The Whiskey Machine: Nanofactory-Based Replication of Fine Spirits and Other Alcohol-Based Beverages

Abstract. Specialized nanofactories will be able to manufacture specific products or classes of products very efficiently and inexpensively. This paper is the first serious scaling study of a nanofactory designed for the manufacture of a specific food product, in this case high-value-per-liter alcoholic beverages. The analysis indicates that a 6-kg desktop appliance called the Fine Spirits Synthesizer, aka. the "Whiskey Machine," consuming 300 W of power for all atomically precise mechanosynthesis operations, along with a commercially available 59-kg 900 W cryogenic refrigerator, could produce one 750 ml bottle per hour of any fine spirit beverage for which the molecular recipe is precisely known at a manufacturing cost of about $0.36 per bottle, assuming no reduction in the current $0.07/kWh cost for industrial electricity. The appliance's carbon footprint is a minuscule 0.3 gm CO_2 emitted per bottle, more than 1000 times smaller than the 460 gm CO_2 per bottle carbon footprint of conventional distillery operations today. The same desktop appliance can intake a tiny physical sample of any fine spirit beverage and produce a complete molecular recipe for that product in ~17 minutes of run time, consuming <25 W of power, at negligible additional cost.

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"Somewhere in the bowels of the cabinet a bartender went into action – a non-human bartender whose electronic soul mixed things not by jiggers but by atom counts, whose ratios were perfect every time, and who could not be matched by all the inspired artistry of anyone merely human."

– Isaac Asimov, *Pebble in the Sky* (1950)

1. Introduction

Specialized nanofactories will be able to manufacture specific products or classes of products very efficiently and inexpensively. This paper is the first serious scaling study of a nanofactory designed for the manufacture of a specific food product, in this case high-value-per-liter alcoholic beverages. The main purpose of this paper is to assess the technical opportunities for the inexpensive chemical analysis and manufacturing of fine spirits and other alcohol-based beverages using the equipment and techniques of atomically precise manufacturing. Of particular practical concern to commercial interests is the vulnerability of existing fine spirits business models to potentially disruptive new sources of atomically indistinguishable replicant products having significantly lower production cost and/or higher consumer desirability than traditionally produced products.

The discussion here focuses on alcohol-based fine spirits, using whiskey[1] as the exemplar beverage product. Other closely related product classes, including distilled spirits such as cognac, rum, brandy, gin, tequila, vodka, Japanese shochu, and Chinese baijiu, other beverages of intermediate alcohol content such as Japanese sake and liqueurs[2] such as Bénédictine, Chartreuse, Grand Marnier, nalewkas, and American schnapps, and fermented and fortified beverages of low alcohol content such as champagne, beer, wine, sherry, and cider, technically could be synthesized by similar methods if product pricing and manufacturing costs permit, as could perfumes and fragrances which are often solvated in fine spirits such as brandy and cognac,[3] but these applications are not discussed extensively in this document. Non-alcoholic beverages – such as coffee, tea, milk,[4] juices, and carbonated sodas – could in principle be manufactured in the same manner but might not be justifiable purely economically unless the cost of energy drops a bit; these also are not discussed further in this document.

While further investigation will be required, the analysis presented here makes a compelling case that the following capabilities may be enabled by the development of nanofactories and atomically precise manufacturing:

(1) Quickly and inexpensively performing a quantitative assay of all organoleptic congeners present in fine spirits, allowing compilation of the complete molecular recipe for a particular spirit.

(2) Quickly and inexpensively manufacturing all organoleptic congeners present in fine spirits.

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[1] The beverage is spelled “whisky” in Scotland but as “whiskey” in the United States and Canada.

[2] http://en.wikipedia.org/wiki/List_of_liqueurs.

[3] http://en.wikipedia.org/wiki/Perfume.

[4] Ryan Pandya, “Making milk without the moo,” *New Scientist*, NS 2975, 30 June 2014; http://www.newscientist.com/article/mg22229750.400-dont-have-a-cow-making-milk-without-the-moo.html.

(3) Manufacturing fine spirits with arbitrarily low concentrations of impurities and contaminants.

(4) Manufacturing replicant fine spirits that are perfect copies of the original material, at perhaps 10 times lower cost than current distillery practice for the original material, given current energy costs.

(5) Synthesizing key valuable vintages or "honey barrel" products on the spot with no need for maintaining historical inventories, thus putting the value of existing inventories of artisanal fine spirits at serious economic risk.

(6) Precise quantification of the organoleptic (sensory) relevance of every chemical component present in any fine spirit, using a combination of rapid product prototyping, selective chemical deletion, and a small cadre of trained human tasters.

(7) Rapid prototyping of novel mixtures, allowing the creation of customized or unique personalized compositions that are specified in molecular detail and thus instantly replicable.[5]

(8) Creating new compositions of whiskey that have not been, or perhaps are even impossible to be, produced by the methods of the traditional distiller's art.

(9) Creating "edited" versions of fine spirits that either (A) have all the deleterious compounds removed without affecting taste, or that (B) include non-deleterious compounds that taste the same as the deleterious ingredients while lacking their harmful effects. Can we go all the way to synthehol?[6] Perhaps.

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[5] In principle we can create a customized "perfect whiskey". Customers could receive a tasting kit with idealized mixtures of various chemicals and perform their own taste comparisons (e.g., does "A" taste better than "B", repeated with many different comparison pairs). If the selection of ingredients is arranged so that an adequate range of taste combinations are exercised, then a statistical analysis might allow a computer to estimate an individual person's "ideal flavor" profile for whiskey. It would then be possible to manufacture a bottle of individualized "ideal whiskey" for that customer, on the spot. After iterating several trial cycles, using ever more subtle changes in comparison to the trial mix, it should be possible to progressively home in on the ideal flavor profile for that customer.

[6] Synthehol is a fictional artificial substitute for alcohol that simulates the appearance, smell, and taste of alcohol, even providing an ethanol-simulating "buzz" that is easily chemically dismissed without any adverse effects such as hangovers (http://science.howstuffworks.com/innovation/edible-innovations/synthehol.htm). It is interesting to review how ethanol affects the human brain. Ethanol enhances the effect of the neurotransmitter GABA (gamma amino butyric acid; http://en.wikipedia.org/wiki/GABA) that acts as an inhibitory neurotransmitter on the central nervous system, producing a sedative effect and causing sleepiness. Ethanol also acts as an antagonist at the NMDA receptor (http://en.wikipedia.org/wiki/NMDA_receptor) for the glutamate neurotransmitter, suppressing the nervous system response to glutamate and enhancing the sedative effect of alcohol, while depressing the behavioral inhibitory centers in the cerebral cortex and raising the dopamine level in the brain's reward center (which creates the "buzz").

Scientists have already created drugs that act like alcohol on the brain. Alcoholics who are trying to quit can take a class of drugs called benzodiazepines. These drugs are also prescribed for anxiety, panic

After a brief summary (Section 2) of the most relevant chemical properties of whiskey – our exemplar fine spirit – we describe traditional methods for producing fine spirits (Section 3) and then review many previous and recent attempts to chemically replicate fine spirits (Section 4). We then describe a new approach for replicating fine spirits, employing the techniques of atomically precise manufacturing, that would use a specialized nanofactory called the Fine Spirits Synthesizer appliance (Section 5).

Following a detailed analysis, we conclude that the replication of fine spirits using nanofactories is possible at a raw production cost of as little as **$0.36/bottle** ($0.51/kg). A 300-watt desktop appliance could produce **1 bottle (750 ml) per hour** – or about 1 "shot" every 2 minutes – of any fine spirit for which it is given the molecular recipe. If provided with a tiny physical sample of any fine spirit using an immersible sampling wand, the appliance could also generate a **complete molecular recipe for the fine spirit in about 17 minutes of run time** at negligible additional cost.

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disorders, insomnia, muscle spasms and some forms of epilepsy (the commonly-prescribed drugs Xanax, Valium and Klonopin are all benzodiazepines). Like alcohol, these drugs are full GABA receptor agonists, meaning that they enhance the effects of the brain chemical GABA. But taking benzodiazepines can cause significant side effects, including dizziness, weakness and upset stomachs, and people who use these drugs can become dependent on them (http://science.howstuffworks.com/innovation/edible-innovations/synthehol1.htm).

In theory, an alcohol alternative could contain a chemical agent that would bind only to the receptors that trigger the positive effects of drinking (relaxation, pleasure), but not to the receptors that contribute to the negative effects (nausea, memory loss). In other words, if you drink it, you'd still get a "buzz" without having some or all of the harmful effects of alcohol on your body. And when the body breaks down this alcohol alternative, it would not produce acetaldehyde, the toxic substance that leads to hangovers and other ill effects of drinking. Finally, if people drank too much of this alcohol alternative, they could take the benzodiazepine antidote flumazenil (brand name Annexate), which would instantly help them sober up so they could drive home. Flumazenil is sometimes used in hospital emergency rooms to awaken patients who are unconscious for no apparent reason.

David Nutt from the University of Bristol proposes making an alcohol alternative that contains a $GABA_A$ partial agonist. It would bind to a $GABA_A$ receptor, but only *partially* activate it, triggering a weaker response. Because a partial agonist takes the place of a true agonist, it blocks the agonist from latching on to the receptor and causing the full effect. (David J. Nutt, "Alcohol alternatives - a goal for psychopharmacology?" *Journal of Psychopharmacology* 20(2006):318-320.) By late 2013, Nutt reported developing an alcohol substitute that mimics the relaxation and sociability that comes with drinking, but without many of drinking's nasty side effects such as aggression and addiction. Take a pill, and the effects disappear. "We've tried the prototypes," Dr. Nutt said. "I've been completely zonked on a high dose, given an antidote and in a matter of five minutes – not at all." Unlike alcohol, these compounds are not considered toxic to any vital organs and would also be less addictive. Nutt had been hoping to start clinical trials by late 2014: "We're looking for the first tranche of investment in January, and then properly scaling up production and figure out the best kind of cocktails to put it in," he said. See: "No more hangovers? New 'alcohol surrogate' comes with antidote that can make you sober again in minutes," *National Post Canada*, 30 December 2013; http://news.nationalpost.com/2013/12/30/no-more-hangovers-new-alcohol-surrogate-comes-with-antidote-that-can-make-you-sober-again-in-minutes/.

Throughout this report, the unit "tonne" refers to a metric ton or 1000 kg, and the energy unit "zJ" refers to the zeptojoule or 10^{-21} joules. The cost of industrial electricity is assumed in all scenarios to be ~\$0.07/kWh ($c_{ElectCost}$ = 1.94 x 10^{-8} \$/J).[7]

[7] U.S. Industrial Sector, \$0.0651/kWh in April 2013. "Electricity Monthly Update, End Use: April 2013, Retail Service by Customer Sector," U.S. Energy Information Administration (EIA); http://www.eia.gov/electricity/monthly/update/end_use.cfm.

2. Chemical Composition of Whiskey

Whiskey has several important chemical constituents.

The largest two by weight and volume – water and ethanol – are closely related and are discussed together in Section 2.1.

The most important class of chemical constituents in terms of aroma and flavor are the congeners (pron. CON-gen-ers). These substances are summarized in Section 2.2.

Finally, the nature of the particulate matter that sometimes may be found in whiskey and other fine spirits is briefly discussed in Section 2.3.

2.1 Water and Ethanol

Whiskey is typically about 60%-63% water, by weight. It is the principal ingredient in most fine spirits.

Whiskey is usually sold at or near an ethanol concentration of 40%, 43%, or 46% alcohol by volume.[8] "Alcohol by volume" (aka. "ABV", "abv", or "alc/vol") is a standard measure, used worldwide, of how much ethanol is contained in an alcoholic beverage, expressed as a percentage of total volume. ABV is defined as the number of milliliters of pure ethanol present in 100 milliliters of solution at 20 °C.[9] The number of milliliters of pure ethanol is the mass of the ethanol divided by its density at 20 °C, which is 0.78924 gm/ml.

Assuming that the density of 43% ABV (86° proof)[10] whiskey, presumably at the standard ABV temperature of 20 °C, is 940.03 gm/liter,[11] then the alcohol content by weight (aka. ABW) for 86° proof whiskey at 20 °C is: (43 ml ethanol/100 ml whiskey) (78.924 gm ethanol/100 ml ethanol) (100 ml whiskey / 94.003 gm whiskey) = 0.361 gm ethanol / gm whiskey, or **36.1% by weight for ethanol**. (As a check, a table of specific gravity for ethanol-water mixtures[12] gives a density of 942.87 gm/liter for 36.1% ABW at 20 °C, which is very close to the estimated 940.03 gm/liter figure for whiskey cited above.) This is also equivalent to 339.4 gm ethanol per liter of 86° proof whiskey.

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[8] http://en.wikipedia.org/wiki/Alcohol_by_volume.

[9] Ethanol-water mixtures have less volume than the sum of their individual components at the given fractions. Mixing equal volumes of miscible ethanol and water results in only 1.92 volumes of mixture. (D.R. Lide, ed., *CRC Handbook of Chemistry and Physics*, 81st Edition, CRC Press, 2000; "Ethanol", *Encyclopedia of Chemical Technology*, Vol. 9, 1991. p. 813.)

[10] In the United States, alcohol content is measured in terms of the percentage of alcohol by volume. The Code of Federal Regulations (27 CFR [4-1-03 Edition] §5.37 Alcohol content) requires that liquor labels must state the percentage of ABV. The same regulation permits, but does not require, a statement of the proof provided that it is printed close to the ABV number. For bottled spirits over 100 ml containing no solids, **actual alcohol content is allowed to vary within 0.15% of ABV stated on the label**. Alcohol proof in the United States is defined as twice the percentage of alcohol by volume. Consequently, 100-proof whiskey contains 50% alcohol by volume, 86-proof whiskey contains 43% alcohol, and so forth; http://en.wikipedia.org/wiki/Alcohol_proof.

[11] http://www.aqua-calc.com/page/density-table/substance/alcoholic-blank-beverage-coma-and-blank-distilled-coma-and-blank-whiskey-coma-and-blank-86-blank-proof.

[12] Robert H. Perry, Don Green, eds., *Perry's Chemical Engineers' Handbook*, 7th Ed., Table 3-110, p. 3-89; http://www.handymath.com/cgi-bin/ethanolwater3.cgi?submit=Entry.

2.2 Congeners

In general, beverage congeners (Latin for "born together") may include organic and inorganic substances, liquid and solid components, flavors and colorants, solvated and suspended materials, and both intentional materials and unintentional or undesirable impurities.[13]

In the alcoholic beverages industry, **congeners** are substances other than alcohol that are produced during fermentation. These substances most typically include small amounts of chemicals such as other alcohols (known as fusel alcohols or fusel oils), acetone, acetaldehyde, esters, tannins, and others such as furfural, glycols, and ethyl acetate. Congeners are responsible for most of the taste and aroma of distilled alcoholic beverages, and contribute to the taste of non-distilled drinks such as beer and wine.[14] Some congeners may contribute nothing to the taste of the beverage. Congeners that contribute something to the sensory experience are called **organoleptics**.

Spirits such as vodka have relatively low concentrations of congeners, whereas other spirits such as whiskey have relatively high levels of congeners. In the context of this document, our emphasis on precisely replicating the congeners of whiskey probably represents one of the most challenging tasks in the fine spirits product sector – that is, the "hardest case" scenario. Replication of the congeners for fine spirits other than whiskey will likely require the manufacture of somewhat smaller quantities of fewer chemical constituents, hence may have moderately lower manufacturing costs with lower product complexity as compared to whiskey.

What are the congeners in whiskey? The composition varies widely in different whiskey products, but according to one of the earliest chemical analyses, a classic pre-Prohibition Era American textbook published in 1919,[15] the congeners in contemporary 85 proof bottled whiskey were 150 parts per 100,000 for volatiles (range 100-250 for various whiskies) and 600 parts per 100,000 for nonvolatiles (range 450-650), total 750 parts per 100,000 for all congeners (range 550-900), presumably measured on a volume basis. Assuming that congeners overall have about the same density as whole whiskey at 20 °C, then the congener content by weight in pre-Prohibition Era whiskey was approximately 0.15% for volatiles, 0.60% for nonvolatiles, and **0.75% by weight for all congeners**. These numbers seem very conservative because they are consistent with general statements from various sources[16] that the total congener content of

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[13] In some sweet liqueurs, the sugar content can be higher than the ethanol content.

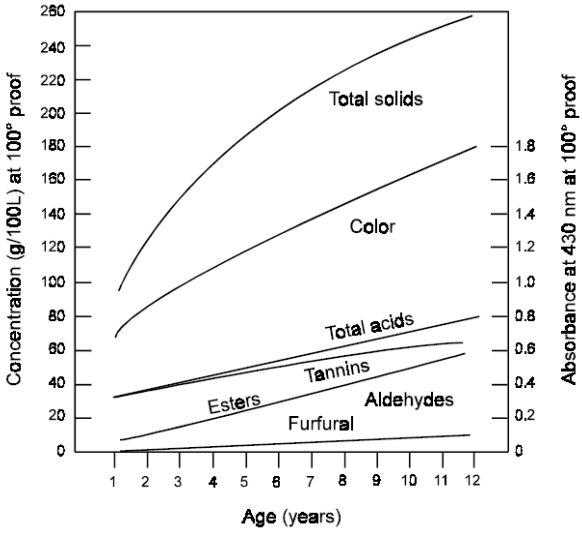
[14] http://www.winesandvines.com/template.cfm?section=features&content=74439.

[15] "Composition of Whiskey," in: Harvey W. Wiley, *Beverages And Their Adulteration: Origin, Composition, Manufacture, Natural, Artificial, Fermented, Distilled, Alkaloidal And Fruit Juices*, P. Blakiston's Son & Co., 1919; http://chestofbooks.com/food/beverages/Adulteration-Origin/Composition-Of-Whisky.html#.U3fw_yjyROQ.

[16] https://www.whisky.de/archiv/experts/alcohol.htm, https://web.archive.org/web/20060902075629/http://ciitn.missouri.edu/testsite/www/212w03ICPR/group02article.html, http://photon.st-and.ac.uk/trapping/images/files/2011/2011_Ashok_3.pdf,

modern whiskey is 1% or less, and because they seem consistent with measured data including: (1) a chemical assay of various modern alcoholic beverages putting the total measured range of whiskey congeners, excluding caramel colorant, at 0.108%-0.786% gm/liter (**0.115%-0.836% by weight**),[17] (2) a 2013 chemical assay that measured the 7 largest congeners in straight bourbon whiskey at **~0.3% by weight**,[18] (3) a 2003 book on whiskey production claiming that congeners of whiskey comprise only **0.1% by volume**,[19] and (4) the data in **Figure 1** that show how total solids in 100° proof Scotch grain whiskey rise with the storage age of the distillate, from **0.100% by weight** (98 gm/100L) in 1 year to **0.274% by weight** (258 gm/100L) by year 12 of storage.

Figure 1. Change in vapor composition (range 0-0.26%) at different trays in Coffey-still rectifier used in the manufacture of Scotch grain whiskey, during 12 yr of storage, on a 100° proof basis.[20]



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https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&ved=0CFQQFjAG&url=https%3A%2F%2Fideals.illinois.edu%2Fbitstream%2Fhandle%2F2142%2F16713%2F1_Lahne_Jacob.pdf%3Fsequence%3D2&ei=29Z3U57AJZHvoASg0oHAAg&usg=AFQjCNEfyQuzAylqI01l-VdFmbx2S_MOIw&sig2=yu1r9Siv-p16YFReLtU2wg&cad=rja.

[17] See totals at bottom of Table 2, below.

[18] "Chemical composition of whiskies produced in Brazil compared to international products," 2013; http://www.dirk-lachenmeier.de/Whiskies_Brazil.pdf.

[19] Ross Aylott, "Chapter 9. Whisky Analysis," in: Inge Russell, Graham Stewart, eds., *Whisky: Technology, Production and Marketing*, Academic Press, 2003; http://books.google.com/books?id=9P3lGgNahvgC&pg=PA278&lpg=PA278&dq=congeners+in+whiskey+concentration&source=bl&ots=xBfgAWGdfF&sig=eE_erMaBalMauxmflU4n08e5Kpc&hl=en&sa=X&ei=tt-kU4esNofyoAS6yoKQDA&ved=0CDgQ6AEwAw#v=onepage&q=congeners%20in%20whiskey%20concentration&f=false.

[20] M. Pyke, "The manufacture of Scotch grain whisky," *Journal of the Institute of Brewing* 71(May-Jun 1965):209-218; http://onlinelibrary.wiley.com/doi/10.1002/j.2050-0416.1965.tb02047.x/epdf.

Our preliminary estimates for the general composition of whiskey, measured as a percentage by weight (e.g., gm component per gm of whole whiskey), are summarized in **Table 1** below.

Table 1. Preliminary estimate of the general composition of whiskey, expressed as a percentage by weight.

Whiskey Component	**% by weight** (gm component / gm whiskey)
Water	63.15 %
Ethanol (in 86 proof whiskey)	36.10 %
Congeners	0.75 %
volatile congeners (0.15 %)	
nonvolatile congeners (0.60 %)	
TOTAL	**100.00 %**

In general, alcohol-based beverages may contain volatile, nonvolatile, and flavorant components that change as the whiskey ages (Figure 1):

Volatiles may include aliphatic carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, hydrocarbons, terpenic compounds, and heterocyclic and aromatic compounds. Volatiles generally originate from three sources: raw materials, fermentation, and the wooden casks in which they are matured. In the distillation procedure (Section 3), it is customary to improve the flavor of the distillate by stripping it of low-boiling and high-boiling compounds to a greater or lesser degree.

Non-volatiles may include unfermented sugars, di- and tri-basic carboxylic acids, coloring substances, tannic and polyphenolic substances, and inorganic salts.

Flavorants: Certain flavored alcoholic beverages may contain, in addition to the natural compounds of the beverages, added synthetic substances and ingredients isolated from herbs and spices. Vermouths, apertifs, bitters, liqueurs and some flavored vodkas frequently include different essential oils or their mixtures. Other synthetic products and coloring substances, such as caramel, may also be added to improve the perceived flavor.

Modern analytical techniques have enabled major advances in the understanding of the compounds responsible for the organoleptic properties of whiskies. However, the first reports on the nature of flavor-producing compounds in whiskies antedate the modern era of Gas Liquid Chromatography (GLC) by nearly half a century. Two publications by Schidrowitz (1902) and Schidrowitz and Kaye (1905), dealing exclusively with Scotch whiskies, reported on the higher

alcohol, acid and ester contents of some 50 different brands.[21] They reported analyses of several Campbeltown Scotch malt whiskies. A report by Mann (1911) published a few years later also quoted values for acidity and levels of furfural, aldehydes, esters and alcohols in Scotch whiskies imported into Australia.[22] Higher alcohols, which are still routinely determined with GLC using a polar stationary phase,[23] are quantitatively the most important. Scotch malt whiskies are richest in higher alcohols, with contents often well over 2 gm/L. Free fatty acids are relatively volatile and make a major contribution to the organoleptic qualities of whiskies. Concentrations of acids in some Scotch malt whiskies can be as high as 0.4-1.0 gm/L absolute alcohol.[24]

Even when analytical methods such as capillary column gas chromatography are linked to a mass selective detector's (GC-MS) sensitivity and discrimination, a major problem in analyzing whiskey by GLC is the overwhelming preponderance of ethanol and water. Only one volatile compound, namely isoamyl alcohol, is likely to be present in a concentration exceeding 0.01%, while most of the others are present in concentrations that rarely exceed 50 parts-per-million (ppm). Indeed many compounds now understood to have an important impact on whiskey flavor are present at parts-per-billion (ppb) levels. For example, Carter-Tijmstra described a technique for measuring dimethyl trisulfide, a compound with a sensory detection threshold of only 0.1 ppb that can be present in whiskey at concentrations below 50 ppb.[25] Conventional chemical analyses are most conveniently conducted on extracted fractions of the different classes of compounds.

The exact compositions of many alcoholic beverages are trade secrets, but there is an extensive literature of the aroma components which are usually present at low levels, more than 1300 of which had been identified by the early 1980s.[26] Information about non-aroma compounds is less extensive, though searches for these compounds occurring in distilled alcoholic beverages[27] and the volatile components of distillates[28] have been in progress for many decades.[29]

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[21] P. Schidrowitz, *Journal of the Chemical Society*, 1902, p. 814; P. Schidrowitz, F. Kaye, *Journal of the Chemical Society*, 1905, p. 585.

[22] E.A. Mann, Government Analyst for Western Australia (Perth, W. Australia), 1911, pp. 1-12.

[23] R.I. Aylott, A.H. Clyne, A.P. Fox, D.A. Walker, "Analytical strategies to confirm scotch whisky authenticity," *Analyst* 119(1994):1741-1746; https://www.researchgate.net/profile/Ross_Aylott/publication/241270949_Analytical_strategies_to_confirm_Scotch_whisky_authenticity/links/0a85e53a0a192acd08000000.pdf.

[24] R.E.B. Duncan, J.M. Philp, "Methods for the analysis of Scotch whisky," *Journal of the Science of Food and Agriculture* 17(May 1966):208-214.

[25] J. Carter-Tijmstra, "Whiskey flavour compound analysis by gas chromatography," Proceedings of Second Aviemore Conference on Malting, Brewing and Distilling, 1986, pp. 413-416.

[26] L. Nykanen, H. Suomalainen, eds., *Handbook of Aroma Research, Book 3: Aroma of Beer, Wine and Distilled Alcoholic Beverages*, Springer, 1983.

[27] R. Ter Heide, "The flavour of distilled beverages," *Developments in Food Science B* 3(1986):239-312.

[28] C. Jouret, J.L. Puech, "Importance of lignin in maturing of rum," *Annales de Technologie Agricole* 24(1975):325-333.

The most important whiskey congeners are listed in **Table 2**, along with their measured concentrations in a variety of whiskey products. (Unavailable data are signified by "n/a".)

[29] J.H. Kahn, P.A. Shipley, E.G. Laroe, H.A. Conner, "Whiskey Composition: Identification of Additional Components by Gas Chromatography-Mass Spectrometry," *Journal of Food Science* 34(November 1969):587-591; http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2621.1969.tb12096.x/abstract.

Table 2. Measured concentrations of some important components of whiskey.[30]

Whiskey Component	Concentration (mg/liter)	Parts-per-million (ppm) by weight (10^6 x gm component / gm whiskey)
Aliphatic monohydric alcohols (aka. fusel alcohols)		
methanol	40-130	43-138
propanol	20-187	21-199
isobutanol (aka. 2-methyl-1-propanol)	100-670	106-713
2-methyl-butanol	60-1390	64-1479
isopentanol (aka. isoamyl alcohol, 3-methyl-1-butanol)	150-2560	160-2723
phenethyl alcohol (2-phenylethanol)	1-131	1-139
Esters of aliphatic acids		
ethyl esters of monocarboxylic acids	360-1010	383-1074
ethyl formate (4-27 mg/L)		
ethyl acetate (180-505 mg/L)		
ethyl caprate (2-10 mg/L)		
ethyl esters of hexadec-9-enoic acid & hexadecanoic acids	*n/a*	
Esters of aromatic acids	n/a	
Phenolic compounds		
tannins (from wooden casks)	230-670	245-713
gallic acid (3,4,5-trihydroxybenzoate, a phenolic acid)	n/a	
ellagic acid (the dilactone of hexahydroxydiphenic acid)	n/a	
phenols	0.003-0.801	0.003-0.852
cresols (0.075 mg/L each of ortho, meta, & para)	0.041-0.160	0.044-0.17
2,6-xylenol	0.001	0.001
7 other phenols	0-0.29	0-0.31

[30] **(1)** L. Nykanen, H. Suomalainen, eds., *Handbook of Aroma Research, Book 3: Aroma of Beer, Wine and Distilled Alcoholic Beverages*, Springer, 1983. **(2)** "Chapter 3. Chemical Composition of Alcoholic Beverages, Additives and Contaminants," in *IARC monographs on the evaluation of carcinogenic risks to humans*, World Health Organization, International Agency for Research on Cancer, Vol. 44, 1988, pp. 71-99; http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CDMQFjAC&url=http%3A%2F%2Fmonographs.iarc.fr%2FENG%2FMonographs%2Fvol44%2Fmono44-7.pdf&ei=Ba12U6qlO9O-oQTPt4CYDg&usg=AFQjCNHBsRwTsJXjwduqbVaU_SzkeSW-9A&sig2=MLE3SUdiLWpb4tVEEQV21Q&bvm=bv.66917471,d.cGU&cad=rja. **(3)** T.P. Lyons, "Chapter 11. Production of Scotch and Irish whiskies: their history and evolution," 1999; http://web.sls.hw.ac.uk/teaching/distilling/files/documents/Lyons1999.pdf. **(4)** Ross Aylott, "Chapter 9. Whisky Analysis," in: Inge Russell, Graham Stewart, eds., *Whisky: Technology, Production and Marketing*, Academic Press, 2003; http://books.google.com/books?id=9P3lGgNahvgC&pg=PA278&lpg=PA278&dq=congeners+in+whiskey+concentration&source=bl&ots=xBfgAWGdfF&sig=eE_erMaBalMauxmflU4n08e5Kpc&hl=en&sa=X&ei=tt-kU4esNofyoAS6yoKQDA&ved=0CDgQ6AEwAw#v=onepage&q=congeners%20in%20whiskey%20concentration&f=false. **(5)** Teemu Strengell, "Whisky Science: Caramel E150," 17 April 2011; http://whiskyscience.blogspot.com/2011/04/caramel-e150.html.

eugenol (4-allyl-2-methoxyphenol, allylguaiacol)	0.583-0.993	0.620-1.06
Aliphatic aldehydes		
acetaldehyde (20-220 mg/L of ethanol)	10-110	11-117
propionaldehyde	1.2	1.3
isobutyraldehyde	20	21
2-methylbutyraldehyde & 3-methylbutyraldehyde	6.3	6.7
Aromatic aldehydes		
furfural (furan-2-carboxaldehyde, furfuraldehyde)	12-30	13-32
syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde)	0-13.8	0-10.9
vanillin (4-hydroxy-3-methoxybenzaldehyde)	0.04-8.13	0.04-8.65
scopoletin (7-hydroxy-5-methoxycoumarin), coniferaldehyde (4-hydroxy-3-methoxycinnamaldehyde), sinapaldehyde (3,5-dimethoxy-4-hydroxycinnamaldehyde), salicylaldehyde, hydroxymethylfurfural, acetovanillone (1-(4-hydroxy-3-methoxyphenyl)ethanone or apocynin)	*n/a*	
Unsaturated aldehydes		
acrolein, propenal, 1,1,3-triethoxypropane	*n/a*	
Aliphatic acids		
acetic acid (50%-95% of total volatile acids)	4.5-805	4.8-856
octanoic acid (caprylic acid), decanoic acid (capric acid), dodecanoic acid (lauric acid), formic acid, palmitic acid, palmitoleic acid ((Z)-hexadec-9-enoic acid), other short-chain acids (propionic, 2-methylpropionic, butyric, 3-methylbutyric, pentanoic), other straight-chain monocarboxylic acids (C_2-C_{18})	12.5-15.1	13.3-16.1
Aliphatic ketones		
acetone	3-10	3-11
Diketones		
2,3-butanedione	0.01-4.4	0.01-4.7
2,3-pentanedione	0.003-0.57	0.003-0.61
Unsaturated monoketones		
tri-6-decen-2-one, penta-6-decen-2-one, hepta-6-decen-2-one	*n/a*	
Rose ketones		
β-damascenone	0.036-0.048	0.038-0.051
Lactones		
cis-whiskey lactone (β-methyl-octalactone, cis-3-methyl-4-octanolide)	5.3-8.37	5.6-8.9
trans-whiskey lactone	1.02-1.30	1.09-1.38
Aromatic acids		
coumaric acid (4-hydroxycinnamic acid)	(small amts)	
gallic acid (3,4,5-trihydroxybenzoic acid), syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid)	*n/a*	
Trace elements		
potassium ion	26-30	28-32
magnesium ion	1.9-28	2.0-30
calcium ion	11-17	12-18
sodium ion	1-3	1-3
Colorants		
spirit caramel (color-balancing additive)	1000-5000	1060-5300
melanoidins (derived from casks)	n/a	
Other components		
glycerol	n/a	

erthritol	n/a	
pyridine	n/a	
α-picoline	n/a	
various pyrazines	n/a	
terpenes and terpenoids (incl. turpentine)	n/a	
sugars *(glucose, fructose, arabinose, xylose, rhamnose, mannose, galactose)*	*n/a*	
sterols *(campesterol, stigmasterol, sitosterol, sitosterol-D-glucoside)*	*n/a*	
Contaminants & undesirables		
copper ion	0.131-0.480	
ethyl carbamate	<0.120 (U.S.)	
dimethyl trisulfide	< 0.050	
urethane	0.03-0.3	0.03-0.3
N-nitrosamines (NDMA, NDEA, NDPA)	0.00015-0.0015	0.00016-0.0016
hydrogen sulfide	n/a	
TOTALS		
all components	**2078-12,859**	**2211-13,679**
excluding spirit caramel colorant	***1078-7859***	***1147-8360***

2.3 Particulates

Visible particulates are known to occur in whiskey. However, no information is readily available that discusses the character, size distribution, and concentrations of potentially organoleptic fine particulates that might be present in final product whiskey. The following is a brief summary of what's known – much of it, unfortunately, only anecdotal.

2.3.1 Floaters and Sediments

When whiskey is removed from the wood casks, it is commonly put through a basic barrier filter to catch fairly large particulates without affecting taste (unless someone's palate actually enjoys mechanical grittiness, which the human tongue can detect down to about 10 microns in particle size). Some observers[31] have reported seeing "tiny strands...very fine but thicker than say human hair, twisted and curled, perhaps 1-2 mm long"; "small floaters... most were very small and white in colour (like tiny shreds of tissue), but some were larger and brown/black in colour."

Another observer[32] reported seeing a lot of "floaters" and specks that looked like "tiny flecks of sawdust and even a few very small black bits from a very old bottle of Clynelish 1976 from the Murray McDavid Mission series, and even posted some images online (**Figure 2**). "They weren't air bubbles or imperfections on the bottle, they floated around. Inspection of the cork revealed no 'corking' or anything untoward. It was less of a haze, more actual particulates."

While the white particles may be fatty acids (Section 2.3.2), the other particles may have a different source. One observer[33] claims that bottles of unfiltered whiskies such as Blackadder Raw Cask[34] may contain "a fairly large amount of ashes, wood shavings, sheep's hair or whatever was in the cask at the time of bottling." Another observer[35] saw "small tiny black colored particles" floating in a miniature bottle of Jack Daniels sour mash whiskey no.7. Apparently it is not uncommon for barrel char to occur in bottlings of American whiskey – bourbons such as George T. Stagg, Booker's, William Larue Weller, etc. – that are otherwise unfiltered, and bits of charcoal may be more common in whiskey produced via the Lincoln County Process.[36] Notes

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[31] http://www.whiskymag.com/forum/viewtopic.php?f=6&t=10448; http://www.connosr.com/wall/discussion/69318/floaters-particles-in-whisky-is-this-normal/.

[32] http://www.whiskymag.com/forum/viewtopic.php?t=5271.

[33] http://www.connosr.com/wall/discussion/69318/floaters-particles-in-whisky-is-this-normal/.

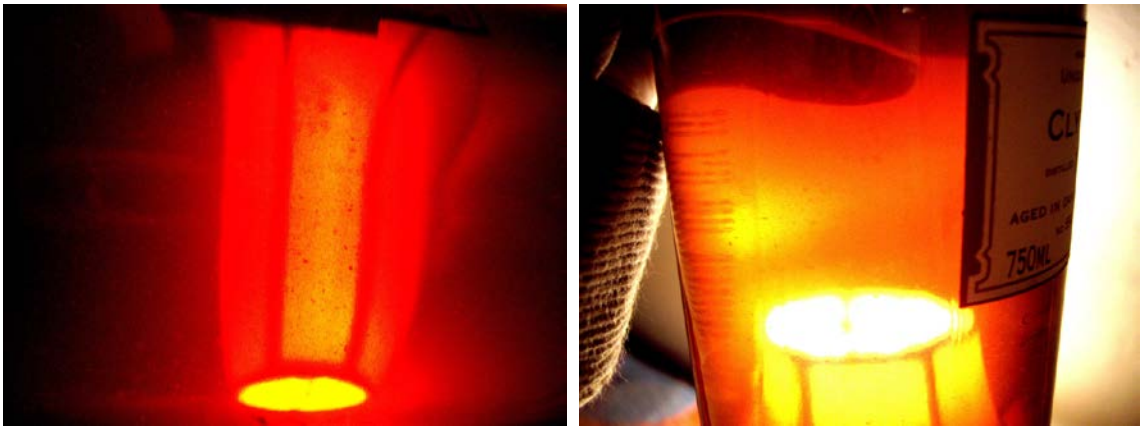
[34] http://www.whiskywebshop.nl/a-11466807/blackadder-bottelingen/caol-ila-1992-islay-schotland-blackadder-raw-cask.

[35] http://www.whiskyportal.com/forum/forum_posts.asp?TID=192.

[36] The Lincoln County Process (http://en.wikipedia.org/wiki/Lincoln_County_Process) is a step used in producing some Tennessee whiskies. The whiskey is filtered through, or steeped in, charcoal chips before

one worker at a distillery that uses old Jack Daniel's casks: "It's simply some charcoal that has managed to make its way through the filtering process from the barrel.... you would not believe how much charcoal comes out when it comes round to emptying!"

Figure 2. Two images of floating sediment in old whiskey[37]



Over a period of time, whiskies – even those that once appeared crystal clear to the eye – can "throw sediment" just like wines. What often transpires is that tiny (initially not discernible) residual particles of oak and/or grape matter and/or other substances bind to one another and precipitate, thereby becoming visible. This phenomenon is not necessarily related to chill filtering (Section 2.3.2). One observer[38] reported "a 50 ml mini of original issue Bowmore Darkest that now displays considerable sediment." Another observer[39] reported buying "a case of Bruichladdich 10 a while back and all 6 bottles had these solid deposits in the bottle. There was quite a bit of it in there, sitting on the bottle bottom until you moved or swirled the bottle about, then the particles would float about, almost unseen when mixed up, only to settle down on the bottle base again after a few minutes. Definitely not a haze. I emailed Mark Reynier at Bruichladdich, just to check that it wasn't the cork stopper that was coming apart (as I thought

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going into the casks for aging. The process is named for Lincoln County, Tennessee, which was the location of Jack Daniel's distillery at the time of its establishment. The charcoal used by Jack Daniel's is created on site, from stacks of two by two inch sugar maple timbers called "ricks". They are primed with 140 proof Jack Daniel's, then ignited under massive hoods that help prevent sparks. Once they have reached the char state, the ricks are sprayed with water to prevent complete combustion. The resulting charcoal is then run through a grinder to reduce it to consistent bean-size pellets. These are then packed into 10-foot (3.0 meter) vats, where they are used to filter impurities from the 140 proof whiskey, after which the whiskey is reduced with water to 125 proof for aging.

[37] http://farm1.static.flickr.com/152/343210727_7ac1285d4e_b.jpg and http://farm1.static.flickr.com/127/343210729_2c8753f94c_b.jpg.

[38] http://www.whiskymag.com/forum/viewtopic.php?f=6&t=10448.

[39] http://www.whiskymag.com/forum/viewtopic.php?t=5271.

that was what it might be, [and] this is the response I received: It is a natural deposit as seen in fine wines – we do not chill-filter or colour the whiskey. It is bottled naturally and so depending on storage temperatures will sometimes throw a deposit." Simple barrier filtration can remove most floaters and sediments. In the past, whiskey has been clarified for bottling by filtration through sheets of cellulose.[40]

2.3.2 Colloidal Particles and Chill-Filtering

As explained by Matthew Fergusson-Stewart,[41] a whiskey connoisseur in Singapore, most food precursors and food products contain lipids (aka. fatty acids or fats). In the case of whiskey, some of the lipid content of the barley used to make the fine spirit persists all the way through gristing, steeping, fermentation, distillation and maturation, and thus is found in the resulting whiskey. Many people believe the presence of these lipids contributes significantly to taste.

When whiskey is above 46% alcohol at room temperature, the appearance of the beverage is unaffected. But if you add enough water, or if you chill the whiskey, or if you do both at the same time by adding ice to your whiskey, the liquid becomes cloudy or "hazy" – losing the classic bright golden shine that is associated with whiskey. Just as each whiskey has different levels of esters, aldehydes or phenols, each can also have different levels of lipids, and some will exhibit this "clouding" behavior more strongly than others.[42] This has led many distillers to remove lipids via chill filtration for almost purely aesthetic reasons. Whether chill filtering noticeably changes the flavor or mouthfeel is a subject of much debate.

The appearance and disappearance of cloudiness in whiskey results from the chemical interactions between the water-ethanol mix and lipids at various temperatures. The lipids in whiskey, like most lipids, have a hydrophilic (water loving) "head" characterized by an electrically charged -OH group, and a hydrophobic (water hating) "tail" typically characterized by one or more long carbon chains (left image, **Figure 3**). It is the dominance of these long hydrophobic carbon chains that prevents oil (oil being fat that is liquid at room temperature) from mixing with water. Ethanol, on the other hand, has a hydrophilic -OH group at one end and a carbon chain at the other, but the carbon chain is very short. The charged -OH group is therefore able to dominate the short carbon chain, allowing ethanol to mix easily with water. In contrast, alcohols with longer carbon chains than ethanol, like hexanol, do not mix readily with water. Fortuitously, the short carbon chain of ethanol is still sufficiently friendly with the long carbon

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[40] A.C. Simpson, "Manufacture of Scotch malt whisky," *Process Biochemistry* 3(Jan 1968):9-14.

[41] Matthew Fergusson-Stewart, "Malt Maniacs E-pistle #2011-06," http://www.maltmaniacs.net/E-pistles/Malt-Maniacs-2011-06-Chill-filtration-and-cloud-formation-in-whisky.pdf.

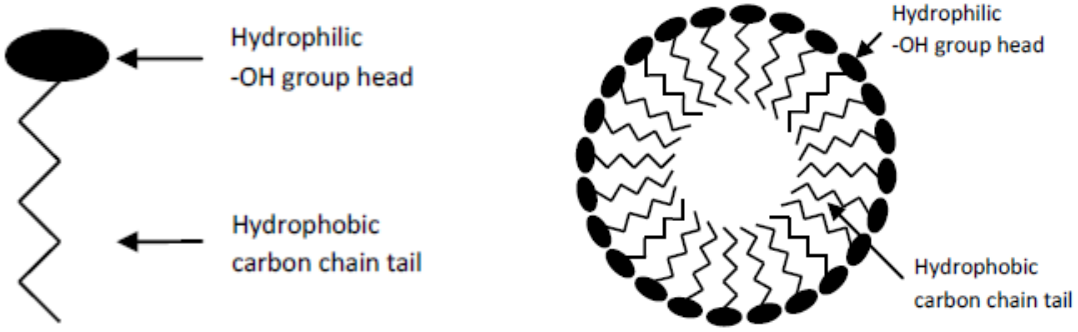
[42] If you pour some whiskey into a glass and add twice as much pure water, you should see the whiskey go cloudy fairly quickly. Gradually adding more water brings out gradually more cloudiness until you reach a maximum. If you put the bottle of whiskey in your freezer, after a few hours of cooling you will see that the entire bottle of whiskey has gone cloudy, even without dilution. Leave the bottle at room temperature and the cloudy haze will slowly disappear with no negative effects. For an incredibly stark example of the same principle, try the same experiments with some Greek Ouzo, which goes from clear to opaque white. Absinthe also gives a very strong result.

chains of lipids to allow them to mix together as well. The ethanol thus participates in the solvation of both.

If ethanol content drops sufficiently, there will no longer be enough of it to keep the oil and water mixed and they will separate. This starts to happen when the ethanol concentration falls below the magic number of 46% ABV at room temperature. At lower temperatures, the oil and water will separate even at higher concentrations of ethanol.

As the lipids and the water stop mixing, the lipids form something called micelles. A micelle is basically a spherical clump of lipid molecules, where the hydrophobic carbon chain "tails" all point in towards the center, away from the water, while the hydrophilic "heads" all point outwards towards the surrounding water (right image, **Figure 3**). Though these clumps of lipid molecules are still tiny, when there are millions of them scattering light in the same glass of whiskey, the result is a cloudy suspension of solid particles in a liquid, called a colloid.[43] Distilleries use chill filtration to remove these lipid micelles under temperature conditions where they will readily form.

Figure 3. Representation of a lipid (left) and a micelle (right).



All non-chill filtered (NCF) whiskey has some level of lipids, and lipids will always contribute to cloudiness when the ethanol content is low enough. However, not all whiskies have the same lipid levels, and cloudiness does not necessarily instantly appear when whiskey first drops just below 46% ABV. The length of the hydrophobic carbon tail (or tails) varies between different lipids, and it is the length of this carbon tail that determines their solubility in ethanol. Longer carbon tails make lipids less soluble, and these lipids form micelles just below 46% ABV ethanol. Other lipids require the ethanol concentration to drop further in order to micellate. The magical 46% ABV is not a switch that flicks cloudiness on and off. Rather, it simply marks one end of the micelle forming range, with each lipid having its own critical micelle concentration. There are a number of non-chill filtered whiskies bottled at 43% ABV. This is low enough for micelle formation to begin, but sometimes for it to be less than obvious. Nonetheless, putting one of

[43] The cell walls in a human body are constructed in an almost identical way. Animal cell walls have an outer layer of lipid molecules, with the hydrophilic heads pointing outwards, and a reversed inner layer, with hydrophilic heads pointing into the cell. The hydrophobic tails of the molecules in each layer point to each other between the layers.

these whiskies side by side with a chill filtered whiskey of similar color often reveals that the 43% ABV non-chill filtered whiskey is not as bright and shiny, a fact that may not be obvious when it is observed alone.

Also present in mature whiskies are sterols[44] which may precipitate in bottled whiskey upon chilling[45] or even when stored at room temperature. Black and Andreasen (1973) found campesterol, stigmasterol and sitosterol in mature bourbon, in addition to sitosterol-D-glucoside, although the possibility that some of these were formed during mashing cannot be excluded.[46]

An important factor to note is that none of these colloidal particulates would have to be added to a chemically synthesized whiskey because their molecular precursors, already present in the mixture, would spontaneously self-assemble in solution under the usual conditions of temperature and dilution required to induce cloudiness.

Chill filtering[47] is a residue-removal method in which whiskey is cooled to between -10 °C and 4 °C Celsius (often roughly 0 °C) and passed through a fine adsorption filter. This prevents the whiskey from becoming hazy when in the bottle, when served, when chilled, or when water or ice is added. It also helps to preclude sedimentation from occurring in the bottles. Chill filtering works by reducing the temperature sufficiently that some fatty acids, proteins and esters (created during the distillation process), including tannin materials,[48] precipitate out so that they are caught on the filter. Single malt whiskies are usually chilled down to 0 °C, while the temperature for blended whiskies tends to be lower since they have lower levels of fatty acid.

Factors affecting the chill filtering process include the temperature, number of filters used, and speed at which the whiskey is passed through the filters. The slower the process and the more filters used, the more impurities will be collected, but at increasing cost. Since this process is believed to sometimes affect the fragrances and taste of the whiskey, for example by removing peat particles that contribute to the "smokiness" of the flavor, some distilleries pride themselves on not using this process.[49] With the current revival of single malt, more and more producers are

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[44] http://en.wikipedia.org/wiki/Sterol.

[45] http://www.google.com/patents/CA1162438A1?cl=en.

[46] R.A. Black, A.A. Andreasen, "Steroids in aged whisky," *Journal of the Association of Official Analytical Chemists* 56(1973):1357-1361.

[47] http://en.wikipedia.org/wiki/Whiskey#Chill_filtration.

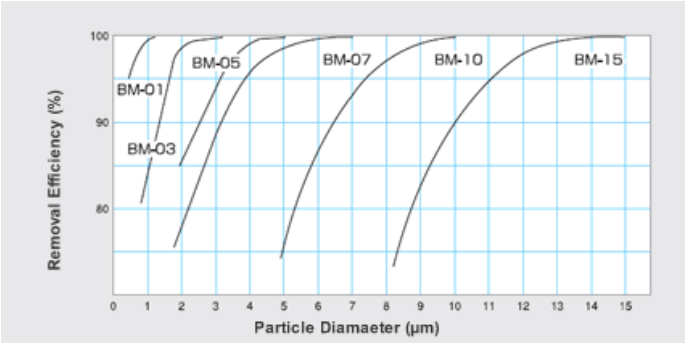
[48] T. Pearse Lyons, "Chapter 14. Production of Scotch and Irish whiskies: their history and evolution," in K.A. Jacques, T.P. Lyons, D.R. Kelsall, eds., *The Alcohol Textbook*, 4th Edition, Nottingham University Press, 2003, pp.193-222, p. 213; http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=14&ved=0CEEQFjADOAo&url=http%3A%2F%2Fwww.ghp-books.com%2Ffreegas%2Falcoholtextbook.pdf&ei=Koi7U7f5OpbhoAST0YDgBw&usg=AFQjCNEecmRthJQJDtqEMuEIfjIWqszUJQ&bvm=bv.70138588,d.aWw&cad=rja.

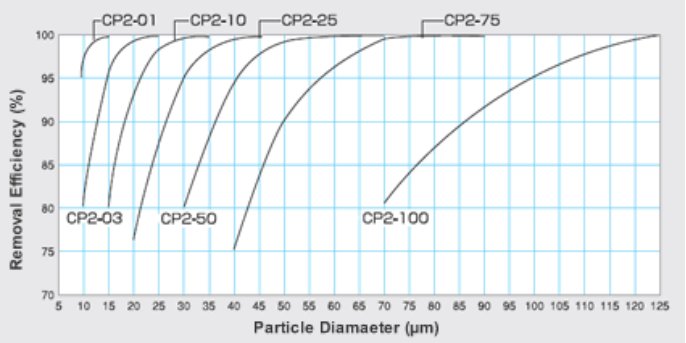
[49] Most Scottish malt distilleries now offer non-chill-filtered versions, including Aberlour, Ardbeg, Arran, Balvenie, Benriach, Bowmore, Brora, Bruichladdich, Caol Ila, Convalmore, Glengoyne, Glenlivet,

bottling their whiskies without chill filtering. Skipping the chill filtering step also reduces production costs.

The typical particle size distribution of particles in whiskey is currently either unknown or, more likely, unpublished. However, JNC Filter Co., Ltd.[50] manufactures and sells filters for various industries, including three types of filters for beer, wine, and fine spirits producers. **Figure 4** shows the particle sizes that can be removed by their BM type and CP-2 type filters, which suggests their customers are interested in removing particles ranging from 0.4 microns up to 125+ microns in size – a range broadly consistent with the size distribution of particles commonly found in tea beverages (**Figure 5**).

Figure 4. BM type[51] (top) and CP-2 type (bottom)[52] particle filters sold by JNC Filter Co., Ltd. for use in the alcohol beverage industry.

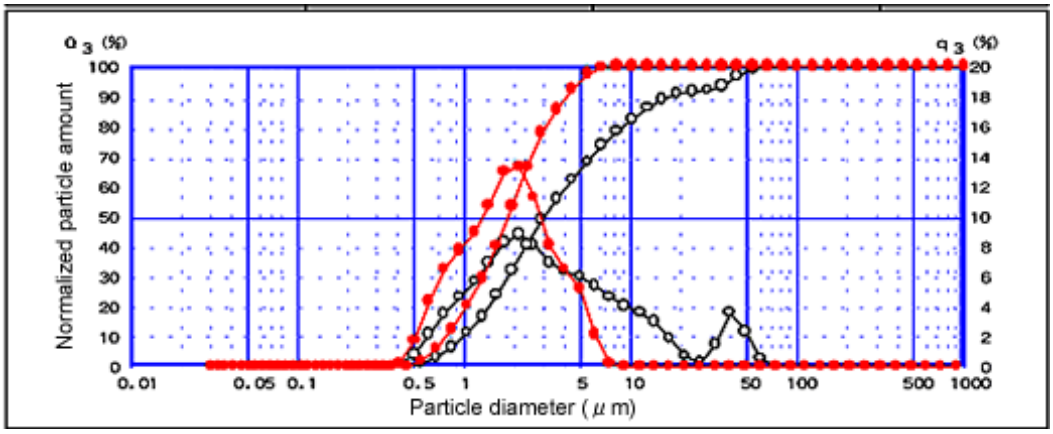




Glenmorangie, Lagavulin, Laphroaig, Longmorn, and Springbank; http://www.whiskymag.com/forum/viewtopic.php?f=6&t=10448. Bourbon is typically chill filtered when pulled from the barrel (http://drinkstraightup.com/2013/01/20/bourbon/).

[50] http://www.jnc-corp.co.jp/filter/english/industry/index.html .
[51] http://www.jnc-corp.co.jp/filter/english/product/bm/index.html.
[52] http://www.jnc-corp.co.jp/filter/english/product/cp2/index.html.

Figure 5. Size distribution of particles in tea.[53]



2.3.3 Radioactive Elements in Whiskey

Radioactivity doesn't contribute to the taste of whiskey, but the isotopic composition of whiskey can attest to the antiquity of the spirits. As a consequence, perfect replication of a fine spirit product may also require duplication of the isotopic profile of the product (e.g., 0.001-1 ppb ^{14}C).

Radiocarbon dating[54] is already widely used to expose counterfeit vintage whiskey. Recently, for example, a bottle of whiskey masquerading as an 1856 Macallan Rare Reserve, which could have sold for tens of thousands of dollars, had to be withdrawn from a Christie's auction because its origin was determined as being sometime after 1950.[55] Researchers at the Oxford Radiocarbon

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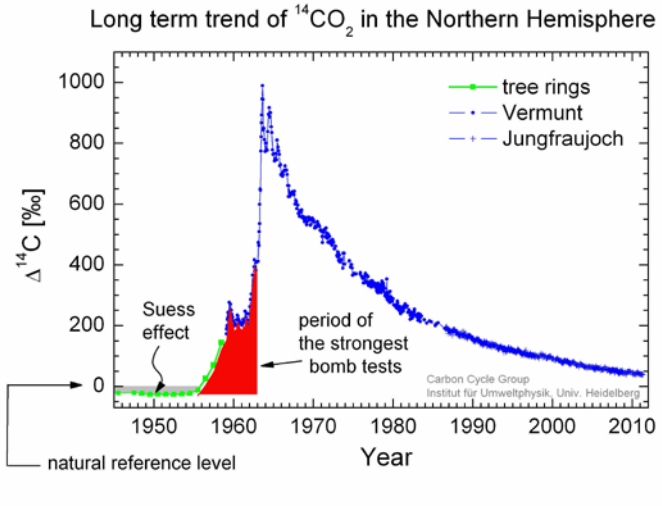
[53] "Particle Size Distribution of Tea Beverage," Shimadzu Analytical and Measuring Instruments, 2014; http://www.shimadzu.com/an/industry/foodbeverages/e8o1ci0000000440_2.htm.

[54] Carbon-12 is the most abundant and nonradioactive isotope of the chemical element carbon. Carbon-14 is a rare (~1 part per trillion) radioactive isotope of carbon found naturally in the atmosphere as carbon dioxide. Plants absorb the radiocarbon (^{14}C) through photosynthesis, and animals then absorb the ^{14}C when they eat plants. The levels of ^{14}C found in plants or animals would then be the same as those found in the atmosphere during its lifetime. After the plant or animal dies, the ^{14}C begins to decay. Radiocarbon dating (http://en.wikipedia.org/wiki/Radiocarbon_dating) works by using the ratio of ^{14}C to stable carbon (^{12}C) found in the organism's remains, along with established knowledge of the rate at which ^{14}C decays, to put an age on the remains. The ratio between these two forms of carbon held consistent for thousands of years, but was altered by two decades of atomic bomb testing after World War II, which increased the amount of radioactive ^{14}C in the atmosphere. Although all organic material collects a certain amount of ^{14}C during its lifetime, elevated levels of radiocarbon present after nuclear bomb testing started in the 1950s causes plants and animals alive after that time to contain an elevated level of ^{14}C. This artificial elevation of the radiocarbon is what gives away a counterfeit whiskey posing as a century-old variety.

[55] http://www.findingdulcinea.com/news/science/2010/mar/How-Do-You-Spot-Vintage-Wine--It-Has-Fewer-Radioactive-Particles.html.

Accelerator Unit (ORAU)[56] are now able to tell if a whiskey was made prior to 1950, thanks in part to the nuclear testing going on at that time.

Organic material that was alive after the start of nuclear testing (see image, below[57]) contains more traces of radioactive carbon-14 than organic material from before the time of nuclear testing. Barley, which is used to make whiskey, is organic material, and thus scientists can examine whiskey for trace amounts of radioactive carbon and determine when it was made. So when a so-called "vintage" is found to have elevated levels of carbon-14, it's a dead giveaway.[58]



Dr. Tom Higham, deputy director of the ORAU, says that the majority of the whiskey samples sent to them end up turning out to be from after the 1950s. Although the radiocarbon dating has helped identify cases of counterfeiting a vintage bottle of whiskey, it can't always identify the exact date of creation.

There are many industrial sources for ^{14}C radiocarbon[59] and ^{14}C-labeled organic radiochemicals.[60]

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[56] Oxford Radiocarbon Accelerator Unit; https://c14.arch.ox.ac.uk/embed.php.

[57] http://www.iup.uni-heidelberg.de/institut/forschung/groups/kk/en/Bilder/14C_NH_longandbomb.jpg.

[58] The majority of the testing is done for the Scotch Whisky Research Institute (http://www.swri.co.uk/), a scientific center that aims to maintain distilled beverage quality, improve distilled beverage manufacturing and preserve the integrity of the industry by authenticating products (such as vintage whiskey). When the lab gets a sample to test, they burn the whiskey and use electricity to charge the resulting gas from the burn, and measure the amount of carbon-14 present. Before the researchers at the ORAU began to authenticate whiskey for buyers and sellers, the Scotch Whisky Research Institute sent them samples of whiskey with already-known dates of creation to ensure that the method worked. The ORAU was able to properly identify the samples provided, and even discovered that one sample had been improperly labeled. Due to its success in authenticating whiskey using radiocarbon dating, the lab started dating wines, although wine dating can be more difficult because of the wider variety of organic material used to make it.

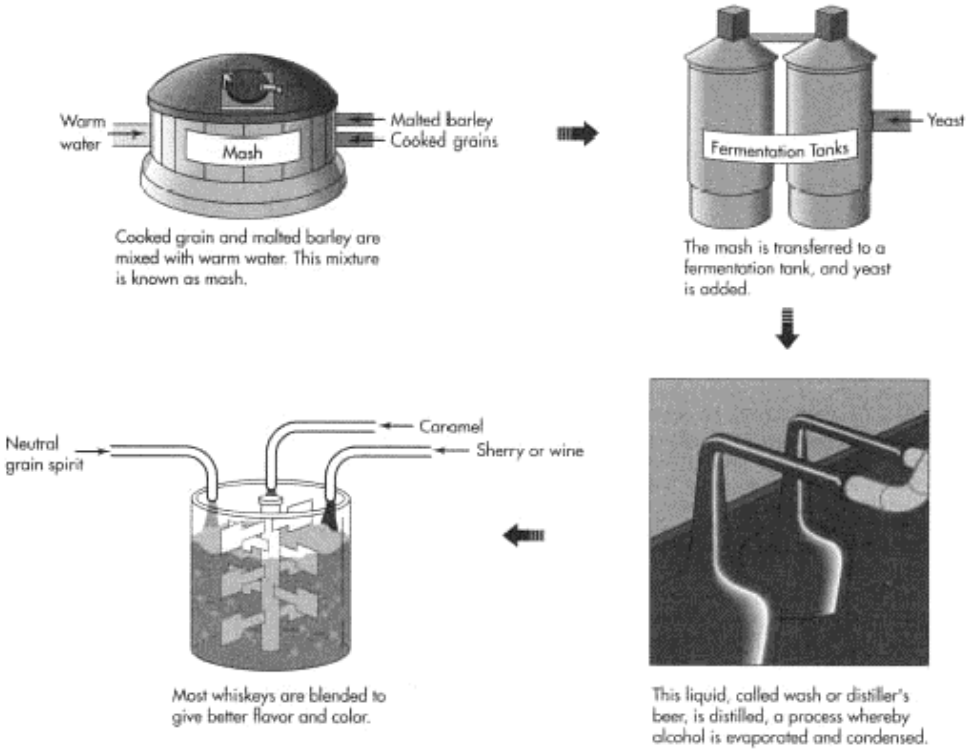
[59] e.g., Spectrum Techniques (https://c14.arch.ox.ac.uk/embed.php).

[60] Perkin-Elmer (http://www.perkinelmer.com/Catalog/Category/ID/New%2014C%20Products), MP Biomedicals LLC (http://www.mpbio.com/search.php?q=radiochemical&s=Search), American Radiolabeled Chemicals, Inc. (http://www.arc-inc.com/index.php?option=com_virtuemart&page=shop.browse&category_id=2&Itemid=53).

3. Traditional Fine Spirits Production

The following is a brief description of the traditional approach to producing fine spirits, and in particular whiskey (**Figure 6**), as it is customarily practiced today.[61] The process of making whiskey takes at least 3 years. If a grain (malted or not) spirit does not stay for at least 3 years in an oak cask, it cannot legally be marketed as "whiskey".

Figure 6. Schematic of the overall process of making whiskey.[62]



Raw materials. Whiskey is made from water, yeast, and grain. Straight whiskies contain no other ingredients, but blended whiskies may contain a small amount of additives such as caramel color and sherry.

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[61] Discussion drawn from several sources: http://www.madehow.com/Volume-2/Whiskey.html; "How is whiskey made – Scotch whisky," http://www.whisky-distilleries.info/Fabrication_EN.shtml; http://en.wikipedia.org/wiki/Whisky#Production; Victoria Gill, "Whisky chemistry: A whisky tour," *Chemistry World*, December 2008, pp. 40-44; http://www.rsc.org/images/whisky_tcm18-138981.pdf.

[62] http://www.madehow.com/Volume-2/Whiskey.html.

The water used is often considered the most important factor in making good whiskey. It should be clean, clear, and free from bad-tasting impurities such as iron. Water that contains carbonates, found in areas that are rich in limestone, is often used in the United States, particularly in Maryland, Pennsylvania, Indiana, and Kentucky. The difference in taste between whiskies coming from various distilleries is partly due to the quality of water used. Scottish water is famous for being suited to making fine whiskey, for reasons that are still somewhat mysterious. (Water in the Highlands is often peaty, which gives it a brownish color. Substances, deriving from peat, are carried by the rivers whose water is used to make whiskey, and can contribute to the original taste of scotch whiskey.)

Every whiskeymaker keeps a supply of yeast available, grown on barley malt and kept free from bacterial contamination. Some whiskeymakers use several kinds of yeast to control the fermentation process precisely.

The type of grain used varies with the kind of whiskey being made, but all whiskies contain at least a small amount of malted barley, which is needed to start the fermentation process. Scotch malt whiskey contains only barley. Other whiskies contain barley in combination with corn, wheat, oats, and/or rye. Corn whiskey must contain at least 80% corn, while Bourbon whiskey and Tennessee whiskey must contain at least 51% corn. Rye whiskey must contain at least 51% rye, and wheat whiskey must contain at least 51% wheat.

Malting. Truckloads of grain are shipped directly from farms to the whiskey manufacturer to be stored in silos until needed. The grain is inspected and cleaned to remove all dust and other foreign particles. All grains except barley are first ground into meal in a gristmill. The meal is then mixed with water and cooked to break down the cellulose walls that contain starch granules. This can be done in a closed pressure cooker at temperatures of up to 311 °F (155 °C) or more slowly in an open cooker at 212 °F (100 °C). Instead of being cooked, barley is malted. The first step in malting barley consists of soaking it in water until it is thoroughly saturated. It is then spread out and sprinkled with water for about three weeks, at which time it begins to sprout.

During this germination the enzyme amylase is produced, which converts the starch in the barley into sugars. The malting art consist of finding the right moment to stop the germination process: not too late but not too early. According to the season, malting takes between 8 and 21 days. Constant attention has to be given to the process. Barley has to be turned over regularly to ensure a constant moisture and temperature and to control the germination of the barley grains (at left).

The sprouting is halted by drying the barley and heating it with hot air from a kiln. For Scotch whiskey, the fuel used in the kiln includes peat, a soft, carbon-rich substance formed when plant matter decomposes in water. The peat gives Scotch whiskey a characteristic smoky taste. The malted barley is then ground like other grains.

Economic reasons obliged many distilleries to abandon their malting floors during the 1960's. Malting now happens mainly at specialized plants, called maltings.

Mashing. When the malt is dry, it is ground in a malt mill (at right) in the distillery to make a kind of coarse flour called grist. Mashing consists of mixing cooked grain with malted barley and warm water. The grist is mixed with hot water in the mash tun (below left), generally one volume of grist with 4 volumes of water. The mix of water and grist looks like a kind of traditional porridge. A mash tun can contain up to 25,000 liters and has rotating blades and a double bottom with thin perforations to let the wort (sugared liquid resulting from the brewing operation) flow out, retaining bigger parts called draff which are sold as cattle food.

The amylase in the malted barley converts the starch in the other grains into sugars. After several hours the mixture is converted into a turbid, sugar-rich liquid known as mash. (In making Scotch malt whiskey the mixture consists only of malted barley and water.) After mashing, the mixture is filtered to produce a sugar-rich liquid known as wort.)

Fermenting. The mash is transferred to a fermentation vessel (at right), usually closed in Scotland and open in the United States. These vessels may be made of wood or stainless steel. Yeast is added to begin fermentation, in which the single-celled yeast organisms convert the sugars in the mash or wort to alcohol and also producing carbon dioxide. The yeast may be added in the form of new, never-used yeast cells (the sweet mash process) or in the form of a portion of a previous batch of fermentation (the sour mash process.) The sour mash method is more often used because it is effective at room temperature and its low pH (high acidity) promotes yeast growth and inhibits the growth of bacteria. The sweet mash method is more difficult to control, and it must be used at temperatures above 80 °F (27 °C) to speed up the fermentation and to avoid bacterial contamination. After three or four days, the end product of fermentation is a liquid containing about 10% alcohol known as distiller's beer in the United States or wash in Scotland.

After this point the processes of making whiskey and of making beer diverge. Beer will be perfumed with hops, while whiskey will be distilled without alterations.

Distilling. A still for making whiskey is usually made of copper, since it removes sulfur-based compounds from the alcohol that would make it unpleasant to drink. Modern stills are made of stainless steel with copper innards (piping, for example, will be lined with copper along with copper plate inlays along still walls).

The simplest standard distillation apparatus is commonly known as a pot still, consisting of a single heated chamber and a vessel to collect purified alcohol. Scottish whiskeymakers often distill their wash in these traditional copper pot stills (**Figure 7**). The wash is heated so that most of the alcohol (which boils at 172 °F / 78 °C) is transformed into vapor but most of the water (which boils at 212 °F / 100 °C) is not. This vapor is transferred back into liquid alcohol in a water-cooled condenser and collected.

Figure 7. Left: Swan necked copper stills in the Glenfiddich distillery. Right: Copper pot stills at Auchentoshan Distillery in Scotland.

Most modern distilleries use a continuous still. This consists of a tall cylindrical column filled with a series of perforated plates. Steam enters the still from the bottom, and distiller's beer enters from the top. The beer is distilled as it slowly drips through the plates, and the alcohol is condensed back into a liquid. Column stills are frequently used in the production of grain whiskey and are the most commonly used type of still in the production of Bourbon and other American whiskies. Column stills behave like a series of single pot stills, formed in a long vertical tube. Whereas a single pot still charged with "wine" might yield a vapor enriched to 40-50% alcohol, a column still can achieve a vapor alcohol content of 95.6%; an azeotropic mixture of alcohol and water.

With either method, the product of the initial distillation – known as "low wine" with 21% ethanol – is distilled a second time in a separate "spirit still" (at left) to produce a product known as "high wine" or new whiskey, which contains about 70% alcohol. Distillation of the spirit gives three fractions – the foreshots that contain the highly volatile components such as acetaldehyde and ethyl acetate, the middle "spirit fraction" that will go on to be matured into whiskey, and the feints which contain the low volatility compounds, including phenols and many nitrogen-containing compounds. During this second distillation, only the spirit fraction or "distillation heart" is casked. The "heads" (foreshots) and "tails" (feints), sometimes collectively called feints, are removed and transferred to the feint

receiver. Because the feints contain some alcohol, they can be mixed with the low wines of the next distillation and thus recycled and redistilled.

The temperature of distillation and other factors determine the proportions of water, alcohol, and congeners in the final product. If the distillate contains more than 95% alcohol it will have no flavor because it has no congeners. This product is known as grain neutral spirit and is often used to add alcohol without adding taste during blending. If the final product has too many congeners of the wrong kind it will taste bad. Distillers remove bad-tasting congeners (usually aldehydes, acids, esters, and higher alcohols) in various ways. Some congeners boil at a lower temperature than alcohol and can be boiled off. Some are lighter than alcohol and will float on top, where they can be poured off.

Tennessee whiskey is unique in that the high wine is filtered through charcoal before it is aged. The charcoal is produced by burning wood from sugar maples. This filtration removes unwanted congeners and results in a particularly smooth whiskey. Premium Tennessee whiskey may be filtered through charcoal again after it is aged to produce an even smoother product.

Aging. Water is added to the high wine to reduce its alcohol content to about 50% or 60% for American whiskies and about 65% or higher for Scotch whiskies. Scotch whiskies are aged in cool, wet conditions, so they absorb water and become less alcoholic. American whiskies are aged in warmer, drier conditions so they lose water and become more alcoholic. Whiskey is aged in wooden barrels (at right), usually made from charred white oak. White oak is used because it is one of the few woods that can hold a liquid without leaking but which also allows the water in the whiskey to move back and forth within the pores of the wood, which helps to add flavor. In the United States these barrels are usually new and are only used once. In most other countries it is common to reuse old barrels. New barrels add more flavor than used barrels, resulting in differences in the taste of American and foreign whiskies.

The aging process is a complex one that is still not fully understood. At least three factors are involved. First, the original mixture of water, alcohol, and congeners react with each other over time. Second, these ingredients react with oxygen in the outside air in oxidation reactions. As oxygen diffuses into the cask, reactions take place between the molecules in the spirit, and between the spirit and the wood. Alcohols and aldehydes are oxidized, and acids react with ethanol to form esters – which are some of the most aromatic of whiskey flavor compounds. Third, the water absorbs substances from the wood as it moves within it. (Charring the wood makes these substances more soluble in water.) All these factors change the flavor of the whiskey. Whiskey generally takes at least three or four years to mature, and many whiskies are aged for ten or fifteen years.

One advantage of oak for maturing alcohol is that it is not airtight. It lets surrounding air enter the cask (which explains the salty taste of a whiskey aging near the sea), but it also lets some ethanol evaporate in the amount of 1%-2%/year, resulting in a diminution of the alcohol

percentage. This is called "the angels share". Assuming a whiskey has about 70% of alcohol when it leaves the spirit still and loses about 1% of alcohol a year, a 30-year-old whiskey would just have an ABV of just 40%, the lowest limit for a whiskey. The nature of the warehouse is also very important. A damp cellar or a dry cellar will influence the evaporation of the spirit differently. In a dry cellar (with a concrete floor), water will evaporate mainly, leaving a drier whiskey with a higher alcohol percentage. In a damp warehouse (beaten-earth floor) more alcohol will evaporate, making a "rounder" whiskey with a smoother taste.

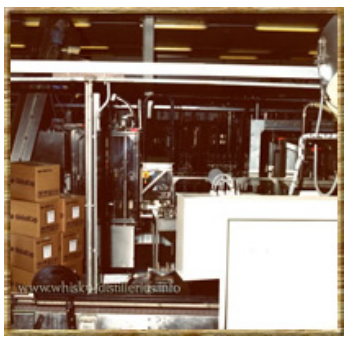
Whiskies do not mature in the bottle, only in the cask, so the "age" of a whiskey is defined as the time between distillation and bottling. This reflects how much the cask has interacted with the whiskey, changing its chemical makeup and taste. Whiskies that have been bottled for many years may have a rarity value, but are not "older" and not necessarily "better" than a more recent whiskey that matured in wood for a similar time. After a decade or two, additional aging in a barrel does not necessarily improve a whiskey.

Sometimes whiskey is aged for a while in bourbon casks, then finishes its aging period in some kind of other cask (e.g., for 6-12 months), in order to give it some new fragrances before bottling. This explains the "wood finish" mentioned on some bottlings – for instance, Glenmorangie specializes in "wood finishes" and some of them are very expensive, probably because of the rarity of the casks. However, this method is also sometimes used to hide some distillation errors, with the casks being warmed up before transferring the whiskey in order to accelerate the fragrance transfer. This is generally considered an unacceptable practice.

Finally, it is maturation in timber casks that gives the whiskey its golden color. Melanoidins (derived from the breakdown of cellulose) help to brown the spirit. Some distilleries use old sherry or rum casks, which also darken the whiskey, as well as contributing to its flavor. The only additive usually allowed, apart from water and pure ethanol, is caramel, which can be added to bring the whiskey to a standard color.

Blending. Straight whiskies and single malt Scotch whiskies are not blended. That is, they are produced from single batches and are ready to be bottled straight from the barrel. All other whiskies are blended. Different batches of whiskey are mixed together to produce a better flavor. Often neutral grain spirit is added to lighten the flavor, caramel is added to standardize the color, and a small amount of sherry or port wine is added to help the flavors blend. Blended Scotch whiskey usually consists of several batches of strongly flavored malt whiskies mixed with less strongly flavored grain whiskies. A few blends contain only malt whiskies. Blending is often considered the most difficult and critical process in producing premium Scotch whiskies. A premium blended Scotch whiskey may contain more than 60 individual malt whiskies which must be blended in the proper proportions.

Bottling. Glass is always used to store mature whiskey because it does not react with it to change the flavor. Modern distilleries use automated machinery (at right) to produce as many as 400 bottles of whiskey per minute.



The glass bottles move down a conveyor belt as they are cleaned, filled, capped, sealed, labeled, and placed in cardboard boxes. The whiskey is then ready to be shipped to liquor stores, bars, and restaurants.

Some residues are left in the whiskey during bottling, causing the distillate to look cloudy.[63] Because this is not always appreciated by the consumer, some distilleries use "chill filtering" (Section 2.3.2) to remove the residues.[64] The problem with chill filtering is that it also removes parts of the fragrances and of the taste. With the current revival of single malt, more and more producers are bottling their whiskies without chill filtering.

Types of whiskey. Whiskey or whiskey-like products are produced in most grain-growing areas. They differ in base product, alcoholic content, and quality. Malt whiskey is made primarily from malted barley. Grain whiskey is made from any type of grains. Malts and grains can be combined in various ways:

Single malt whiskey is whiskey from a single distillery made from a mash that uses only one particular malted grain. Unless the whiskey is described as single-cask, it contains whiskey from many casks, and different years, so the blender can achieve a taste recognizable as typical of the distillery. In most cases, single malts bear the name of the distillery, with an age statement and perhaps some indication of some special treatments such as maturation in a port wine cask. Single-malts represent about 5% of the whiskey market today.

Blended malt whiskey is a mixture of single malt whiskies from different distilleries. If a whiskey is labeled "pure malt" or just "malt" it is almost certain a blended malt whiskey. This was formerly called a "vatted malt" whiskey.

Blended whiskey is made from a mixture of different types of whiskey. A blend may contain whiskey from many distilleries so that the blender can produce a flavor consistent with the brand. The brand name may, therefore, omit the name of a distillery. Most Scotch, Irish and Canadian whiskey is sold as part of a blend, even when the spirits are the product of one distillery, as is common in Canada. American blended whiskey may contain neutral spirits.

Cask strength (also known as barrel proof) whiskies are rare, and usually only the very best whiskies are bottled in this way. They are bottled from the cask undiluted or only lightly diluted.

Single cask (also known as single barrel) whiskies are bottled from an individual cask, and often the bottles are labeled with specific barrel and bottle numbers. The taste of these whiskies may vary substantially from cask to cask within a brand.

A few other well-known types of whiskey include:

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[63] Additionally, in whiskies of high ethanol concentration, there are congeners (other molecules, usually quite large ones, and often carrying much of the taste of the whiskey) which are less soluble in water than in ethanol. As more water is added, the solubility of these in the mixture thus decreases. They precipitate out of solution, usually as very fine particles, too small to settle by gravity. This is visible as a haze or cloudiness in the beverage. https://www.whisky.de/archiv/experts/alcohol.htm.

[64] http://en.wikipedia.org/wiki/Whiskey#Chill_filtration.

Light whiskey is produced in the US at more than 80% alcohol by volume and stored in used or uncharred new oak containers.

Spirit whiskey is a mixture of neutral spirits and at least 5% of certain stricter categories of whiskey.

Bourbon whiskey is made from mash that consists of at least 51% corn (maize).

Corn whiskey is made from mash that consists of at least 80% corn.

Malt whiskey is made from mash that consists of at least 51% malted barley.

Rye whiskey is made from mash that consists of at least 51% rye.

Rye malt whiskey is made from mash that consists of at least 51% malted rye.

Wheat whiskey is made from mash that consists of at least 51% wheat.

Irish whiskey is thrice-distilled pot whiskey made in Ireland.

Scotch whisky is twice-distilled whiskey made in Scotland. Scotch whisky is divided into five distinct categories: single malt Scotch whisky, single grain Scotch whisky, blended malt Scotch whisky (formerly called “vatted malt” or “pure malt”), blended grain Scotch whisky, and blended Scotch whisky.

4. Bulk Chemical Replication of Fine Spirits

Given that the distillation of fine spirits has traditionally been a labor-, capital-, and time-intensive process, the question naturally arises whether or not it might be possible to simply assemble the relevant chemicals comprising the congeners, dissolve them in an ethanol-water mixture in the appropriate concentrations, and directly replicate a fine spirit beverage from scratch?

This Section examines the possibilities and limitations of the bulk chemical replication approach. A brief summary of the principal required ingredients – bulk water (Section 4.1), ethanol (Section 4.2), and congeners (Section 4.3) – is followed by a discussion of the history and details of the possibilities for the bulk chemical replication of whiskey (Section 4.4).

4.1 Water

Of the three necessary ingredient classes in bulk chemical replicant fine spirits, water seems the most straightforward. Extremely pure multiply-distilled water with impurities at the parts-per-billion level would be the obvious starting point. It is true that some people who drink purified water often prefer a certain brand or "taste" in the water, with different filtered water bottle companies using different filtering techniques to impart the taste that their customers prefer. Some companies use very pure water while others start with purified water and then add minute amounts of magnesium sulfate, sodium chloride and potassium chloride to enhance the flavor of the water.[65] The choice of a particular source of water by a distillery almost certainly affects the taste of the final product, given that inorganic metal ions have been measured in whiskey at the 40,000-80,000 ppb level (Table 2) and because many substances known to affect whiskey flavor are only present at ppb levels.[66] For our purposes here, any desired "impurities" in the water should be regarded as inorganic congeners to be included on the congener ingredient list of the replicant whiskey "recipe".

Given a water concentration by weight at the 631,500,000 ppb level in whiskey (Table 1), the input water would ideally be cleaned to about the 99.9999999% (9N or "nine nines") purity level if we seek to ensure that no contaminant can exceed ~1 ppb in concentration. These levels of purity are currently available both in desktop purification units and in the semiconductor industry (see Table 4 footnote).

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[65] "Whiskey, A Mystery No More", http://ciitn.missouri.edu/cgi-bin/pub_view_project_ind.cgi?g_num=2&c_id=2003001.

[66] T.P. Lyons, "Chapter 11. Production of Scotch and Irish whiskies: their history and evolution," 1999; http://web.sls.hw.ac.uk/teaching/distilling/files/documents/Lyons1999.pdf.

4.2 Ethanol

The second largest ingredient in our bulk chemical replicant fine spirits is ethyl alcohol, aka. ethanol. Presumably this could be fermentation-derived multiply-distilled extremely pure ethanol containing non-water impurities that are also at the parts-per-billion level. A small amount of water-only impurity is acceptable because an azeotropic mixture (95%+) of ethanol and water should have negligible congeners and thus should have no flavor. Among distillers this product is known as neutral spirit and is often used to add alcohol without adding taste during blending.[67]

The ethanol employed in fine spirits is produced by natural biological processes via the interaction of yeast with the mash, during fermentation, which is followed by distillation. Ethanol can also be synthesized from ethylene obtained from cracked petroleum hydrocarbons. The alcohol beverage industry has generally agreed not to use synthetic ethanol manufactured from ethylene for the production of alcoholic beverages, due to the presence of inconvenient impurities.[68] It might be possible to use petroleum-derived ethanol in replicant spirits, but extreme purity would probably be required by regulatory and industry entities to ensure both that no medically harmful constituents were present at meaningful concentrations and that no additional flavors were being introduced into the final product. Given an ethanol concentration by weight at the 361,000,000 ppb level in whiskey (Table 1), such petroleum-derived alcohol would have to be cleaned to almost the 99.9999999% (9N or "nine nines") purity level if we sought to ensure that no contaminant exceeds ~1 ppb. Even 99.999% (5N) purity would be required to avoid any impurities at the 1 ppm (1000 ppb) level in the petroleum-sourced material, a level that might remain unacceptable for legal, safety, and taste reasons.

Impurities in commercially available ultrapure (99.99%+) ethanol are generally found in the ppm range and are typically less than 0.002% (20 ppm).[69] The largest contaminant for natural grain-derived ethanol is methanol, which is usually removed with only trace amounts (<10 ppm, <0.001%) left in the product. The largest contaminant in synthetic ethylene-derived ethanol is isopropyl alcohol, which is usually removed down to the <25 ppm level. The most significant marker of synthetic ethanol as compared to natural alcohol is the presence of 2-butanol, a chemical not found at all in fermentation ethanol. Other good markers of synthetic ethanol are acetone and crotonaldehyde which are much larger contaminants in synthetic than in natural

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[67] http://www.madehow.com/Volume-2/Whiskey.html.

[68] "Chapter 3. Chemical Composition of Alcoholic Beverages, Additives and Contaminants," in *IARC monographs on the evaluation of carcinogenic risks to humans*, World Health Organization, International Agency for Research on Cancer, Vol. 44, 1988, pp. 71-99; http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CDMQFjAC&url=http%3A%2F%2Fmonographs.iarc.fr%2FENG%2FMonographs%2Fvol44%2Fmono44-7.pdf&ei=Ba12U6qlO9O-oQTPt4CYDg&usg=AFQjCNHBsRwTsJXjwduqbVaU_SzkeSW-9A&sig2=MLE3SUdiLWpb4tVEEQV21Q&bvm=bv.66917471,d.cGU&cad=rja.

[69] "Grain and Synthetic Ethanol Production," Pharmaco-Aaper and Commercial Alcohols, February 2002; http://www.pharmcoaaper.com/pages/TechLibrary/tech_docs_ethyl_alcohol/grain_vs_synthetic_ethanol_production.pdf.

ethanol.[70] Organoleptic modifiers, typically Bitrex[71] (at 10-30 ppm) or related impurities,[72] are also often added as part of the denaturation process to impart an unpleasant bitter taste.

[70] S.A. Savchuk, G.M. Kolesov, "Markers of the Nature of Ethyl Alcohol: Chromatographic Techniques for Their Detection," *J. Anal. Chem.* 60(2005):1102-1113.

[71] https://en.wikipedia.org/wiki/Denatonium.

[72] http://www.inchem.org/documents/sids/sids/64175.pdf.

4.3 Congeners

The third and key flavor ingredient in our bulk chemical replicant fine spirits is the congeners (Table 1). At least 1300 specific chemical substances had been detected in whiskey by the early 1980s,[73] though many of these substances may not measurably contribute to taste or aroma (i.e., some may be non-organoleptics). There are many sources for these substances. For instance, microorganisms create massively diverse flavor profiles during fermentation through production of secondary metabolites. In addition to yeast, Simpson *et al.* (2001) found 64 different bacterial species in the fermentation of whiskey from a number of samples in Scotland.[74] Another author[75] lists multiple additional mechanisms for generating chemical flavor diversity in whiskey:

- thousands of pre-existing chemical compounds within barley, yeast, and bacteria;
- secondary metabolites generated by yeast, bacteria, and other fungus during fermentation;
- chemical reactions during barley germination, drying, peating, and fermentation;
- chemical reactions that occur from heating the wash and reactions that occur between the metal of the stills and the wash;
- chemical reactions between individual compounds in the finished spirit; and
- chemical reactions between the spirit and the wood cask.

While there may be some minor variation in the congeners from bottle to bottle of the same product, major variations in chemical composition occur among different fine spirits and between whiskies of different types, sources, ages, or bottling years. Each product has a unique chemical signature. Creating a bulk chemical replicant whiskey will require us first to identify all chemical substances that actually contribute something to flavor, then measure the concentration of each such organoleptic chemical substance that is present in the beverage. With this chemical recipe in hand, the appropriate chemicals could be purchased commercially and solvated in the correct amounts in an ethanol-water mixture, essentially creating the replicant whiskey from scratch.

Which chemical substances contribute to flavor in whiskey? Here is one description[76] of the five most interesting compounds among many that contribute significantly to taste in single-malt whiskey:

Whiskey lactone. 3-methyl-4-octanolide or as it is commonly called "whiskey lactone" is a chiral compound that comes in two forms, *cis* or *trans*. The *trans*-3-methyl-4-octanolide is a

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[73] L. Nykanen, H. Suomalainen, eds., *Handbook of Aroma Research, Book 3: Aroma of Beer, Wine and Distilled Alcoholic Beverages*, Springer, 1983.

[74] Simpson KL1, Pettersson B, Priest FG, "Characterization of lactobacilli from Scotch malt whisky distilleries and description of Lactobacillus ferintoshensis sp. nov., a new species isolated from malt whisky fermentations," *Microbiology* 147(April 2001):1007-16; http://www.ncbi.nlm.nih.gov/pubmed/11283296.

[75] "What's Inside Scotch Whisky," 5 April 2011; http://www.drbunsen.org/whats-inside-scotch-whisky/.

[76] "What's Inside Scotch Whisky," 5 April 2011; http://www.drbunsen.org/whats-inside-scotch-whisky/.

natural insect repellent, while *cis*-3-methyl-4-octanolide is extremely fragrant and is the most important form for flavoring whiskey. Whiskey lactone is primarily found in American oak wood and the compound becomes infused into the whiskey after years of storage within oak casks. The high alcohol content of whiskey functions to extract whiskey lactone from the cask and into the spirit. This process infuses whiskey with a wonderfully sweet flavor that is often described as coconut with subtle roasted and/or woody qualities. Unsurprisingly, the compound is used as a flavor additive for candies and other sweets. Whiskey lactone is most noticeable in tasting single malts from Glenrothes[77] and some malts from anCnoc.[78]

Ellagic acid. Ellagic acid is a phenolic compound derived from tannins in barley. Tannins are hydrolyzed during barley germination to generate ellagic acid. In recent years, considerable interest in ellagic acid has surfaced in the scientific community. It is speculated to have potent anti-cancer properties related to its ability to inhibit cell growth and trigger cell death.[79] Based on a number of scientific studies, ellagic acid is now being marketed as a health supplement. Ellagic acid imparts a pungent and astringent quality into whiskey. Balvenie[80] malts are especially known for their high ellagic acid content.

Acetovanillone. No talk of the composition of scotch whiskey would be complete without highlighting peat. One interesting compound particularly abundant in peat-infused whiskey from Islay and Orkney is acetovanillone.[81] Acetovanillone has numerous useful pharmacological properties. Acetovanillone is a potent anti-inflammatory used to treat arthritis and atherosclerosis, and the compound has even been shown to be effective in treating Lou Gehrig's disease in mice.[82] In whiskey, acetovanillone adds a strong vanilla flavor that may be most noticeable in Bunnahabhain[83] malts.

Furfural. Furfural is a ubiquitous organic compound found in many single malts. It is generated from a barley sugar polysaccharide precursor called hemicellulose. When barley is germinated, enzymes inside the barley become activated and convert hemicellulose to another sugar called

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[77] http://www.theglenrothes.com/.

[78] http://ancnoc.com/.

[79] Heber D. Multitargeted therapy of cancer by ellagitannins. Cancer Lett. 2008 Oct 8;269(2):262-8; http://www.ncbi.nlm.nih.gov/pubmed/18468784.

[80] http://www.thebalvenie.com/.

[81] Harrison BM, Priest FG. Composition of peats used in the preparation of malt for scotch whisky production - influence of geographical source and extraction depth. J Agric Food Chem. 2009 Mar 25;57(6):2385-91; http://www.ncbi.nlm.nih.gov/pubmed/19243172.

[82] Harraz MM, Marden JJ, Zhou W, Zhang Y, Williams A, Sharov VS, Nelson K, Luo M, Paulson H, Schöneich C, Engelhardt JF. SOD1 mutations disrupt redox-sensitive Rac regulation of NADPH oxidase in a familial ALS model. J Clin Invest. 2008 Feb;118(2):659-70; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2213375/.

[83] http://www.bunnahabhain.com/.

xylose though a hydrolysis reaction. During the distillation process, xylose then undergoes a dehydration reaction to make furfural. Furfural is toxic and even lethal at high concentrations. Furfural is characterized as having an almond or caramel taste and is common component of many single malts, but is most readily apparent in beer, especially Belgian beer like the St. Bernardus Tripel.[84]

***Ortho*-cresol**. *Ortho*-cresol is a phenolic compound that is toxic and corrosive with disinfectant and antiseptic activity. It is used as a disinfectant and/or solvent in many industrial applications. Cresol is found in Lysol[85] disinfectant spray and a number of commonly used industrial cleaning products. Flavor-wise, *ortho*-cresol has a musty, coal-tar, and phenolic taste and is frequently found in relatively high concentrations in whiskey for the Islay Region. The *ortho*-cresol taste seems especially pronounced in Talisker[86] malts.

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[84] http://www.beeradvocate.com/beer/profile/259/722/.

[85] http://www.wisegeek.com/what-is-o-cresol.htm.

[86] http://en.wikipedia.org/wiki/Talisker.

4.4 Attempts to Chemically Replicate Whiskey

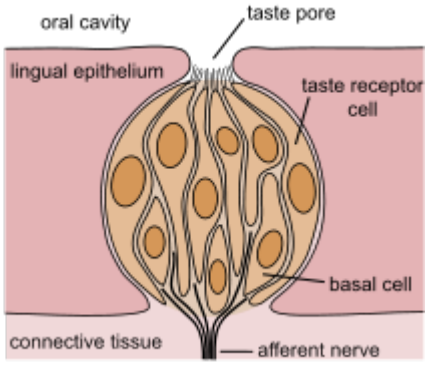
We start with a brief summary of the limits of the human gustatory (taste) and olfactory (smell) apparatuses (Section 4.4.1). We follow with a review of historical efforts to chemically replicate whiskey (Section 4.4.2), then quantify these efforts in terms of material (Section 4.4.3) and analytical (Section 4.4.4) costs. Chemical sensor technologies are summarized in **Appendix A**.

4.4.1 Limits of Human Taste Sensitivity to Fine Spirits Chemicals

Leaving aside the visual, acoustic and mechanical senses, the human sensory experience with fine spirits is primarily chemically driven by the sense of taste (mouth) and the sense of smell (nose).

Taste. Taste is the sensation produced when a substance in the mouth reacts chemically with taste receptor cells located on taste buds.[87] Taste, along with smell (olfaction) and trigeminal nerve stimulation (registering texture, pain, and temperature), determines the flavors of foods, beverages, and other substances.

The tongue is covered with thousands of small bumps called papillae that are easily visible to the naked eye. There are hundreds of taste buds within each papilla, except for the filiform papillae that do not contain taste buds. There are ~12,000 taste buds in total, located on the back and front of the tongue, or on the roof, sides, and back of the mouth, or in the throat including the epiglottis. Each taste bud contains 50 to 100 taste receptor cells. Human taste buds normally have a lifetime of ~10 days. Taste perception fades with age: on average, people lose half their taste receptors by time they turn 20 years old.



There are five basic sensations of taste: **sweet**, **sour**, **salty**, **bitter**, and **umami** (aka. savory). Taste buds produce these sensations by detecting a chemical interaction with different molecules or ions. Sweet, umami, and bitter tastes are triggered by the binding of molecules to G protein-coupled receptors on the cell membranes of taste buds.[88] Saltiness and sourness are perceived when alkali metal or hydrogen ions enter taste buds, respectively. The basic tastes can be classified as aversive or appetitive – e.g., sweetness identifies energy-rich foods, while bitterness warns of poisons.[89] Different molecules can produce different intensities of a given taste. For

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[87] http://en.wikipedia.org/wiki/Taste.

[88] A.A. Bachmanov, G. K. Beauchamp, "Taste receptor genes", *Annu. Rev. Nutr.* 27(2007):389-414; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721271/.

[89] Greg Miller, "Sweet here, salty there: Evidence of a taste map in the mammalian brain," *Science* 333(2 Sep 2011):1213;

instance, fructose tastes 1.4 times sweeter than sucrose, glucose (a sugar in honey and vegetables) tastes 0.75 times as sweet, and lactose (a milk sugar) tastes 0.5 times as sweet. The average human detection thresholds are 10 millimoles/L for sucrose and 30 millimoles/L for lactose, running down to only 0.002 millimoles/L for 5-nitro-2-propoxyaniline.

The tongue can also feel sensations that are not transmitted by taste buds, but rather via elements of the somatosensory system,[90] particularly chemesthesis[91] – the chemical sensibility of the skin and mucous membranes. Much of the chemesthetic flavor sensations are transmitted by the trigeminal nerves, which are relatively large and important nerves that mediate pain, touch, and thermal perception. There are perhaps half a dozen categories of chemicals that can stimulate the trigeminal nerves:

(1) **Pungency** (aka. "spiciness", "hotness"): Substances such as ethanol and capsaicin cause a burning sensation by inducing a trigeminal nerve reaction together with normal taste reception. The sensation of heat is caused by the food's activating nerves that express TRPV1 and TRPA1 receptors. Foods like chili peppers activate nerve fibers directly – the sensation interpreted as "hot" results from the stimulation of somatosensory (pain/temperature) fibers on the tongue.

(2) **Coolness**: Some substances activate cold trigeminal receptors even when not at low temperatures. This "fresh" or "minty" sensation can be tasted in spearmint, menthol, ethanol, and camphor, and is caused by activation of the same mechanism that signals cold, TRPM8 ion channels on nerve cells.

(3) **Astringency**: Some foods (tea, red wine, rhubarb, and unripe persimmons and bananas) contain tannins or calcium oxalate that cause an astringent or puckering sensation of the mucous membrane of the mouth.

(4) **Metallicness**: A metallic taste may be caused by food and drink, certain medicines or amalgam dental fillings, caused by galvanic reactions in the mouth.[92] Some artificial sweeteners are perceived to have a metallic taste, which is detected in part by the TRPV1 receptors, and blood is considered by many people to have a metallic taste.

(5) **Stinging**: Carbon dioxide is the trigeminal stimulant in carbonated beverages that produces the stinging or tingling sensation of carbonation in the nose and mouth.

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http://www.nidcr.nih.gov/AboutUs/Councils/NADCRC/DirectorsReport/ArchiveofDirectorsReports/Documents/1213.full.pdf.

[90] http://en.wikipedia.org/wiki/Somatosensory_system.

[91] http://en.wikipedia.org/wiki/Chemesthesis.

[92] Electrogustometry is the measurement of taste threshold by passing controlled anodal current through the tongue, giving a unique and distinct metallic taste. http://en.wikipedia.org/wiki/Electrogustometry.

(6) And possibly: **Calcium**: In 2008, geneticists discovered a CaSR calcium receptor on the tongues of mice which, along with the "sweet" T1R3 receptor, can detect calcium as a taste.[93] **Fattiness**: A potential taste receptor called CD36, also found in mice, reacts to fatty acids.[94] **Numbness**: Sichuan pepper and other plant extracts produce a time-delayed numbing, almost anesthetic, feeling on the tongue.[95] **Heartiness**: Also known as "kokumi" or "mouthfulness", this sensation may be triggered by a number of γ-L-glutamyl peptides which may activate a calcium-sensing glutathione-sensitive receptor.[96]

Because chemoresponsive nerve fibers are present in all types of skin, chemesthetic sensations can be aroused from anywhere on the body's surface as well as from mucosal surfaces in the nose, mouth, eyes, etc. Mucus membranes are generally more sensitive to chemesthetic stimuli because they lack the barrier function of cornified skin.

Smell. An odor or fragrance (commonly referred to as a smell) is caused by one or more volatilized chemical compounds, generally at a very low concentration, that humans or other animals perceive by the sense of olfaction.[97] The sense of smell gives rise to the perception of odors, mediated by the olfactory nerve. The olfactory receptor (OR) cells are neurons present in the olfactory epithelium, a small patch of tissue in back of the nasal cavity. There are millions of olfactory receptor neurons that act as sensory signaling cells. Each neuron has cilia in direct contact with air. The olfactory nerve is considered the smell mediator with the axon connecting the brain to the external air. Odorous molecules act as a chemical stimulus with molecules binding to receptor proteins extended from cilia, initiating an electric signal.

Unlike mouth taste, which offers perhaps a dozen distinctive sensations, the nasal perception of odors is vastly more complex.[98] Humans have a surprisingly good sense of smell even though they only have 350 functional olfactory receptor genes compared to the 1,300 found in mice, correlated to an evolutionary decline in sense of smell. With their receptors, humans are believed to be able to identify about 10,000 structurally distinct odorant ligands,[99] though perhaps we can

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[93] http://www.scientificamerican.com/article/osteoporosis-calcium-taste-chalk/.

[94] http://www.scientificamerican.com/article/potential-taste-receptor/.

[95] http://gernot-katzers-spice-pages.com/engl/Zant_pip.html.

[96] Navam S. Hettiarachchy, Kenji Sato, Maurice R. Marshall, eds., *Food proteins and peptides: chemistry, functionality interactions, and commercialization*, CRC Press, Boca Raton FL, 2010, p. 290.

[97] http://en.wikipedia.org/wiki/Odor.

[98] The characteristic scent of a rose, for example, is produced by a mixture of 275 components, although typically, only a small percentage of components contribute to the perceived smell. G. Ohloff, *Scent and Fragrances: The Fascination of Odors and Their Chemical Perspectives*, translated by W. Pickenhagen and B.M. Lawrence, Springer-Verlag, Berlin, 1994.

[99] E. C. Crocker, L. F. Henderson, "Analysis and classification of odors: An effort to develop a workable method," *Am. Perfum. Essent. Oil Rev.* 22(1927):325. Randall R. Reed, "How Does the Nose Know?" *Cell* 60(12 Jan 1990):1-2. J. A. Gottfried, in *Taste and Smell: An Update*, T. Hummel, A. Welge-Lüssen, Eds. (Karger, Basel, 2006), p. 46. A. N. Gilbert, *What the Nose Knows* (Crown Publishers, New York, 2008),

distinguish a much larger number of multiplexed odor sensations[100] just as we can distinguish millions of colors while having only trichromatic color vision (i.e., 3 cone types each sensitive only to red (500-700 nm), green (450-630 nm), or blue (400-500 nm) light).[101]

The widest range of odors arise from organic compounds, although some simple compounds not containing carbon, such as hydrogen sulfide and ammonia, are also odorants. Odor sensation usually depends on the concentration available to the olfactory receptors. A single odorant stimulus type is typically recognized by multiple receptors, and different odorants are recognized by combinations of receptors, the patterns of neuron signals helping to identify the smell. The olfactory system does not interpret a single compound, but instead the whole odorous mix, not necessarily corresponding to concentration or intensity of any single constituent.[102] Nevertheless, humans can discriminate between two odorants that differ in concentration by as little as 7%.[103]

Habituation affects the ability to distinguish odors after continuous exposure. The sensitivity and ability to discriminate odors diminishes with exposure, and the brain tends to ignore continuous stimulus and focus on differences and changes in a particular sensation. When odorants are mixed, the conditioned odorant is blocked out because of habituation. A human's odor detection threshold is variable. Repeated exposure to an odorant leads to enhanced olfactory sensitivity and decreased detection thresholds for a number of different odorants.[104]

How differently does the same whiskey taste to different people? Some persons may be missing some receptors, producing taste-blindness to a few specific chemicals, and individuals will differ somewhat in the numbers of their receptors, so some people may be more or less sensitive to particular organoleptic chemicals than others. This means that the perceptual experience should differ somewhat, but perhaps not wildly so, from one person to the next. Unlike the immune system, which is capable of generating receptors (antibodies) specific to ~10 billion distinct antigen epitopes[105] (but with only ~10 million of them found in any single human[106]), the human

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pp. 1-5. E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, A. J. Hudspeth, *Principles of Neural Science* (McGraw-Hill Companies, ed. 5, 2013).

[100] C. Bushdid, M.O. Magnasco, L.B. Vosshall, A. Keller, "Humans Can Discriminate More than 1 Trillion Olfactory Stimuli," *Science* 343(21 Mar 2014):1370-1372; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4483192/.

[101] http://en.wikipedia.org/wiki/Color_perception.

[102] Richard Axel, "The molecular logic of smell," *Scientific American* 273(Apr 1995):154; http://bg.bilkent.edu.tr/jc/topics/Cellular%20and%20Molecular%20Logic%20of%20Smell/papers/the%20molecular%20logic%20of%20smell.pdf.

[103] W.S. Cain, "Differential sensitivity for smell: 'noise' at the nose," *Science* 195(1977):796-798.

[104] W.S. Cain, J.F. Gent, "Olfactory sensitivity: reliability, generality, and association with aging," *J. Exp. Psychol.: Hum. Percept. Perform.* 17(1991):382-91.

[105] http://en.wikipedia.org/wiki/Antibody#Immunoglobulin_diversity.

olfactory receptor system seems fairly ancient and conservative. Humans evolved to be able to smell certain specific chemicals in their environment because those chemicals were relevant to survival. The human olfactory apparatus is sufficiently uniform to allow some standardization of the responses of panels of human odor judges, which possibly might be calibrated using a measurement metric such as the European Odor Unit, corresponding to the common human ability to detect n-butanol at a concentration of ~40 ppb by volume.[107]

4.4.2 Some Historical and Recent Whiskey Replication Efforts

Over the decades there have been numerous attempts to create synthetic whiskey from bulk chemicals. For example, in 1972, in order to assess the contributions made by whiskey components to the odor of these spirits, Salo *et al.*[108] concocted a synthetic whiskey with components that chromatographic analysis had revealed were present in a light-flavored Scotch whiskey. The synthetic whiskey was made using 576 gm of a mixture of higher alcohols, 90 mg of acids, 129 mg of esters and 17.4 mg of carbonyl compounds in highly-rectified grain spirit diluted to 34° G.L.[109] in water that had been ion-exchanged and treated with activated charcoal. This imitation whiskey contained 13 alcohols in addition to ethanol, 21 acids, 24 esters and 9 carbonyl compounds. Caramel coloring was used to give it the color of a distilled and matured whiskey. Odor thresholds of the individual compounds and groups of compounds were determined as previously described by Salo.[110] Experienced taste panel participants were easily able to distinguish the imitation whiskey from a blended Scotch whiskey. But when the concoction was mixed with an equal amount of the Scotch, only 6% correct judgments above chance were made. This suggested that the concentrations of, and interactions between, the components of the synthetic whiskey were not greatly dissimilar from those in the Scotch that was used for comparison. It also hints that a significant number of organoleptic congeners may be present in whiskey at very low concentrations that are close enough to the detection limit of the human taste sensorium such that a mere 2:1 dilution drops them below this limit.

In more recent times, the Brown-Furman Company enlisted professional taste testers to determine which organoleptic compounds are fundamental to the unique taste of Jack Daniel's whiskey –

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[106] Daniel C. Adelman, Abba Terr, "Allergic and Immunologic Disorders," in Lawrence M. Tierney, Jr., Stephen J. McPhee, Maxine A. Papadakis, eds., *Current Medical Diagnosis and Treatment*, 35th Edition, Appleton and Lange, Stamford, CT, 1996, pp. 694-718.

[107] A.P. Van Harreveld, P. Heeres, H. Harssema, "A review of 20 years of standardization of odor concentration measurement by dynamic olfactometry in Europe," *J. Air & Waste Management Assoc.* 49(1999):705-715.

[108] P. Salo, L. Nykänen, H. Suomalainen, "Odor thresholds and relative intensities of volatile aroma components in an artificial beverage imitating whisky," *Journal of Food Science* 37(1972):394-396.

[109] G.L. = % grain ethyl alcohol = 68° U.S. proof. https://web.anl.gov/PCS/acsfuel/preprint%20archive/Files/25_4_SAN%20FRANCISCO_08-80_0309.pdf.

[110] P. Salo, "Determining the odor thresholds for some compounds in alcoholic beverages," *Journal of Food Science* 35(1970):95-99.

the venerable whiskey distilled in Lynchburg, Tennessee, since 1866. Their results,[111] presented at a 2002 ACS (American Chemical Society) meeting in Boston, showed that the trademark taste comes from **3 organic flavor compounds** that are formed during the storage portion of the whiskey making process, wherein many organic compounds that are present in oak react with the whiskey during its maturation process. The three chemical compounds that most govern the unique Jack Daniel's taste are gallic acid,[112] syringic acid and coniferaldehyde.[113]

In the Jack Daniel's experiments,[114] the researchers distilled out all of the alcohol and other components that could evaporate away and separated the rest into two parts: one water soluble, the other not. They then spiked each into young, one-year-old Jack Daniel's and asked a panel of trained tasters their opinions of the taste. The whiskey spiked with the water-soluble compounds like glucose and fructose sugars tasted smoother and sweeter. The whiskey spiked with the nonwater-soluble compounds – organic chemicals like vanillin and syringic acid – had more vanilla and flavors and was somewhat more face-puckering astringent, the tasters reported. But actual Tennessee whiskey, in addition to being made in Tennessee, also, by law, adds a step: dripping the whiskey through 10 feet of maple sugar wood charcoal before putting it into the barrels for aging. The charcoal takes out the fruitiness by absorbing compounds known as esters that give flavors of apple, pear, peach and citrus fruits.

At the same 2002 ACS meeting,[115] Dr. Peter H. Schieberle, a professor of food chemistry at the Technical University of Munich (Germany), presented similar research about the flavor chemistry of bourbon whiskey. In the German bourbon research, Schieberle distilled away the alcohol and volatile compounds and examined the leftover brown sludge, about 1-2 % of the original bourbon. Of the 400-500 or so compounds found in the sludge, the researchers identified **28 critical compounds** that seemed to give the most flavor to the bourbon, including β-damascenone which adds the taste of cooked apples, lactones which provide coconut flavors, and eugenol from the oak barrels which provides clovelike flavors. When the 28 critical compounds were added to the alcohol and other volatile compounds, the result was said to be a "pretty good bourbon". "**Many people couldn't tell the difference between the whiskey and the recombinant**," Schieberle said.

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[111] http://ciitn.missouri.edu/cgi-bin/pub_view_project_ind.cgi?g_num=2&c_id=2003001.

[112] Tannins, well-known in wine, are the constituents of oak that react to form gallic acid. These are a specific type of tannin known as gallotannins (tannins from plant galls) that are hydrolysable. The hydroxyl groups of these compounds are partially esterified with phenolic groups, and hydrolysis of the tannin then yields the gallic acid. Reactions of tannins can also form other important flavor compounds involved in the taste of Jack Daniel's.

[113] Lignin, an organic chemical in oak, yields the coniferaldehyde and syringic acid flavor compounds.

[114] "What's in That Bottle of Jack Daniel's? A Chemistry Mystery," 5 November 2002; https://web.archive.org/web/20060902075629/http://ciitn.missouri.edu/testsite/www/212w03ICPR/group02article.html.

[115] "What's in That Bottle of Jack Daniel's? A Chemistry Mystery," 5 November 2002; https://web.archive.org/web/20060902075629/http://ciitn.missouri.edu/testsite/www/212w03ICPR/group02article.html.

More recently at the Fall 2013 ACS annual meeting, Thomas Collins, director of food science research at the University of California at Davis, described work[116] aimed at chemically distinguishing different whiskies: "Right now, we can do a pretty good job of separating, for example, Scotch whiskies from bourbons and other American whiskies and also Canadian and Irish whiskies. When you narrow it down into whiskies from a particular region, the process gets a little more difficult because they're more similar to each other." [117]

Collins and his team used two common chemical techniques – high-performance liquid chromatography (HPLC) and high-resolution mass spectrometry – to see if they could determine the chemical differences among 60 different whiskies: 38 straight bourbon whiskies, 10 rye whiskies, five Tennessee whiskies and seven other American whiskies, varying in age from two-to-15 years old. What they found was a spectacular testament to the spirit's complex chemistry: over **4,000 different non-volatile compounds** across the different samples. (And there may be several hundred additional volatile compounds as well.) There was a fair amount of overlap among the different spirits. But each spirit contains unique compounds, or unique concentrations of compounds, that can be used to distinguish a scotch from a bourbon, or a Tennessee whiskey from a bourbon, simply by looking at the liquor's chemistry.

According to Collins, the relative concentrations of 50-100 chemicals can distinguish any two given whiskies from one another. These chemicals predominantly include turpentine-derived terpenes and terpenoids, which may come from either the barrel or the grain; fatty acids, which may come from either yeasts or plants; and polyphenols, such as tannins, which come from the aging barrels and vary by both distiller and a whiskey's age. Chemically, it's often a question of concentration: how much of a plant-derived compound does a spirit have? Sometimes there are certain compounds that are only found in one spirit or the other, but more often there are compounds that are present in both but at different concentrations. Collins and his team have yet to embark on the obvious next step in their experiments – relating the differences in chemical makeup to potential sensory differences in aroma and flavor – but he feels fairly confident that the two are related.

In 2008, Poisson and Schieberle[118] used liquid-liquid extraction, fractionation, Solvent-Assisted Flavor Evaporation (SAFE), and dilution analysis (AEDA) to identify the most potent odorants in

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[116] Thomas S. Collins, Jerry Zweigenbaum, Susan E. Ebeler, "Profiling bourbons and American whiskies using UHPLC/QTOF-MS," Monday, 9 Sep 2013, 246th ACS National Meeting and Exposition; http://abstracts.acs.org/chem/246nm/program/view.php?obj_id=207497&terms=.

[117] "Chemical Analysis Finds A Whiskey's Unique Fingerprint: How to tell different whiskies apart scientifically," *Popular Science*, 9 Sep 2013, http://www.popsci.com/science/article/2013-09/fyi-what-chemicals-make-whiskey; "How Chemistry Can Explain the Difference Between Bourbon and a Tennessee Whiskey: The unique flavor of a whiskey or scotch might be more than pure luck – it might be a science," *Smithsonian*, 9 Sep 2013, http://www.smithsonianmag.com/arts-culture/how-chemistry-can-explain-the-difference-between-bourbon-and-a-tennessee-whiskey-5175998/?no-ist.

[118] L. Poisson, P. Schieberle, "Characterization of the most odor-active compounds in an American Bourbon whisky by application of the aroma extract dilution analysis," *J. Agric. Food Chem.* 56(2008):5813-5819.

a single American bourbon whiskey. They also identified highly volatile aroma-active compounds by static headspace olfactometry (SHO) and dilution analysis. Altogether, 45 compounds with significant dilution factors (FDs) were identified in the extract, while 23 aroma-active compounds were identified in the headspace. Of these compounds, β-damascenone, γ-nonalactone, cis-(3S,4S)-β-methyl-γ-octanolide (whiskey lactone), γ-decalactone, eugenol, and vanillin were identified as the most potent odorants, being the compounds with the highest FDs. The compounds identified by these researchers are substantially similar to those expected and previously identified in rye whiskey.

The same researchers[119] quantified the compounds identified as among the most important odorants in bourbon whiskey using stable-isotope dilution analysis (SIDA). They then used the quantification data in order to construct model whiskies and to conduct aroma omission studies, which in turn allowed them to validate the importance of the compounds identified through AEDA. They successfully quantified 31 of the 45 important odorants previously identified (**Figure 8**) using SIDA. They then constructed model whiskies using the quantification data, and conducted sensory omission studies, confirming to their satisfaction that they had constructed accurate models, and therefore had identified the most important odorants in bourbon whiskey. It is worth noting, however, that they used only an orthonasal (sniffing) sensory test – a retronasal (tasting) test might provide more interesting results.

Figure 8. Absolute concentrations of important odorants in a bourbon whiskey, as calculated using Stable Isotope Dilution Analysis (SIDA) by Poisson and Schieberle (2008).

compound	concentration [μg/L][a]	standard deviation [%][b]
ethanol	316000000	
3-methylbutanol	1060000	2
1,1-diethoxyethane	15300	1
2-phenylethanol	13900	2
ethyl octanoate	8340	9
3-methylbutyl acetate	2590	7
(3*S*,4*S*)-*cis*-whiskylactone	2490	6
4-hydroxy-3-methoxybenzaldehyde	2130	2
ethyl hexanoate	1990	1
2-phenylethyl acetate	1940	2
ethyl propanoate	793	4
ethyl butanoate	551	5
3-methylbutanal	342	10
(3*S*,4*R*)-*trans*-whiskylactone	337	8
4-allyl-2-methoxyphenol	240	1
2-methylpropanal	233	9
ethyl 2-methylpropanoate	134	10
γ-nonalactone	120	10
4-ethyl-2-methoxyphenol	59	3
2-methoxyphenol	56	7
ethyl 3-methylbutanoate	52	6
(*E*,*E*)-2,4-decadienal	39	6
2,3-butandione	33	10
(*S*)-ethyl 2-methylbutanoate	30	10
(*E*)-damascenone	11	5
(*E*)-2-nonenal	9	5
(*E*,*E*)-2,4-nonadienal	2.4	10
(*E*)-2-decenal	1.8	3
trans-ethyl cinnamate	1.7	10
γ-decalactone	1.6	10
(*E*,*Z*)-2,6-nonadienal	0.9	10

[a] The mean value obtained by analyzing three different samples taken from the same bottle. [b] The standard deviation of the mean value [%].

[119] L. Poisson, P. Schieberle, "Characterization of the key aroma compounds in an American Bourbon whisky by quantitative measurements, aroma recombination, and omission studies," *J. Agric. Food Chem.* 56(2008):5820-5826.

4.4.3 Quantified Raw Materials Cost of Chemical Replication

Obviously, the precise identity and quantification of the taste-relevant constituents of whiskey – the organoleptic components – is key to replication. To this end, the aroma profile and most potent odorants of two American rye whiskies (Wild Turkey and Rittenhouse) were examined in 2010 during the Masters Thesis work of Jacob Lahne.[120] Using two dilution analysis methods for Gas Chromatography-Olfactometry (GCO), rye whiskey was found to be a complex aroma system with no single odorant responsible for its characteristic aroma, but among the key aroma compounds identified were 3-methyl-1-butanol, 2-phenylethanol, *cis*-(3S,4S)-whiskey lactone, guaiacol, syringol, and vanillin. These compounds likely mainly originate from either yeast metabolism (in the case of fusel alcohols) or lignin pyrolysis. All key odorants were quantified, with concentrations ranging from 2560 ppm (3-methyl-1-butanol) to 7 ppb (ethyl cinnamate), and with acetaldehyde also identified as a significant odorant.

Lahne then used these quantified components, properly adjusted,[121] to construct an artificial "model whiskey" from the 30 most potent odorant congeners of rye whiskey using the recipe concentrations, chemical purities, and sources indicated in **Table 3**. Note that several compounds were present at the parts-per-billion level. A panel of nonprofessional judges was unable, in many cases, to nasally distinguish the artificial "Model B" whiskey from the actual commercial Wild Turkey rye whiskey.

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[120] Jacob Lahne, "Aroma Characterization Of American Rye Whiskey By Chemical And Sensory Assays," Master's Thesis, Graduate College of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, 2010; https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&ved=0CFQQFjAG&url=https%3A%2F%2Fideals.illinois.edu%2Fbitstream%2Fhandle%2F2142%2F16713%2F1_Lahne_Jacob.pdf%3Fsequence%3D2&ei=29Z3U57AJZHvoASg0oHAAg&usg=AFQjCNEfyQuzAylqI01l-VdFmbx2S_MOIw&sig2=yu1r9Siv-p16YFReLtU2wg&cad=rja.

[121] Model A was based on chemical composition results from direct chemical assay of four whiskies. Model B was based on a comparison of Model A and authentic Wild Turkey rye whiskey by internally standardized GC-FID using a procedure described in the thesis. In Model B, roughly half (17 compounds) were corrected, and acetaldehyde was added to the model. Many corrections were relatively minor, but some were quite dramatic. For example, 2-phenylethanol was more than quadrupled in concentration, while isoamyl acetate was decreased by a factor of 3.

Table 3. Recipe for "Model B" whiskey using the 31 most potent odorant chemicals found in American rye whiskey, from Lahne (2010).[122]

Whiskey Component	Concentration (mg/L) (~ppm)	Purity	Source for "Model B" Chemical
3-methyl-1-butanol	2800.000	≥ 98 %	Fisher (Fair Lawn, NJ)
2-methyl-1-propanol	820.000	≥ 98 %	Baker (Phillipsburg, NJ)
acetic acid	640.000	≥ 98 %	Fisher (Fair Lawn, NJ)
2-phenylethanol	92.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
syringaldehyde	62.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
acetaldehyde	40.000	≥ 98 %	Fisher (Fair Lawn, NJ)
vanillin	8.100	≥ 98 %	Fluka (Switzerland)
cis-whiskeylactone	8.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
phenylacetic acid	8.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
isoamyl acetate	3.900	≥ 98 %	Fluka (Switzerland)
guaiacol	3.800	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
ethyl hexanoate/caproate	3.600	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
isovaleric acid	3.100	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
2,6-dimethoxyphenol	3.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
butyric acid	2.900	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
4-ethyl-2-methoxyphenol (aka. 4-ethylguaiacol)	2.200	≥ 98 %	Alfa Aesar (Lancaster, UK)
ethyl butyrate	1.700	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
2-phenylethyl acetate	1.700	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
γ-nonalactone	1.500	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
ethyl propanoate (aka. ethyl propionate)	1.300	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
trans-whiskeylactone	1.300	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
ethyl isobutyrate	1.000	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
eugenol	0.890	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
p-vinylguaiacol (aka. 2-methoxy-4-vinylphenol)	0.850	≥ 98 %	Avocado (Lancaster, UK)
ethyl vanillate	0.840	≥ 98 %	Alfa Aesar (Lancaster, UK)
4-ethylphenol	0.800	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
ethyl isovalerate	0.290	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
β-damascenone	0.048	≈ 95 %	Firmenich (Switzerland)
p-cresol	0.041	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
β-ionone	0.032	≥ 98 %	Sigma-Aldrich (St. Louis, MO)
trans-ethyl cinnamate	0.007	≥ 98 %	Alfa Aesar (Lancaster, UK)

[122] Jacob Lahne, "Aroma Characterization Of American Rye Whiskey By Chemical And Sensory Assays," Master's Thesis, Graduate College of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, 2010; https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&ved=0CFQQFjAG&url=https%3A%2F%2Fideals.illinois.edu%2Fbitstream%2Fhandle%2F2142%2F16713%2F1_Lahne_Jacob.pdf%3Fsequence%3D2&ei=29Z3U57AJZHvoASg0oHAAg&usg=AFQjCNEfyQuzAylqI01l-VdFmbx2S_MOIw&sig2=yu1r9Siv-p16YFReLtU2wg&cad=rja.

Table 4 presents an estimate of the production cost of Lahne's "Model B" whiskey using commercial sourcing of the 33 chemicals, assuming that the recipe given in Table 3 was sufficient and complete. The first two columns of Table 4 list the names and required concentrations of the water, ethanol, and 31 critical congeners needed to make the "Model B" product. The third column gives the minimum purity level for each compound, on the assumption that impurities in any one compound cannot be allowed to add more than 1 ppb of total impurities to the final product. The fourth column lists the U.S. prices for all compounds at the highest purity readily available in the largest quantity available (i.e., giving the cheapest unit price) from Sigma-Aldrich in 2014.[123] The fifth column gives the estimated price per gram of the chemical at the minimum purity level specified in column 3, assuming material densities approximating that of water and conservatively assuming that each additional "9" of purity increases the cost of a chemical by roughly 6-fold.[124] The sixth and final column gives the contribution of each ingredient to the total cost of making one liter of the synthetic "Model B" whiskey mixture.

[123] http://www.sigmaaldrich.com/united-states.html.

[124] For example, Sigma-Aldrich lists the prices for acetic acid as $0.019/ml at 99% purity, $0.10/ml at 99.7% purity, and $0.67/ml at 99.99% purity, a progression that is crudely consistent with the following purity-cost model: $C_{ultrapure} = C_{Sigma\text{-}Aldrich} * M_9\text{^}[\log_{10}(100\% - p_{Sigma\text{-}Aldrich}) - \log_{10}(100\% - p_{ultrapure})]$, where $p_{Sigma\text{-}Aldrich}$ is the percentage purity available from Sigma-Aldrich (e.g., 99.5), $p_{ultrapure}$ is the ultrapurity percentage required for the replicant whiskey (e.g., 99.999), M_9 is the cost multiplier per extra "9" of purity added (i.e., $M_9 = 6$ fold in our "six 9s" example), $C_{Sigma\text{-}Aldrich}$ is the product cost from Sigma-Aldrich at the indicated commercially-available purity level $p_{Sigma\text{-}Aldrich}$, and $C_{ultrapure}$ is the estimated product cost at the enhanced purity level $p_{ultrapure}$.

Table 4. Estimated production cost of "Model B" whiskey, assuming a required purity level of ~1 ppb for each compound and assuming a log-linear cost/purity function.

Whiskey Component	Needed Concen-tration (mg/L)	Minimum Purity Req'd to meet 1 ppb standard (%)	2014 cost of chemical at the indicated available purity level from Sigma Aldrich	Estimated cost of chemical at min. req'd purity level ($/gm)	Cost to make 1 liter of "Model B" mixture
water[125]	656100.	99.9999998	$0.03/ml (≥99.9997%)	$0.000005	<$0.01
ethanol[126]	339400.	99.9999997	$0.08/ml (≥99.9975%)	$89.97	$30,535.82
3-methyl-1-butanol	2800.	99.999964	$0.64/ml (≥99%)	$1,836.74	$5,142.87
2-methyl-1-propanol	820.000	99.99988	$0.41/ml (99.5%)	$268.86	$220.47
acetic acid	640.000	99.99984	$0.67/ml (99.99%)	$16.73	$10.71
2-phenylethanol	92.000	99.9989	$0.20/ml (≥99%)	$40.11	$3.69
syringaldehyde	62.000	99.9984	$0.66/gm (≥98%)	$169.59	$10.51
acetaldehyde	40.000	99.9975	$0.25/ml (≥99.5%)	$15.43	$0.62
vanillin	8.100	99.988	$0.14/gm (99%)	$4.37	$0.04
cis-whiskeylactone	8.000	99.988	$0.94/gm (≥98%)	$50.36	$0.40
phenylacetic acid	8.000	99.988	$2.55/gm (≥99%)	$79.66	$0.64

[125] The formula using Sigma-Aldrich prices estimates an $8.88/gm cost at <1 ppb, but the cost of water with <ppb purity requirements intended for high-volume use in the semiconductor manufacturing industry was reported in 2003 (http://www.reticlecarbon.com/3_application_water_10.htm) as only $20/1000 gallons, or **$0.005/kg**, using a multiplicity of industrial processes applied sequentially including ion exchange, ozone-injection, degassing, thermal treatment, and ultraviolet oxidation. Production of water with Total Organic Content <0.5 ppb appears standard in this industry – for example, Ovivo's ultrapure water plants (large industrial facilities) are said to employ a long list of processes to achieve ultrahigh purity including reverse osmosis, ultrafiltration, membrane degasser, EDI, ion exchange, adsorption, UV, ozone, flocculation, precoat filtration, sedimentation, multimedia filter, advanced oxidation, and activated carbon filters (http://www.ovivowater.com/content/files/data/Ovivo_Industry_Semiconductor_69519e80200c4004a7556bb0c8b19f90.pdf). Small desktop units that are capable of producing ultrapure water with Total Organic Content <2 ppb at liter/minute flow rates, using replaceable cartridges, are available, e.g., for $6900 from Sartorius (http://www.sartorius.us/fileadmin/fm-dam/sartorius_media/Lab-Products-and-Services/Lab-Water-Systems/Data-Sheets/Data_arium_pro_SLG2051-e.pdf); operating costs aren't given, but if $100 worth of cartridges had to be replaced daily to maintain this flow rate, then the water cost would be **$4/kg**. Note also that ultrapure (ppb) water is not normally used in traditional whiskey manufacture, so requiring such high purity might be considered overkill.

[126] At Sigma-Aldrich: Ethyl alcohol, pure, 200 proof, meets USP testing specifications, evap. residue ≤0.0025%, **$0.08/ml** (http://www.sigmaaldrich.com/catalog/product/sial/493546?lang=en&region=US); Ethyl alcohol, pure, 200 proof, HPLC/spectrophotometric grade, evap. residue ≤0.001%, water ≤0.2%, **$0.07/ml** (http://www.sigmaaldrich.com/catalog/product/sial/459828?lang=en&region=US). An unnamed Chinese supplier claims to offer 99.9% pure ethanol at $800/tonne, or roughly **$.001/ml** (http://www.alibaba.com/product-detail/2013-hot-sell-ethyl-alcohol-99_630556962.html).

isoamyl acetate	3.900	99.974	$0.19/ml (≥99%)	$3.25	$0.01
guaiacol	3.800	99.974	$0.03/gm (≥98%)	$0.88	<$0.01
ethyl hexanoate/caproate	3.600	99.972	$0.28/ml (≥99%)	$4.52	$0.02
isovaleric acid	3.100	99.967	$0.03/gm (≥99%)	$0.43	<$0.01
2,6-dimethoxyphenol	3.000	99.967	$1.26/gm (99%)	$17.91	$0.05
butyric acid	2.900	99.966	$0.02/gm (≥99%)	$0.28	<$0.01
4-ethyl-2-methoxyphenol	2.200	99.955	$0.56/gm (≥98%)	$10.73	$0.02
ethyl butyrate	1.700	99.941	$0.06/ml (99%)	$0.54	<$0.01
2-phenylethyl acetate	1.700	99.941	$2.29/gm (≥99%)	$20.72	$0.04
γ-nonalactone	1.500	99.933	$0.02/gm (≥98%)	$0.28	<$0.01
ethyl propanoate	1.300	99.923	$0.05/ml (99%)	$0.37	<$0.01
trans-whiskeylactone	1.300	99.923	$0.94/gm (≥98%)	$11.85	$0.02
ethyl isobutyrate	1.000	99.90	$0.12/ml (99%)	$0.72	<$0.01
eugenol	0.890	99.89	$0.25/gm (99%)	$1.39	<$0.01
p-vinylguaiacol	0.850	99.88	$3.96/gm (≥98%)	$35.36	$0.03
ethyl vanillate	0.840	99.88	$3168.00/gm (≥98%)	$28,285.79	$23.76
4-ethylphenol	0.800	99.88	$0.31/gm (99%)	$1.61	<$0.01
ethyl isovalerate	0.290	99.66	$0.04/gm (≥98%)	$0.16	<$0.01
β-damascenone	0.048	97.9	$2.10/gm (95%)	$4.12	<$0.01
p-cresol	0.041	97.6	$0.49/gm (≥99%)	$0.25	<$0.01
β-ionone	0.032	96.9	$0.05/gm (≥97%)	$0.05	<$0.01
trans-ethyl cinnamate	0.007	85.7	$0.23/gm (99%)	$0.03	<$0.01
TOTALS					
all components	1,000,000				**$35,949.72**
ex. ethanol	4,513				***$5,413.90***
ex. 2 costliest items	1,713				***$271.03***
ex. 3 costliest items	893				***$50.56***

Lahne's initial attempt, "Model A", was strictly based on chemical quantifications from actual samples of commercial whiskies, yet the 17 "naive judges" described the replicant as "medicinal", "barnyard", and "banana" – "whiskey" or "whiskey-like" descriptors were not forthcoming. "Model B" attempted to correct the initial recipe to be more like Wild Turkey rye whiskey and apparently tasted much closer to whiskey, though the best the author could report was that the "judges were unable in some but not all cases to discriminate between the model and the commercial whiskies, indicating that the model and the quantification it was based on were a partial success."

It is possible the taste judges were reacting negatively to the subtle aromas of some unidentified objectionable impurities, given that the chemicals Lahne used were at best 98% pure and the analysis presented in Table 4 suggests that ~99.95% purity may be required for any chemical that will be used at ~ppm concentrations, assuming we wish to hold impurities to ppb levels that might be undetectable to the human nose. However, it is also possible that Lahne's proposed "Model B" recipe for rye whiskey is simply incomplete. We probably need to include a lot more chemicals to make the bulk chemical replicant whiskey taste right. Indeed, to be a true replicant whiskey, we'd ideally want to include *all* of the chemical constituents down to the ppb level unless there is decisive evidence that a particular chemical has absolutely *no* impact whatsoever on taste.

To account for these additional chemical constituents, **Table 5** includes a list of the estimated maximum concentrations of 113 additional congener ingredients that have been identified by chemical assay to be found in some whiskies but which were not included in Lahne's "Model B" replicant rye whiskey. These additional ingredients are taken from Table 1 and from several

other sources,[127] then assembled in a format similar to that of Table 4. (The cost of the four metal ions is taken from their respective chloride salts.)

Table 5. Estimated cost of 113 additional whiskey congeners, not included in "Model B", assuming a required purity level of ~1 ppb for each compound and assuming a log-linear cost/purity function.

Whiskey Component	Assumed or Max. Concen-tration (mg/L)	Minimum Purity Req'd to meet 1 ppb standard (%)	2014 cost of chemical at the indicated available purity level from Sigma-Aldrich	Estimated cost of chemical at min. req'd purity level ($/gm)	Incremental cost to make 1 L of repli-cant whiskey mixture
2-methyl-butanol	1390	99.99993	$0.04/gm (≥99%)	$68.42	$95.10
ethyl acetate	716	99.99986	$0.04/ml (≥99.9%)	$6.65	$4.76
1-propanol	187	99.99947	$0.03/ml (≥99.5%)	$6.19	$1.16
methanol	130	99.99923	$0.04/ml (≥99.93%)	$1.34	$0.17
ethyl decanoate	44	99.9977	$0.19/ml (≥99%)	$21.46	$0.94
ethyl dodecanoate	32	99.9969	$0.54/ml (≥98%)	$82.94	$2.65
furfural	30	99.9967	$0.04/ml (≥99%)	$3.41	$0.10
potassium ion	30	99.9967	$0.14/gm (≥99%)	$11.94	$0.36
magnesium ion	28	99.9964	$7.71/gm (≥99.99%)	$17.07	$0.48
ethyl formate	27	99.9963	$0.02/gm (≥97%)	$3.67	$0.10
gallic acid	25	99.9960	$0.57/gm (≥98%)	$71.79	$1.79
ellagic acid	25	99.9960	$57.00/gm (≥95%)	$14,646.68	$366.17
ethyl 9-decenoate	22	99.9955	$0.02/gm (≥98%)	$2.30	$0.05
isobutyraldehyde	20	99.9950	$0.47/ml (≥99.5%)	$16.92	$0.34
acetovanillone	20	99.9950	$0.23/gm (≥98%)	$24.35	$0.49
calcium ion	17	99.9941	$21.25/gm (≥99.99%)	$32.04	$0.54
1,1-diethoxyethane	15.3	99.9935	$0.19/ml (99%)	$9.56	$0.15
ethyl palmitate	10	99.990	$3.60/gm (≥99%)	$129.60	$1.30
salicylaldehyde	10	99.990	$0.57/ml (≥99%)	$20.52	$0.21
hydroxymethylfurfural	10	99.990	$5.92/gm (≥99%)	$213.12	$2.13
acrolein	10	99.990	$92.80/ml (≥99%)	$3,340.80	$33.41
1,1,3-triethoxypropane	10	99.990	$1.92/gm (≥95%)	$241.83	$2.42
acetone	10	99.990	$0.03/ml (≥99.9%)	$0.18	<$0.01
ethyl octanoate	8.34	99.988	$0.24/gm (≥99%)	$7.50	$0.06
1-hexanol	6.71	99.985	$0.10/ml (≥99%)	$2.63	$0.02
2-methylbutyraldehyde	6.3	99.984	$0.28/gm (98%)	$11.99	$0.08
isovaleraldehyde	6.3	99.984	$0.20/ml (97%)	$11.74	$0.07
ethyl lactate	5.3	99.981	$0.02/gm (≥98%)	$0.75	<$0.01
octanoic acid	5	99.980	$0.37/ml (≥99%)	$7.77	$0.04

[127] Henk Maarse, *Volatile Compounds in Foods and Beverages*, CRC Press, 1991; L. Poisson, P. Schieberle, "Characterization of the most odor-active compounds in an American Bourbon whisky by application of the aroma extract dilution analysis," *J. Agric. Food Chem.* 56(2008):5813-5819; L. Poisson, P. Schieberle, "Characterization of the key aroma compounds in an American Bourbon whisky by quantitative measurements, aroma recombination, and omission studies," *J. Agric. Food Chem.* 56(2008):5820-5826.

decanoic acid	5	99.980	$0.22/gm (≥99%)	$4.62	$0.02
dodecanoic acid	5	99.980	$0.19/gm (≥99%)	$3.99	$0.02
formic acid	5	99.980	$0.09/ml (≥95%)	$6.61	$0.03
palmitic acid	5	99.980	$1.89/gm (≥99%)	$39.68	$0.20
palmitoleic acid	5	99.980	$185.20/gm (≥98.5%)	$5,329.94	$26.65
propionic acid	5	99.980	$0.03/ml (≥99.5%)	$0.37	<$0.01
isobutyric acid	5	99.980	$0.29/ml (≥99.5%)	$3.55	$0.02
isovaleric acid	5	99.980	$0.03/gm (≥99%)	$0.63	<$0.01
valeric acid	5	99.980	$0.02/gm (≥99%)	$0.42	<$0.01
syringic acid	5	99.980	$6.16/gm (≥95%)	$452.42	$2.26
2,3-butanedione	4.4	99.977	$0.26/ml (97%)	$11.51	$0.05
sodium ion	3	99.967	$0.04/gm (≥99.5%)	$0.33	<$0.01
diethyl succinate	1.97	99.95	$0.02/gm (≥99%)	$0.21	<$0.01
scopoletin	1.6	99.94	$824.00/gm (≥99%)	$7,357.16	$11.77
1,1-diethoxy-2-methylpropane	1.24	99.92	$200.00/gm (99%?)	$1,427.55	$1.77
propionaldehyde	1.2	99.92	$0.14/ml (97%)	$2.35	<$0.01
4-hexen-1-ol	1.11	99.91	$2.83/gm (≥96%)	$54.20	$0.06
coniferaldehyde	1	99.90	$38.50/gm (98%)	$396.15	$0.40
tri-6-decen-2-one	1	99.90	n/a	---	---
penta-6-decen-2-one	1	99.90	n/a	---	---
hepta-6-decen-2-one	1	99.90	n/a	---	---
coumaric acid	1	99.90	$3.32/gm (≥98%)	$34.16	$0.03
glycerol	1	99.90	$0.08/ml (≥99.5%)	$0.08	<$0.01
erythritol	1	99.90	$2.25/gm (≥99%)	$13.50	$0.01
pyridine	1	99.90	$0.13/ml (≥99.9%)	$0.13	<$0.01
α-picoline	1	99.90	$0.06/ml (98%)	$0.62	<$0.01
turpentine	1	99.90	$0.05/ml (99%)	$0.30	<$0.01
δ-nonalactone	1	99.90	$0.27/gm (98%)	$2.78	<$0.01
1-tetradecanol	0.91	99.89	$0.45/gm (97%)	$5.89	$0.01
ethyl myristate	0.59	99.83	$0.74/ml (99%)	$2.94	<$0.01
2,3-pentanedione	0.57	99.82	$0.83/gm (97%)	$7.41	<$0.01
hexadecanol	0.54	99.81	$0.04/gm (≥99%)	$0.15	<$0.01
benzaldehyde	0.45	99.78	$0.25/ml (≥99.5%)	$0.47	<$0.01
2-methylbutyl acetate	0.24	99.58	$0.01/gm (99%)	$0.02	<$0.01
3-methylbutyl decanoate	0.21	99.52	$0.70/ml (99%?)	$1.24	<$0.01
sinapaldehyde	0.2	99.50	$64.40/gm (98%)	$189.40	$0.04
tetradecyl acetate	0.11	99.09	n/a	---	---
1-decanol	0.1	99.00	$1.06/gm (≥99%)	$1.06	<$0.01
2-isopropyl-3-methoxypyrazine	0.1	99.00	$3.18/gm (99%)	$3.18	<$0.01
ethyl phenylacetate	0.1	99.00	$0.12/gm (99%)	$0.12	<$0.01
4-methyl acetophenone	0.1	99.00	$0.04/gm (≥95%)	$0.14	<$0.01
α-damascone	0.1	99.00	$6.42/ml (≥90%)	$38.52	<$0.01
2-phenylethyl propionate	0.1	99.00	$0.02/gm (≥98%)	$0.03	<$0.01
sugar lactone	0.1	99.00	$5.07/gm (≥97%)	$11.92	<$0.01
(Z)-6-dodeceno-γ-lactone	0.1	99.00	n/a	---	---
2-acetylfuran	0.09	98.89	$0.07/gm (≥99%)	$0.06	<$0.01
isoamyl octanoate	0.08	98.75	$0.06/gm (≥98%)	$0.09	<$0.01
1-dodecanol	0.08	98.75	$0.04/gm (98%)	$0.06	<$0.01
2-methylbutyl decanoate	0.08	98.75	n/a	---	---
o-cresol	0.075	98.7	$0.02/gm (≥99%)	$0.02	<$0.01
m-cresol	0.075	98.7	$0.03/gm (≥98%)	$0.04	<$0.01
ethyl linoleate	0.07	98.6	$18.34/gm (≥99%)	$14.12	<$0.01
isobutyl decanoate	0.06	98.3	$50.00/gm (99%?)	$33.09	<$0.01
2-phenylethyl decanoate	0.06	98.3	n/a	---	---
citric acid tributyl ester acetate	0.06	98.3	$0.02/gm (≥98%)	$0.02	<$0.01
ethyl isovalerate	0.052	98.1	$0.04/gm (≥98%)	$0.04	<$0.01
dimethyl trisulfide	0.05	98.0	$0.80/gm (≥98%)	$0.80	<$0.01
1-octanol	0.05	98.0	$0.08/ml (≥99%)	$0.05	<$0.01
ethyl 5-hydroxymethyl-2-furoate	0.05	98.0	n/a	---	---
ethyl nonanoate	0.05	98.0	$0.02/gm (≥98%)	$0.02	<$0.01
farnesyl acetate	0.05	98.0	$18.40/gm (95%)	$37.54	<$0.01
1,1-diethoxy-3-methylbutane	0.04	97.5	n/a	---	---

phenethyl octanoate	0.04	97.5	$0.13/gm (≥99%)	$0.06	<$0.01
isoamyl laurate	0.04	97.5	$0.37/gm (≥97%)	$0.43	<$0.01
ethyl oleate	0.04	97.5	$5.12/gm (98%)	$4.30	<$0.01
(E,E)-2,4-decadienal	0.039	97.4	$1.52/gm (≥89%)	$4.67	<$0.01
1,1-diethoxy-2-methylbutane	0.03	96.7	n/a	---	---
1-heptanol	0.03	96.7	$0.05/ml (98%)	$0.03	<$0.01
phenol	0.03	96.7	$0.09/gm (≥99%)	$0.04	<$0.01
2-heptanone	0.03	96.7	$0.02/gm (≥98%)	$0.01	<$0.01
ethyl heptanoate	0.03	96.7	$0.63/gm (≥98%)	$0.43	<$0.01
2-methylbutyl octanoate	0.03	96.7	n/a	---	---
dodecyl acetate	0.03	96.7	$2.66/gm (97%)	$2.47	<$0.01
farnesol	0.03	96.7	$1.51/gm (95%)	$2.09	<$0.01
ethyl *(S)*-2-methylbutanoate	0.03	96.7	$0.16/gm (≥98%)	$0.11	<$0.01
hexyl acetate	0.02	95.0	$0.02/gm (≥98%)	$0.01	<$0.01
(E)-2-heptenal	0.02	95.0	$1.03/gm (≥95%)	$1.03	<$0.01
ethyl valerate	0.01	90.0	$0.03/gm (≥98%)	$0.01	<$0.01
(E)-2-nonenal	0.009	88.9	$0.53/gm (≥93%)	$0.37	<$0.01
(E,E)-2,4-nonadienal	0.0024	any	$1.48/gm (≥89%)	[$1.48]	<$0.01
(E)-2-decenal	0.0018	any	$0.40/gm (≥92%)	[$0.40]	<$0.01
γ-decalactone	0.0016	any	$1.50/gm (≥97%)	[$1.50]	<$0.01
2,6-xylenol	0.001	any	$0.03/gm (≥99%)	[$0.03]	<$0.01
(E,Z)-2,6-nonadienal	0.0009	any	$7.94/gm (≥95%)	[$7.94]	<$0.01
TOTALS					
all 113 new components	2938				**$558.43**
ex. costliest ingredient	2913				***$192.26***
ex. costliest 2 ingredients	1523				***$97.16***
ex. costliest 3 ingredients	1513				***$63.75***
ex. costliest 4 ingredients	1508				***$37.10***

Given that there may be at least ~4000 non-volatile chemicals present at the ppb level,[128] and perhaps several hundred additional volatile compounds, the 144 congeners listed in Table 4 and Table 5, while representative, may include less than 3% by number of all the substances found in whiskey, or only 1/30th of the total number. However, most of these as-yet unquantified substances are likely to be present in only tiny amounts, hopefully not adding appreciably to the cost of manufacture. The 144 congeners listed in the tables total 7451 mg/L or about 0.792% by weight, roughly consistent with the previously estimated total congener mass budget of 0.75% (Table 1). Assuming that we have properly accounted for all of the highest-mass expensive chemicals, then the raw materials cost to produce 1 liter of bulk chemical replicant whiskey (**Table 6**) would be $36,508.15 for all 146 components listed in both Table 4 and Table 5 at the ideal purity levels.

[128] Thomas S. Collins, Jerry Zweigenbaum, Susan E. Ebeler, "Profiling bourbons and American whiskies using UHPLC/QTOF-MS," Monday, 9 September 2013, 246th ACS National Meeting and Exposition; http://abstracts.acs.org/chem/246nm/program/view.php?obj_id=207497&terms=.

Table 6. Estimated materials cost of 1 liter of bulk chemical replicant whiskey.		
Whiskey Components	**Excluding the Next Costliest Ingredient:**	**Remaining Cost, in $ per liter**
Water, ethanol, and 144 congeners	---	$36,508.15
ex. costliest ingredient	ethanol	$5,972.33
ex. costliest 2 ingredients	3-methyl-1-butanol	$829.46
ex. costliest 3 ingredients	ellagic acid	$463.29
ex. costliest 4 ingredients	2-methyl-1-propanol	$242.82
ex. costliest 5 ingredients	2-methyl-butanol	$147.72
ex. costliest 6 ingredients	acrolein	$114.31
ex. costliest 7 ingredients	palmitoleic acid	$87.66
ex. costliest 8 ingredients	ethyl vanillate	$63.90
ex. costliest 9 ingredients	scopoletin	$52.13
ex. costliest 10 ingredients	acetic acid	$41.62

However, this cost might fall to $41.62 per liter if we could eliminate the high cost of the 10 most expensive ingredients. How might this be done?

Perhaps surprisingly, the most expensive chemical ingredient in a liter of whiskey appears to be ethanol. This is driven by our perhaps excessive demand that no impurities be present above the 1 ppb level (e.g., 99.9999997% purity, or almost 9N, for ethanol that will constitute 36.1% by weight of the final mixture). This seems to be well beyond the present capabilities of commercial suppliers. For example: "Pharmaco-Aaper stands apart as the premier producer and manufacturer of the highest purity pharmaceutical and analytical grade ethanol in the world. We operate the most rigorous quality system, fully integrated into a dedicated manufacturing process that provides a chain of custody and control of quality from raw materials to finished product."[129] Pharmaco-Aaper's best ethanol product is called "World/GMP grade ethyl alcohol" ("Absolute, Dehydrated, Anhydrous, 200 Proof, Pure Ethanol"), that formally assays at 99.99% with impurities of <5 ppm methanol, no acetal or acetaldehyde or benzene detected (probably to the 1 ppm level), and <50 ppm total for all other impurities with solid residues <10 ppm.[130] This is a factor of 10,000X more impure than we would be seeking with a 1 ppb minimum standard. However, if research can demonstrate that this higher level of ethanol impurities is non-organoleptic, then Pharmaco-Aaper's material could be used at a cost that is likely considerably less than the $89.97/gm estimated in Table 4. Ethanol at 99.99% should otherwise be safe enough for human consumption, since 99.9% ethanol (albeit fermentation-derived) and even

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[129] "Pharma Ethanol"; http://www.cpichem.com/index.php/ct-menu-item-4/ct-menu-item-8.

[130] CPI Chemicals for Pharmacy and Industry, "GMP Grade Ethyl Alcohol 99,9%"; http://www.cpichem.com/index.php/ct-menu-item-4/ct-menu-item-8/ethanol-product-summary/gmp-grade-ethyl-alcohol-99-9.

somewhat lesser grades are approved for use in human foodstuffs and beverages where the precise taste is not an important factor. Alternatively, research funding could be directed into finding new filtration and purification methods aimed at producing ultrapure ethanol at low cost.

A similar R&D strategy applied to the other nine of the top 10 most expensive ingredients – which are costly mainly because of the unusually high purity required – could conceivably push the raw materials component of the manufacturing cost for bulk chemical replicant whiskey down into the $50-$100/liter range.

However, the above materials cost analysis must be regarded as a lower-bound estimate because our calculations assume that the impurities present in each of potentially ~4,000 intentionally added compounds are entirely uncorrelated. This seems unlikely. For example, if two separate compounds in the recipe share the same impurity in an amount that would separately add 1 ppb to the replicant mixture, then the total concentration of that impurity in the final mixture would rise to 2 ppb. In the extreme case where all ~4,000 commercially purchased constituents had exactly 1 ppb of the same impurity, the total concentration of that impurity in the final mixture would rise to ~4000 ppb. In order to ensure that the replicant product contained at most 1 ppb of any one impurity, we would have to increase the required initial purity level of all ingredients by ~4,000-fold, raising the total materials cost by another factor of $\sim 6^{[\log 10(4000)]}$ or ~640-fold, from perhaps $50/liter up to as much as (640 x $50/liter =) $32,000/liter. Without access to atomically precise manufacturing (Section 5), there is no easy way to remove these numerous contaminants once they've been added to the replicant mixture, and it is difficult to know how the presence of such large amounts of one or more impurities might interact with the other ingredients in a manner that could affect the replicant taste.

It seems most likely that many but not all ingredients will share some but not all of the same impurities, a research question that can only be resolved by further testing and analysis. If we're lucky, the per-compound impurity-contribution target may only have to be lowered from 1 ppb to 0.1 ppb or so, not all the way down to 0.0016 ppb, to deal with the correlated-contaminant effect described above. For now, we can only say that the materials cost of manufacturing a complete bulk chemical replicant whiskey, even after employing the cost-reduction steps described above for the 10 costliest ingredients, is probably in the $50-$32,000/liter range. The geometric mean of this range is ~$1300/liter, giving a not-unreasonable mid-range materials cost estimate of ~**$1000/bottle** for the standard 750-ml bottle size. This exceeds the retail price even of most connoisseur-level whiskies and thus appears to be, for most purposes, commercially impractical.

4.4.4 Quantified Cost of Analysis for Chemical Replication

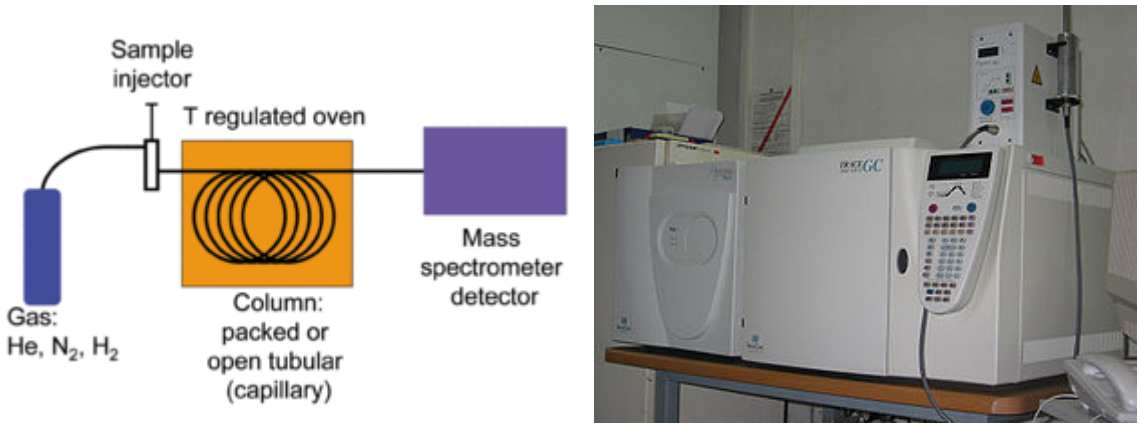
Before we can solvate a set of chemicals to create a synthetic whiskey, we must first have the precise chemical recipe for the target whiskey. If a generic whiskey-like taste is all that we desire, then a generic recipe could be developed once and then used. But if the goal is to exactly replicate the taste of a treasured existing whiskey that was produced by traditional methods, then the cost to perform a comprehensive chemical assay must be added to the cost of each replication. For all further discussion here, we'll assume that 10,000 chemicals must be correctly identified and quantified to adequately replicate whiskey, roughly matching the 10,000 structurally distinct odorant ligands believed to be detectable by the human olfactory apparatus (Section 4.4.1)

In one scenario, a small sample of the whiskey to be replicated would be submitted to a chemical analysis laboratory that performs a precise quantitative analysis of the 10,000 distinct organic

chemicals anticipated to be present, essentially reverse-engineering the recipe for the replicant chemical mixture by starting from the original product.

GC-MS. A key workhorse technique for this task would be Gas Chromatography–Mass Spectrometry (GC-MS),[131] an analytical method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a test sample (**Figure 9**). GC-MS is extensively used for the analysis of organic compounds including esters, fatty acids, alcohols, aldehydes, terpenes, etc., that are found in foods, beverages and perfumes. GC-MS has been widely heralded as the "gold standard" for forensic substance identification because it is used to perform a specific test that can positively identify the actual presence of a particular substance in a given sample.

Figure 9. GC-MS schematic (left) and a typical laboratory GC-MS instrument (right).



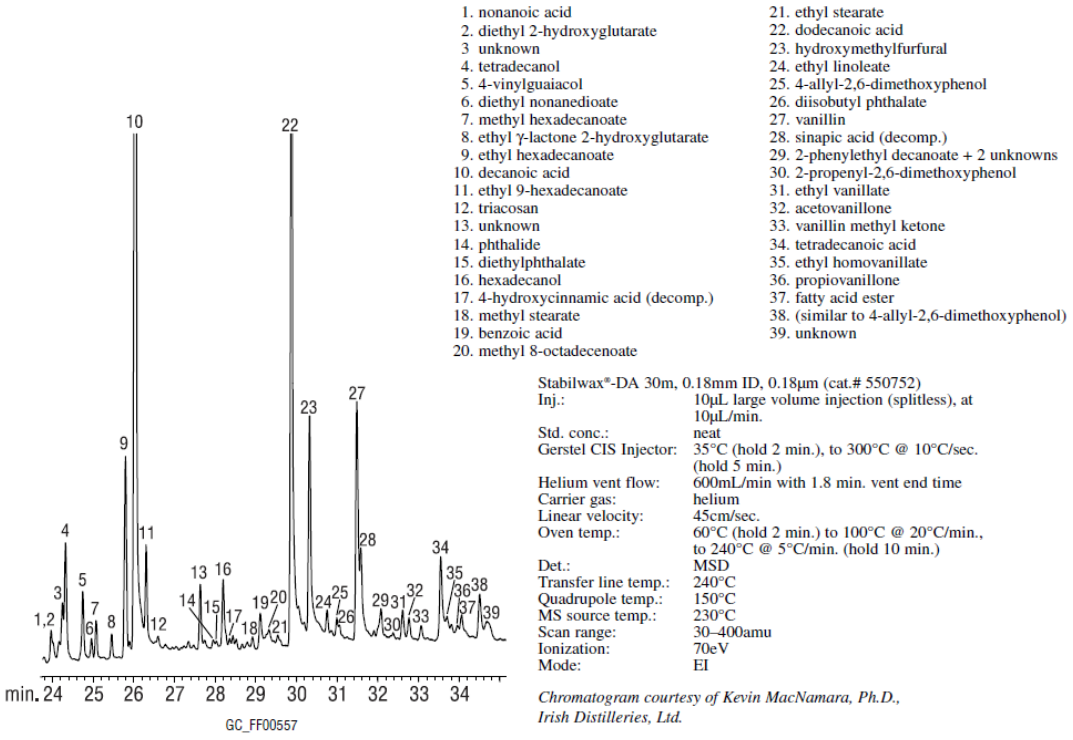
The GC-MS is composed of two major building blocks: the gas chromatograph and the mass spectrometer. The gas chromatograph utilizes a capillary column which depends on the column's dimensions (length, diameter, film thickness) and chemical properties. The difference in the chemical properties between different molecules in a mixture and their relative affinity for the stationary phase of the column promotes separation of the molecules as the sample travels the length of the column. The molecules are retained by the column and then elute (come off) from the column at different times (called the retention time), and this allows the mass spectrometer downstream to capture, ionize, accelerate, deflect, and detect the ionized molecules separately. The mass spectrometer does this by breaking each molecule into ionized fragments and detecting these fragments using their mass-to-charge ratio.

When used together, the GC and the MS allow a much finer degree of substance identification (**Figure 10**) than either unit used separately. It is not possible to make an accurate identification of a particular molecule by gas chromatography or mass spectrometry alone. The mass spectrometry process normally requires a very pure sample, while gas chromatography using a traditional detector (e.g., flame ionization detector) cannot differentiate between multiple

[131] http://en.wikipedia.org/wiki/Gas_chromatography%E2%80%93mass_spectrometry.

molecules that happen to take the same amount of time to travel through the column (i.e., have the same retention time) yielding two or more molecules that co-elute. Sometimes two different molecules can also have a similar pattern of ionized fragments in a mass spectrometer (i.e., their "mass spectrum"). Combining the two processes reduces the possibility of error, as it is extremely unlikely that two different molecules will behave in the same way in both a gas chromatograph and a mass spectrometer. Therefore, when an identifying mass spectrum appears at a characteristic retention time in a GC-MS analysis, it typically increases certainty that the analyte of interest is in the sample.

Figure 10. Gas chromatogram of flavor compounds in a sample of Irish malt whiskey.[132]



The primary goal of instrumented analysis is to quantify an amount of substance. This is done by comparing the relative concentrations among the atomic masses in the generated spectrum. Comparative analysis essentially compares the given mass spectrum to a spectrum library to see if its characteristics are present for some sample in the library. Another method of analysis measures the peaks in relation to one another, wherein the tallest peak is assigned 100% of the value and the other peaks are assigned proportionate values. The total mass of the unknown compound is normally indicated by the parent peak and the value of the parent peak can be used to fit with a chemical formula containing the various elements (also identified by isotope pattern) which are believed to be in the compound. Once a chemical formula is matched to the spectrum,

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[132] http://www.restek.com/images/cgram/gc_ff00556.pdf.

the molecular structure and bonding can be identified, and must be consistent with the characteristics recorded by GC-MS. Typically, this identification is done automatically by programs that come with the instrument, given a list of the elements which could be present in the sample.

LC-MS. Liquid chromatography–mass spectrometry (LC-MS, or alternatively HPLC-MS) is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry (MS).[133] LC-MS is a powerful technique that has very high sensitivity and selectivity and so is useful in many applications. Its application is oriented towards the separation, general detection and potential identification of chemicals of particular masses in the presence of other chemicals (i.e., in complex mixtures) – as, for example, for identifying specific natural products in natural-products extracts and for identifying pure substances in mixtures of chemical intermediates. Preparative LC-MS systems can be used for rapid mass-directed purification of specific substances from such mixtures that are important in basic research and in pharmaceutical, agrochemical, food, and other industries.

HPLC. High-performance liquid chromatography (aka. high-pressure liquid chromatography) is a technique in analytic chemistry used to separate the components in a mixture, to identify each component, and to quantify each component.[134] It relies on pumps to pass a pressurized liquid solvent containing the sample mixture through a column filled with a solid adsorbent material. Each component in the sample interacts slightly differently with the adsorbent material, causing different flow rates for the different components and leading to the

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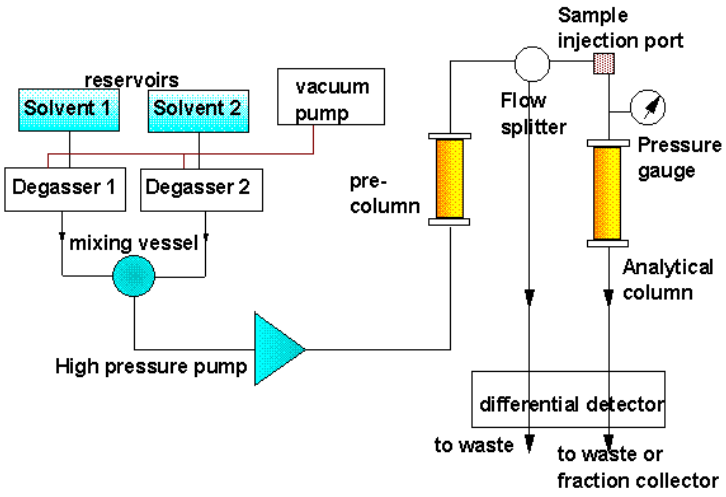
[133] http://en.wikipedia.org/wiki/Liquid_chromatography-mass_spectrometry.

[134] http://en.wikipedia.org/wiki/High_performance_liquid_chromatography.

separation of the components as they flow out the column. HPLC has been used for medical (e.g., detecting vitamin D levels in blood serum), legal (e.g., detecting performance enhancement drugs in urine), research (e.g., separating the components of a complex biological sample, or of similar synthetic chemicals from each other), and manufacturing (e.g., during the production process of pharmaceutical and biological products) applications.



HPLC relies on pumps to pass a pressurized liquid (e.g., ~400 atm) and a sample mixture through a column filled with a sorbent, leading to the separation of the sample components. The active component of the column, the sorbent, is typically a granular material made of solid particles (e.g., silica, polymers, etc.), 2-50 microns in size. The components of the sample mixture are separated from each other due to their different degrees of interaction with the sorbent particles. The pressurized liquid is typically a mixture of solvents (e.g., water, acetonitrile and/or methanol) and is referred to as a "mobile phase". Its composition and temperature play a major role in the separation process by influencing the interactions taking place between sample components and sorbent. These interactions are physical in nature, such as hydrophobic (dispersive), dipole–dipole, or ionic, and most often a combination thereof. HPLC separations have theoretical parameters and equations to describe the separation of components into signal peaks when detected by instrumentation such as by a UV detector or a mass spectrometer.

Resource and Cost Estimates. Using these instruments along with many other specialized analytical tests, we assume that we will need to characterize and quantify the presence of up to 10,000 distinct organic chemicals in our test sample of whiskey.

To get an idea of the likely time, cost, and personnel/equipment requirements to accomplish such a task, the author posed a crisply-defined problem statement to an experienced PhD bench chemist,[135] as follows: Assume that we have a mixture of 10,000 organic compounds, all of which are solvated in an alcohol-water mixture, and that we know the names, molecular structures, and basic physicochemical properties of all 10,000 compounds. The compounds are a broad assortment of common alcohols, aliphatic and aromatic acids and their esters, phenolic compounds, aliphatic and aromatic aldehydes, ketones, lactones, terpenes, sterols, sugars, and other simple organics – with few having more than 1-2 dozen carbon atoms per molecule and most nearer the low end of this range – but some passingly similar to each other, e.g., 2-methyl-butanol, 3-methyl-1-butanol, and 2-methyl-1-propanol. We further assume the following

[135] Personal communication with Michael Drew, PhD; 24-25 Jul 2014.

approximate distribution of concentrations among the 10,000 compounds: 10 compounds at 10-1000 ppm, 100 compounds at 1-10 ppm, 1000 compounds at 0.1-1 ppm, and 8890 compounds at 0.001-0.1 ppm (1-100 ppb). The challenge: How to measure the concentration of each of the 10,000 compounds, accurate to at least one, or ideally two, significant figures?

After some analysis, the bench chemist concluded that the project would require at least a GC-MS and likely an LC-MS and HPLC. Organic constituents that are volatile liquids at room temperature (i.e., molecular weight <300 gm/mole) and would separate by boiling point would be the easiest to analyze by GC-MS which is extremely sensitive and capable of detecting the presence of compounds down to the parts per billion level using only microliters of test sample. However, with such a complex mixture there are so many compounds present that separation at high sensitivity would prove difficult. And if the mixture has chiral molecules, then we'd have isomers that would also need to be separated and analyzed on chiral columns,[136] likely adding more time and expense to the analysis.

In the somewhat analogous case of crude oil purification, the constituent compounds are usually separated by boiling point using an enormous fractional distillation apparatus. A similar technique might be helpful here, though the large number of molecules at ppb concentrations might prove challenging to separate and analyze. However, if 10 liters of test sample was available (e.g., 1 ml of test sample per analyte x 10,000 analytes), this might provide enough working material to separate the analyte and perform the analysis using 1 ml aliquots for each of the 10,000 compounds present in the test sample. Once component chemical classes are separated by boiling point, it would be possible to extract the acidic molecules (e.g., carboxylic acids, phenols) by a chemically active extraction. The alcohols could be separated from ketones/esters by modification by silyl group (e.g., trimethylsilyl chloride or many others). The general process is called fractional distillation and you would need a batch processor perhaps similar to the system (at right) that is commercially available from Pope Scientific.[137]

It would likely not be feasible to simply inject each sample into the apparatus as such a complex mixture, so the samples would be needed to be pre-separated into mixtures of perhaps 20-30 compounds. This effort might take about 1-2 years to separate compounds into distinguishable groups and then another 12-18 months to analyze them by class and boiling point. You would need a PhD-level analytical chemist to make sure the machines were running, and at least one other experienced PhD process chemist to set up and keep the distillation running smoothly. These processes would likely be set up at the same initial time. After the analytical instruments

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[136] http://en.wikipedia.org/wiki/Chiral_column_chromatography.

[137] Pope Scientific Inc., "Fractional Distillation Equipment: Distillation Systems & Components. Fractional Distillation Systems for Purification, Fractionation, and Solvent Recovery"; http://www.popeinc.com/still-products/fractional-distillation-systems#tab-1.

and batch process system has been set up, you would need another 3 B.S.-level technicians to help with processing those thousands of runs and prepping the samples. The distillation equipment would likely be in use ~50% of the time, whereas the analytical equipment would be in use full-time once it is set up because it can be automated and run 24/7 if necessary.

The analytical equipment is estimated to cost $700K-$800K, which includes $250K-$350K for the LC-MS, $250K for the GC-MS, $200K for the HPLC, plus another $200K-$250K for the fractional distillation equipment, a total capital outlay of about $1M. Taking into account all expenses for equipment, consumables, and labor, we estimate a total cost of $500-$1000 per analyte over the lifetime of the project. Making the reasonable assumption that the project might be even more difficult than it looks, we'll conservatively adopt the $1000/analyte estimate for the rest of this discussion. Since the project would require 24-42 months to complete, we can probably assume that the equipment would be fully depreciated by the end and might have to be replaced if we desired to repeat the project on a new 10-liter test sample. It seems doubtful that a commercial contract laboratory could perform all parts of the project more inexpensively, if at all – so it should be faster and much more economical to hire personnel specific for the project, yielding the aforementioned cost estimates.

In sum, we estimate that to fully quantify the constituents of a single traditionally-manufactured fine spirit product that we wish to replicate will cost $10M, require the destruction of 10 liters of the product, and will require: (a) between 2 and 3.5 years to complete, (b) 5 full-time scientific personnel including 2 PhDs, and (c) an initial capital outlay of at least $1M for equipment. The yield is one recipe for just one whiskey product.

4.4.5 Economic Feasibility of the Bulk Chemical Replication of Whiskey

Are there any circumstances under which bulk chemical whiskey replication might make economic sense?

High-end specialty market for whiskey. In this market, for example, in July 2014 the Wine Searcher website listed four bottles of a rare 750 ml bottle of Knappogue Castle 1951 (right), believed to be one of the oldest Irish whiskies around, for sale at prices ranging from **$750-$2200/bottle**.[138] Whiskey connoisseurs routinely order $51 shots of "K51" at bars in Manhattan,[139] and a chart (below)[140] shows that the retail price of K51 during 2007-2014, in all countries exclusive of local tax, has varied in the $500-$1500/bottle range. K51 was distilled in 1951 at the now-defunct B. Daly

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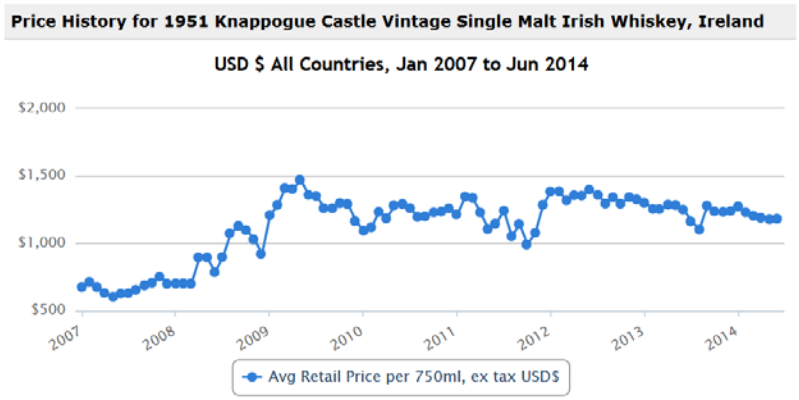
[138] http://www.wine-searcher.com/find/knappogue+castle+single+malt+whisky+ireland/1951.

[139] "Ten Must-Drink Irish Whiskies," *Forbes*, 13 March 2007; http://www.forbes.com/2007/03/12/drink-whiskey-irish-forbeslife-cx_pl_0313irishwhiskey.html.

[140] http://www.wine-searcher.com/wine-95152-1951-knappogue-castle-vintage-single-malt-irish-whiskey-ireland.

Distillery in Tullamore, aged in sherry casks for 36 years, and bottled in 1987. Fewer than 1000 bottles of K51 are still extant. You can easily pay more. For example, an ancient bottle of 1882 Bushmills went for **$2600** from a private collector in 2006, Port Ellen 1983 is available[141] for **$3065**/bottle, and the current world record for a single bottle of whiskey is apparently a 6-liter crystal decanter of Macallan Imperiale "M" sold for **$628,000** by Sotheby's in Hong Kong in January 2014.[142] More affordable super-premium Irish whiskies are readily available including Redbreast 12-year-old at **$50**/bottle, Green Spot at **$60** (only 500 bottles released per year), Jameson 18-year-old at **$65**, Bushmills 21-year-old single malt at **$115**, and Midleton Very Rare at **$150**.



Consider that the entire remaining (at most) 1000-bottle global inventory of the extremely rare Knappogue Castle 1951, if priced near the central $1000/bottle level, would have an aggregate market value of $1M. The $10M analysis cost to obtain the chemical recipe of this product greatly exceeds the total market value of the surviving inventory of K51. Let's assume a whiskey entrepreneur decided to invest $10M to obtain the complete molecular recipe for K51. At a materials cost of ~$1000/bottle for bulk chemical replication (Section 4.4.3), it would be impossible for the entrepreneur to obtain any positive return on his investment because the profit per bottle is effectively zero at the current market price of ~$1000/bottle.

The situation is aggravated as soon as the market learns that there has been a sudden increase in available supply due to the entrepreneur's activities. Assuming constant market demand for the product (e.g., drinkers remain as enchanted with whiskey as ever, and regard the original and the replicant as having equal desirability), and assuming the known price elasticity of demand (E_d) of approximately -1.5 for fine spirits generally,[143] then doubling the supply from 1000 bottles to 2000 bottles should cause the price of K51 to fall from $1000/bottle down to $333/bottle, turning a $0/bottle profit into a -$667/bottle loss for the entrepreneur.[144] There's a loss of -$0.67/bottle

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[141] http://www.masterofmalt.com/whiskies/port-ellen/port-ellen-30-year-old-1983-cask-671-tantalus-duncan-taylor-whisky/.

[142] Bronte Lord, "The world's most expensive whisky," CNN Money, 21 Jan 2014; http://money.cnn.com/2014/01/21/news/economy/whisky-auction/. See also: http://richieast.com/bottle-macallan-m-whisky-made-sensation-auction-hong-kong/.

[143] http://en.wikipedia.org/wiki/Price_elasticity#Selected_price_elasticities.

[144] The manufacturer's profit is $G_{mfg} = (P_1 - K_{mfg})\, Q_{mfg}$ ($) or G_{mfg}/Q_{mfg} ($/bottle), where $P_1 = P_0\,(1 + (Q_1 - Q_0) / (E_d\, Q_0))$, taking P_0 = the original market price (e.g., $1000/bottle), Q_0 = the original quantity of

even if only 1 bottle of replicant whiskey is produced and sold at the slightly depressed price of $999/bottle (given the slightly enlarged extant inventory of 1000 + 1 = 1001 bottles), and the losses grow steadily larger as more bottles are produced. With no operating profits, the $10M investment in the recipe can never be recouped and so the proposed venture makes no economic sense.

A similar result is obtained if we optimistically assume that the materials cost for bulk chemical replication can be brought down tenfold, to $100/bottle. In this circumstance, the highest total profit to the entrepreneur is $304K which occurs at a net profit of $450/bottle on a manufacturing run of 675 bottles and a depressed market price of $550/bottle. If the entrepreneur produces more bottles, his profit falls because adding the extra bottles to aggregate supply depresses the price ever further, thus reducing his profit margin per bottle – i.e., at 1000 bottles of replicant production, profit per bottle is lower at $233/bottle on a depressed market price of $333/bottle, and total profits are also lower at $233K. If the entrepreneur produces fewer bottles, his profit per bottle is higher but he sells less so his total profit again declines – i.e., if only 1 bottle of replicant whiskey is produced, profit per bottle is highest at $899/bottle on a market price of $999/bottle, but total profits are also lowest at $0.9K). With at most an operating profit of $0.304M the $10M investment in the chemical recipe can never be recouped, and again the proposed venture makes no economic sense.

If 900 of the outstanding 1000 bottles of K51 were either consumed or destroyed, leaving only 100 bottles extant instead of 1000, our mathematical model predicts that the price should rise to $1600/bottle. In this circumstance, and still optimistically assuming a $100/bottle materials cost for bulk chemical replication, the highest total profit to the entrepreneur is $844K which occurs at a net profit of $750/bottle on 1125 bottles at a depressed market price of $850/bottle. Yet again, the proposed venture makes no economic sense.

Only by making a series of unreasonably overoptimistic assumptions can we get our entrepreneur anywhere near financial break-even. Assume that the market price for an extremely rare vintage whiskey is $3000/bottle (the highest we've seen), the inventory of this mystery vintage is gigantic at 10,000 bottles, and we can somehow get the materials cost for bulk chemical replication down to $100/bottle. In this circumstance, the highest total profit to the entrepreneur is $10.5M which occurs at a net profit of $1450/bottle on 7250 bottles at a depressed market price of $1550/bottle. The entrepreneur finally recoups his $10M investment in the chemical recipe but has earned only $500K or ~$100K/year over the perhaps 5-year duration of the project. This hardly seems worth his time and financial risk.

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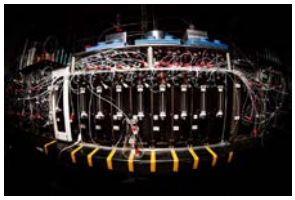
inventory (e.g., 1000 bottles), Q_1 = the new available supply = $Q_0 + Q_{mfg} - Q_{consumed}$ with Q_{mfg} = the quantity of manufactured replicant whiskey (bottles) and $O_{consumed}$ = the quantity of original inventory consumed or destroyed (bottles), and K_{mfg} = the materials cost of manufacturing bulk chemical replicant whiskey (e.g., $1000/bottle). $E_d = (\Delta Q/Q) / (\Delta P/P)$ is the classical own-price elasticity of demand, where ΔQ is the change in quantity Q and ΔP is the change in price P that is attributable to the change in quantity (http://en.wikipedia.org/wiki/Price_elasticity_of_demand).

Low-end consumer market for whiskey. In this market, millions of liters are sold annually at prices in the $10-$35/bottle range.[145] U.S. sales of all fine spirits in 2011 were reportedly[146] $19.9B/year, with 198M cases sold (= 2.376B bottles/year assuming the standard 9 liters/case), implying a surprisingly low average U.S. sales price of $8.38/bottle for fine spirits (possibly the wholesale price?). In 2012-13, Jameson Irish Whiskey reportedly[147] sold 4.3M cases (= 52M bottles/year) distributed amongst at least 5 product lines (Jameson Black Barrel Irish Whiskey, Jameson 12 Year Old Special Reserve, Jameson Gold Reserve, Jameson 18 Year Old Limited Reserve, and Jameson Rarest Vintage Reserve). Assuming an average ~$25/bottle across the entire line and assuming equal sales for all 5 products, these five whiskies might be averaging ~$260M/year in sales per product line or ~$1.3B/year for all five. (Worldwide revenues (sales) for the top 10 fine spirits companies totaled $40B in 2007.)[148]

With $260M/year in sales for each product, it would be an easy matter to invest $10M to obtain the bulk chemical recipe for each product because this cost would represent only ~4% of annual sales over just a single year.

However, at the anticipated ~$1300/liter ($1000/bottle) materials cost for bulk chemical replication (Section 4.4.3), it would impossible to profitably manufacture and sell these low-end products because their materials costs would well exceed the sales prices commanded by such products in the marketplace. This remains true even if we could achieve the lowest plausible ~$50/liter ($38/bottle) materials cost.



Finally, there is no evidence to suggest that the net cost of bulk replication would be significantly lower by employing recently-announced automated small-molecule synthesis techniques.[149]

We conclude that the bulk chemical replication of whiskey and other fine spirits appears to be economically infeasible when competing against traditionally distilled products in both low-end and high-end market segments.

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[145] http://drinks.seriouseats.com/2014/01/best-affordable-bourbon-under-twenty-old-fitzgerald-beam-evan-williams-barton-heaven-hill-cheap-whiskey.html, http://www.buzzfeed.com/andrewgauthier/good-cheap-whiskeys#q7zl1e, http://whiskey.findthebest.com/saved_search/Best-Cheap-Whiskey.

[146] "State of the Spirits Industry 2013," Demeter Group Investment Bank; http://demetergroup.net/sites/default/files/news/attachment/State-of-the-Spirits-Industry-2013.pdf.

[147] Pernod-Ricard, 2012/2013 Annual Report, p. 131; http://pernod-ricard.com/files/fichiers/Commun/Documents/RA2012_13_VGB_MiseEnLigne_28102013.pdf .

[148] Diageo ($15.1B), Pernod Ricard ($9.5B), Bacardi ($5.7B), Fortune Brands ($2.7B), Brown-Forman ($2.3B), Thai Beverage ($1.7B), Belvedere ($1.0B), Campari ($1.0B), and William Grant ($1.0B); http://www.globalbusinessinsights.com/content/rbcg0201m.pdf.

[149] Li J, Ballmer SG, Gillis EP, Fujii S, Schmidt MJ, Palazzolo AM, Lehmann JW, Morehouse GF, Burke MD. Synthesis of many different types of organic small molecules using one automated process. *Science* 347(13 Mar 2015):1221-6; http://www.sciencemag.org/content/347/6227/1221.full.pdf. See also https://news.illinois.edu/blog/view/6367/204395, the process machine illustrated in the image above.

5. NEW APPROACH: Nanofactory Replication of Fine Spirits

In this Section we shall propose and discuss a fundamentally new way of replicating fine spirits, which may be called "nanofactory replication" using the techniques of atomically precise manufacturing as exemplified by a nanofactory. A nanofactory is a manufacturing system for building atomically precise products in macroscale (e.g., kilogram) quantities.

The overall new approach to nanofactory replication of fine spirits may be summarized as follows:

(1) First, use scanning probe microscope-derived molecular tools that can build atomically precise diamondoid structures using the methods of mechanosynthesis (Section 5.1.1).

(2) Second, use the aforementioned molecular tools to build a nanofactory (Section 5.1.2).

(3) Third, use the nanofactory to build a **Fine Spirits Synthesizer** or "Whiskey Machine" (Section 5.4).

The Fine Spirits Synthesizer would be a commercial appliance composed of a large number of nanomachinery parts, all of which can be built by the nanofactory. The Synthesizer incorporates an Assay Unit and a Synthesis Unit, along with some support infrastructure.

The **Assay Unit** (Section 5.2) consists of ~10 million Lab Modules, each about 1 micron^3 in size, that can quantify all of the compounds in the test sample of fine spirits product. The Assay Unit creates the molecular recipe for a particular whiskey.

The **Synthesis Unit** (Section 5.3) consists of an even larger number of Fab Modules, each about 0.001 micron^3 in size, that can synthesize all of the compounds in the fine spirits product whose molecular recipe was previously provided by the Assay Unit. The Synthesis Unit makes whiskey.

The **Fine Spirits Synthesizer** (Section 5.4) begins working when a tiny sample (less than 1 droplet) of original whiskey is injected into the input port of the Assay Unit. The chemical composition of the sample is rapidly analyzed and precisely quantified in the Assay Unit, allowing the exact molecular recipe for the whiskey to be compiled. Alternatively, a previously compiled or designed fine spirits molecular recipe might be provided from a customer or a library of such molecular recipes, in which case no sample analysis will be required for the replication process to proceed.

The molecular recipe is then passed to the Synthesis Unit, whereupon basic feedstock chemicals are mechanosynthetically combined into each of perhaps ~4000 congener chemicals that comprise the particular fine spirit molecular recipe. The molecules of these chemicals have been manufactured one by one, almost atom by atom, hence are exactly what was ordered with essentially zero contaminants or impurities. These near-absolute purity individual chemical ingredients are then combined to form a mixed-congener package that would be sufficient to reconstruct, say, a 750 ml quantity of the desired replicant whiskey.

Ethanol of extreme purity can be supplied from commercial sources, if available inexpensively. Conceivably, it might also be extracted at ultra-high purity from almost any semi-solid or liquid

material in which free ethanol is a chemical component – e.g., alcoholic beverages of any kind,[150] fermenting mashes or fruit juices, cheap technical-grade ethanol produced from fermented or hydrocarbon sources, cheap denatured alcohols,[151] gasohol (grade "E10" is 10% ethanol),[152] mouthwashes[153] or literally hundreds of other consumer products[154] – using sorting rotors (Section 5.3.3) equipped with binding sites for ethyl alcohol. These sorting rotors, possibly arranged in a sequential cascade to enhance filtrate concentration, would extract the ethanol molecules one by one in pure fraction from the source and pass them along to the mixing chamber of the Synthesizer. Alternatively, ethanol of extreme purity could be manufactured mechanosynthetically like the congeners if deemed convenient and economical (Section 5.3.2).

Water of extreme purity, the final ingredient, can be supplied from the tap or other sources, including highly impure or even polluted sources if necessary. As with ethanol, sorting rotors with binding sites for water molecules could extract the water molecules from these impure sources in pure fraction and pass them along to the mixing chamber of the Synthesizer (Section 5.3.3). Since water has the smallest molecules of any ingredient in fine spirits (with the possible exception of a few metallic ions), a simple size-based separation system (e.g., a nanosieve with holes too small to pass anything but water molecules; Section 5.3.4) may be another alternative.

The ultrapure water, ethanol, and congeners – in appropriate quantities, as dictated by the molecular recipe – are combined in the Synthesizer mixing chamber. This yields a bottle of nanofactory replicant fine spirits that is an exact chemical duplicate of the original whiskey sample down to the ~1 ppb concentration level. The replicant whiskey will include all organoleptic chemicals specified in the recipe and no unwanted impurities. While some non-organoleptic chemicals might be missing, their absence is inconsequential because those compounds contribute nothing to the drinker's sensory experience.

Section 5.1 provides a brief introduction to the techniques of atomically precise manufacturing, including mechanosynthesis (Section 5.1.1) and the nanofactory (Section 5.1.2). This is followed by a discussion of the operation of the Assay Unit (Section 5.2) that generates molecular recipes given a sample of fine spirits, and the Synthesis Unit (Section 5.3) that manufactures replicant fine spirits following a molecular recipe. We conclude with a systems-level description of the structure and operations of the Fine Spirits Synthesizer appliance or "Whiskey Machine" (Section 5.4).

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[150] http://en.wikipedia.org/wiki/Alcoholic_beverage.

[151] http://en.wikipedia.org/wiki/Denatured_alcohol.

[152] http://en.wikipedia.org/wiki/Ethanol_fuel.

[153] http://en.wikipedia.org/wiki/Mouthwash#Alcohol.

[154] http://scorecard.goodguide.com/chemical-profiles/consumer-products.tcl?edf_substance_id=64-17-5.

5.1 Generic Description of a Nanofactory

The nanofactory is a high quality, extremely low cost, and very flexible manufacturing system in which products are built atom by atom – an atomically precise manufacturing system employing controlled molecular assembly. Nanofactories will enable the creation of fundamentally novel products having the intricate complexity and reliability currently found only in biological systems, but operating with greater speed, power, predictability, and, most importantly, entirely under human engineering control.

The principal inputs to a nanofactory may be simple hydrocarbon feedstock molecules such as natural gas or propane, along with water and small supplemental amounts of other simple molecules containing trace atoms of a few additional chemical elements needed to make useful products, such as oxygen, nitrogen, sulfur, or silicon. The nanofactory must also be provided with electrical power and a means for cooling the working unit.

5.1.1 Mechanosynthesis, Tools, and Nanoparts

At the most primitive level of the manufacturing process, atomically precise objects will be built atom by atom using a process called mechanosynthesis. Mechanosynthesis, involving molecular positional fabrication, is the formation of covalent chemical bonds using precisely applied mechanical forces to build, e.g., organic molecules or diamondoid[155] structures. Mechanosynthesis employs chemical reactions driven by the mechanically precise positioning of extremely reactive chemical species in an ultra-high vacuum environment. Mechanosynthesis may be automated via computer control, enabling programmable molecular positional fabrication.

Atomically precise fabrication involves holding feedstock atoms or molecules, and a growing nanoscale workpiece, in the proper relative positions and orientations so that when they touch they will chemically bond in the desired manner. In this process, a mechanosynthetic tool is brought up to the surface of a workpiece. One or more transfer atoms are added to, or removed from, the workpiece by the tool (**Figure 11**). Then the tool is withdrawn and recharged. This process is repeated until the workpiece (e.g., a growing nanopart) is completely fabricated to

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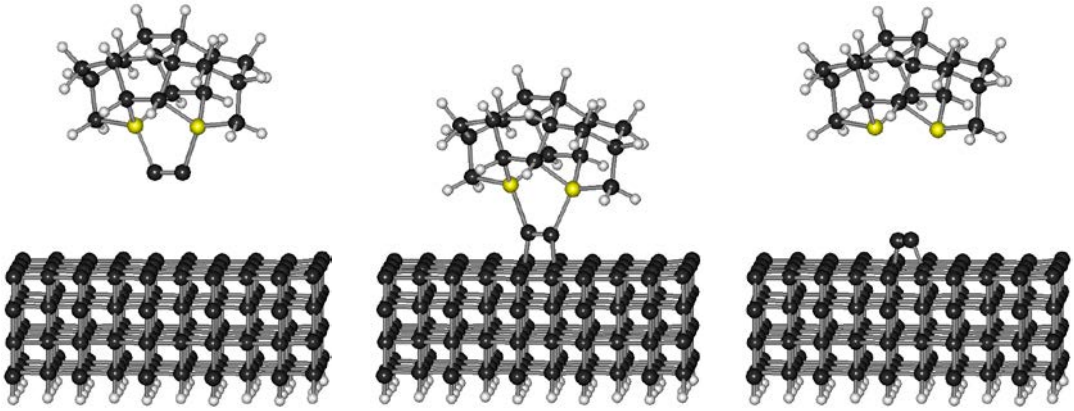
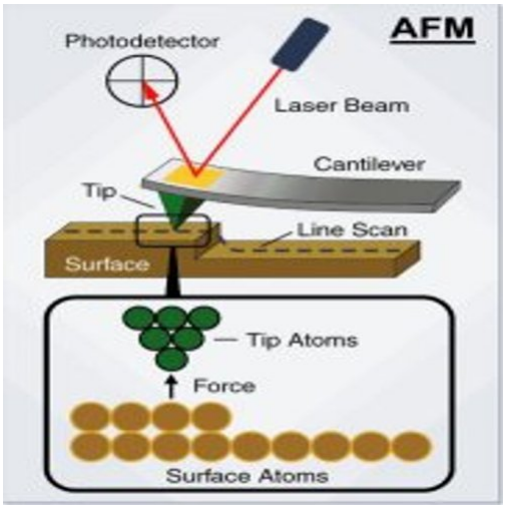
[155] Most diamondoids resemble ceramics. First and foremost, diamondoid materials include pure diamond, the crystalline allotrope of carbon. Among other exceptional properties, diamond has extreme hardness, high thermal conductivity, low frictional coefficient, chemical inertness, a wide electronic bandgap, and is the strongest and stiffest material presently known at ordinary pressures. Diamondoid materials also may include any stiff covalent solid that is similar to diamond in strength, chemical inertness, or other important material properties, and possesses a dense three-dimensional network of bonds. Examples of such materials are carbon nanotubes and fullerenes, several strong covalent ceramics such as silicon carbide, silicon nitride, and boron nitride, and a few very stiff ionic ceramics such as sapphire (monocrystalline aluminum oxide) that can be covalently bonded to pure covalent structures such as diamond. Of course, large pure crystals of diamond are brittle and easily fractured. The intricate molecular structure of a diamondoid nanofactory macroscale product will more closely resemble a complex composite material, not a brittle solid crystal. Such atomically precise products, and the nanofactories that build them, should be extremely durable in normal use.

molecular precision with each atom in exactly the right place. Note that the transfer atoms are under positional control at all times to prevent unwanted side reactions from occurring. Side reactions are also prevented using proper reaction design so that the reaction energetics help us avoid undesired pathological intermediate structures.

Figure 11. Three frames at the top show the DCB6Ge tooltip depositing two carbon atoms on a diamond surface. The tooltip is attached to a much larger tool handle structure (not shown) which is attached, in turn, to the macroscale tip of a laboratory-scale scanning probe microscope (e.g., see schematic, lower left, and image, lower right, of a UHV scanning probe microscope).

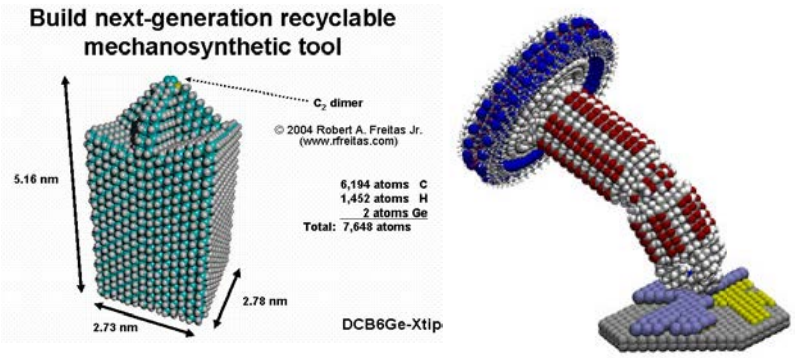




Mechanosynthesis has been extensively discussed in the theoretical literature since 1992,[156] was first demonstrated experimentally in 2003[157] and repeatedly in later years,[158] with the first U.S.

[156] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992; R.A. Freitas Jr., R.C. Merkle, "A minimal toolset for positional diamond

patent on mechanosynthesis issued to Freitas in 2010.[159] Mechanosynthesis has not yet achieved widespread mainstream acceptance because historically it has proven experimentally challenging to accomplish, but it can be rapidly developed using cryogenic UHV scanning probe technology of the kind illustrated in **Figure 11**.



A scanning probe-based system would enable the fabrication of more precise, more easily rechargeable, and generally much improved mechanosynthetic tools. These more capable tools may include more stable handles of standardized dimensions, such as the rechargeable DCB6Ge dimer placement tool with the more reliable crossbar design (above, left),[160] or tools with more complex handles incorporating moving components (above, right).

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mechanosynthesis," *J. Comput. Theor. Nanosci.* 5(2008):760-861; http://www.molecularassembler.com/Papers/MinToolset.pdf.

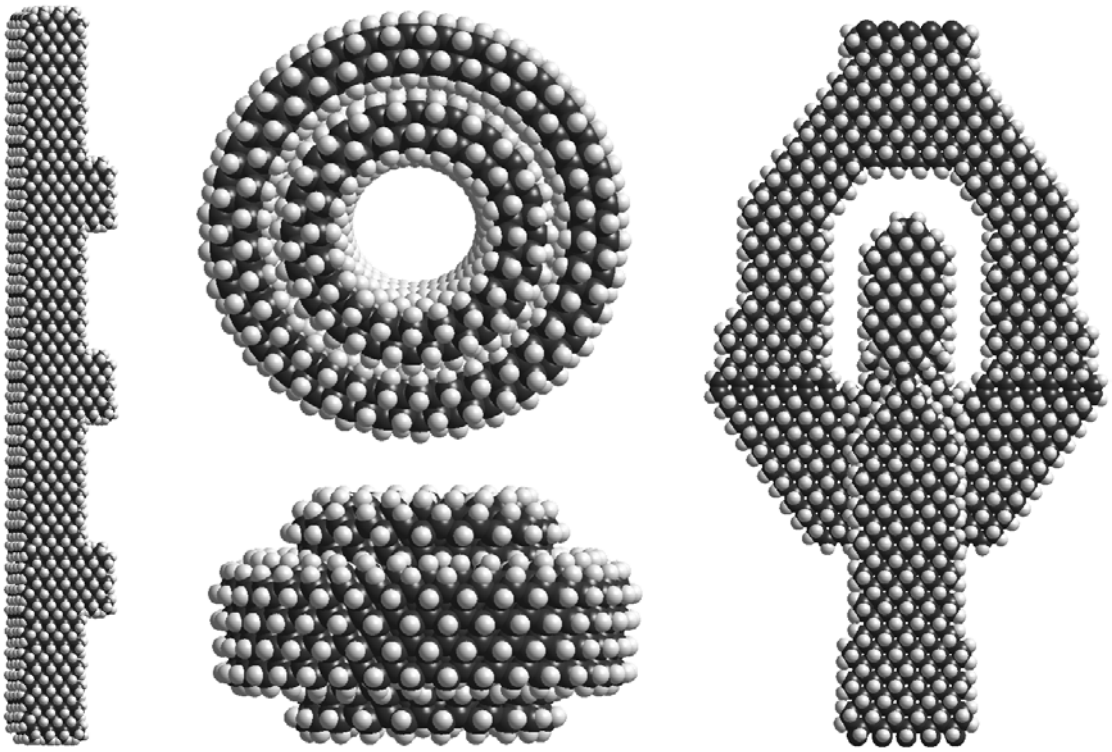
[157] N. Oyabu, O. Custance, I. Yi, *et al.*, "Mechanical vertical manipulation of selected single atoms by soft nanoindentation using near contact atomic force microscopy," *Phys. Rev. Lett.* 90(2003):176102; http://link.aps.org/abstract/PRL/v90/e176102.

[158] N. Oyabu, O. Custance, M. Abe, S. Moritabe, "Mechanical vertical manipulation of single atoms on the Ge(111)-c(2x8) surface by noncontact atomic force microscopy," *Abstracts of Seventh International Conference on Non-Contact Atomic Force Microscopy*, Seattle, Washington, USA, 12-15 September, 2004, p. 34; http://www.engr.washington.edu/epp/afm/abstracts/15Oyabu2.pdf. Y. Sugimoto, P. Pou, O. Custance, P. Jelinek, M. Abe, R. Perez, S. Morita, "Complex patterning by vertical interchange atom manipulation using atomic force microscopy," *Science* 322(2008):413-417; http://www.sciencemag.org/cgi/content/full/322/5900/413. Shigeki Kawai, *et al.*, "Atom manipulation on an insulating surface at room temperature," *Nature Communications* (2014), DOI: 10.1038/ncomms5403.

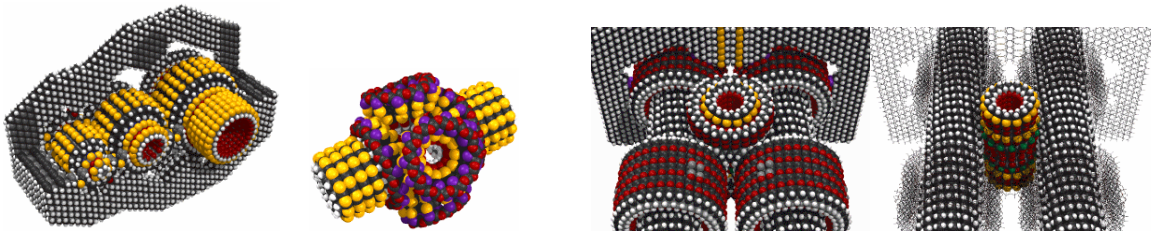
[159] Robert A. Freitas Jr., "Simple Tool for Positional Diamond Mechanosynthesis, and its Method of Manufacture," U.S. Patent 7,687,146 (30 March 2010); http://www.google.com/patents/US7687146.

[160] J. Peng, R.A. Freitas Jr., R.C. Merkle, *et al.*, "Theoretical analysis of diamond mechanosynthesis. Part III. Positional C_2 deposition on diamond C(110) surface using Si/Ge/Sn-based dimer placement tools," *J. Comput. Theor. Nanosci.* 3(2006):28-41; http://www.MolecularAssembler.com/Papers/JCTNPengFeb06.pdf.

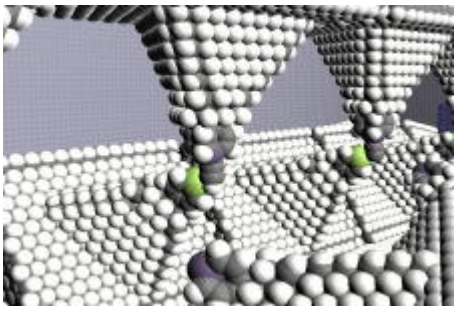
Later systems will incorporate more complex components such as the all-hydrocarbon diamond logic rod (below, left), the hydrocarbon bearing (below, center), the diamond universal joint (below, right), and related devices. The end result of this iterative development process will be a mature set of efficient, positionally controlled mechanosynthetic tools that can reliably build atomically precise diamondoid structures – including more mechanosynthetic tools.



Once mechanosynthetic tooltips are developed for a few additional element types, a still wider variety of nanomachines can be fabricated incorporating atoms other than hydrogen, carbon and germanium (e.g., silicon, oxygen, nitrogen, and sulfur). Examples of these more varied diamondoid nanomachines include the speed reduction gear (below, left), in which the train of gears reduces the speed from the high-speed one on the left to the half-speed one on the right, and the differential gear (below, center) that smoothly converts mechanical rotation in one direction into mechanical rotation in the opposite direction. The largest publically reported molecular machine model that has been simulated using molecular dynamics is the worm drive assembly (below, pair at right), consisting of 11 separate components and over 25,000 atoms. The two tubular worm gears progress in opposite directions, converting rotary into linear motion.



Using computer-automated tooltips performing positionally-controlled mechanosynthesis in lengthy programmed sequences of reaction steps, we will be able to fabricate simple diamondoid nanomechanical parts such as bearings, gears, struts, springs, logic rods and casings, to atomic precision. Early tools will rapidly progress from single tools manipulated by laboratory scanning-probe-like mechanisms, to more complex multitip tools and jigs which the simple tools could initially fabricate, one at a time. In a factory production line (below), individual mechanosynthetic tooltips may be affixed to rigid moving support structures and guided through repeated contact events with workpieces, recharging stations, and other similarly-affixed opposable tooltips. These "molecular mills" can then perform repetitive fabrication steps using simple, efficient mechanisms in the manner of a production line. Such production lines can, in principle, be operated at very high speeds – with positionally constrained mechanosynthetic encounters possibly occurring at up to megahertz frequencies.



5.1.2 Conceptual Description of a Nanofactory

The ultimate goal of molecular nanotechnology is to develop a manufacturing technology able to inexpensively manufacture most arrangements of atoms that can be specified in molecular detail – including complex arrangements involving millions or billions of atoms per product object. This will provide the ultimate manufacturing technology in terms of precision, flexibility, and low cost. To be practical, a nanofactory must also be able to assemble very large numbers of identical atomically precise nano- or microstructures very quickly. Two central technical objectives thus form the core of our current strategy for atomically precise manufacturing: (1) programmable positional assembly including fabrication of diamondoid structures using molecular feedstock, as discussed above, and (2) massive parallelization of all fabrication and assembly processes, briefly discussed below.

Conceptually, nanofactory systems capable of massively parallel fabrication[161] might employ, at the lowest level, large arrays of mechanosynthesis-enabled scanning probe tips all building similar diamondoid product structures in unison. Analogous approaches are found in present-day larger-scale systems. For example, simple mechanical ciliary arrays consisting of 10,000 independent microactuators on a 1 cm^2 chip have been made at the Cornell National Nanofabrication Laboratory for microscale parts transport applications, and similarly at IBM for mechanical data storage applications.[162] Active probe arrays of 10,000 independently-actuated

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[161] Robert A. Freitas Jr., Ralph C. Merkle, *Kinematic Self-Replicating Machines*, Landes Bioscience, Georgetown, TX, 2004; Section 5.7, pp. 182-184; http://www.MolecularAssembler.com/KSRM/5.7.htm.

[162] "1000 Tips for Ultrahigh-Density Data Storage," *IBM News*, Zurich Research Lab, 11 October 1999, http://www.zurich.ibm.com/news/99/millipede.html; IBM Research: Millipede, http://domino.research.ibm.com/Comm/bios.nsf/pages/millipede.html; P. Vettiger, G. Cross, M. Despont, U. Drechsler, U. Duerig, B. Gotsmann, W. Haeberle, M. Lantz, H. Rothuizen, R. Stutz, G. Binnig, "The Millipede – nanotechnology entering data storage," Technical Report, IBM Zurich Research Lab;

microscope tips have been developed by Mirkin's group at Northwestern University for dip-pen nanolithography using DNA-based "ink".[163] Almost any desired 2D shape can be drawn using 10 tips in concert. A million-tip DPN array has been fabricated by the Micro Nano Technology Research Group at the University of Illinois,[164] and another microcantilever array manufactured by Protiveris Corp. has millions of interdigitated cantilevers on a single chip.[165] Martel's group at École Polytechnique Montreal has investigated using fleets of independently mobile wireless instrumented microrobot manipulators called NanoWalkers to collectively form a nanofactory system that might be used for positional manufacturing operations.[166] Zyvex Corp. (http://www.zyvexlabs.com) received a $25 million, five-year, National Institute of Standards and

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http://domino.research.ibm.com/Comm/bios.nsf/pages/millipede.html/$FILE/pv7201-preprint.pdf; also published in: P. Vettiger, G. Cross, M. Despont, *et al.*, "The Millipede – nanotechnology entering data storage," *IEEE Trans. Nanotechnol.* 1(June 2002):39-55.

[163] Seunghun Hong, Chad A. Mirkin, "A nanoplotter with both parallel and serial writing capabilities," *Science* 288(9 June 2000):1808-1811; http://www.nanotechnology.northwestern.edu/press/Science%20.Vol288.9june2000.pdf; Ming Zhang, David Bullen, Kee S. Ryu, Chang Liu, S. Hong, S. Chung, Chad Mirkin, "Passive and active probes for dip pen nanolithography," First IEEE Conference on Nanotechnology, 28-30 October 2001, Maui, HI; http://mass.micro.uiuc.edu/publications/papers/64.pdf; D. Bullen, M. Zhang, C. Liu, "Thermal-mechanical optimization of thermally actuated cantilever arrays," Smart Electronics, MEMS, and Nanotechnology Conference (4700), SPIE's 9th Annual International Symposium on Smart Structures and Materials, 17-21 March 2002, San Diego, CA; http://mass.micro.uiuc.edu/publications/papers/70.pdf; Ming Zhang, David Bullen, Sung-Wook Chung, Seunghun Hong, Kee S. Ryu, Zhifang Fan, Chad A. Mirkin, Chang Liu, "A MEMS nanoplotter with high-density parallel dip-pen nanolithography probe arrays," *Nanotechnology* 13(April 2002):212-217; http://mass.micro.uiuc.edu/publications/papers/72.pdf; X. Wang, D. Bullen, J. Zou, K. Ryu, C. Liu, S.W. Chung, C. Mirkin, "Linear probe arrays for dip-pen nanolithography," Intl. Conf. on Micro & Nano Systems (ICMNS 2002), 11-14 August 2002, Kunming, China; http://mass.micro.uiuc.edu/publications/papers/74.pdf; D. Bullen, S. Chung, X. Wang, J. Zou, C. Liu, Chad Mirkin, "Development of parallel dip pen nanolithography probe arrays for high throughput nanolithography," (Invited) Symposium LL: Rapid Prototyping Technologies, Materials Research Society Fall Meeting, Boston, MA, Proceedings of the MRS, Vol. 758, 2-6 December 2002; http://mass.micro.uiuc.edu/publications/papers/84.pdf; D. Bullen, X. Wang, J. Zou, S. Hong, S. Chung, K. Ryu, Z. Fan, C. Mirkin, C. Liu, "Micromachined arrayed dip pen nanolithography probes for sub-100 nm direct chemistry patterning," Proc. 16th IEEE International Micro Electro Mechanical Systems Conference, MEMS 2003, Kyoto, Japan, 19-23 January 2003; http://mass.micro.uiuc.edu/publications/papers/86.pdf; Jun Zou, David Bullen, Xuefeng Wang, Chang Liu, Chad A. Mirkin, "Conductivity-based contact sensing for probe arrays in dip-pen nanolithography," *Appl. Phys. Lett.* 83(2003):581.

[164] "MNTR Research Focus Slide Show: Passive Parallel DPN Array," 2006, http://mass.micro.uiuc.edu/research/current/nanolithography/2006-focus-intro/slide11.html.

[165] "Microcantilever Arrays," Protiveris Corp., 2003; http://www.protiveris.com/cantilever_tech/microcantileverarrays.html.

[166] S. Martel, I. Hunter, "Nanofactories based on a fleet of scientific instruments configured as miniature autonomous robots," Proc. 3rd Intl Workshop on Microfactories; 16-18 Sep 2002; Minneapolis MN, pp. 97-100.

Technology (NIST) contract to develop prototype microscale assemblers using microelectromechanical systems.[167]

At the end of a carefully focused development program, analogous work could lead to the design and fabrication of numerous production lines comprising a nanofactory, both for diamondoid mechanosynthesis and for component assembly operations. Ultimately, atomically precise macroscale products – including components of additional nanofactories – could be manufactured in desktop nanofactories efficiently designed for this purpose. The nanofactory system will include a progression of fabrication and assembly lines at several different physical scales (**Figure 13**).

In one conceivable design, at the smallest scale, molecular mills could manipulate individual molecules to fabricate successively larger submicron-scale building blocks. These would be passed to larger block assemblers that assemble still larger microblocks, which would themselves be passed to even larger product assemblers that put together the final product. The microblocks would be placed in a specific pattern and sequence following construction blueprints created using modern "Design for Assembly" and "Design for Manufacturability" (DFM) philosophies. As plane after plane is completed, the product extrudes outward through the surface of the nanofactory output platform.

Of course, these images represent idealized conceptualizations of just one possible nanofactory architecture. Other architectural approaches may readily be conceived.[168]

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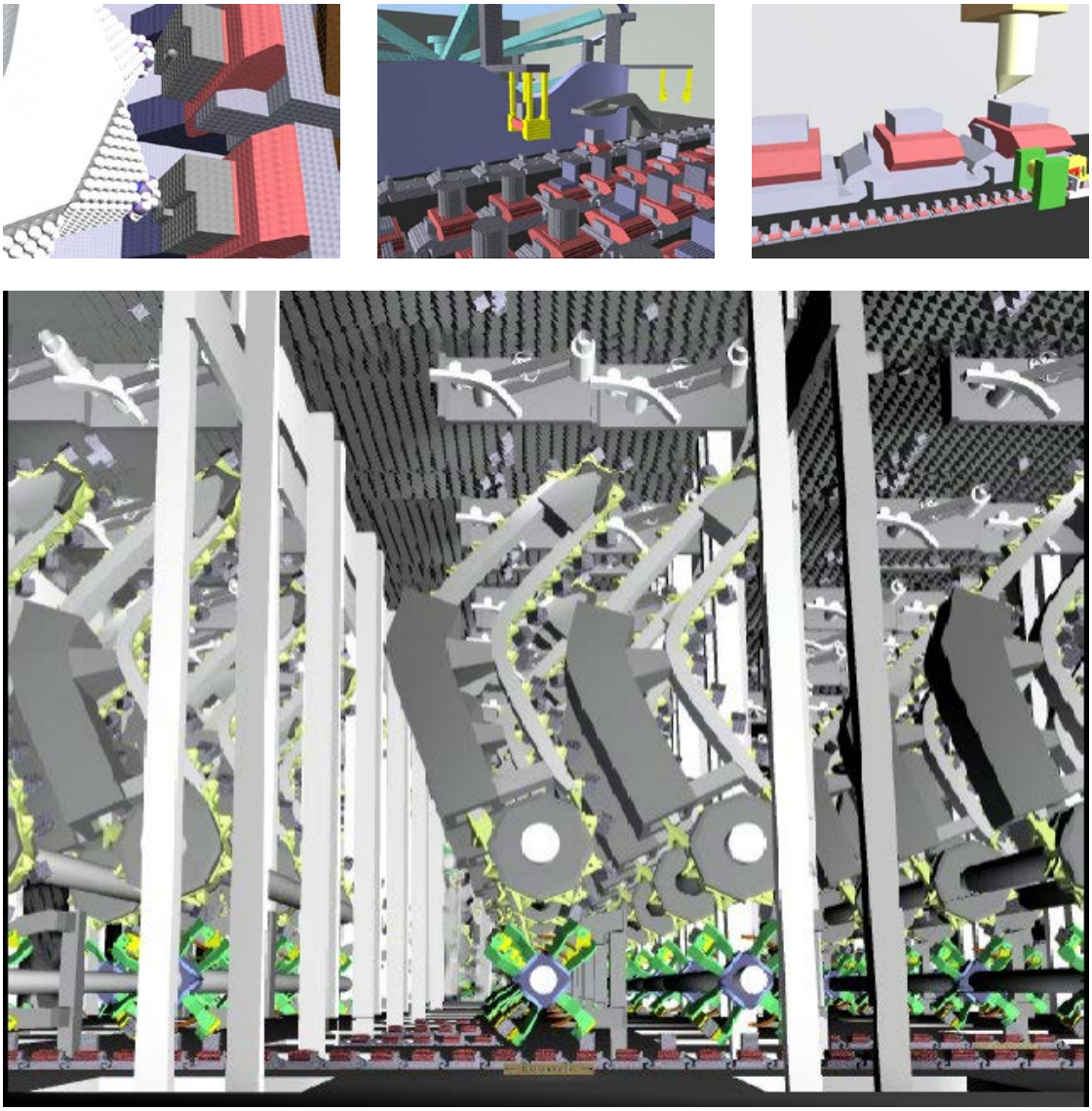
[167] Robert A. Freitas Jr., Ralph C. Merkle, *Kinematic Self-Replicating Machines*, Landes Bioscience, Georgetown, TX, 2004; Section 4.20, p. 144; http://www.MolecularAssembler.com/KSRM/4.20.htm.

[168] Robert A. Freitas Jr., Ralph C. Merkle, *Kinematic Self-Replicating Machines*, Landes Bioscience, Georgetown, TX, 2004; Section 4; http://www.molecularassembler.com/KSRM/4.htm.

Figure 13. Assembly of nanoparts into larger components and product structures using mechanical manipulators at various size scales (e.g., perhaps 0.01 µm, 0.1 µm, 1 µm, and 10 µm in the four images below) on interconnected production lines inside a diamondoid nanofactory.[169]



As shown in the conceptual image of the desktop nanofactory below (**Figure 14**), the finished product in this example is a billion-CPU laptop supercomputer, built to molecular precision all the way down to its constituent atoms. The laptop supercomputer product is emerging from the output port at the top of the nanofactory at the end of a production cycle.

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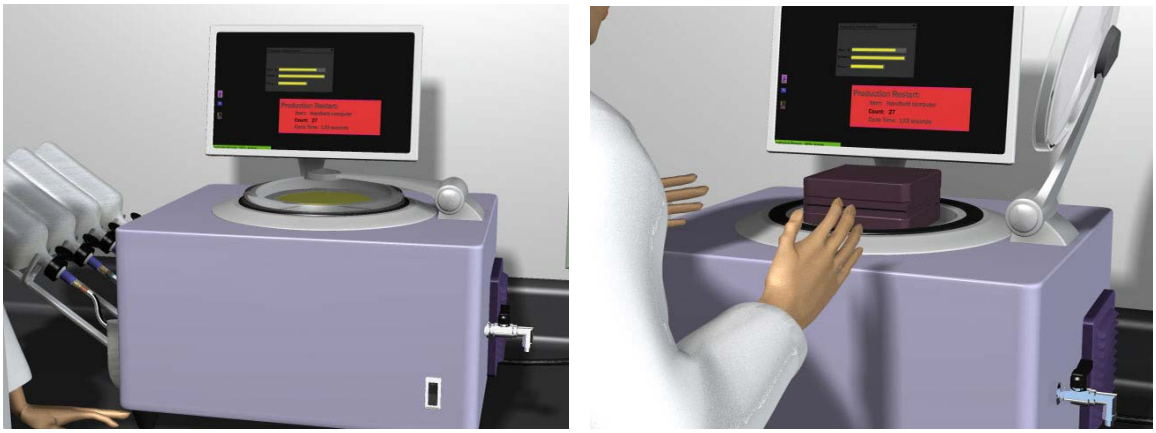
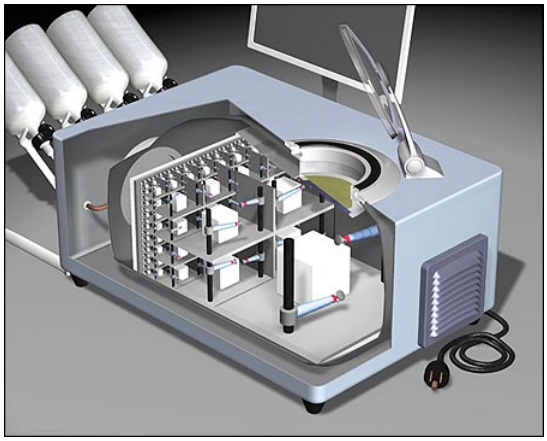
[169] John Burch nanofactory website, http://www.lizardfire.com/html_nano/nano.html.

Figure 14. Conceptual vision of a desktop nanofactory appliance.[170]



While this discussion has centered on the atomically precise manufacture of rigid diamondoid products, a properly configured nanofactory can also be employed to fabricate organic molecules such as the congeners of whiskey in bulk quantities, as described in Section 5.3.1 below.

More specifically, the nanofactory can be used to build the components of a desktop **Fine Spirits Synthesizer**. The Fine Spirits Synthesizer would itself be a specialized type of limited-use nanofactory optimized for the production of highly deterministic solutions of extremely pure organic compounds solvated in an ultrapure ethanol-water solvent. The Fine Spirits Synthesizer might look something like the machine pictured in Figure 14, except that a bottle of fine whiskey would be emerging from the output platform at the top of the device instead of a folded laptop supercomputer.



The end result of a dedicated nanofactory development program would be the creation of extremely clean, efficient, and inexpensive manufacturing systems capable of producing macroscale quantities of atomically precise products. Nanofactories will make possible the manufacture of both (A) mostly covalently-bonded products (e.g. machines) having the intricate complexity and reliability of biological systems combined with the greater speed, power, and predictability of engineered mechanical systems, and (B) a second class of mostly noncovalently-bonded products (e.g., liquid chemical mixtures of designer molecules) of unprecedented specificity, purity, and personalization to the customer.

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[170] John Burch nanofactory website, http://www.lizardfire.com/html_nano/nano.html.

5.2 Assay Unit

We propose the quick and inexpensive replication of fine spirits using an appliance called the **Fine Spirits Synthesizer** (Section 5.4), which itself may be built using the nanofactory described in Section 5.1.

The Fine Spirits Synthesizer is a limited-use nanofactory that can only manufacture alcoholic beverages and nothing else. It consists of two major active subsystems: the **Assay Unit** (described here, in Section 5.2) and the **Synthesis Unit** (described in Section 5.3).

The first step in the nanofactory replication of fine spirits is to obtain the precise molecular recipe for the beverage product that we wish to replicate. This is accomplished by feeding a tiny quantity of the target liquid product to be replicated into the input port of the Assay Unit. The chemical composition of the sample is analyzed and precisely quantified, allowing compilation of the exact molecular recipe for the target whiskey or other fine spirit. This molecular recipe then guides the quantitative synthesis of all required congeners in the Synthesis Unit.

In this Section, we outline one possible architecture for the Assay Unit which employs a scanning probe-based **chemohaptic analysis** approach (Section 5.2.1). We discuss the use of atomic force microscopy (AFM) to determine the structure (Section 5.2.2) and element types of the atoms (Section 5.2.3) and functional groups (Section 5.2.4) of individual sample molecules, and identify procedures for dealing with a few difficult cases (Section 5.2.5). We then describe the minimum possible microscale laboratory module that could be employed to perform these single-molecule examinations (Section 5.2.6) and estimate the performance characteristics of a complete Assay Unit comprised of such microscale laboratory modules (Section 5.2.7), closing with a brief summary description of the Assay Unit (Section 5.2.8). Further research is required to add more detail to this architecture, to examine additional possible architectures, and to analyze technical tradeoffs among competing architectures to help choose the ideal final design for the Assay Unit.

5.2.1 Chemohaptic Analysis

Haptic perception[171] is a generic process of recognizing objects through touch. The phrase is usually applied to a macroscale human sensory activity involving a combination of somatosensory perception of patterns on the skin surface (e.g., edges, curvature, and texture) and proprioception of hand position and conformation, but in the present context we are referring to an activity that takes place at the nanoscale. In particular, chemohaptic analysis is the process of inferring the chemical composition of a molecule by "touching" that molecule, after it is placed on some suitable surface, with the sharp tip of a scanning probe microscope such as the atomic force microscope (AFM) previously illustrated schematically in Figure 11. Chemohaptic analysis is the application of chemohaptics to the systematic identification of an unknown molecular structure. Today this field exists in only nascent form, though after the advent of nanofactories it will likely come into common use for the rapid characterization of unknown organic molecules.

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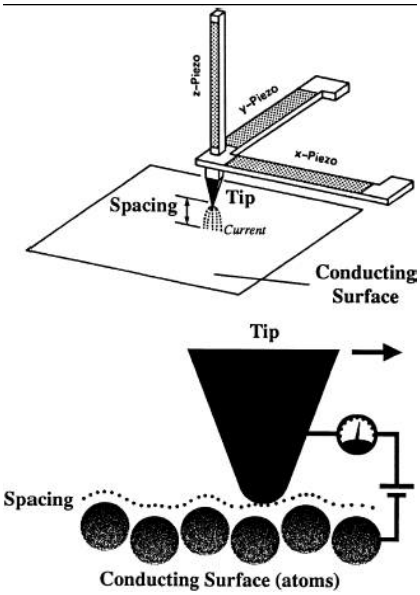
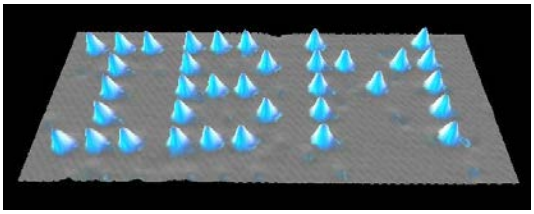
[171] http://en.wikipedia.org/wiki/Haptic_perception.

Before we go much further, it is useful to first review a bit of background on scanning probe microscopy (SPM) which is the key to understanding the basic process of chemohaptic analysis. In the following discussion, please keep in mind that the diameters of individual atoms in covalently bonded molecules are approximately 76 pm for hydrogen, 146 pm for oxygen, 150 pm for nitrogen, and 154 pm for carbon,[172] where 1 picometer (pm) = 0.01 Angstroms (Å) = 0.001 nanometers = 10^{-12} meter.

The first of the SPMs was the Scanning Tunneling Microscope (STM) developed in the late 1970s and early 1980s by Gerd Karl Binnig and Heinrich Rohrer at an IBM research lab in Zurich, Switzerland,[173] earning these scientists, along with Ernst Ruska, the 1986 Nobel Prize in Physics. The STM was initially used as an imaging device, capable of resolving individual atoms by recording the quantum tunneling current that occurs when an extremely sharp conductive probe tip (usually tungsten, nickel, gold, or platinum-iridium) is brought to within about one atomic diameter of an atom, and then adjusting the position of the tip to maintain a constant current as the tip is scanned over a bumpy atomic surface (at right). A height change as small as 100 pm can cause tunneling current to double. The tip is connected to an arm that is moved in three dimensions by stiff ceramic piezoelectric transducers that provide sub-nanometer positional control. If the tip is atomically sharp, then the tunneling current is effectively confined to a region within ~100 pm of the point on the surface directly beneath the tip, thus the record of tip adjustments generates an atomic-scale topographic map of the surface. STM tips can scan samples at ~KHz frequencies, although slower scans are used for very rough surfaces and in some modern STMs the sample is moved while the tip is held stationary. Perhaps most iconic is the classic 1989 picture of the IBM logo spelled out with 35 xenon atoms arranged on a nickel surface (at left).[174] These atoms were imaged by an STM tip after lateral positioning of the individual atoms using the same tip.





[172] http://en.wikipedia.org/wiki/Atomic_radii_of_the_elements_(data_page).

[173] G. Binnig, H. Rohrer, "Scanning tunneling microscopy," *Helv. Phys. Acta* 55(1982):726-735; G. Binnig, H. Rohrer, C. Gerber, E. Weibel, "Surface studies by scanning tunneling microscopy," *Phys. Rev. Lett.* 49(1982):57-61 and *Phys. Rev. Lett.* 50(1983):120-123; Gerd Binnig, Heinrich Rohrer, "The Scanning Tunneling Microscope," *Sci. Am.* 253(August 1985):50-56; G. Binnig, H. Rohrer, "Scanning tunneling microscopy," *IBM J. Res. Develop.* 30(1986):355-369; Gerd Binnig, Heinrich Rohrer, "Scanning tunneling microscopy from birth to adolescence," *Rev. Modern. Phys.* 59(July 1987):615-625.

[174] D.M. Eigler, E.K. Schweizer, "Positioning Single Atoms with a Scanning Tunnelling Microscope," *Nature* 344(5 Apr 1990):524-526; http://www.nature.com/nature/journal/v344/n6266/abs/344524a0.html.

A major limitation of the STM was that it only worked with conducting materials such as metals or semiconductors, but not with insulators or biological structures such as DNA.[175] To remedy this situation, in 1986 Binnig, Quate and Gerber developed the Atomic Force Microscope (AFM)[176] which is sensitive directly to the forces between the tip and the sample, rather than a tunneling current. An AFM can operate in at least three modes. In "attractive" or non-contact mode (NC-AFM or FM-AFM), the tip is held some tens of nanometers above the sample surface where it experiences the attractive combination of van der Waals, electrostatic, or magnetostatic forces. In "repulsive" or contact mode (C-AFM), the tip is pressed close enough to the surface for the tip and sample electron clouds to overlap, generating a repulsive electrostatic force of ~10 nN (nanonewtons), in operation much like the stylus riding a groove in an old record player. There is also intermittent-contact mode (IC-AFM), which is sometimes called "tapping" mode. In any of these modes, a topographic map of the surface is generated by recording the up-and-down motions of the cantilever arm as the tip is scanned. These motions may be measured either by the deflection of a light spot reflected from a mirrored surface on the cantilever (**Figure 11**) or by tiny changes in voltage generated by piezoelectric transducers attached to the moving cantilever arm. Typical laboratory AFM cantilevers have lengths of 100-400 microns, widths of 20-50 microns, and thicknesses between 0.4-3 microns. AFM tips may be positioned with ~10 pm precision, compressive loads as small as 1-10 pN of force are routinely measured,[177] and the tips may even be operated in liquids.[178] STM technology has also much improved over the last few decades, now regularly achieving resolutions of ~1 pm in the z direction (vertical) and ~10 pm in the xy (horizontal) plane, which is better than atomic resolution.

5.2.2 Structure Determination by AFM

The AFM is essentially a way to "touch" a molecule and to "feel" the shapes of the atoms comprising the molecule, while the molecule is resting on a surface. In 2009, researchers at IBM Zurich used an AFM in constant-height non-contact mode in ultra-high vacuum (UHV) at cryogenic temperatures (5 K) to scan an organic molecule that had been deposited either on a flat copper Cu(111) conductive surface, or on the same copper surface coated with a 2-monolayer

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[175] Gil U. Lee, Linda A. Chrisey, Richard J. Colton, "Direct Measurement of the Forces Between Complementary Strands of DNA," *Science* 266(4 Nov 1994):771-773; T. Boland, B.D. Ratner, "Direct measurement of hydrogen bonding in DNA nucleotide bases by atomic force microscopy," *Proc. Natl. Acad. Sci. USA* 92(1995):5297-5301.

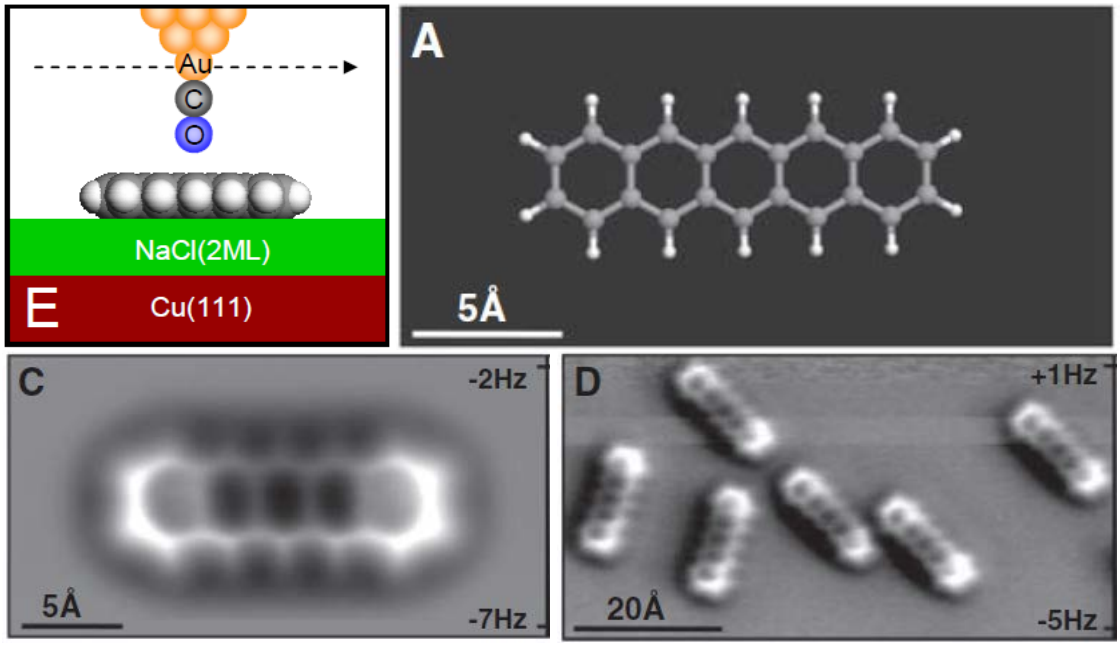
[176] G. Binnig, C.F. Quate, Ch. Gerber, "Atomic Force Microscopy," *Phys. Rev. Lett.* 56(3 Mar 1986):930-933.

[177] A.L. Weisenhorn, P.K. Hansma, T.R. Albrecht, C.F. Quate, "Forces in atomic force microscopy in air and water," *Appl. Phys. Lett.* 54(1989):2651-2653; C. Julian Chen, *Introduction to Scanning Tunneling Microscopy*, Oxford University Press, Cambridge, 1993; R. Wiesendanger, *Scanning Probe Microscopy and Spectroscopy: Methods and Applications*, Cambridge University Press, Cambridge, MA, 1994.

[178] T.E. Schaffer, J.P. Cleveland, F. Ohnesorge, D.A. Walters, P.K. Hansma, "Studies of vibrating atomic force microscope cantilevers in liquid," *J. Appl. Phys.* 80(1996):3622-3627.

thickness of insulating NaCl film (**Figure 15**).[179] Scan forces ranged from 0-100 pN. The first organic molecule they looked at – pentacene ($C_{22}H_{14}$), a linear polycyclic hydrocarbon consisting of five fused benzene rings – has 22 carbon atoms and thus lies nearer to the large end of the size spectrum in comparison to most of the congeners likely to be present in fine spirits. By 2014 the Zurich group had imaged their largest molecule to date, a clover-shaped nanographene molecule with 22 fused benzene rings ($C_{78}H_{36}$).[180]

Figure 15. Top left: The AFM tip is gold atoms to which a single carbon monoxide (CO) molecule has been attached, making a very sharp tip. The pentacene molecule rests on the surface. Top right: The molecular structure of pentacene (gray = carbon, white = hydrogen). Bottom left: A single pentacene molecule on Cu(111), with all of its atoms clearly resolved. Bottom right: Again on Cu(111), six atomically-resolved pentacene molecules are in one image.



In similar manner, the IBM team used their AFM to distinguish, by "touch" alone, the carbon atom "bond order" – that is, whether adjacent carbon atoms have single- (C–C), double- (C=C), or triple (C≡C) bonds – in various scanned individual organic molecules including polycyclic

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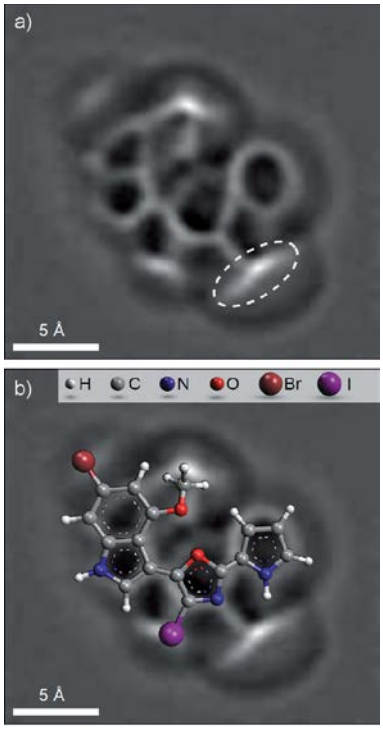
[179] Leo Gross *et al.*, "The Chemical Structure of a Molecule Resolved by Atomic Force Microscopy," *Science* 325(28 Aug 2009):1110-4.

[180] Bruno Schuler *et al.*, "From Perylene to a 22-Ring Aromatic Hydrocarbon in One-Pot," *Angew. Chemie* 53(18 Aug 2014):9004-9006; https://www.researchgate.net/profile/Sara_Collazos/publication/263707042_From_Perylene_to_a_22-Ring_Aromatic_Hydrocarbon_in_One-Pot/links/560522cc08aea25fce32191f.pdf.

hydrocarbons and fullerenes.[181] Along with the charge distribution within individual surface-bound molecules,[182] the positioning of the sample molecule on the surface can be determined with very high precision using AFM, including the deposited molecule's lateral adsorption position to atomic resolution, its adsorption height differences to a precision of 3 pm, and the tilts of its molecular plane to within 0.2°.[183]



In 2010, the Zurich team used the same technique (i.e., the sample molecule is deposited on a Cu(111) surface and scanned by a CO-functionalized AFM tip) to determine the exact pattern of atomic connectivity in a natural organic molecule of previously undetermined structure, a metabolite called cephalandole A.[184] By 2012, a larger collaboration of researchers[185] used a combination of the same atomic resolution AFM, along with Density-Functional Theory (DFT) quantum chemistry structure calculations and computer-aided structure elucidation (CASE), to solve the structure (at right) of the natural compound breitfussin A (molecular formula $C_{16}H_{11}N_3O_2BrI$, from high-resolution mass spectrometry), a member of a chemical family of molecules that include sterols, polyhalogenated monoterpenes, and anthracenone derivatives. (The white-dashed encircled region marks a non-intrinsic molecule feature.) Remarkably, AFM could be used to determine all the connection positions of the cyclic systems as well as those of the substituent groups (MeO, Br, and I) – information that is difficult to obtain with other techniques.

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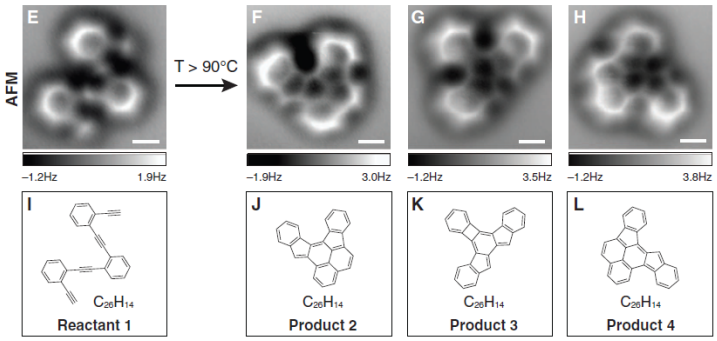
[181] Leo Gross, Fabian Mohn, Nikolaj Moll, Bruno Schuler, Alejandro Criado, Enrique Guitián, Diego Peña, André Gourdon, Gerhard Meyer, "Bond-Order Discrimination by Atomic Force Microscopy," *Science* 337(14 Sep 2012):1326-9.

[182] Fabian Mohn, Leo Gross, Nikolaj Moll, Gerhard Meyer, "Imaging the charge distribution within a single molecule," *Nature Nanotechnology* (26 Feb 2012):1-5.

[183] B. Schuler, W. Liu, A. Tkatchenko, N. Moll, G. Meyer, A. Mistry, D. Fox, L. Gross, "Adsorption geometry determination of single molecules by atomic force microscopy," *Phys. Rev. Lett.* 111(5 Sep 2013):106103.

[184] Leo Gross *et al.*, "Organic structure determination using atomic-resolution scanning probe microscopy," *Nature Chemistry* 2(Oct 2010):821-825; http://home.cc.umanitoba.ca/~hultin/chem2220/Support/CoolStuff/MolecularStructure/nchem.765.pdf.

[185] K.O. Hanssen *et al.*, "A Combined Atomic Force Microscopy and Computational Approach for the Structural Elucidation of Breitfussin A and B: Highly Modified Halogenated Dipeptides from *Thuiaria breitfussi*," *Angew. Chem. Int. Ed.* 51(2012):1-6.



AFM is now regularly used to record the changes in chemical structure that occur as an individual molecule undergoes a complex reaction on a surface. For example, Crommie's group at U.C. Berkeley used a cryogenic UHV non-contact AFM to track the transformations of an individual molecule of 1,2-bis((2-ethynylphenyl)ethynyl)benzene on a silver Ag(100) surface as it underwent a series of cyclization processes (above; scale bar = 3 Å).[186] With the assistance of DFT-based quantum chemistry calculations, these bond-resolved single-molecule AFM images were sufficient to identify the structure of the original reactant and its successor product molecules.

5.2.3 Element Typing of Atoms by AFM

If we have the molecular formula – that is, if we know how many atoms of each element are present – then it is clearly possible to use AFM to infer the geometric structure and bonding pattern of an unknown molecule, provided it doesn't deviate too far from linear or planar form. But what if we don't have the molecular formula? Even then, in many cases, the sample molecule's geometric structure, its bond lengths and angles, the number of bonds per atom, and the measured bond order, may be enough to strongly infer, if not always unambiguously identify, the element type of a particular atom in an unknown organic molecule.

In limited cases, cryogenic STM-based single-molecule inelastic electron tunneling spectroscopy can provide electron tunneling spectra that serve as fingerprints of the vibrational properties of adsorbed molecules (e.g., C-H and C-D stretch modes,[187] ^{12}C-O and ^{13}C-O vibrational excitations,[188] N-H stretching vibrations[189]) and of the electronic properties of magnetic impurity atoms (e.g., Co-Au electronic resonance,[190] Ce-Ag tunneling spectra anti-resonance[191]), thereby

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[186] Dimas G. de Oteyza *et al.*, "Direct Imaging of Covalent Bond Structure in Single-Molecule Chemical Reactions," *Science* 340(21 Jun 2013):1434-7.

[187] B.C. Stipe *et al.*, "Single-Molecule Vibrational Spectroscopy and Microscopy," *Science* 280(12 Jun 1998):1732-5.

[188] A.J. Heinrich, C.P. Lutz, J.A. Gupta, D.M. Eigler, "Molecular Cascades," *Science* 298(15 Nov 2002):1381-7.

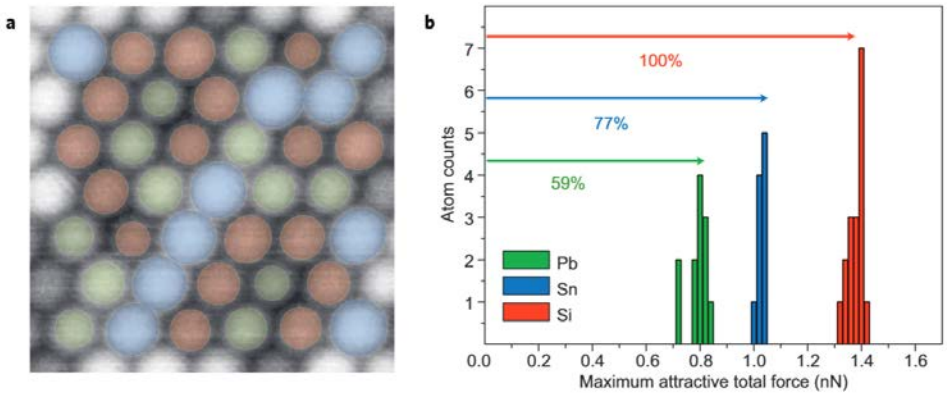
[189] J.I. Pascual, N. Lorente, Z. Song, H. Conrad, H.-P. Rust, "Selectivity in vibrationally mediated single-molecule chemistry," *Nature* 423(29 May 2003):525-528.

[190] V. Madhavan, W. Chen, T. Jamneala, M.F. Crommie, N.S. Wingreen, "Tunneling into a Single Magnetic Atom: Spectroscopic Evidence of the Kondo Resonance," *Science* 280(24 Apr 1998):567-9.

allowing direct elemental identification of a particular atom. Non-destructive low-voltage EELS (Electron Energy-Loss Spectroscopy) single-atom spectroscopy has also correctly identified atoms of the elements Ca, La, Ce and Er,[192] and other related methods have been disclosed.[193]

Another more useful way to detect element type is via dynamic force microscopy (NC-AFM), which can image insulator, semiconductor and metal surfaces with true atomic resolution by detecting and precisely measuring the short-range forces that arise with the onset of chemical bonding between the apical tip atom and surface atoms. These forces depend sensitively upon the chemical identity of the atoms involved. For example, Custance[194] reports using room temperature chemical force measurements as the basis for atomic recognition by imaging a surface alloy containing equal proportions of Si, Sn, and Pb atoms on an Si(111) substrate, and successfully identifying the element types of all surface atoms (**Figure 16**) – even though these three elements exhibit very similar chemical properties and identical surface position preferences that render any discrimination attempt based on topographic measurements alone very difficult.

Figure 16. At left: NC-AFM image of a surface alloy composed of Si, Sn and Pb atoms blended in equal proportions on a Si(111) substrate. The color coding (Pb = green, Sn = blue, Si = red) corresponds to the chemical species as determined by room temperature force distance spectroscopy. At right: Atom counts as a function of the maximum measured attractive force above the Pb, Sn and Si atoms. The three different elements are clearly distinguished by their respective maximum forces.



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[191] Jiutao Li, Wolf-Dieter Schneider, Richard Berndt, Bernard Delley, "Kondo Scattering Observed at a Single Magnetic Impurity," *Phys. Rev. Lett.* 80(30 Mar 1998):2893-6.

[192] Kazu Suenaga *et al.*, "Visualizing and identifying single atoms using electron energy-loss spectroscopy with low accelerating voltage," *Nature Chemistry* 1(2009):415-418.

[193] "Simultaneous topographic and elemental chemical and magnetic contrast in scanning tunneling microscopy," U.S. Patent App. 20140259235, http://www.freepatentsonline.com/y2014/0259235.html.

[194] Yoshiaki Sugimoto, Pablo Pou, Masayuki Abe, Pavel Jelinek, Ruben Perez, Seizo Morita, Oscar Custance, "Chemical identification of individual surface atoms by atomic force microscopy," *Nature* 446(1 Mar 2007):64-7.

5.2.4 Element Typing of Functional Groups by AFM

Besides element typing of specific atoms, we can also chemically recognize particular functional groups that consist of a small number of atoms (e.g., –OH, $–CH_3$, etc.). This may be accomplished using another variant of atomic force microscopy called **Chemical Force Microscopy** (CFM).[195] Recall that with AFM, structural morphology is probed using simple tapping or contact modes that utilize van der Waals interactions between tip and sample to maintain a constant probe deflection amplitude (constant force mode) or maintain height while measuring tip deflection (constant height mode). But CFM, on the other hand, uses chemical interactions between functionalized probe tip and sample. A typical laboratory setup might involve a gold-coated tip to which R-SH thiols have been attached using gold-thiol bonding, the "R" being an organic functional group of interest such as –COOH or $–CH_3$. When the R-functionalized tip is brought close to a test molecule on a surface, the R-group experiences a chemical interaction with the sample, creating an identifiable force profile that enables the CFM to determine the chemical nature of the sample surface, irrespective of its specific morphology. Typically, CFM is limited by thermal vibrations within the cantilever holding the probe. This limits force measurement resolution to ~1 pN which is still very suitable considering that weak $COOH/CH_3$ interactions are ~20 pN per pair.[196] A recent review paper[197] notes CFM applications including titration-AFM to obtain the apparent *pKa* value at the surface, determination of adhesive forces and energy on a surface, finding a specific substance by measuring single intermolecular forces (e.g., host-guest interaction in a complex environment), detection of specific chemical groups, determining surface heterogeneity, and studies of surface chemical reactions on the nanoscale and in real time.

Initially developed by Charles Lieber at Harvard University in 1994, CFM (aka. chemical force spectroscopy[198]) was originally demonstrated using hydrophobicity (i.e., repulsion from water) where polar molecules (e.g., COOH) tend to have the strongest binding to each other, followed by nonpolar molecules (e.g., CH_3-CH_3) bonding, and lastly a combination of the two being the weakest. Thus, a scan of a sample with a tip functionalized with a –COOH or a $–CH_3$ group can allow us to detect the presence and location of either group on a sample surface. Other tip functionalizations will probably be needed to identify other common organic ligand groups such

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[195] http://en.wikipedia.org/wiki/Chemical_force_microscopy.

[196] C.D. Frisbie, L.F. Rozsnyai, A. Noy, M.S. Wrighton, C.M. Lieber, "Functional Group Imaging by Chemical Force Microscopy," *Science* 265(1994):2071; A. Noy, C.D. Frisbie, L.F. Rozsnyai, M.S. Wrighton, C.M. Lieber, "Chemical Force Microscopy: Exploiting Chemically-Modified Tips to Quantify Adhesion, Friction, and Functional Group Distributions in Molecular Assemblies," *J. Am. Chem. Soc.* 117(1995):7943-7951; A. Noy, D.V. Vezenov, C.M. Lieber, "Chemical Force Microscopy," *Annu. Rev. Mater. Sci.* 27(1997):381; C.M. Lieber, D. Vezenov, A. Noy, C. Sanders, "Chemical Force Microscopy," *Microscopy and Microanalysis* 3(1997):1253-1254.

[197] Clarice Steffens, Fabio L. Leite, Carolina C. Bueno, Alexandra Manzoli, Paulo Sergio De Paula Herrmann, "Atomic Force Microscopy as a Tool Applied to Nano/Biosensors," *Sensors (Basel)* 12(2012):8278-8300, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3436029/.

[198] A. Noy, "Strength in numbers: probing and understanding intermolecular bonding with chemical force microscopy," *Scanning* 30(Mar-Apr 2008):96-105.

as $–NH_2$ (amine),[199] –OH (hydroxyl),[200] –SH (thiol),[201] $–PO_4$ and $–PO_2H$ (phosphate),[202] $–C_6H_5$ (phenyl),[203] and the like, that might also be present on an unknown organic congener molecule, and might incorporate Br or Xe at the tip.[204] For example, Wong *et al.*[205] in Lieber's group prepared nanotube tips by oxidation in air at 700 °C, burning off all but 2% of the original material and leaving the ends covered with carboxyl (COOH) groups whose chemistry is rich and well understood. Four different kinds of tips were created: (1) the original carboxyl tip, which is acidic; (2) an amine-terminated tip (made by forming an amide bond to one of the amine groups in ethylenediamine ($H_2NCH_2CH_2NH_2$)), which is basic; (3) a hydrocarbon-terminated tip (made by forming an amide bond to benzylamine ($C_6H_5CH_2NH_2$)), which is hydrophobic; and (4) a biotin-terminated tip (made by forming an amide bond to a biotin derivative), which shows specific binding to streptavidin. AFM contact forces between tips and selected samples varied in a deterministic manner and were shown to be sensitive to pH and to the chemical details of the sample surface in ways consistent with the tips' intended chemistry.

A biological implementation of CFM at the nanoscale level is the unfolding of proteins with functionalized tip and surface.[206] Due to the increased contact area, the tip and the surface act as anchors holding protein bundles while they separate. As uncoiling ensues, the required force jumps in steps, indicating various stages of uncoiling such as: (1) separation into bundles, (2) bundle separation into domains of crystalline protein held together by van der Waals forces, and (3) linearization of the protein upon overcoming the secondary bonding. Information on the

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[199] M. Hibino, T. Nakano-Nishida, "Chemical force microscopy using functionalized ZnO whisker probe tips," *J. Nanosci. Nanotechnol.* 14(Apr 2014):3080-6.

[200] P.D. Ashby, C.M. Lieber, "Ultra-sensitive imaging and interfacial analysis of patterned hydrophilic SAM surfaces using energy dissipation chemical force microscopy," *J. Am. Chem. Soc.* 127(11 May 2005):6814-8.

[201] T. Mandal, M.D. Ward, "Determination of specific binding interactions at L-cystine crystal surfaces with chemical force microscopy," *J. Am. Chem. Soc.* 135(17 Apr 2013):5525-8.

[202] K. Wuttisela, W. Triampo, D. Triampo, "Chemical force mapping of phosphate and carbon on acid-modified tapioca starch surface," *Int. J. Biol. Macromol.* 44(1 Jan 2009):86-91; D.I. Kreller, G. Gibson, G.W. vanLoon, J.H. Horton, "Chemical force microscopy investigation of phosphate adsorption on the surfaces of iron(III) oxyhydroxide particles," *J. Colloid Interface Sci.* 254(15 Oct 2002):205-13.

[203] J. Patete, J.M. Petrofsky, J. Stepan, A. Waheed, J.M. Serafin, "Hofmeister effect on the interfacial free energy of aliphatic and aromatic surfaces studied by chemical force microscopy," *J. Phys. Chem. B.* 113(15 Jan 2009):583-8, *J. Phys. Chem. B.* 114(11 Nov 2010):14110.

[204] Fabian Mohn, Bruno Schuler, Leo Gross, Gerhard Meyer, "Different tips for high-resolution atomic force microscopy and scanning tunneling microscopy of single molecules," *Appl. Phys. Lett.* 102(2013):073109, http://dx.doi.org/10.1063/1.4793200.

[205] S.S. Wong, E. Joselvich, A.T. Woolley, C.L. Cheung, C.M. Lieber, "Covalently functionalized nanotubes as nanometer probes for chemistry and biology," *Nature* 394(2 Jul 1998):52-55.

[206] J. Zlatanova, S.M. Lindsay, S.H. Leuba, "Single molecule force spectroscopy using the atomic force microscope," *Prog. Biophys. Mol. Biol.* 74(2000):37.

internal structures of these complex proteins and a better understanding of constituent interactions is provided with this method.

Similarly, the measured force required to peel a single-stranded DNA molecule away from a single-crystal graphite surface during retraction of an oligonucleotide-functionalized AFM tip differs for pyrimidine bases (e.g., 85.3 pN for thymine and 60.8 pN for cytosine), allowing their presence in a strand of DNA to be distinguished.[207] AFM tips functionalized with specific single-strand DNA oligonucleotides (mixed multi-base strands) can discriminate between their biological binding partner and other molecules on a heterogeneous substrate.[208] The partial sequencing of a single DNA molecule (the unambiguous identification of all guanines, as distinct from the other 3 bases) on a copper Cu(111) surface via high-resolution STM was first reported in 2009.[209]

Functionalized AFM tips have been created to exploit the chemical forces involved in antibody-antigen recognition,[210] protein-carbohydrate recognition,[211] enzyme-ligand recognition,[212] and charge-transfer complexes.[213] A wide variety of methods for attaching biological molecules to AFM tips are known.[214] Tips with embedded electrical charges can also probe the electrostatic structure of sample organic molecules.[215]

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[207] S. Manohar, A.R. Mantz, K.E. Bancroft, C.Y. Hui, A. Jagota, D.V. Vezenov, "Peeling single-stranded DNA from graphite surface to determine oligonucleotide binding energy by force spectroscopy," *Nano Lett.* 8(Dec 2008):4365-72; http://pubs.acs.org/doi/abs/10.1021/nl8022143.

[208] A. Noy, D.V. Vezenov, J.F. Kayyem, T.J. Meade, C.M. Lieber, "Stretching and breaking duplex DNA by chemical force microscopy," *Chem. Biol.* 4(Jul 1997):519-27; L.T. Mazzola, C.W. Frank, S.P. Fodor, C. Mosher, R. Lartius, E. Henderson, "Discrimination of DNA hybridization using chemical force microscopy," *Biophys. J.* 76(Jun 1999):2922-33.

[209] H. Tanaka, T. Kawai, "Partial sequencing of a single DNA molecule with a scanning tunnelling microscope," *Nature Nanotech.* 4(2009):518-522.

[210] Peter Hinterdorfer, Werner Baumgartner, Hermann J. Gruber, Kurt Schilcher, Hansgeorg Schindler, "Detection and localization of individual antibody-antigen recognition events by atomic force microscopy," *Proc. Natl. Acad. Sci. USA* 93(16 Apr 1996):3477-3481.

[211] For example, the measured rupture force between one molecule of mannose and the concanavalin A protein is 95 ± 10 pN. X. Zhang, V.K. Yadavalli, "Functionalized self-assembled monolayers for measuring single molecule lectin carbohydrate interactions," *Anal. Chim. Acta.* 649(1 Sep 2009):1-7.

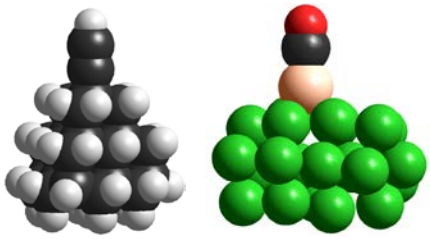
[212] M. Fiorini, R. McKendry, M.A. Cooper, T. Rayment, C. Abell, "Chemical force microscopy with active enzymes," *Biophys. J.* 80(May 2001):2471-6.

[213] R. Gil, J.C. Fiaud, J.C. Poulin, E. Schulz, "Charge-transfer complexes interactions evidenced by chemical force microscopy," *Chem. Commun. (Camb).* 2003(7 Sep 2003):2234-5.

[214] R. Barattin, N. Voyer, "Chemical modifications of atomic force microscopy tips," *Methods Mol. Biol.* 736(2011):457-83.

[215] W.F. Heinz, J.H. Hoh, "Relative surface charge density mapping with the Atomic Force Microscope," Biophys. J. 76(Jan 1999):528-538; http://www.sciencedirect.com/science/article/pii/S0006349599772218.

We can also use mechanosynthesis to build much sharper scanning probe tips, such as the hydrogenated ethynyl on an adamantane handle (leftmost image), whose apical hydrogen atom (white) is smaller than the apical oxygen atom (red) of the IBM Zurich C-O tip (rightmost image) which is mounted on a single gold atom attached to a much larger and poorly characterized field of copper (green) atoms coating a standard silicon probe tip.



5.2.5 Chemohaptic Analysis of More Difficult Cases

What if the sample molecule deviates significantly from linear or planar form? A review of the 144 congener molecules listed in Table 4 and Table 5 reveals no 3D cage or caltrops-shaped molecules that might prove extremely challenging to tip-scan. The molecular structures for all 31 of the "most potent odorants" in rye whiskey from Table 4 are listed in **Appendix B**. All are fairly small molecules and appear quite amenable to AFM-based tip-scanning. Many have one or a few methyl groups that protrude beyond the primary plane of the molecule, but most of these congener molecules are either long chains, single rings, or a ring + chain combination with 1-3 small side groups attached. The 113 additional congener molecules listed in the much longer Table 5 appear to follow the same pattern.

For those few unknown congener molecules that might still present modest difficulties, at least four approaches may be considered to obtain the full characterization information that we need.

First, the scanning mechanism should include a procedure by which a molecule, once scanned and mapped, is physically rotated to a new position on the surface and then re-scanned. This procedure, which will bring new atoms and side groups into view, could be repeated 10 times or more if necessary until the data sets from all repeat tip scans can be matched up to yield a consistent picture of the molecular shape. The sample molecule could also be placed in a special jig to position it in a manner most conducive to useful data collection. The use of pattern-matching, based on our library of known ~10,000 targets, could help here.

Second, a "pin-cushion" type receptor could be employed as a general-purpose molecular shape sensor (http://www.nanomedicine.com/NMI/3.5.7.4.htm).

Third, a hydrogen abstraction tool could be used to abstract any hydrogen present on the molecule, then a second tool of known configuration could be covalently bonded to the sample molecule at that position. The sample molecule is now securely held by a "hand" and can be translated, rotated, pushed, squeezed, stretched, or re-scanned at odd angles by a third tip acting as an examination tool to obtain any missing information about shape or composition.

Fourth, in difficult cases we could employ a protocol for progressive subtractive mechanosynthesis in which the sample molecule is disassembled group by group, or even atom by atom, with full re-scan after each disassembly step so that the original molecular structure can be inferred.

We conclude that mechanical tip-scanning should suffice to determine both elemental identity and molecular geometry (including bond order) for most if not all of the congener molecules expected to be present in whiskey and other fine spirits.

5.2.6 Minimum Size of Lab Module for Chemohaptic Analysis

The smallest possible Lab Module for performing a chemohaptic analysis on one molecule at a time might include at least the following components and subsystems:

(1) a means to accept a single sample molecule to be tested into the apparatus;

(2) an examination surface upon which the sample molecule will be immobilized, prior to being tip-scanned;

(3) an evacuated (UHV) test chamber large enough to accommodate (a) the largest anticipated sample molecule, (b) the examination surface, and (c) the intrusion of all the tools that must work on the sample molecule;

(4) a large set of exchangeable probe tips with various functionalizations that serve different scanning purposes, and a means for storing these probe tips between uses;

(5) a means for extending, retracting, and exchanging probe tips, and a motorized means for performing the mechanical scanning process;

(6) a sensor system for measuring forces between scanning probe and sample molecule;

(7) a means for recording and transmitting the scanned force data;

(8) a small local computational system to analyze the raw data and to modify the testing regimen on the fly, in response to particular patterns detected in the data;

(9) specialized tools for manipulating the sample molecule;

(10) a set of mechanosynthetic tools for performing subtractive mechanosynthesis, if necessary, and a means for recharging spent tools; and

(11) a means for disposing of the sample molecule after the analysis is complete.

Table 7 compiles our best estimates for atom count, mechanism volume, power consumption, and time budget to complete one analysis cycle for one sample molecule using a Lab Module consisting of appropriate sets of mechanisms and devices representing each of the aforementioned 11 categories of essential components and subsystems.

Table 7. System parameters for a Lab Module that performs a single-molecule structural and elemental characterization.				
Components or Subsystems	**Carbon Atom Count** *(millions)*	**Volume** *(nm^3)*	**Maximum Power Consumption** *(nW)*	**Time Budget** *(msec)*
(1) input one sample molecule[216]	28.0	156,000		0.25
(2) exam table[217]	1.8	10,000		
(3) UHV chamber[218]	6,652.8	500,000,000		
(4) probe tips and tool rack[219]	2.0	10,000		
(5) tip exchange & scanning the molecule[220]	90.0	1,020,000	0.002	30.00
(6) force sensors[221]	1.0	8,000	0.002	4.00

[216] (1): We'll assume a transfer arm that is 250 nm long and 625 nm^2 in cross-section, giving ~156,000 nm^3 and 28 million C atoms for this mechanism. Since it only operates twice or a small number of times during an examination cycle, the continuous power draw is negligible. If the sample molecule must be moved 250 nm at 1 mm/sec, the transfer time is 0.25 msec.

[217] (2): The largest congener molecule likely to be tested should be no more than 1-2 nm in diameter, but we'll allocate 100 nm^2 for the examination surface, also assumed to be 10 nm thick. We'll also allocate 10 of these to accommodate the possibility of using different surfaces and with specialty jigs on these surfaces, giving a total ~10,000 nm^3 and 1.8 million C atoms for these surfaces.

[218] (3): Assuming a 0.5 $micron^3$ cubic chamber with six 0.63 $micron^2$ walls that are 10 nm thick to support internal vacuum at ambient pressure, then we have 0.0378 $micron^3$ of solid diamond wall that incorporates 6.6528 billion C atoms. A chamber wall thickness of 10 nm should be more than sufficient because to avoid bursting, an analogous spherical pressure vessel wall thickness $t_{wall} \geq \Delta P\ R_{vessel} / 2\ \sigma_{wall} = 0.002$ nm, taking $\Delta P = 1$ atm $= 10^5$ N/m^2, $R_{vessel} = (3V_{vessel}/4\pi)^{1/3} = 492$ nm for $V_{vessel} = 0.5$ $micron^3$, and working stress $\sigma_{wall} \sim 10^{10}$ N/m^2 for diamond; *Nanomedicine, Vol. I*, Section 10.3.1.)

[219] (4): We assume the Lab Module has 100 probe tips of various types, each tip having ~10,000 C atoms or ~50 nm^3 of volume. Allowing an equal volume for the tool rack to hold the 100 exchangeable probe tips we have a total of ~2 million C atoms and ~10,000 nm^3 of total volume for the probe tips.

[220] (5): We allocate a $(100\ nm)^3$ volume of machinery that is 50% filled with diamondoid mechanical actuators, levers, gears, and so forth to drive the tip scan process and to enable tip changeout, and we'll use a linear dielectric drive motor that can produce 10 nN of force while consuming 2 pW of power in a ~2000 nm^3 volume at a power density of 10^{12} W/m^3. We also assume 10 redundant motors, operated one at a time but continuously. This gives a 1,020,000 nm^3 volume, 90 million C atoms, and ~2 pW power draw. If up to 100 exchangeable probe tips must be moved through a round-trip distance of 200 nm between tool rack and sample molecule at 1 mm/sec, then the total transfer time is (100 tips) (200 nm/tip) / (1 mm/sec) = 20 msec. Allowing 0.1 msec/tip for probe tip attachment and detachment at the tool rack adds another 10 msec to the time budget for this process.

[221] (6): AFM tip scans typically measure up to 100 pN of force, but assuming we must accommodate forces up to ~10 nN from a tip that is scanning at a continuous speed of ~1 mm/sec, then a ~20 nm force sensor (*Nanomedicine, Vol. I*, Section 4.4.1) has an 8000 nm^3 volume, ~1 million C atoms, and up to ~10 pW

(7) data recording, processing, and transmission[222]	3,000.0	20,000,000	0.006	400.00
(8) computer[223]	35,000.0	264,000,000	60.060	
(9) molecule manipulation tools[224]	100.0	500,000	0.004	
(10) subtractive mechanosynthesis tools/operations[225]	26.1	1,000,000	0.010	100.0
(11) disposal of sample molecule[226]				0.25
Subtotals	44,901.7	786,704,000	60.084	534.50
Unallocated resources	15,098.3	213,296,000	39.916	465.50
TOTALS	**60,000.0**	**1,000,000,000**	**100.000**	**1,000.00**

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power draw if operated continuously. The smallest features visible in Fig. 15 are larger than 10 pm and the field of view for a single molecule is ~2 nm. If we raster scan along 2000 pm long lines with 10 pm separation between lines across the entire field of view using a tip moving at 1 mm/sec, then the tip travels 2000 pm x (2000 pm / 10 pm) = 400,000 pm (0.4 micron) per scan and each scan requires 0.4 msec to complete. A series of 10 tip-scans thus would require up to 4 msec.

[222] (7): Allocate another 10% of the computer memory budget from item (8) for this item: 0.02 micron^3, 3 billion C atoms, 6 pW power draw. A scanning tip moving at 1 mm/sec and recording 10 pm features will encounter 10^8 features/sec, implying 100 MHz operation – well within the anticipated ~GHz processing and transmission speeds of nanocomputers, nanoswitches, and other nanomechanical systems. Assuming 10 bits per feature gives a data flow of 10^9 bits/sec during the 4 msec while the 10 tip-scans are in progress. If 100 computational operations must be performed on every bit to achieve molecular structure identification and element typing, then the total data processing time per 10 tip-scans is 400 msec.

[223] (8): The local computer can be a 1-gigaflop mechanical nanocomputer occupying a volume of 0.064 micron^3 with an atom count of ~5 billion C atoms, mass ~10^{-16} kg, and a 60 nW power draw (*Nanomedicine, Vol. I*, Section 10.2.1), paired with 10^6 bits of fast-access (10^{10} bit/sec) mechanical memory and 10^9 bits of slow-access (10^9 bit/sec) spooled hydrofluorocarbon memory with a combined ~0.2 micron^3 volume (*Nanomedicine, Vol. I*, Section 10.2.1), giving a ~30 billion C atom count and a 60 pW power draw (*Nanomedicine, Vol. I*, Section 7.2.6).

[224] (9): Assume 10 manipulators, each having 10 million C atoms and 50,000 nm^3 of displaced volume, but they're operated at most 2 at a time at a cost of 2 pW per manipulator; this yields a total of 500,000 nm^3, 100 million C atoms, and a 4 pW power draw, assuming continuous operation.

[225] (10): A nanoscale fabricator might include 3 small mechanosynthetic manipulators and one large manipulator, 20 toolheads and a toolrack, occupying 1,000,000 nm^3 of displaced volume with 26.1 million C atoms, burning ~10 pW of power when in continuous use. It could fabricate structures at the ~10 msec/atom rate if presentation of feedstock molecules is not a time-limiting factor, as would be the case during disassembly rather than fabrication, where we are breaking bonds in a molecule at hand rather than making bonds between a workpiece and an imported moiety. Assuming ~10 C atoms for the "typical congener", the disassembly portion of the analysis procedure, if needed, could be done in ~100 msec. (The 10 scan times for 9 disassembly steps are already accounted for under item (6), above.)

[226] (11): Mechanisms already included in (1); if the sample molecule or its remains must be moved 250 nm at 1 mm/sec, the transfer time is 0.25 msec.

5.2.7 Size and Performance of the Assay Unit

From Table 7, each diamondoid molecular machine-based Lab Module incorporates $n_{C\text{-}LM}$ = 60 billion carbon atoms of total mass $M_{LM} = m_C\ n_{C\text{-}LM} = 1.2 \times 10^{-15}$ kg (taking $m_C = 2 \times 10^{-26}$ kg/C atom), has a volume V_{LM} = 1 micron^3, a power consumption up to P_{LM} = 100 nW in continuous operation, and requires τ_{LM} ~ 1 sec/molecule in continuous operation to determine the molecular structure and element types of all atoms in an unknown congener molecule. A set of N_{LM} = 10 million Lab Modules, comprising the analytical core of the Assay Unit, can process n_{LM} / τ_{LM} = 10 million molecules randomly chosen from the fine spirits sample every second. After t_{sample} = 1000 sec, the Assay Unit has processed $n_{AssayUnit} = n_{LM}\ t_{sample} / \tau_{LM}$ = 10 billion molecules with a ~93% probability[227] of having captured between 5-15 copies of any molecule that is present at the 1 ppb concentration. Preparatory pre-extraction of water and ethanol molecules from the sample via sorting rotors (Section 5.3.3) could improve Assay Unit productivity by up to 100-fold.

The Lab Module Block of the Assay Unit, incorporating 10 million Lab Modules, has a total volume of $V_{LMB} = N_{LM}\ V_{LM}$ = 0.01 mm^3 and a mass of $M_{LMB} = N_{LM}\ M_{LM}$ = 0.000012 gram.

The maximum power consumption of the Lab Module Block of the Assay Unit is $P_{LMB} = N_{LM}\ P_{LM}$ = 1 watt. Power density for the Lab Module Block is a quite reasonable $P_{d\text{-}LMB} = P_{LMB} / V_{LMB} = 10^{11}$ W/m^3, exactly midway between the ~10^{10} W/m^3 power density estimated for molecular transport[228] and the ~10^{12} W/m^3 power density estimated for mechanical computation.[229]

Scanning operations perform more effectively at lower temperatures, so we should examine the impact of a decision to hold Lab Modules at cryogenic temperatures. In the most simpleminded approach, we might import either liquid nitrogen (77 K or -196 °C for LN2) or liquid helium (4 K or -269 °C for LHe) as cryogen coolants. The cost of liquid cryogens if consumed as coolants may be estimated as $c_{cryo} = (p_{Lcryo})\ (MW_{Lcryo}) / (H_{vapLcryo})$ = \$1.2 x 10^{-6}/watt-sec for liquid nitrogen (= $c_{cryoLN2}$) or \$0.0054/watt-sec for liquid helium (= $c_{cryoLHe}$), taking cryogen price p_{Lcryo} = \$0.247/kg (\$0.20/liter @ 0.808 kg/liter density at b.p.)[230] for LN2 or \$112/kg (\$14/liter @ 0.125 kg/liter density at b.p.)[231] for LHe, molecular weight MW_{Lcryo} = 28 gm/mole for LN2 or 4 gm/mole for LHe, and heat of vaporization $H_{vapLcryo}$ = 5560 J/mole for LN2[232] or 82.9 J/mole for LHe[233]. In this scheme, the cost of keeping the Lab Module Block cooled to 4 K is about $c_{LMB\text{-}LHe} = P_{LMB}\ t_{sample}\ c_{cryoLHe}$ = **\$5.40/sample** using LHe coolant, or about $c_{LMB\text{-}LN2} = P_{LMB}\ t_{sample}\ c_{cryoLN2}$ = **\$0.0012/sample** using LN2 coolant if we can tolerate operation at 77 K. In the ideal design, thermoelectric cooling[234] (e.g., Peltier cooling) or similar methods including portable liquid

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[227] assuming a binomial distribution; http://en.wikipedia.org/wiki/Binomial_distribution.
[228] http://www.nanomedicine.com/NMI/6.5.6.htm#A.
[229] http://www.nanomedicine.com/NMI/6.5.6.htm#E.
[230] The cheapest we've seen: http://van.physics.illinois.edu/qa/listing.php?id=1685.
[231] http://physics.illinois.edu/research/liquefier.asp.
[232] http://en.wikipedia.org/wiki/Nitrogen.
[233] http://en.wikipedia.org/wiki/Helium.

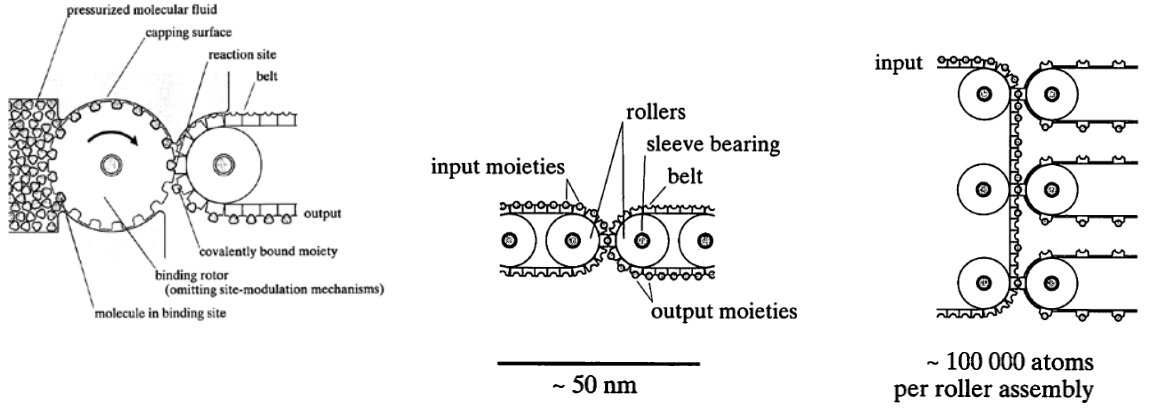
[234] S.R. Harutyunyan, V.H. Vardanyan, A.S. Kuzanyan, V.R. Nikoghosyan, S. Kunii, K.S. Wood, A.M. Gulian, "Thermoelectric cooling at cryogenic temperatures," *Appl. Phys. Lett.* 83(Sep 2003):2142-4, http://dx.doi.org/+10.1063/1.1610810.

nitrogen generator units[235] or miniaturized Joule-Thomson refrigerators[236] could be applied to establish cryogenic temperatures inside the unit, entirely eliminating the need for externally-supplied cryogen consumables. However, it should be pointed out that the element typing described in Section 5.2.3 was performed at room temperature, and the acceptable upper temperature limits of AFM-based congener molecule structure determination (aka. chemohaptic scanning) have yet to be determined.

Besides the possible requirement for cryogenic refrigeration, the Assay Unit will need to provide the large number of Lab Modules with access to infrastructure utilities including sample molecule preparation and distribution, electrical power distribution, a central computer providing process guidance and library functions, a materials distribution system for feedstock and waste, and a communications system linking all the Lab Modules to each other and to the external control interface.

A complete system design is beyond the scope of this document, but it appears that at least the sample molecule distribution system should have negligible mass and power draw. **Figure 17** shows a proposed system of molecule transport, starting with a pressurized fluid phase (near the sample input port) from which individual molecules are acquired, bound to reagent-binding devices mounted on nanoscale conveyor belts moving over ~10 nm rollers, then transported to elsewhere in the system one molecule at a time.

Figure 17. Schematic diagrams of mechanisms for: (1) removing individual molecules from a liquid sample and covalently binding them to a moving conveyor belt (left), (2) transfer of molecules from one conveyor belt to another (center), and (3) fan-out of multiple conveyors from a single conveyor input (right).[237]



[235] For example: http://www.elan2.com/ or http://www.cryomech.com/products/liquid-nitrogen-plants/.

[236] Miniaturized cryogenic cooling systems available from MMR Technologies have a mass of 10-60 gm and a size of a few centimeters, with a cooling capacity of 0.25-0.5 watts while drawing less than 12 watts of power; http://www.mmr-tech.com/PDFs/jThomson_broch.pdf.

[237] K. Eric Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, Wiley, 1992, Figs. 13.5 and 13.7.

According to one analysis of this theoretical design,[238] a 20-roller conveyor line 1 micron long might have a ~2 micron long belt with 500 closely packed reagent devices measuring 4 nm x 4 nm x 2 nm (32 nm^3), while delivering $\alpha_{transport} = 10^6$ molecules/sec at a belt speed of 4 mm/sec, with a total conveyor line mass of $M_{conveyor} \sim 6 \times 10^{-20}$ kg (~3 million carbon atoms). Operation is in cryogenic UHV vacuum conditions. Total power dissipation is $P_{conveyor} \sim 1.4 \times 10^{-18}$ watts, a rate of ~0.001 zJ per moiety (or per reagent device) delivered or $\sim 10^{-6}$ zJ/nm traveled per reagent device. If $n_{AssayUnit} = 10^{10}$ molecules must be transported from the pressurized sample droplet to the Lab Modules in a distribution time of $t_{transport} = 100$ msec, then we need a set of $N_{conveyors} = n_{AssayUnit} / (\alpha_{transport}\ t_{transport}) = 100{,}000$ conveyor lines of total mass $M_{transport} = N_{conveyors}\ M_{conveyor} = 6 \times 10^{-15}$ kg and total power draw of $P_{transport} = N_{conveyors}\ P_{conveyor} = 0.14$ pW during the $t_{transport} / \tau_{LM} = 10\%$ of the 1-second single-molecule analysis cycle that the import transport system is operating. These estimates do not include the mass of the motors, gearing, housings, control systems, and other support mechanisms, but are consistent with the assumption that the import transport system as a whole should have negligible power and mass requirements compared to the rest of the system. An export transport system of similar size and design will likely also be needed to carry the sample molecule or its component pieces out of the Assay Unit for proper external disposal.

The size of the whiskey test sample that we require for recipe compilation is astonishingly small. Using the gross composition of fine spirits given in Table 1, the approximate molecular number density $\delta_{MolNumDen} \sim 63\%$ water x $(33.5 \text{ molecules/nm}^3)^{-1}$ + 36% ethanol x $(13.1 \text{ molecules/nm}^3)^{-1}$ + 1% congeners x $(\sim 5 \text{ molecules/nm}^3)^{-1} \sim 0.048$ nm^3/molecule (~20.8 molecules/nm^3) for well-mixed room-temperature liquid whiskey.[239] Thus the minimum volume of the test sample for the entire 1000-second Assay Unit molecular recipe run of 10 billion molecules is $V_{aliquot} = n_{AssayUnit}\ \delta_{MolNumDen} =$ **0.483 micron^3**. For perspective, a single pharmaceutical "drop" of liquid[240] has a volume of 1/20th ml or **50 billion micron^3**. Alternatively, our minimum-volume test sample aliquot comprises only **0.00000000000006%** (~6×10^{-16}) of a standard 750 ml bottle of whiskey. In other words, we should be able to obtain the molecular recipe for any extant whiskey using an utterly negligible quantity of representative test sample.

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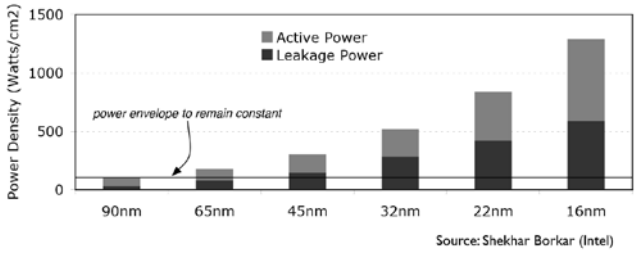
[238] Robert A. Freitas Jr., *Nanomedicine, Vol. I: Basic Capabilities*, Landes Bioscience, 1999, Section 3.4.3; http://www.nanomedicine.com/NMI/3.4.3.htm.

[239] The largest-by-weight whiskey congener is 3-methyl-1-butanol ($C_5H_{12}O$) with $\rho = 810.4$ kg/m^3, MW = 0.088148 kg/mole = 9193.6 moles/m^3 = 5.54 molecules/nm^3. A lesser-weight but twice-larger congener molecule is eugenol ($C_{10}H_{12}O_2$) with $\rho = 1060$ kg/m^3, MW = 0.1642 kg/mole = 6455.5 moles/m^3 = 3.89 molecules/nm^3. Given this range, we conservatively choose ~5 molecules/nm^3 as "typical" for congeners. For water (H_2O): $\rho = 1000$ kg/m^3, MW = 0.018 kg/mole = 55,555 moles/m^3 = 33.5 molecules/nm^3. For ethanol (C_2H_5OH): $\rho = 789$ kg/m^3, MW = 0.046 kg/mole = 21,739 moles/m^3 = 13.1 molecules/nm^3.

[240] http://en.wikipedia.org/wiki/Drop_(unit).

5.2.8 Summary of Assay Unit

The Assay Unit may be a cube-shaped stand-alone device of volume ~1 cm^3, mass ~ 1 gm, and power draw ~1 watt, giving an overall power dissipation through each of the six cube faces of <1 W/cm^2 at the surface, far cooler than the ≥100 W/cm^2 of modern computer processor chips (right).[241] The Assay Unit can detect and characterize, with atomic structural and elemental precision, all unknown congeners present in a sample of fine spirits down to the ~1 ppb concentration level in a total run time of ~1000 sec (17 min), with virtually no operating costs because there are no material inputs other than a tiny physical sample and a small trickle of electricity. There are no significant human labor inputs because the system can be largely automated.



[241] http://www.cs.columbia.edu/~sedwards/classes/2012/3827-spring/advanced-arch-2011.pdf.

5.3 Synthesis Unit

This document proposes the quick and inexpensive replication of fine spirits using an appliance called the **Fine Spirits Synthesizer** (Section 5.4), a limited-use nanofactory that can only manufacture beverages and nothing else. It consists of two major active subsystems: the **Assay Unit** (described in Section 5.2) and the **Synthesis Unit** (described here, in Section 5.3).

After the precise molecular recipe for the beverage product that we wish to replicate has been provided by the Assay Unit, this molecular recipe then guides the quantitative synthesis of up to 10,000 different molecular species of congeners in the Synthesis Unit, followed by the combination of these ingredients in solution phase, thus permitting quick and inexpensive replication of a particular sample of whiskey or other fine spirits.

In this Section, we outline one possible architecture for the Synthesis Unit. We describe the mechanosynthesis of individual congener molecules (Section 5.3.1) and macroscale quantities of congeners (Section 5.3.2), using the ethanol molecule as our exemplar. A discussion of receptor-based sourcing of ultrapure ethanol and water (Section 5.3.3) and non-receptor-based sourcing of ultrapure water (Section 5.3.4) is followed by a brief summary of the entire Synthesis Unit (Section 5.3.5). Again, further investigation is required to add more detail to this architecture, to examine additional possible architectures, and to analyze technical tradeoffs among competing architectures to help choose the ideal final design for the Synthesis Unit.

5.3.1 Mechanosynthesis of Ethanol and Congener Molecules

Rather than a conventional bulk chemical synthesis process, the Synthesis Unit builds congener molecules one at a time, usually on a surface via one or more tooltips that transfer reactive moieties from a source of small simple feedstock molecules (e.g., CH_4, H_2O) or surface-bound substituents (e.g., $–CH_3$, –OH, =O, –H) to the “workpiece” (i.e., the molecule that is being built).

To reiterate from Section 5.1.1: Atomically precise fabrication involves holding feedstock atoms or molecules, and a growing nanoscale workpiece, in the proper relative positions and orientations so that when they touch they will chemically bond in the desired manner. In this process, a mechanosynthetic tool is brought up to the surface of a workpiece. One or more transfer atoms are added to, or removed from, the workpiece by the tool. Then the tool is withdrawn and recharged. This process is repeated until the workpiece is completely fabricated to molecular precision with every atom in exactly the right place. Note that the transfer atoms are under positional control at all times to prevent unwanted side reactions from occurring. Side reactions are also prevented using proper reaction design so that the reaction energetics help us avoid undesired pathological intermediate structures.

The mechanosynthetic fabrication of most fine spirit congener molecules will generally require the ability to build and join together just five basic types of organic building blocks made from the elements carbon, hydrogen, and oxygen, including:

(1) hydrocarbon chains, e.g., $–CH_2–CH_2–$;

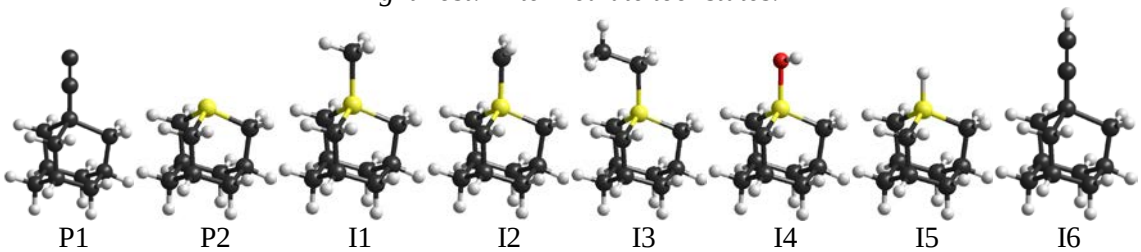
(2) linear esters with a carbon chain interrupted by an oxygen atom, e.g., $–RCO_2R'–$, where R,R′ = hydrocarbon chain;

(3) cyclic phenyl and phenylene groups, e.g., $–C_6H_5R$ and $–C_6H_4RR'$, where R,R′ = CH_3, OH, or other organic side group;
(4) cyclic lactones, e.g., $–O(C=O)(CH_2)_2(CHR)–$ or $–O(C=O)(CH_2)(CHR)(CHR')–$; and
(5) simple terminating groups, e.g., $–CH_3$, –OH, =O, –H, and –COOH.

It is proposed that an ethanol molecule or any organic congener molecule consisting solely of the elements C, H, and O can be built, atom by atom or group by group, by the sequential application of a surprisingly short list of mechanosynthetic tools. As few as 2 primary tools and 6 intermediate tool states (see list below and **Figure 18**; radical site = *) might suffice for manufacturing ethanol and many similar organic molecules.

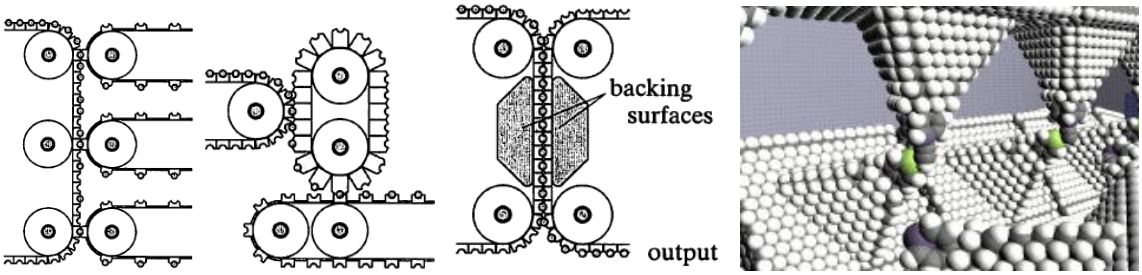
Primary #1: H abstraction "HAbst*" tool ($*CC–C_{10}H_{15}$) to remove an H atom;
Primary #2: Ge radical "*GeRad" tool ($*GeC_9H_{15}$) for moiety transfer with weak bonding and for abstraction tool recharge reactions;
Intermediate #1: CH_3 transfer tool ($CH_3–GeC_9H_{15}$) to acquire a CH_3 group;
Intermediate #2: CH_2 donation tool ($*CH_2–GeC_9H_{15}$) to add a CH_2 group;
Intermediate #3: CH_3CH_2 donation tool ($CH_3CH_2–GeC_9H_{15}$) to add a CH_3CH_2 group;
Intermediate #4: OH donation tool ($OH–GeC_9H_{15}$) to add an OH group;
Intermediate #5: H donation tool ($H–GeC_9H_{15}$) to add an H atom; and
Intermediate #6: spent abstraction tool "HAbstH" ($H–CC–C_{10}H_{15}$) needing recharge.

Figure 18. Possible minimal toolset for building linear, planar, branching, or cyclic organic molecules containing only the elements C (black), H (white), and O (red). In this example, many tooltips also include Ge (yellow) atoms at the working apex. Two leftmost: primary tools. Six rightmost: intermediate tool states.



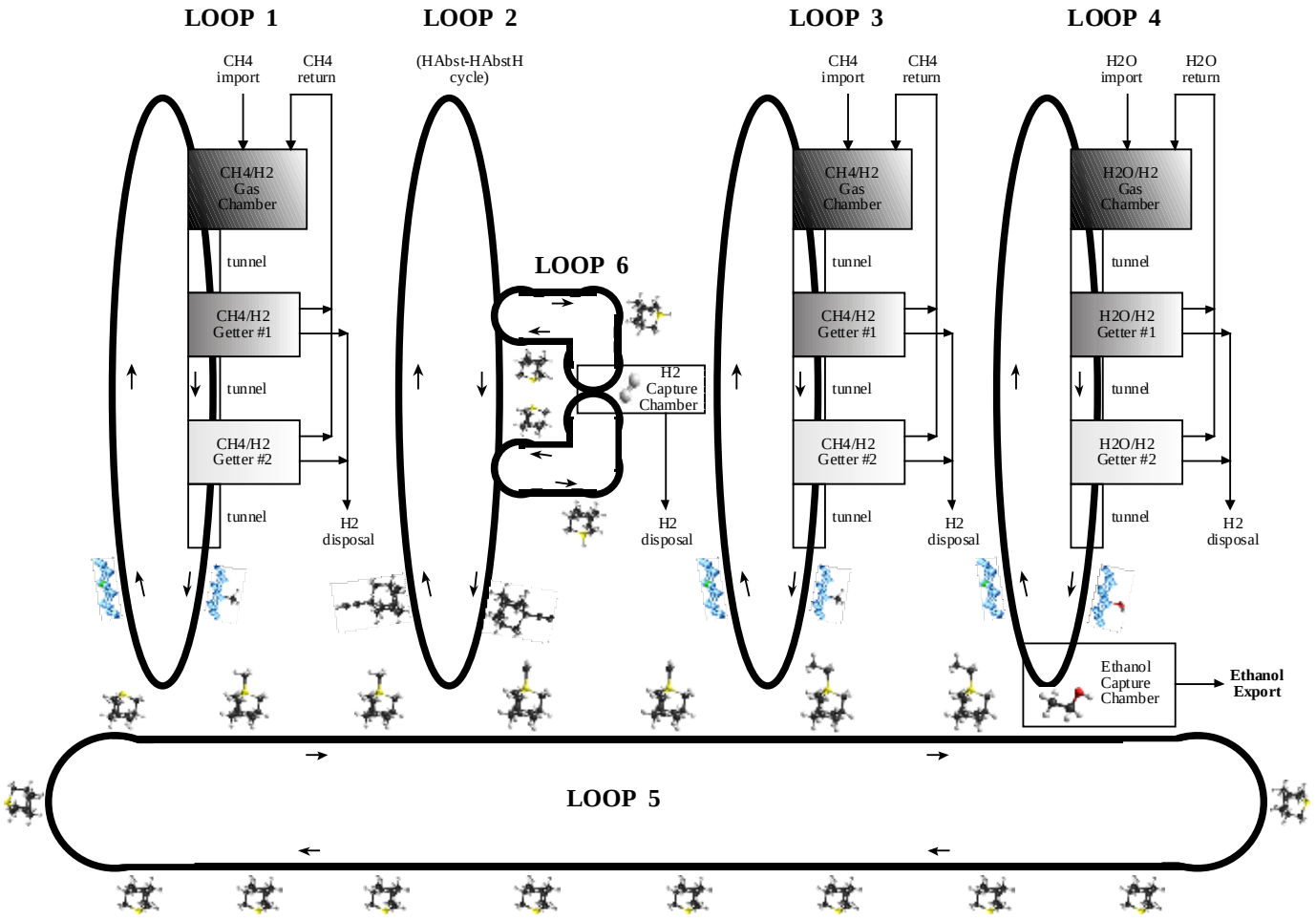
Each of these tooltips – all built on a single adamantane cage – is attached to a larger tool handle structure (not shown) that is mounted on a reagent device that is attached, in turn, to moving conveyor belt mechanisms (below) as previously described in a somewhat different context (Section 5.2.7). Note the "backing surfaces" in the mechanism at center (below) – these may be used to apply high crushing forces to opposing moieties in constrained volumes to overcome reaction barriers if necessary.[242]

[242] K. Eric Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, Wiley, 1992, Figs. 13.7(b), 13.7(c), 13.7(d).



The following is a brief description of a hypothetical mechanosynthetic production line that could be used to build ethanol molecules in a cryogenic vacuum environment, using conveyor belts to move reactive molecules at high speed and to precisely control the location and nature of the interaction between these reactive molecules. The chemistry we describe is believed to be plausible but has not yet been computationally or experimentally validated. Nevertheless, even if this particular reaction sequence and specific set of tools proves flawed upon more detailed analysis, we're confident that other reaction sequences and toolsets can be found that will provide a convenient path to the same result.

Figure 19. Schematic of a hypothetical mechanosynthetic production line for ethanol molecules (black = C, white = H, yellow = Ge, red = O, blue = metal or Ge surface).



The hypothetical ethanol production line (**Figure 19**) has inputs of methane (CH_4) and water (H_2O) and outputs of ethanol (C_2H_5OH) and hydrogen gas (H_2). The production line consists of six interacting continuous or stepwise-moving conveyor loops as described below.

Loop 1: First methyl feedstock pickup

A conveyor belt using carriers having an outer coating of germanium (Ge)[243], platinum (Pt)[244], rhodium (Rh)[245], or iridium (Ir)[246] passes through a chamber containing methane gas molecules (CH_4). The coating surface strips one H off; the carrier is given enough residence time in the chamber to allow any H to migrate across the surface to recombine with another H on the surface, then to leave the surface as H_2 gas while remaining trapped in the chamber. This leaves a CH_3 bound to the Loop 1 carrier surface (right). The Loop 1 carriers then traverse a series of tunnels tight enough to prevent most stray CH_4 or H_2 molecules from following the carriers through the tunnel. At intervals the tunnels open up into small getter chambers equipped with sorting rotors (Section 5.3.3) having binding sites for CH_4 and H_2 to collect and remove any that happen to slip through.

Cleared of any bound molecules other than the desired CH_3, the conveyor belt finally emerges into a vacuum where each carrier is brought into firm contact with carriers from another

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[243] A partially methylated germanium surface may provide a source of positionally controlled single-carbon feedstock. Such a surface can be prepared by thermal adsorption and reaction of CH_4 gas on Ge(100) [J. Murota, M. Sakuraba, Tohoku-Cambridge Forum Hall in Peterhouse, University of Cambridge, Organizers: M. Koyanagi, W. I. Milne), International Workshop on Nano-Technology, Nano-Materials, Nano-Devices, and Nano-Systems, 11 June 2004] or by ion bombardment of clean Ge(111) at low substrate temperature (<470 K) using low-energy *CH_3 ions, a strongly exoergic radical coupling reaction. After hydrocarbon CVD on Ge surfaces, absorption spectra indicate that bonding is mainly type sp^3 with CH, CH_2, and CH_3 bonds [J. Franks, *J. Vac. Sci. & Technol. A* 7(1989):2307]. It may also be possible to prepare a CH_3-decorated Ge surface via conventional solution-phase chemical methylation [W. Sundermeyer, W. Verbeek, *Angew. Chemie Intl. Ed. Engl.* 5(1966):1; H.P. Mayer, S. Rapsomanikis, *Appl. Organomet. Chem.* 6(1992):173; J.M. Buriak, *Chem. Rev.* 102(2002):1271], since methylated germanium is found in the natural environment.

[244] Methane impinging on Pt(111) causes methyl to adsorb at 120 K [C. Papp *et al., J. Phys. Chem. C* 111(2007):2177-2184]. On Pt(111) surface, the dissociative chemisorption of methane to CH_3 and H is downhill by 6.5 kcal/mole. Breaking the second C-H bond to form CH_2 adsorbed on the surface is 1.2 kcal/mole uphill; forming CH adsorbed is then downhill by 21.7 kcal/mole [Jeremy Kua, William A. Goddard III, "Chemisorption of Organics on Platinum. 2. Chemisorption of C2Hx and CHx on Pt(111)," *J. Phys. Chem. B* 102(1998):9492-9500; http://www.wag.caltech.edu/home/ch120/References/InterstitialElectrons3.pdf].

[245] Methane adsorbs dissociatively to the Rh(111) surface [M. Mavrikakis *et al., J. Chem Phys.* 117(2002):6737-44].

[246] Methane dissociatively adsorbs on Ir(111) surface [e.g., G. Henkelman, H. Jónsson, *Phys. Rev. Lett.* 86(2001):664-7]. It may be possible to start with ethylene which deposits on Ir surface as ethylidyne (C-CH_3) at 300 K. Abstraction of the CH_3 by GeRad may be possible because the C-C bond is apparently weak – the hydrocarbon decomposes at 500 K leaving only a C layer on the surface [K.L. Kostov, T.S. Marinova, *Reaction Kinetics Catalysis Lett.* 32(Jan 1986):141-146].

conveyor belt (Loop 5) whose carriers protrude a *GeRad tool. The CH_3 group hops from the Loop 1 carrier onto the *GeRad tool because this transfer is favored energetically, making a CH_3-GeRad intermediate on the Loop 5 carriers. The empty Ge-, Pt-, Rh- or Ir-coated carriers are returned to the starting point, re-entering the methane chamber ready for the next cycle without further processing.

Loop 2: Hydrogen abstraction from first methyl

Each carrier that is attached to the Loop 2 conveyor belt protrudes an HAbst* tool and operates entirely in vacuum. The Loop 2 carriers are brought into firm contact with a CH_3 bound to a CH_3-GeRad intermediate in Loop 5, abstracting one of the H atoms from the bound CH_3 and leaving a *CH_2-GeRad intermediate bound to the carrier of System 5. The spent (hydrogenated) HAbstH intermediates on the carriers of Loop 2 are brought into contact with a recharge subsystem (Loop 6) whereupon the excess H is removed and disposed of, after which the reclaimed and reactivated HAbst* tools resume the next cycle of Loop 2 operation without further processing.

Loop 3: Second methyl feedstock pickup

This conveyor belt system is exactly the same as Loop 1, and runs parallel to and in synchrony with it. Once the second -CH_3 group has been transferred (see Loop 5), the empty carriers are returned to the starting point, ready for the next cycle without further processing.

Loop 4: Hydroxyl feedstock pickup

The Loop 4 conveyor belt system is almost the same as Loop 1, except that the feedstock attached to the carriers is an -OH group rather than a -CH_3 group (right). The bulk input is a chamber containing water (H_2O), which, like the methane, has had one H dissociatively removed, yielding in this case a migrating H and an –OH group bound to the carrier.[247] Once the -OH group has been transferred, the empty carriers are returned to the starting point ready for the next cycle without further processing.

Loop 5: Build ethanol from two methyl groups and one hydroxyl group, then release

Note that this is the previously-mentioned vacuum-residing conveyor belt system whose carriers initially protrude a *GeRad tool. A molecule of ethanol is assembled on each carrier as the Loop 5 belt encounters, in sequence, carriers from Loop 1, Loop 2, Loop 3, and Loop 4.

Encounter with Loop 1: When brought into contact with a Loop 1 carrier, a CH_3 group transfers from that carrier onto the Loop 5 *GeRad tool, making a CH_3-GeRad intermediate on

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[247] A Cu(110) surface catalyzes water dissociation into H and OH under ambient conditions, and autocatalytic water dissociation is believed to be a general phenomenon on metal surfaces [Klas Andersson *et al., J. Am. Chem. Soc.* 130(2008):2793-2797]. An $(IrO_2)_n$ (n=1-5) cluster when exposed to one H_2O molecule with 15.1 kcal/mole energy added can be driven uphill to form $IrO_2.H_2O$, which then exoergically transforms to $IrO(OH)_2$ which is downhill by -17.9 kcal/mole [Xin Zhou, Jingxiu Yang, Can Li, *J. Phys. Chem. A* 116(2012):9985-9995]. Oxygen-assisted water dissociation reaction (OWD: $H_2O + O \rightarrow 2OH$), based on a tunnel mechanism of H transfer, has activation energies much lower than those of water dissociation on clean metal (Pt, Cu, Ni, Rh) surfaces [Ernst D. German, Moshe Sheintuch, *J. Phys. Chem. C* 115(2011):10063–10072]. OH groups rest stably on the Rh(111) surface with the H pointing away from the surface [M. Mavrikakis *et al., J. Chem Phys.* 117(2002):6737-6744].

the Loop 5 carrier. The empty Loop 1 carrier is returned to the starting point, ready for the next cycle without further processing.

Encounter with Loop 2: The CH_3-GeRad intermediate on the Loop 5 carrier is next brought into contact with an HAbst* tool on a Loop 2 carrier, which abstracts one of the H atoms from the bound CH_3 group, leaving a *CH_2-GeRad intermediate on the Loop 5 carrier.

Encounter with Loop 3: The *CH_2-GeRad intermediate on the Loop 5 carrier is next brought into contact with a Loop 3 carrier, whereupon a snap-on reaction occurs because there is an energetic preference for the CH_3 group on the Loop 3 carrier to be bonded to the C atom of the *CH_2-GeRad intermediate on the Loop 5 carrier rather than to the Ge/metal atom holding the CH_3 group onto the Loop 3 carrier. This leaves a CH_3CH_2-GeRad intermediate on the Loop 5 carrier. The empty Loop 3 carrier is returned to the starting point, ready for the next cycle without further processing.

Encounter with Loop 4: The CH_3CH_2–GeRad intermediate on the Loop 5 carrier is then pressed into contact with the OH-metal intermediate on the Loop 4 carrier inside an ethanol collection chamber. The hydroxyl group should have some energetic preference to be bonded to the Ge-bonded C atom of the CH_3CH_2–GeRad intermediate rather than to the metal atom holding the OH- group on the Loop 4 carrier,[248] so a metal-Ge bond may form as the -OH group inserts into the Ge-C bond on the CH_3CH_2–GeRad intermediate on the Loop 5 carrier, creating a CH_3-CH_2-OH molecule of ethanol that is released into the ethanol collection chamber. The Loop 4 and Loop 5 carriers are then pulled apart, breaking the temporary bond between them. This leaves an empty carrier on Loop 4 and a *GeRad tool on Loop 5, both of which are returned to the starting point in their respective loops, ready for the next cycle without further processing.

Loop 6: HAbstH tool recharge

The recharge subsystem required for Loop 2 may involve two identical tracks and two pairs of specially configured *GeRad tools. In each pair, the first *GeRad tool alternatively bonds and unbonds to the distal C atom of the ethynyl C_2 group on an HAbstH intermediary on Loop 2, a process that can cycle endlessly. The second *GeRad tool of the pair approaches the excess H atom on the HAbstH intermediary and abstracts it, making an H-GeRad intermediary on a Loop 6 carrier and restoring the active HAbst* tool on a Loop 2 carrier. The second pair of *GeRad tools performs the same operations on a second HAbstH intermediary on Loop 2. The two H-GeRad intermediaries are then brought into forcible contact while parked inside a separate hydrogen capture chamber, creating a Ge-Ge bond between the two tools and releasing an H_2 gas molecule into the chamber which can be safely exhausted from the system. The two Loop 6 tools are then pulled apart, removed from the H_2 capture chamber, and returned to the starting point ready for the next recharge cycle without further processing. Alternatively, the H-GeRad intermediaries could be re-routed to a reaction sequence for building some molecule other than ethanol in which a hydrogen donation was required.

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[248] Since metal-oxygen and metal-germanium bond energy data were not readily available, we assumed for the purposes of this calculation that the OH group on Loop 4 is bonded to a GeRad. In this case, the reaction would be plausibly estimated to be exoergic because we are breaking one C-Ge bond (2.47 eV) and one (Loop 4) Ge-O bond (2.81 eV), total +5.28 eV, while creating one (Loop 4-Loop 5) Ge-Ge bond (1.95 eV) and one C-O bond (3.71 eV), total -5.66 eV, therefore the reaction appears energetically favored by **-0.38 eV**. Sources: http://www.wiredchemist.com/chemistry/data/bond_energies_lengths.html and Jan Felix Binder, *Electronic and Structural Properties of the Ge/GeO2 Interface through Hybrid Functionals*, PhD Thesis, École Polytechnique Fédérale de Lausanne, 2012, p.30 and Fig. 3.9/p.37 (for estimate of Ge-O bond strength); http://infoscience.epfl.ch/record/176949/files/EPFL_TH5363.pdf.

A similar process may be applied to build any congener molecule whose structure and elemental composition is reported back from the Assay Unit. Many reaction sequences can be determined in advance and can be hard-coded. Production lines could use switchyards (right) to route carriers from one Loop to another Loop on the fly, essentially creating a reprogrammable production network. But in order to be able to handle any unknown congener that is composed only of C, H, and O atoms and one or more of the five basic types of organic building blocks mentioned earlier, we will also need automated mechanosynthetic sequence generation to minimize or eliminate the human labor requirement. This seems do-able, given the relative structural simplicity of the molecular targets and the relatively small number of primary tools and core reactions that we need to use (i.e., we have a relatively small mechanosynthetic alphabet). In sum: If we know the chemical formula and structure of an organic congener molecule, we can just build that molecule mechanosynthetically, functional group by functional group.

Adding a few more elements such as sulfur, nitrogen, and phosphorus would raise the complexity level and increase the tooltype count – but probably tolerably so, while greatly extending the scope of manufacturable molecules to the full range of biologicals including amino acids, peptides, nucleic acids, proteins and DNA. However, most of these extensions are not likely to be required for the replication of the congeners that are present in whiskey and other fine spirits.

5.3.2 Quantitative Production of Ethanol and Congeners

The 6-loop schema described in Section 5.3.1 appears to fabricate individual molecules of ethanol fairly efficiently using only methane and water as the bulk inputs and generating hydrogen gas as the only waste product. Assuming that each conveyor belt/roller mechanism requires ~1 million carbon atoms,[249] then six of these, along with infrastructure support including ~1 million atoms for the sorting rotor "getters" plus 5 million atoms for each of 11 chamber/getter boxes with tunnels and equipment housings, gets us up to 62 million carbon atoms. Adding in motors, controllers, and other hardware, each mechanosynthetic **Fab Module** incorporates perhaps $n_{C\text{-}FM}$ ~ 100 million carbon atoms of total mass $M_{FM} = m_C\ n_{C\text{-}FM} = 2 \times 10^{-18}$ kg (taking $m_C = 2 \times 10^{-26}$ kg/C atom). Each Fab Module may occupy a $(100\ nm)^3$ cube having a volume $V_{FM} \sim 0.001$ $micron^3$, with about half of this volume occupied by machinery and the rest in vacuum (empty space).

While mechanosynthetic production lines are thought to be operable at MHz frequencies,[250] to keep power consumption low we assume here that each Fab Module will be operated at a frequency of only $\nu_{FM} = 0.1$ MHz, producing $r_{congener} = 10^5$ molecules/sec of congener or ethanol

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[249] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Section 13.3.5.

[250] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Table 14.4.

molecules. This represents a production rate of $R_{FM} = r_{congener}\ MW_{congener} / N_A = 7.6 \times 10^{-21}$ kg/sec of congener per Fab Module, taking molecular weight as $MW_{congener} \sim MW_{ethanol} = 0.046$ kg/mole (for ethanol, our exemplar manufactured molecule; Section 5.3.1), with Avogadro's number $N_A = 6.023 \times 10^{23}$ molecules/mole. Similar production rates should be achievable for congener molecules of reasonable size (Appendix B), perhaps averaging ~0.090 kg/mole, simply by adding a few more fabrication loops to Fab Module production lines.

For scaling purposes, we'll assume that the Fab Module Block of the Synthesis Unit must produce near-absolute purity ethanol at a production rate of $R_{FMB} = N_{FM}\ R_{FM} = 0.071$ gm/sec.[251] This requires $N_{FM} = 9{,}342$ trillion Fab Modules having a volume of $V_{FMB} = N_{FM}\ V_{FM} = 9.3\ cm^3$ and a mass of $M_{FMB} = N_{FM}\ M_{FM} = 18.7$ gm. (Note that $N_{FM} \sim 100$ trillion Fab Modules if only congeners, and no ethanol, are mechanosynthetically manufactured; Section 5.4.3 and Table 11.)

To estimate the power consumption for performing mechanosynthesis, we note that the standard enthalpy of formation for liquid ethanol is 470 zJ/molecule.[252] With an efficient design, we should be able to closely approach this figure, but we'll conservatively assume that we can only achieve 50% energy efficiency, giving a net energy dissipation of $E_{diss} = 940$ zJ/molecule.[253] Adopting this estimate, the Fab Module Block would produce ethanol at an energy cost of $E_{ethanol} = E_{diss}\ N_A / MW_{ethanol} = 12.3$ MJ/kg and the Fab Module Block would have a power draw of $P_{FMB} = R_{FMB}\ E_{diss}\ N_A / MW_{ethanol} =$ **874 W** when operated at the $R_{FMB} = 0.071$ gm/sec ethanol production rate. Power density for the Fab Module Block would then be $P_{d\text{-}FMB} = P_{FMB} / V_{FMB} \sim 10^8\ W/m^3$, well below the $\sim 10^{10}\ W/m^3$ power density estimated for molecular transport[254] and significantly lower than the $\sim 10^{11}\ W/m^3$ power density estimated for the Lab Module Block of the Assay Unit (Section 5.2.7).

While mechanosynthetic operations have been successfully demonstrated at room temperature,[255] our present assumption is that high-reliability mechanosynthetic operations should take place in vacuum and at cryogenic temperatures. Liquid nitrogen (LN2) temperature (77 K) should suffice to ensure high-reliability mechanosynthesis. As noted in Section 5.2.7, the cost of LN2 cryogen if consumed as coolant is $c_{cryoLN2} = \$1.2 \times 10^{-6}$/watt-sec, hence the cost for manufacturing ethanol or congener mechanosynthetically is the sum of the electricity cost of mechanosynthetic energy dissipation plus the cooling cost, or $C_{ethanol} = C_{congener} = (c_{electricity} + c_{cryoLN2})\ E_{ethanol} =$ **$15/kg**,

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[251] This rate is consistent with a ~1 bottle/hour fine spirits production rate.

[252] http://en.wikipedia.org/wiki/Standard_enthalpy_change_of_formation_(data_table).

[253] Even if we pessimistically assumed that all mechanosynthetic bond-breaking and bond-making events were completely dissipative, the energy cost would only be about 5-fold higher, around 5350 zJ/molecule of ethanol. This includes breaking a C-H bond (671 zJ) and making a C-Ge bond (391 zJ) at Loop 1, breaking a C-H bond (671 zJ) at Loop 2, breaking a C-H bond (671 zJ) and making a C-C bond (556 zJ) at Loop 3, breaking an O-H bond (753 zJ) and making a C-O bond (575 zJ) at Loop 4, breaking a C-Ge bond (391 zJ) at Loop 5, and breaking a C-H bond (671 zJ) at Loop 6.

[254] http://www.nanomedicine.com/NMI/6.5.6.htm#A.

[255] For example: Y. Sugimoto, P. Pou, O. Custance, P. Jelinek, M. Abe, R. Perez, S. Morita, "Complex patterning by vertical interchange atom manipulation using atomic force microscopy," *Science* 322(2008):413-417; http://www.sciencemag.org/cgi/content/full/322/5900/413.

taking $c_{electricity}$ = 1.94 x 10^{-8} $/J (=$0.07/kWh, the industrial electricity cost), $c_{cryoLN2}$ = $1.2 x 10^{-6}/watt-sec (Section 5.2.7), and $E_{ethanol}$ = $E_{congener}$ = 12.3 MJ/kg.

Setting ethanol aside, all congeners comprise 0.75% by weight of whiskey (Table 1). A standard 750 ml bottle of 43% ABV whiskey at the standard ABV temperature of 20 °C has a density of 940.03 gm/liter (Section 2.1), implying a liquid mass of 705 gm with a total congener mass of $M_{bottleCongener}$ = 5.3 gm/bottle, an ethanol mass of $M_{bottleEthanol}$ = 254.5 gm/bottle, and a water mass of $M_{bottleWater}$ = 445.2 gm/bottle. The energy cost to manufacture all the congeners in a bottle of whiskey is therefore only $C_{bottleCongener}$ = $C_{congener}$ $M_{bottleCongener}$ = **$0.08/bottle for congeners**. This may be at least 50-100 times cheaper than traditional methods of manufacture.

In terms of the production costs for replicant whiskey, ethanol is the only component with significant impact simply because there is so much of it in a bottle of product, about 36.10% by weight (Table 1). Taking $C_{congener}$ = $15/kg for ethanol, the energy cost to manufacture all the ethanol in a bottle of whiskey is $C_{bottleEthanol}$ = $C_{congener}$ $M_{bottleEthanol}$ = **$3.82/bottle for ethanol**.

Due to the high sensitivity of production cost to the cost of mechanosynthetic ethanol manufacture, the following Section 5.3.3 explores an alternative less-expensive source of ultrapure ethanol for the manufacture of replicant fine spirits.

5.3.3 Receptor-Based Purification of Ethanol and Water

As previously suggested, ethanol could be extracted at ultra-high purity from almost any low-quality semi-solid or liquid source material in which free ethanol is a chemical component – e.g., cheap alcoholic beverages of any kind,[256] fermenting mashes or fruit juices, cheap technical-grade ethanol produced from fermented or hydrocarbon sources, cheap denatured alcohols,[257] gasohol,[258] mouthwashes,[259] and literally hundreds of other consumer products[260] – using sorting rotors (see below) that are equipped with "receptors" or "binding sites" for ethyl alcohol molecules. These sorting rotors would extract the ethanol molecules one by one in pure fraction from the source material and pass them along to the mixing chamber of the Synthesizer.

Similarly, water of extreme purity could be sourced from the tap, local wells, or springs, or from other sources, even including highly impure or polluted sources if necessary. As with ethanol, sorting rotors with binding sites for water molecules could extract the water molecules from these impure sources in pure fraction and pass them along to the mixing chamber of the Synthesizer.

How does this work? A sorting rotor-based molecular filter consists of a barrier or wall that is penetrated by one or more nanomechanical devices that act as molecule-specific pumps, analogous to the transporter pumps found on the surfaces of living biological cells. One simple such pump is a nanomechanical device called a "molecular sorting rotor" that is capable of selectively binding molecules from solution and then transporting these bound molecules against

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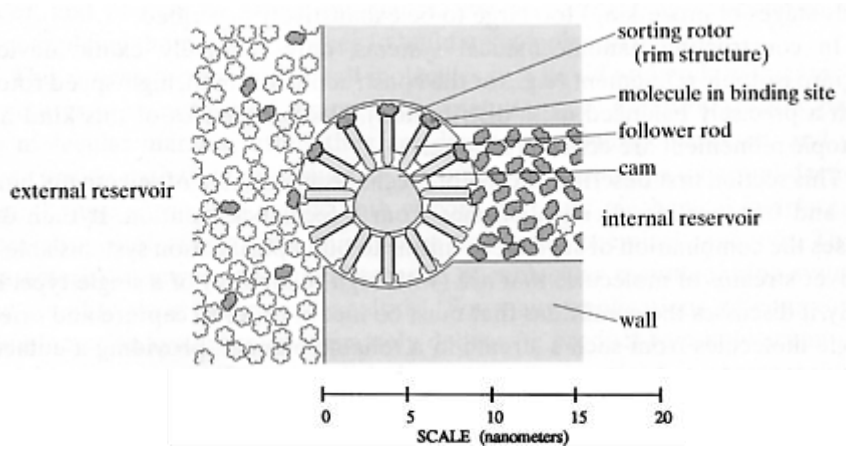
[256] http://en.wikipedia.org/wiki/Alcoholic_beverage.
[257] http://en.wikipedia.org/wiki/Denatured_alcohol.
[258] http://en.wikipedia.org/wiki/Ethanol_fuel.
[259] http://en.wikipedia.org/wiki/Mouthwash#Alcohol.
[260] http://scorecard.goodguide.com/chemical-profiles/consumer-products.tcl?edf_substance_id=64-17-5.

concentration gradients (**Figure 20**), moving only the molecules of a specific type (such as ethanol or water molecules) from one side of the wall to the other. Each pump mechanically transports individual molecules, one by one, through the barrier. The molecular filter is simply a sheet with large numbers of surface-embedded pumps.

Figure 20. Exemplar molecular sorting rotor design, with target molecules (dark) passing from left to right as the rotor turns in the clockwise direction.



The archetypal sorting rotor illustrated above is a disk about 10 nm in diameter and about 3 nm thick having 12 binding site "pockets" along the rim that are exposed alternately to the source fluid at left and the receiving chamber at right by the clockwise axial rotation of the disk. (Other designs may have more, or fewer, pockets.) Each pocket selectively binds a specific molecule when exposed to the source fluid at left. The rotor turns clockwise, moving the pocket containing the bound molecule through the wall from left to right. Once the binding site has rotated far enough to expose it to the receiving chamber at right, the bound molecules are forcibly ejected by rods thrust outward by the cam surface. Other means, whether mechanical or electronic, could also be used to reversibly alter the binding site affinity for the transported molecule during the transport process.

Molecular sorting rotors can be designed from about 100,000 atoms (including rotor housing and pro rata share of the mechanical drive system), measuring roughly 7 nm (wide) x 14 nm (tall) x 14 nm (deep) in size with a mass of about $m_{rotor} = 2 \times 10^{-21}$ kg if composed mostly of diamondoid structure. The classic sorting rotor turns at about 86,000 rev/sec which exposes 1 million binding sites per second to the source fluid,[261] giving a conservative rim speed of 2.7 mm/sec, sorting and transporting small molecules like ethanol at a rate of 10^6 molecules/sec assuming laminar flow as in the case of an aqueous source fluid and assuming high ethanol concentrations $\geq$1 gm/L. Given mid-range concentrations of ethanol in various source materials, the binding sites may not be fully occupied at that rim speed so that speed might have to be reduced. Binding site occupancy

[261] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Section 13.2.1(a).

is critically determined by the as-yet undetermined dissociation constant for the interaction between target molecule, binding site, and solvent, but a reasonable estimate is that sortation speed may fall to 10^5 molecules/sec at moderate ethanol concentrations of ~100 mg/L (~10^{-3} molecules/nm^3) and to 10^2 molecules/sec at a relatively low ~0.1 mg/L ethanol concentration (~10^{-6} molecules/nm^3 or ~100 ppb). We will conservatively assume that this lower 10^2 molecules/sec sortation rate will apply to all sorting rotor-based filtration scenarios discussed elsewhere in this document.

Molecular pumps generally operate in a four-phase sequence: (1) recognition (and binding) by the transporter of the target molecule, with selective extraction of the target from a collection of dissimilar molecules presented to the pump in the source fluid; (2) translocation of the target molecule through the wall, inside the transporter mechanism; (3) release of the molecule by the transporter mechanism; and (4) return of the transporter to its original condition, so that it is ready to accept another target molecule. It should be noted that molecular transporters that rely on protein conformational changes are ubiquitous in biological systems.

The minimum energy required to pump uncharged molecules is the change in free energy ΔG (joules) in transporting the species from one environment having concentration c_1 to a second environment having concentration c_2, given by:[262]

$$\Delta G = k_B T \ln(c_2/c_1) \qquad (1)$$

where k_B = 0.01381 zJ/K (Boltzmann constant) and T = temperature in kelvins. So for example, transport of one uncharged molecule from a low concentration to a high concentration environment across a $c_2/c_1 = 1000$ gradient (typical in biology) costs ΔG ~ 30 zJ/molecule at 300 K (~room temperature). A more aggressive $c_2/c_1 = 10^6$ concentration gradient costs ΔG ~ 60 zJ/molecule, and $c_2/c_1 = 10^9$ concentration gradient would cost ΔG ~ 90 zJ/molecule. (For computational convenience we will ignore the entropic cost to separate, say, ethanol from water, readily estimated as about 10-20 zJ/molecule at 300 K for 5%-50% ethanol solutions but whose more exact calculation[263] is beyond the scope of this paper and does not materially affect the conclusions.)

Plausibly assuming the use of low-friction molecular bearings inside the rotor mechanism, the primary source of energy loss is speed-dependent viscous drag of the rotor surface as it moves through the fluid environment on either side of the barrier wall. For a source material fluid environment having the approximate viscosity of water (~10^{-3} kg/m-sec at 20 ºC) on both sides of the wall, the sorting rotor described as above has an estimated continuous drag power loss of 10^{-16} W while transporting 10^6 molecules/sec,[264] or ~0.1 zJ/molecule transported. At lower speeds,

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[262] Robert A. Freitas Jr., *Nanomedicine, Vol. I: Basic Capabilities*, Landes Bioscience, 1999, Section 3.4.3, Eqn. 3.18, p. 80.

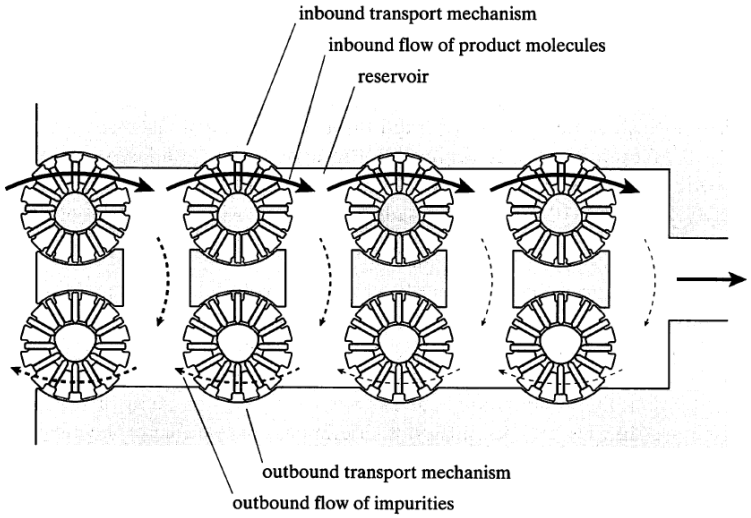
[263] e.g., T. Sato, A. Chiba, R. Nozaki, "Dynamical aspects of mixing schemes in ethanol-water mixtures in terms of the excess partial molar activation free energy, enthalpy, and entropy of the dielectric relaxation process," J. Chem. Phys. 110(1 Feb 1999):2508-2521.

[264] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Section 13.2.1(e).

drag power scales as the square of velocity, so rotors turning 10,000 times slower would dissipate negligible energy in overcoming drag forces.

Staged cascades can be employed to achieve progressively higher purification of input streams (**Figure 22**). Note that a 1000-fold increase in purity at each stage can produce a trillion-fold increase in purity after just 4 stages.

Figure 22. Schematic diagram of a staged cascade process based on sorting rotors, with progressively purer fractions of the receptor-targeted ethanol molecule moving to the right via the topmost rotors, and stray impurity molecules counterflowing to the left (via receptors for those molecules) in the bottommost rotors.[265]



The strength of the binding of the target molecule to the artificial receptor site can be designed to be sufficient to achieve high occupancy of all pockets (e.g., 99%) at the relatively low speeds of rotor rotation assumed here. The mechanical energy consumed to force the target molecule out of its binding site into the receiving chamber is delivered from the cam to the rods, but this energy can be largely returned with minimal losses to the cam on the source side by the compression of the rods during the binding of the target molecule to the receptor, a process that generates mechanical energy. The artificial receptors are best designed for high affinity binding in the presence of a dominant background of quite different molecules. Analogies with antibodies suggest that a rotor with binding pockets of this type could deliver a product stream with impurity fractions up to 10^{-4} to 10^{-9} (i.e., 99.99% to 99.9999999% purity or better) depending on affinities, specificities, and the concentrations of the effectively competing ligands.[266]

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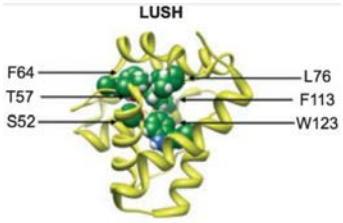
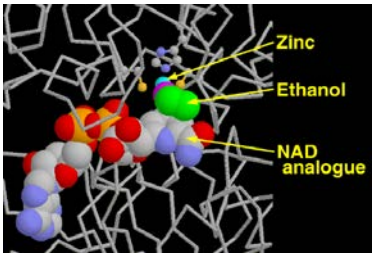
[265] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Fig. 13.4.

[266] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Section 13.2.2(b).



A computational modeling and simulation effort will be required to create highly-selective binding site designs for ethanol. A number of receptors for ethanol are already known in the biological literature. Several proteins are known whose function is altered by ethanol, including the Drosophila odorant-binding protein LUSH (right), human PKCα and human Glycine Receptor α1. For instance, coordination of ethanol in LUSH includes hydrogen bonding of S52 and T57 with the alcohol hydroxyl group and hydrophobic interactions of F64, L76, F113, and W123 with the alkyl chain.[267] Ethanol also binds directly to the receptors for acetylcholine, serotonin, and GABA, and to the NMDA receptors for glutamate.[268] Ethanol also binds to the 9 amino-acid hydrophobic core of the alcohol dehydrogenase enzyme (left), although the site binds other alcohols besides ethanol.[269] One researcher reports[270] developing ultrasensitive ethanol receptors (USERs) by manipulating the Loop 2 (L2) structure of glycine receptors (GlyRs) and γ-amino butyric acid subtype-A receptors (GABAARs) which can significantly increase ethanol sensitivity of mutant receptors and can create ethanol receptors that respond to extremely low ethanol concentrations (≤ 1 mM or ≤46 mg/L) that would be too low to affect native receptors.



It might also be useful to have binding sites for methane (CH_4),[271] to assist in its extraction in very pure form when starting from a conventional commercial natural gas feedstock.

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[267] R.J. Howard *et al.*, "Alcohol-binding sites in distinct brain proteins: the quest for atomic level resolution," *Alcohol Clin. Exp. Res.* 35(Sep 2011):1561-73.

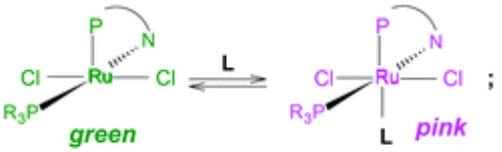
[268] S. Murail *et al.*, "Microsecond Simulations Indicate that Ethanol Binds between Subunits and Could Stabilize an Open-State Model of a Glycine Receptor," *Biophys. J.* 100(Apr 2011):1642-50.

[269] http://www.chembio.uoguelph.ca/educmat/chm455/adh.ppt.

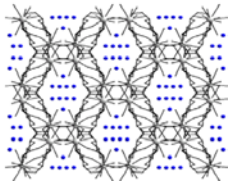
[270] Karan Muchhala, *Developing Ultrasensitive Ethanol Receptors (USERS) As Novel Tools for Alcohol Research: Optimizing Loop 2 Mutations in alpha1 GlyRs*, PhD thesis, Univ. Southern California, 2013; http://gradworks.umi.com/15/51/1551520.html.

[271] P. Nordlund *et al.*, "The active site structure of methane monooxygenase is closely related to the binuclear iron center of ribonucleotide reductase," *FEBS Lett.* 307(3 Aug 1992):257-262; M.K. Rana *et al.*, "Methane Storage in Metal-Substituted Metal–Organic Frameworks: Thermodynamics, Usable Capacity, and the Impact of Enhanced Binding Sites," *J. Phys. Chem. C* 118(2014):2929-2942.

A few binding sites are also known for water. For example, helical transmembrane proteins acquire "buried water" in internal voids,[272] a lithium-organic framework reversibly binds water,[273] and the five-coordinate, square-pyramidal *trans*-$RuCl_2(P–N)(PPh_3)$ complex reversibly binds water, methanol and ethanol (above, right).[274] Various materials also form 3D networks that can reversibly bind crystallization water molecules (left).[275]



R = phenyl, *p*-tolyl ; L = H_2O, MeOH, EtOH



With good receptor designs in hand, we could create macroscale molecular filters for ethanol, water, and methane. In the basic molecular filter design, the sorting rotors are operated as pumps requiring external power input to transport the target molecule from a relatively low-concentration environment in the source fluid to a high-concentration collection system. In this scheme, the molecular filter is comprised entirely of sorting rotors tightly packed side by side to form a thin sheet of adjacent mechanical devices. This solid sheet of rotors (ensconced in their mechanically stiff housings) must be of sufficient thickness to withstand pressure differentials perhaps on the order of ~1 atm without tearing. We might envision the sheet of rotors rolled into a seamless tube through which extracted ethanol molecules may flow for collection downstream. The minimum wall thickness of a cylinder wall of radius R_{cyl} = 1 mm made of diamondoid material with a conservative failure strength of $\sigma_w = 10^{10}$ N/m^2 (~0.2 times the failure strength of diamond) that can withstand a pressure differential of ΔP = 1 atm without bursting is $t_{wall} \geq R_{cyl} \Delta P / \sigma_w$ = 10 nm, roughly equivalent to the 14 nm thickness of the exemplar sorting rotor housing described earlier. These tubes will be short enough in length to avoid significant energy losses due to Poiseuille fluid flow drag.

An exemplar sorting rotor design would include a channel ~5 nm deep that can be employed to carry off the chosen fluid molecules once they have been selectively removed from the source fluid in which the molecular filter resides. The most efficient filter system architecture has yet to be determined, but might consist of a multiscale branching collection system roughly analogous to the structure of the human lung – an architecture that nature has already optimized for efficient gas exchange and transport – but using continuous unidirectional flow rather than the pulsatile flow commonly employed in biological lungs. The lowest-level branches might possibly be some tens of nanometers in diameter. Filtered fluids would pass to progressively larger branches,

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[272] Robert Renthal, "Buried water molecules in helical transmembrane proteins," *Protein Sci.* 17(Feb 2008):293-8.

[273] Racha El Osta, Michel Frigoli, Jérôme Marrot, Nathalie Guillou, Hubert Chevreau, Richard I. Walton, Franck Millange, "A lithium–organic framework with coordinatively unsaturated metal sites that reversibly binds water," *Chem. Commun.* 48(2012):10639-10641.

[274] Erin S. F. Ma, Brian O. Patrick, Brian R. James, "Reversible binding of water, methanol, and ethanol to a five-coordinate ruthenium(II) complex," *Dalton Trans.* 42(2013):4291-98.

[275] Y. Zheng, D. Kustaryono, N. Kerbellec, O. Guillou, Y. Gérault, F. Le Dret, C. Daiguebonne, "The lanthanide-containing cyclohexane-tri-carboxylate coordination polymers re-investigated," *Inorganica Chimica Acta* 362(2009):2123-2126.

finally reaching the uppermost branches measuring on the order of millimeters in diameter, whereupon the ethanol collects in a drainage tube that empties into a large macroscale collection reservoir for further processing.

Given that we'd like to produce 99.9999997% pure ethanol (Table 4) for our replicant whiskey, a purity level in the ~1 ppb range is required. If we use sorting rotors to extract the ethanol from a concentrated source (e.g., a bottle of cheap spirits, wine, denatured alcohol, or mouthwash, at ≥100 gm/L), then the impurities must be held to 1 part in 10^9; if we extract the ethanol from a more dilute source down to ≤1 mg/L (ppm levels), then we must increase the concentration of ethanol molecules relative to all the competing non-ethanol molecules by a billion-fold to ensure an impurity level of only 10^{-9}. Thus the rotors must either increase the concentration of ethanol molecules by a factor of 10^9 or decrease the impurities to 10^{-9}, which we see from Eqn. (1) will cost $\Delta G_{ethanol}$ ~ 90 zJ/molecule. Conservatively assuming that a single sorting rotor can increase concentration by only 10^3-fold,[276] then a cascade of $N_{rotorcascade}$ ~ 3 rotors in series (Figure 22) is required to achieve a total increase in concentration of $(10^3)^{Nrotorcascade} = 10^9$-fold as required, with an energy cost of $\Delta G_{ethanolRotor} = \Delta G_{ethanol} / N_{rotorcascade}$ ~ 30 zJ/molecule at each rotor in the series.

Using this figure and the conservatively-assumed sortation rate of $R_{SortEthanol} = 10^2$ molecules/rotor-sec, the energy cost of ultrapure ethanol production by extraction from impure sources using sorting rotors may cost up to $C_{SortEthanol} = \Delta G_{ethanol}\ c_{ElectCost}\ N_A / MW_{ethanol}$ = **$0.023/kg for ethanol** ($0.0059/bottle) taking $c_{ElectCost} = 1.94 \times 10^{-8}$ $/J = $0.07/kWh for electricity, ethanol molecular weight $MW_{ethanol} = 0.046$ kg/mole, and Avogadro's number $N_A = 6.023 \times 10^{23}$ molecules/mole. This appears to be about 100-1000 times cheaper than the mechanosynthetic fabrication of ethanol molecules, one by one, as described earlier in Section 5.3.1 and quantified in Section 5.3.2. (The entropic cost of extracting ethanol from such low-purity sources, which this analysis has ignored, would at most double the ethanol extraction cost per kilogram as estimated above, depending on the starting concentration and other factors.)

Taking the mass sortation rate for ethanol as $M_{SortEthanol} = R_{SortEthanol}\ MW_{ethanol} / N_A = 7.6 \times 10^{-24}$ kg/rotor-sec, then to match the R_{FMB} = **0.071 gm/sec ethanol** production rate of the Fab Module Block (Section 5.3.2) will require a bank of $N_{EthanolRotors} = N_{rotorcascade}\ R_{FMB} / M_{SortEthanol} = 2.8 \times 10^{19}$ sorting rotors having a total mass of $M_{EthanolRotors} = N_{EthanolRotors}\ m_{rotor}$ = **56 gm of sorting rotors**, for $m_{rotor} = 2 \times 10^{-21}$ kg/rotor. Taking the volume as half-filled with machinery having the density of diamond $\rho_{diamond} = 3510$ kg/m^3, the total volume of the rotors comprising the Ethanol Sortation Module is $V_{EthanolRotors} = 2\ M_{EthanolRotors} / \rho_{diamond}$ = **32 cm^3 of sorting rotors**. The rotor bank will consume power and generate waste heat at the rate of $P_{EthanolRotors} = \Delta G_{ethanolRotor}\ N_{EthanolRotors}\ R_{SortEthanol}$ = **84 watts**, a very modest power density of only $P_{D\text{-}EthanolRotors} = P_{EthanolRotors} / V_{EthanolRotors} \sim 3 \times 10^6$ W/m^3.

Roughly similar considerations and results apply to the extraction of water from impure sources. Assuming the same energy cost for water sortation as for ethanol sortation, then $\Delta G_{water} = \Delta G_{ethanol}$ ~ 90 zJ/molecule and $\Delta G_{waterRotor} = \Delta G_{water} / N_{rotorcascade}$ ~ 30 zJ/molecule. Taking the same sortation rate of $R_{SortWater} = R_{SortEthanol} = 10^2$ molecules/rotor-sec, the cost of ultrapure water production by extraction from impure liquid sources using sorting rotors may cost up to $C_{SortWater} = \Delta G_{water}\ c_{ElectCost}\ N_A / MW_{water}$ = **$0.058/kg for water**, taking $c_{ElectCost} = 1.94 \times 10^{-8}$ $/J =

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[276] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, New York, 1992, Section 13.2.2(b), p. 382.

$0.07/kWh for electricity, molecular weight MW_{water} = 0.018 kg/mole for water, and Avogadro's number $N_A = 6.023 \times 10^{23}$ molecules/mole. Taking the mass sortation rate for water as $M_{SortWater} = R_{SortWater}\ MW_{water} / N_A = 3.0 \times 10^{-24}$ kg/rotor-sec, then to achieve an $R_{WaterNanosortation}$ = **0.124 gm/sec water** production rate[277] requires a bank of $N_{WaterRotors} = N_{rotorcascade}\ R_{WaterNanosortation} / M_{SortWater} = 12.4 \times 10^{19}$ sorting rotors having a total mass of $M_{WaterRotors} = N_{WaterRotors}\ m_{rotor}$ = **248 gm of sorting rotors**, for $m_{rotor} = 2 \times 10^{-21}$ kg/rotor. Taking the volume as half-filled with machinery that is the density of diamond $\rho_{diamond}$ = 3510 kg/m^3, the total volume of the rotors comprising a Water Sortation Module would be $V_{WaterRotors} = 2\ M_{WaterRotors} / \rho_{diamond}$ = **141 cm^3 of sorting rotors**. The rotor bank will consume power and generate waste heat at the rate of $P_{WaterRotors} = \Delta G_{waterRotor}\ N_{WaterRotors}\ R_{SortWater}$ = **372 watts**, a very modest power density of only $P_{D\text{-}WaterRotors} = P_{WaterRotors} / V_{WaterRotors} \sim 3 \times 10^6$ W/m^3.

In principle, all of the ~10,000 congeners potentially present in fine spirits could be similarly extracted from cheap impure sources of mixed chemicals, using sorting rotors to separate out and purify the fractions of each pure molecular ingredient, with costs likely 10-100 times cheaper than the mechanosynthetic route of production. This would, however, require us to design effective receptors for each of the ~10,000 target molecules. These receptors wouldn't have to be perfectly selective – a few percent of preference for the desired molecular species compared to all other species present might be enough to achieve desired final purity levels, given a sufficiently lengthy staged cascade of sorting rotors (Figure 22) – though this could also significantly increase system mass and volume. To follow this path, it would be extremely useful, and probably essential for practicality, to entirely automate the design of receptor sites. This alternative processing architecture is worth further investigation but lies beyond the scope of the present document.

5.3.4 Non-Receptor Nanosieve-Based Purification of Water

Water has the smallest molecules of any ingredient in fine spirits – with the possible exception of a few metallic ions and a few gas molecules like O_2, N_2, and CO_2 which should have only modest relevance to whiskey taste. Therefore a simple size-based separation system – e.g., a membrane with holes too small to pass anything but water molecules – appears to be a viable alternative for the inexpensive extraction of ultrapure water (~1 ppb contaminants) from impure sources.[278] Molecular sieves[279] can be produced in bulk and are commonly used to separate water from ethanol, e.g., in the corn ethanol industry.[280] Additional analysis will be required to

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[277] This rate is consistent with a ~1 bottle/hour fine spirits production rate.

[278] Hydrogen-decorated pores in single-atom-thick graphene sheets may be an excellent selective filter for water molecules; see: Alberto Ambrosetti, Pier Luigi Silvestrelli, "Gas Separation in Nanoporous Graphene from First Principle Calculations," *J. Phys. Chem. C* (1 Aug 2014), http://pubs.acs.org/doi/abs/10.1021/jp504914u.

[279] http://en.wikipedia.org/wiki/Molecular_sieve.

[280] http://en.wikipedia.org/wiki/Corn_ethanol#Production_process.

determine if nanosieving or sortation via sorting rotors (Section 5.3.3) is preferable in a particular application.

For the simple nanosieving of small molecules (r_{pore} ~ 0.32 nm), an exemplar $V_{nanosieve}$ = 1 micron^3 sieving device is estimated[281] to have a processing rate of $R_{nanosieve} = 1.5 \times 10^9$ molecules/device-sec, power draw $P_{nanosieve}$ = 400 pW and power density $P_{d\text{-}nanosieve} = 4 \times 10^8$ watts/m^3. This gives a cost for ultrapure water extraction from impure sources of $C_{NanosieveWater} = P_{d\text{-}nanosieve}\ V_{nanosieve}\ c_{ElectCost}\ N_A / (R_{nanosieve}\ MW_{water})$ = **$0.17/kg for nanosieved water**,[282] taking $c_{ElectCost} = 1.94 \times 10^{-8}$ $/J = $0.07/kWh for electricity, molecular weight MW_{water} = 0.018 kg/mole for water, and Avogadro's number $N_A = 6.023 \times 10^{23}$ molecules/mole. Cost per 750 ml whiskey bottle is $C_{bottleWater} = C_{NanosieveWater}\ M_{bottleWater}$ = **$0.08/bottle for nanosieved water**, for $M_{bottleWater}$ = 445.2 gm/bottle.

Taking the mass nanosieving rate for water as $M_{NanosieveWater} = R_{nanosieve}\ MW_{water} / N_A = 4.5 \times 10^{-17}$ kg/nanosieve-sec, then to achieve a simple $R_{NWater} = R_{WaterNanosortation}$ = **0.124 gm/sec** production rate[283] will require a bank of $N_{AllNanosieves} = R_{NWater} / M_{NanosieveWater} = 2.76 \times 10^{12}$ nanosieves having a total volume of $V_{AllNanosieves} = N_{AllNanosieves}\ V_{nanosieve}$ = **2.75 cm^3 of nanosieves**. Assuming the nanosieve volume as half-filled with machinery having the density of diamond $\rho_{diamond}$ = 3510 kg/m^3, the total mass of all nanosieves that might comprise a Water Nanosieving Module would be $M_{AllNanosieve} = V_{AllNanosieves}\ \rho_{diamond} / 2$ = **4.84 gm for all nanosieves**. Total power draw would be $P_{AllNanosieves} = V_{AllNanosieves}\ P_{d\text{-}nanosieve}$ = **1100 watts for all nanosieves**.

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[281] Robert A. Freitas Jr., *Nanomedicine, Vol. I: Basic Capabilities*, Landes Bioscience, 1999, Section 3.3.1, p. 78; http://www.nanomedicine.com/NMI/3.3.1.htm#p15.

[282] This **$0.17/kg** energy cost for nanosieved water (~2.4 kWh/m^3) compares favorably to the **~$0.14/kg** (~2 kWh/m^3) cost of seawater desalination currently reported in well-designed experimental seawater reverse osmosis (SWRO) systems and controlled pilot-scale studies, and also to the **~$0.21-$0.28/kg** (3-4 kWh/m^3) required for current state-of-the-art SWRO plants, which also emit 1.4-1.8 kg CO_2 per cubic meter of produced water. Menachem Elimelech, William A. Phillip, "The Future of Seawater Desalination: Energy, Technology, and the Environment," *Science* 333(5 Aug 2011):712-717.

[283] This rate is consistent with a ~1 bottle/hour fine spirits production rate.

5.4 Description of the Fine Spirits Synthesizer Appliance

What might a practical system to analyze and replicate fine spirits look like?

We propose the quick and inexpensive replication of fine spirits using a commercial appliance called the **Fine Spirits Synthesizer**. The Fine Spirits Synthesizer is a limited-use nanofactory that can only manufacture beverages and nothing else. This Section briefly summarizes the components of a complete appliance which consists of an **Assay System** and a **Synthesis System**, along with some support infrastructure.

The Fine Spirits Synthesizer will be a commercial appliance scaled to a production rate of ~1 bottle (750 ml) of fine spirits per hour. This is equivalent to a production rate of one 30 ml (1 U.S. fluid ounce) "jigger" or "shot" glass[284] every 144 seconds (2.4 min) as might be appropriate for bartender use in pubs, bars, or cocktail lounges. In the event that the molecular recipe for the beverage product is already available either in a pre-existing library stored in the appliance or via an online data repository that lies behind a corporate paywall, or can be provided by the customer to the bartender (perhaps from the customer's iPhone or iPad), then the product manufacturing cost is primarily the cost of synthesis. However, if the objective is to use the appliance to replicate a physical whiskey sample provided by a customer, then the use of the Assay Unit must be included. Compiling a fine spirits molecular recipe *de novo* will add an extra ~1000 sec (~17 min) to the processing time for the initial batch of replicant fine spirits, while imposing very little extra cost or power demand.

A standard 750 ml bottle of 43% ABV whiskey at the standard ABV temperature of 20 °C has a density of 940.03 gm/liter (Section 2.1), hence a liquid mass of 705 gm with a total congener mass (0.75%) of $M_{bottleCongener}$ = 5.3 gm/bottle, an ethanol mass (36.10%) of $M_{bottleEthanol}$ = 254.5 gm/bottle, and a water mass (63.15%) of $M_{bottleWater}$ = 445.2 gm/bottle (Table 1). The ability to manufacture all three quantities together in 1 hour – i.e., production rates of $R_{bottleCongener}$ = 0.0015 gm/sec for congeners, $R_{bottleEthanol}$ = 0.071 gm/sec for ethanol, and $R_{bottleWater}$ = 0.124 gm/sec for water – is the principal performance specification for the Fine Spirits Synthesizer appliance.

We discuss water sourcing in Section 5.4.1, ethanol production in Section 5.4.2, and congener production in Section 5.4.3, then quantitatively describe a complete Fine Spirits Synthesizer appliance in Section 5.4.4.

5.4.1 Water Sourcing

Table 8 lists several methods by which the required $R_{bottleWater}$ = 0.124 gm/sec production rate for water can be acquired for our appliance.

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[284] http://en.wikipedia.org/wiki/Shot_glass.

Table 8. Possible sources of water for the Fine Spirits Synthesizer appliance.			
Water Source	**Cost**		**Power Draw scaled to 1 bottle/hour Production Rate** *(W)*
	($/kg)	*($/bottle)*	
Tap water[285]	$0.0005/kg	$0.0002/bottle	0 W
Semiconductor process water at ppb purity[286]	$0.005/kg	$0.002/bottle	some power required
Tap water + Brita[287] deionizer	$0.05/kg	$0.02/bottle	0 W
Sortation from tap water (Section 5.3.3)	$0.06/kg	$0.03/bottle	372 W
Water distillation appliances[288]	$0.10/kg	$0.04/bottle	322 W
Tap water + ZeroWater[289] deionizer	$0.13/kg	$0.06/bottle	0 W
Nanosieving from tap water (Section 5.3.4)	$0.17/kg	$0.08/bottle	1100 W
Pre-packaged distilled water from Walmart	$0.25/kg	$0.11/bottle	0 W
Pre-packaged distilled glacier water[290]	$0.53/kg	$0.23/bottle	0 W
Sartorius desktop ultrapure units[291]	$4.00/kg	$1.78/bottle	some power required
Sterile-filtered bioreagent water[292]	$21.17/kg	$9.42/bottle	0 W

[285] The average cost of municipal tap water is $2 per 1000 gallons or $0.0005/kg, essentially free; http://water.epa.gov/lawsregs/guidance/sdwa/upload/2009_08_28_sdwa_fs_30ann_dwsrf_web.pdf.

[286] This involves multiple complex chemical processes at industrial scale in large plants. See Table 4, *supra*; http://www.reticlecarbon.com/3_application_water_10.htm.

[287] Brita faucet water filter systems (Models SAFF-100 and FF-100) require a filter change every 100 gallons (https://www.brita.com/using-your-brita/faqs/) and cost $18.99/filter (https://www.brita.com/products/faucet-water-filter-system/faucet-filters-1-pack-white/), hence the operating cost is $0.1899/gallon or $0.05/kg, apparently producing water in the 10-100 ppm TDS range.

[288] A coffeepot-size water distillation appliance able to produce ~1 liter/hr (~1 kg/hr) at a claimed total cost of $0.38/gallon or $0.10/kg are commercially available for $149 (http://www.a1-water-distiller.com/). Heating and boiling 1 kg of room temperature (20 °C) water requires $E_{heatboil} = 2.59 \times 10^6$ J/kg of energy, indicating a power draw of $P_{distill} = E_{heatboil} R_{bottleWater} = 322$ W.

[289] ZeroWater (http://www.zerowater.com/technology-product.aspx) claims a cost of $0.50/gallon ($0.132/kg) to produce water with ≤1 ppm of Total Dissolved Solids (TDS).

[290] High-quality Nestle distilled glacier water (http://www.restockit.com/nestle-distilled-water-1-gal-(nes100604).html) sells for $418.25 for 210 gallons, or $0.526/kg; lesser-quality distilled water is reportedly available at WalMart for around $0.25/kg.

[291] Small desktop units that are capable of producing ultrapure water with Total Organic Content <2 ppb at liter/minute flow rates, using replaceable cartridges, are available, e.g., for $6900 from Sartorius (http://www.sartorius.us/fileadmin/fm-dam/sartorius_media/Lab-Products-and-Services/Lab-Water-Systems/Data-Sheets/Data_arium_pro_SLG2051-e.pdf); operating costs aren't available online, but if $100 worth of cartridges must be replaced daily to maintain this flow rate, then water cost would be **$4/kg**.

For a practical appliance, we are seeking the lowest possible cost and power draw at an acceptable purity level. Direct use of municipal tap water is unacceptable, due to heavy mineral content[293] and chlorination[294] in many locales that will clearly affect flavor in the final product. The lowest-cost alternative that eliminates both these problems with zero power consumption is tap water that has been passed through a deionizing filtration system such as the Brita faucet water filter system (at right), as mentioned in Table 8.

Rather than attempting to produce or provide an ultrapure water source having <1 ppb impurities, we might simply use tap water that has been passed through an unpowered in-line conventional deionizer that has zero power draw and requires only inexpensive periodic filter replacement. This filtration method may suffice to remove almost all significant organoleptic contaminants yielding readily-available source water at about $0.02/bottle with zero power consumption. This eliminates the need for more sophisticated sortation- or nanosieve-based active filtration systems that could draw 372-1100 W of power to meet the specified $R_{bottleWater}$ = 0.124 gm/sec water production rate for the appliance. The resulting filtered tap water will probably be of comparable or higher purity than the water employed in the traditional production of fine spirits[295] and is cheaper and more convenient than requiring the commercial user to purchase pre-packaged distilled water from grocery stores or other even more highly purified research-grade water that may be available commercially. For our exemplar system, we shall henceforth assume that the water supply requires zero power draw and can be provided at a ~$0.02/bottle ($0.05/kg) cost.

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[292] Research-quality sterile-filtered bioreagent water is available from Sigma-Aldrich for $21.17/kg; http://www.sigmaaldrich.com/catalog/product/sigma/w3500?lang=en&region=US.

[293] Mineral content primarily includes ions of Mg, Ca, Na and K at the 0.1-100 ppm level but also smaller quantities of Cu, Fe, Mn, P, and Zn. See: "Mineral content of drinking water, 100 USA cities," http://www.mgwater.com/mgrank.shtml; and see: Pamela Pehrsson, Kristine Patterson, Charles Perry, "The Mineral Content of US Drinking and Municipal Water," USDA, Agricultural Research Service, Human Nutrition Research Center, Nutrient Data Laboratory, Beltsville, MD, http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Articles/NDBC32_WaterMin.pdf.

[294] In the U.S., the Environmental Protection Agency requires treated tap water to have a detectable level of chlorine to help prevent contamination; up to 4 ppm is allowed in drinking water. http://www.waterandhealth.org/chlorine-in-tap-water-is-safe-to-drink/. Chlorinating agents may include monochloramine, gaseous or liquid elemental chlorine, or chlorine dioxide; http://water.epa.gov/drink/contaminants/basicinformation/disinfectants.cfm.

[295] For example, most of the water in Scotland (where "Scotch whisky" is made) is very "soft", allowing it to absorb more from the malted barley than "hard" water will absorb (http://www.royalmilewhiskies.com/viewindex.asp?article_id=wb_making). "Soft" water is water from which most of the calcium, magnesium, and several other metal cations have been removed (http://en.wikipedia.org/wiki/Soft_water). "Peaty water" is sometimes employed to add flavor to whiskey, but any organoleptic components present in such water will have been detected by the Assay Unit and incorporated into the recipe for synthesizing that particular fine spirit, hence no longer need to be provided opportunistically by the water source.

If after further study it is determined that 99.9999998% pure water is truly essential for taste, this can probably be provided at modest additional cost by desktop units in commercial systems or at industrial scale using process plant technologies commonly available for bulk water ultrapurification in the semiconductor fabrication industry.[296]

5.4.2 Ethanol Production

Operation of the Fine Spirit Synthesizer appliance at the 1 bottle/hour pace requires an $R_{bottleEthanol}$ = 0.071 gm/sec production rate for ethanol. **Table 9** lists several sources of cheap bulk ethanol.

Table 9. Cheap sources of pure and adulterated bulk ethanol.

Ethanol Source	Cost *($/kg)*	Ethanol Concentration *(%)*	Net Cost of the Ethanol *($/bottle)*
Homebrew stills and "moonshine"[297]	$0.25/kg	95%	$0.07/bottle
Biofuel startup company[298]	$0.25/kg	99.7%	$0.06/bottle
Corn-derived bulk ethanol[299]	$0.55/kg	95%	$0.15/bottle
Bulk "neutral spirits", beverage (India)[300]	$1.01/kg	96.9%	$0.27/bottle
Ethyl alcohol, food/cosmetics (India)[301]	$1.04/kg	99.5%	$0.27/bottle
Bulk denatured alcohol[302]	$1.08/kg	99.6%	$0.28/bottle

[296] http://www.reticlecarbon.com/3_application_water_10.htm.

[297] Informal sources confirm the possibility of an ethanol production cost as low as $0.25/kg, e.g., http://running_on_alcohol.tripod.com/id1.html.

[298] At least one biofuel startup company has claimed it could produce 99.7% pure ethanol as cheaply as ~$0.25/kg; http://archive.wired.com/cars/energy/news/2008/01/ethanol23.

[299] The Midwest wholesale cash price for corn-derived bulk ethanol was ~$0.55/kg in Aug 2014 (http://www.extension.iastate.edu/agdm/energy/xls/agmrcethanolplantprices.xlsx). Anhydrous 200-proof corn ethanol is blended with about 5% denaturant such as natural gasoline (http://www.ethanolrfa.org/pages/how-ethanol-is-made).

[300] Extra Neutral Ethyl Alcohol, $0.80/liter, 30 Aug 2014; http://www.alibaba.com/product-detail/Neutral-Spirits_133860803.html.

[301] US$0.82/liter; http://www.alibaba.com/product-detail/Ethyl-Alcohol-Ethanol-_144602833.html.

[302] Price quote: http://www.alibaba.com/product-detail/Denatured-Absolute-Alcohol_122279527.html. "Denatured alcohol or methylated spirits is ethanol that has additives to make it poisonous, extremely bad tasting, foul smelling or nauseating, to discourage recreational consumption. Because of the diversity of industrial uses for denatured alcohol, hundreds of additives and denaturing methods have been used. The

Ethanol micro-distillery plant (rural Kenya)[303]	$1.17/kg	95% ?	$0.31/bottle
Industrial ethanol, medicine grade (China)[304]	$1.45/kg	99.9%	$0.37/bottle
Bowman's Vodka[305]	$5.89/kg	40%	$3.75/bottle
Retail "neutral spirits" (e.g., Everclear)[306]	$28.32/kg	95%	$7.59/bottle

Two methods for ethanol production have been described in this document.

First, ultrapure ethanol having ≤1 ppb impurities could be mechanosynthetically manufactured at a cost of $C_{bottleEthanol}$ = **$3.82/bottle** and a power demand of P_{FMB} = **874 W** when operated at the specified $R_{bottleEthanol}$ = 0.071 gm/sec production rate. This could be accomplished using an **18.7 gm** mass of Fab Modules having a volume of **9.3 cm^3** (Section 5.3.2).

Second, the same 99.9999997% pure ethanol could be extracted from a cheap concentrated bulk source shipped internationally in industrial drums (at left) using an array of sorting rotors at an energy cost for sortation of $C_{SortEthanol}$ = $0.023/kg for ethanol. To this must be added the cost of the cheap feedstock ethanol source (Table 9). If we can assume availability at $C_{BulkEthanol}$ = $1.00/kg ($0.79/liter) and if the alcohol source is at least $\alpha_{ethanol}$ = 94% pure ethanol,[307] then the total cost of sortation-based ethanol is $C_{totalEthSort} = C_{SortEthanol} + (C_{BulkEthanol} / \alpha_{ethanol})$ = $1.09/kg,

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main additive has traditionally been 10% methanol, giving rise to the term "methylated spirits". Other typical additives include isopropyl alcohol, acetone, methyl ethyl ketone, methyl isobutyl ketone, and denatonium. In many countries, it is also required that denatured alcohol be dyed blue or purple with an aniline dye"; http://en.wikipedia.org/wiki/Denatured_alcohol.

[303] http://sites.duke.edu/adhoc_httpssitesdukeedubioethanolpro/business-plan-specifics/economic-feasibility-analysis-of-micro-distillery-plant/.

[304] Industrial Ethanol 99.9% - Absolute Alcohol, Anhydrous Ethyl Alcohol, 30 Aug 2014; http://www.alibaba.com/product-detail/Industrial-Ethanol-99-9-Absolute-Alcohol_1961629751.html.

[305] Beverage recommended as the "cheapest way to get drunk", containing the maximum amount of ethanol per retail dollar, 30 Aug 2014: Bowman's Vodka, 40% ABV, $9.69/1.75 liter; http://getdrunknotfat.com/get-drunk-not-broke/.

[306] "Rectified spirit, also known as neutral spirits or rectified alcohol, is highly concentrated ethanol which has been purified by means of repeated distillation, a process that is called rectification. It typically contains 95% alcohol by volume (ABV) (190 US proof). The purity of rectified spirit has a practical limit of 95.6% ABV when produced using conventional distillation processes, because a mixture of ethanol and water becomes an azeotrope at this concentration." (http://en.wikipedia.org/wiki/Rectified_spirit) For example, **Everclear** is a brand name of rectified spirit sold by American spirits company Luxco, bottled at 190-proof (95% ABV), though its sale is prohibited in 14 U.S. states (California, Florida, Hawaii, Iowa, Maine, Maryland, Massachusetts, Michigan, Minnesota, Nevada, New Hampshire, New York, North Carolina, Ohio, and Washington); http://en.wikipedia.org/wiki/Everclear_(alcohol). On 30 Aug 2014, Everclear was available at retail for $16.99 for a 750 ml bottle (~600 gm); http://www.winechateau.com/sku1004371_EVERCLEAR-GRAIN-ALCOHOL-190@-750ML.

[307] For example, in 2013 the European Union agreed to a denaturant mixture of 100 liters ethanol, 3 liters isopropyl alcohol, 3 liters methyl ethyl ketone, and 1 gm denatonium benzoate (aka. Bitrex), yielding a

equivalent to $C_{totalEthSortBTL} = C_{totalEthSort}\ M_{bottleEthanol}$ = **$0.28/bottle**. (Using a $0.25/kg source would reduce sortation-based ethanol cost to $C_{totalEthSortBTL}$ = $0.07/bottle, taking $\alpha_{ethanol}$ = 99.7%.) The power demand is $P_{EthanolRotors}$ = **84 W** when the Ethanol Sortation Module is operated at an R_{FMB} = 0.071 gm/sec production rate. This could be accomplished using a **56 gm** mass of sorting rotors having a volume of **32 cm^3** (Section 5.3.3). The Ethanol Sortation Module can be water-cooled.

Despite the slightly higher mass of machinery, both cost and power draw are reduced 10-fold if we use sortation rather than mechanosynthesis to produce the ethanol. Rather than attempting to mechanosynthetically manufacture ultrapure ethanol having <1 ppb impurities, we will simply purchase bulk denatured alcohol as our ethanol source, then apply cheaper sortation methods to extract the ethanol at the same high purity level. The ~15 gm of denaturants remaining after extracting the ethanol to make 1 bottle of fine spirits can be safely disposed in a sink drain.

5.4.3 Congener Production

Operation of the Fine Spirit Synthesizer appliance at the 1 bottle/hour pace requires an $R_{bottleCongener}$ = 0.0015 gm/sec production rate for congeners. Here we shall assume that only congener molecules will be fabricated "from scratch" in the Fab Module Block (Section 5.3.2) using mechanosynthesis and our methods for atomically precise manufacturing.

We start by assuming a Fab Module production rate of $R_{FM} = r_{congener}\ MW_{congener} / N_A$ = 1.5 x 10^{-20} kg/sec of congener per Fab Module, taking $r_{congener}$ = 10^5 molecules/sec of congener molecules per Fab Module, a mean molecular weight for congener molecules (Appendix B) of $MW_{congener}$ = 0.090 kg/mole, and Avogadro's number N_A = 6.023 x 10^{23} molecules/mole. For scaling purposes, we further assume that the Fab Module Block of the Synthesis Unit must produce high-purity congeners at a production rate of $R_{FMB} = R_{bottleCongener} = N_{FM}\ R_{FM}$ = 0.0015 gm/sec.[308] This requires N_{FM} = 100 trillion Fab Modules having a total collective volume of $V_{FMB} = N_{FM}\ V_{FM}$ = **0.1 cm^3** and a total mass of $M_{FMB} = N_{FM}\ M_{FM}$ = **0.2 gm**. We assume that 100 cm^3 (~100 gm) of physical support structure (feedstock distribution, mixing chamber, etc.) will suffice for the Fab Module Block.

Following the estimation methods previously employed in Section 5.3.2, we assume E_{diss} = 1880 zJ/molecule (i.e., twice the value used for ethanol, which has half the molecular weight), in which case the energy cost of fabricating congener molecules is $E_{congener} = E_{diss}\ N_A / MW_{congener}$ = 12.6 MJ/kg and the Fab Module Block would have a power draw of $P_{FMB} = R_{FMB}\ E_{diss}\ N_A / MW_{congener}$ = **19 W** (a modest ~2 x 10^8 W/m^3 power density) when operated at the R_{FMB} = 0.0015 gm/sec congener production rate.

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mixture that is ~94% pure ethanol by volume; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:049:0055:0061:EN:PDF. In the U.S., denatured alcohol is more often ~91% pure ethanol.

[308] This rate is consistent with a ~1 bottle/hour fine spirits production rate.

A refrigeration system is required to maintain the Fab Module Block at liquid nitrogen (LN2) temperature (77 K) to ensure high-reliability mechanosynthetic operations. One way to carry off the P_{FMB} = 19 W of waste heat generated by the Fab Module Block is to boil liquid nitrogen, using liquid nitrogen from an LN2 generator that can produce $q_{LN2} = P_{FMB}\ MW_{LN2} / \rho_{LN2}\ H_{vapLcryo}$ = 1.18 x 10^{-7} m^3/sec ~ **10 liters/day of LN2**, taking LN2 heat of vaporization $H_{vapLcryo}$ = 5560 J/mole,[309] molecular weight MW_{LN2} = 0.028 kg/mole, and LN2 density ρ_{LN2} = 808 kg/m^3.

The elan2 **Liquid Nitrogen Generator** Autotransfer Station[310] (at right) produces **8 liters/day** (using N_2 extracted from air) and has a 20 liter storage tank. The Generator draws $P_{LN2Generator}$ = **900 W** of power, runs with regular 115 VAC electricity, measures 37 cm x 89 cm x 94 cm (~**11 ft^3** in volume) and weighs **59 kg**. The flexitube carrying the liquid nitrogen could be plugged directly into the Fine Spirits Synthesizer appliance, rather than into the top of the storage dewar as shown at lower right in the image above. Alternatively, a wide variety of cryocoolers[311] or cryorefrigerators[312] could be used to cool the Fab Module Block.

The carbon atoms needed to fabricate congener molecules is conveniently sourced from abundant commercial natural gas (mostly methane; **Table 10**) after purification using sorting rotors.

The cost of mechanosynthetic feedstock is negligible,[313] so the operating cost for manufacturing congeners mechanosynthetically is the sum of the electricity cost of mechanosynthetic energy dissipation plus the cooling cost, or $C_{congener} = (P_{FMB} + P_{LN2Generator})\ c_{electricity}$ = $0.064/hr = **$0.064/bottle** ($12.08/kg), taking $c_{electricity}$ = 1.94 x 10^{-8} $/J (=$0.07/kWh, the industrial cost of electricity). This is very close to the $0.08/bottle for congener synthesis calculated earlier in Section 5.3.2, using a slightly different estimation method for the cooling costs.

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[309] http://en.wikipedia.org/wiki/Nitrogen.

[310] http://www.elan2.com/product_elan2AT.asp.

[311] http://en.wikipedia.org/wiki/Cryocooler.

[312] http://www.cryomech.com/products/cryorefrigerators/.

[313] The cost of methane feedstock to make congeners is about $C_{methane}$ = (0.0015 gm/sec) ($0.60/kg for CH_4) / (1 whiskey bottle/hr) = **$0.0032/bottle**. See: "Natural Gas Prices," U.S. Energy Information Administration, http://www.eia.gov/dnav/ng/NG_PRI_SUM_DCU_NUS_M.htm.

Table 10. Composition of commercial natural gas derived from LNG sources.[314]		
Gas Component	**Formula**	**Concentration** (mole %)
methane	CH_4	95%
ethane*	C_2H_6	2.5-3.2%
propane*	C_3H_8	0.2%
butane*	C_4H_{10}	0.06%
pentane*	C_5H_{12}	0.01-0.02%
hexane + higher HCs*	C_6H_{14} + …	0.01%
hydrogen*	H_2	0.01%
mercaptan odorant*	$C_4H_{10}S$	0.00015%
nitrogen**	N_2	1.0-1.6%
carbon dioxide**	CO_2	0.5-0.7%
oxygen**	O_2	0.02%
water**	H_2O	0.002-0.004%
** non-CH_4 combustible*		*2.8-3.5%*
*** non-CH_4 incombustible*		*1.5-2.3%*

5.4.4 Quantitative Summary of the Appliance

The Fine Spirits Synthesizer appliance – aka. the "Whiskey Machine" – comes in two parts: a desktop appliance (see mock-up image, **Figure 23**) and a Liquid Nitrogen (LN2) Generator positioned on the floor or in a nearby cabinet (see image, Section 5.4.3).

[314] http://www.uniongas.com/about-us/about-natural-gas/Chemical-Composition-of-Natural-Gas (Union Gas), https://www.enbridgegas.com/gas-safety/about-natural-gas/components-natural-gas.aspx (Enbridge), and http://en.wikipedia.org/wiki/Tert-Butylthiol.

Figure 23. The "Whiskey Machine"

As summarized in **Table 11**, the desktop appliance weighs about 6 kg and has a volume of ~10,500 cm^3, approximately the size of a small box measuring ~22 cm (~9 inches) on a side. It has two hose connections (center left in photo), one to a natural gas supply and another to a source of tap water. The tap water hose also provides a means for disposing of a small flow of waste water to a sink drain. A third thermally-insulated cryogenic flexitube (silver hose, at top in photo) allows liquid nitrogen to flow up to the appliance from the LN2 Generator located below. A 1-liter bottle containing inexpensive ethanol feedstock is attached to the left side of the appliance. There is also a power cord for electricity (center right in photo).

The LN2 Generator (see image, Section 5.4.3) sits on the floor below or near the appliance. It provides liquid nitrogen coolant fluid to the appliance. The LN2 Generator weighs 59 kg with a volume of 0.31 m^3 (~11 ft^3), and consumes 900 W while it is running, producing enough refrigerant to keep critical components of the desktop appliance cryogenically cool. The refrigerant, nitrogen (N_2) gas, is drawn from the air and liquefied, then is returned harmlessly to the air after it rewarms due to absorbing waste heat from the appliance.

The Fine Spirits Synthesizer appliance alone consumes about 300 W of power while in continuous operation. It is designed to manufacture 1 bottle (750 ml) per hour – or about 1 "shot" every 2 minutes – of any fine spirit for which it is given the molecular recipe. If provided with a tiny physical sample of a fine spirit liquid using the sampling wand, the appliance can also generate a complete molecular recipe for any fine spirit in about 17 minutes of run time while consuming only about 25 watts of power when the Assay Unit alone is running, at negligible additional cost (i.e., a few cents' worth of electrical power).

Total power draw for the entire system is 1200 W.

The appliance manufactures fine spirits products at a cost of **$0.36/bottle** ($0.51/kg), which includes $0.02/bottle ($0.05/kg) for the water, $0.28/bottle ($1.09/kg) for the ethanol, and $0.06/bottle ($12.08/kg) for the congeners.

How does $0.36/bottle compare to the distillers' cost of making whiskey? It is difficult to give a precise answer because this information is extremely proprietary, with the cost varying with the type of product, the volume of the product run, the changing wholesale cost of ingredients, the cost of capital for the producer (incorporating plant age, producer's creditworthiness, etc.), and many other factors. Anecdotal evidence[315] suggests a typical operating cost of "several dollars per liter" excluding fixed capital costs might be plausible. If our estimates are correct, a raw production cost of $0.36/bottle might therefore represent a perhaps 10-fold improvement over current costs of production at the major distilleries, especially when the fixed capital and labor costs are taken into account. If the widespread deployment of nanofactories worldwide permits the cost of industrial electricity to fall significantly,[316] the production cost of nanofactory manufactured spirits could fall by at least another order of magnitude (e.g., another 10-fold) from our initial $0.36/bottle figure.

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[315] http://www.straightbourbon.com/forums/showthread.php?161-The-Cost-Of-Bourbon.

[316] Robert A. Freitas Jr., "The Nanofactory Solution to Global Climate Change: Atmospheric Carbon Capture; Section 6.6," IMM Report No. 45, December 2015; http://www.imm.org/Reports/rep045.pdf.

Table 11. Mass, volume, and power budget for a desktop Fine Spirits Synthesizer appliance, assuming sortation-sourced ethanol.			
Components or Subsystems	**Mass** *(gm)*	**Volume** *(cm^3)*	**Maximum Power Consumption** *(W)*
Assay System			
Sampling Wand[317]	3.2	1	~0
Sample Preparation and Distribution System[318]	10	10	~0
Assay Unit (Section 5.2)	1	1	1
Assay Unit Refrigeration System[319]	120	60	< 24
Sample Disposal System[320]	10	10	~0
Assay System subtotals	*144.2*	*82*	*25*
Synthesis System			
Methane Supply			
Natural Gas Hookup[321]	150	20	0
Methane Conditioning System[322]	153	152	5

[317] The Sampling Wand is assumed to be a cylindrical device 30 cm long and 1 mm in diameter (0.8 gm, 0.2 cm^3, if solid diamond mechanism), attached to a transfer hose perhaps three times longer that is affixed to the appliance. The Wand is dipped into the bottle of fine spirits to be replicated and collects either a representative sample of the liquid's molecules from the entire container (if the Wand is stirred) or a stratigraphic sample from a particular height within the bottle (if not stirred). The sample is passed through the transfer hose to the input port of the Assay Unit. Power requirements are negligible because only ~0.483 $micron^3$ of sample fluid is being collected.

[318] Samples could be conveyed to the 10 million Lab Modules in the Assay Unit using the system of 100,000 conveyor lines described in Section 5.2.7, but extended 10^5-fold from 1 micron to a maximum of 10 cm in length. In that case, the total conveyor mass would be 6 x 10^{-7} gm, volume ~2 x 10^{-7} cm^3, and the power draw would be 1.4 x 10^{-8} watts for ~100 sec during the ~1000 sec of total runtime needed to analyze one sample. We assume that an additional 10 cm^3 of passive infrastructure having a mass of ~10 gm will be sufficient to provide physical support for the 1 cm^3 material volume of the Assay Unit.

[319] The Lab Module Block generates ~1 watt of waste heat and must be cryogenically cooled. Miniaturized cryogenic cooling systems of total mass ~120 gm and total volume of perhaps ~60 cm^3 can perform this service at a cost of <24 watts (e.g., http://www.mmr-tech.com/PDFs/jThomson_broch.pdf).

[320] This system is similar to the Sample Distribution System described earlier. The small number of organic sample molecules to be removed from the Assay Unit after analysis (~10^{10} molecules, volume ~0.5 $micron^3$) are conveyed to the Waste Combustion System for final disposal.

[321] This is just a conventional valved hose bib to allow the appliance to receive commercial natural gas from a conventional wall-mounted outlet.

Water Supply			
Tap Water Hookup[323]	150	20	0
Water Conditioning System (Section 5.4.1)	150	150	0
Ethanol Supply			
Ethanol Source Material Container[324]	100	1000	0
Ethanol Sortation Module (Section 5.4.2)	56	32	84
Specialty Feedstock Supply[325]	~100	~100	~0
Fab Module Block (Section 5.4.3)	0.2	0.1	19
Fab Module Physical Support Structure (Section 5.4.3)	~100	~100	~0
Waste Combustion and Water Coolant System[326]	~100	~100	47

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[322] The largest component is a simple replaceable bulk filtration unit that removes any particulates from the gas stream, assumed to be 150 gm with a 150 cm^3 volume. The most important component is a set of sortation- or nanosieve-based filters that selectively extracts pure methane from the natural gas feedstock supply. With a congener-only fabrication requirement of $R_{bottleCongener}$ = 0.0015 gm/sec of congener, if the required rate of methane extraction is approximately the same then this extraction can be performed using, e.g., $M_{MethaneRotors} = N_{rotorcascade}\ R_{bottleCongener}\ N_A\ m_{rotor} / R_{SortMethane}\ MW_{methane}$ = **3.4 gm of sorting rotors** of volume $V_{MethaneRotors} = M_{MethaneRotors} / \rho_{rotors}$ = 1.7 cm^3, consuming $P_{MethaneRotors} = V_{MethaneRotors}\ P_{D\text{-}MethaneRotors}$ = 5.1 W of power, taking $N_{rotorcascade}$ = 3 rotors in the sortation cascade, mass $m_{rotor} = 2 \times 10^{-21}$ kg/rotor, rotor sort rate $R_{SortMethane} = 10^2$ molecules/rotor-sec, rotor power density $P_{D\text{-}MethaneRotors} = 3 \times 10^6$ W/m^3, rotor mass density ρ_{rotors} = 2000 kg/m^3, molecular weight $MW_{methane}$ = 0.016 kg/mole, and Avogadro's number $N_A = 6.023 \times 10^{23}$ molecules/mole.

[323] This is just a conventional valved hose bib to allow the appliance to receive common tap water from a conventional wall-mounted outlet.

[324] Glass bottle of ~1 liter volume into which the cheap ethanol source material (e.g., bulk ethyl alcohol, denatured alcohol, etc.) is poured. This should include a replaceable particulate filter at the top of the bottle.

[325] This is a small replaceable canister or cartridge containing specialty feedstock molecules providing atoms of nitrogen, sulfur, phosphorus, or any other elements that may be required in trace amounts for the manufacture of a few specialty congeners.

[326] The waste stream from the natural gas feed will include 3% $R_{bottleCongener}$ = 0.000045 gm/sec of combustible non-methane gases and 2% $R_{bottleCongener}$ = 0.000030 gm/sec of incombustible non-methane gases (Table 10). The waste stream from the Synthesis Unit includes at most (4 $MW_{hydrogen}/MW_{methane}$) $R_{bottleCongener}$ = 0.000375 gm/sec of H_2 effluent from the mechanosynthesis of congeners. The combustible sample organics left over from the Assay Unit are a negligible 0.483 $micron^3$ or $<10^{-12}$ gm. The combustible waste organics are burned in oxygen drawn from the air. Assuming for scaling purposes the following combustion formula for the organics: C_2H_5OH (46 gm) + $3O_2$ (96 gm) → $2CO_2$ (88 gm) + $3H_2O$ (54 gm), then the appliance generates (0.000045 gm/sec) (88/46) = 0.31 gm/hr = 0.31 gm/bottle of CO_2 effluent, (0.000045 gm/sec) (54/46) = 0.17 gm/hr = 0.17 gm/bottle of H_2O effluent, and (0.000045 gm/sec) (3×10^7 J/kg for C_2H_5OH; http://en.wikipedia.org/wiki/Energy_density) = 1.4 W of waste heat. For hydrogen combustion: $2H_2$ (4 gm) + O_2 (32 gm) → $2H_2O$ (36 gm), so the appliance generates (0.000375 gm/sec) (36/4) = 12.15 gm/hr = 12.15 gm/bottle of H_2O effluent and (0.000375 gm/sec) (1.2×10^8 J/kg for H_2; http://en.wikipedia.org/wiki/Energy_density) = 45 W of waste heat. That's a combustion total of ~0.3 gm/hr CO_2, ~12.3 gm/hr of H_2O, and ~47 W of waste heat. These low-toxicity effluents along with the ~0.1 gm/hr of incombustible non-methane waste gases, plus the 47 W waste heat generated by the combustion chamber and the 84 W of waste heat generated by the Ethanol Sortation Module, totaling ~131 W of waste heat, are injected into a small stream of tap water that is discharged into a common sink drain. A wastewater flow of $F_{water} = P_{water} / \rho_{water}\ H_{water}\ \Delta T$ = 11 liters/hr (~3 gallons/hr) can carry off P_{water} ~ 131

Synthesis System subtotals	*1059.2*	*1674.1*	*155*
Support Infrastructure			
Liquid Nitrogen (LN2) Generator (Section 5.4.3)	59,000	309,542	900
Subtotals	60,203.4	311,298.1	1080
Unallocated resources	4,796.6	8,701.9	120
TOTALS ***excluding LN2 Generator***	**65,000** ***6,000***	**320,000** ***10,458***	**1200** ***300***

W of waste heat with a modest water temperature rise of only $\Delta T = 10$ °C, taking $\rho_{water} = 1000$ kg/m^3 and $H_{water} = 4179$ J/kg-°C. Note that using the water stream to carry away the raw waste chemicals without combustion is also possible but may not be advisable, especially given the presence of mercaptan odorant in natural gas that must be disposed of.

6. Conclusions

We have reviewed many previous and recent attempts to chemically replicate fine spirits (Section 4). Our analysis suggests that to obtain the precise molecular recipe for a single fine spirits product that we might wish to replicate, using conventional techniques, will cost ~$10M, require the destruction of 10 liters of the original product, and will also require: (a) between 2 and 3.5 years to complete, (b) 5 full-time scientific personnel including 2 PhDs, and (c) an initial capital outlay of at least $1M for equipment (Section 4.4.4). Once we have the molecular recipe, it will require approximately $1000/bottle, plus or minus a factor of 10, in materials cost alone to manufacture a complete bulk chemical replicant whiskey (Section 4.4.3). We conclude that the bulk chemical replication of whiskey and other fine spirits is economically infeasible when competing against traditionally distilled products in both low-end and high-end market segments (Section 4.4.5).

A nanofactory-based approach gives dramatically different results. In particular, a 6-kg desktop appliance called the **Fine Spirits Synthesizer** that consumes 300 W for synthesis operations, along with a 59-kg 900 W cryogenic refrigerator, could produce one 750 ml bottle per hour of any fine spirit beverage for which the molecular recipe is known, at a cost of about $0.36 per bottle (Section 5.4.4). The appliance's carbon footprint is a minuscule 0.3 gm CO_2 emitted per bottle,[327] more than 1000 times smaller than the 460 gm/bottle carbon footprint of Pernod-Ricard's current distillery operations.[328]

The same desktop appliance could intake a tiny physical sample of any fine spirit beverage and produce a complete molecular recipe for that product in about 17 minutes of run time, consuming under 25 W of power, at negligible cost. A standalone molecular recipe analysis appliance, which perhaps might be called a Fine Spirits Analyzer, could readily be abstracted from the design for the Fine Spirits Synthesizer, simply by deleting all Synthesis System components from the component list given in Table 11.

How much might it cost to build the first prototype Fine Spirits Synthesizer appliance? Strictly speaking, only the Assay Unit (1 gm), the Ethanol Sortation Module (56 gm), the sortation component of the Methane Conditioning System (3.4 gm), and the Fab Module Block (0.2 gm) of the appliance, totaling 0.0606 kg of atomically precise machinery, must be built by the nanofactory described in Section 5.1. But let's conservatively assume that the entire 1.2 kg of the Assay System and Synthesis System described in Table 11 must be built to molecular specificity using the methods of atomically precise manufacturing.

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[327] See Note 326, Table 11. This figure is the same regardless of whether the ethanol is acquired externally and then purified using sorting rotors, as proposed here, or is manufactured *in situ* mechanosynthetically.

[328] All Pernod-Ricard production sites emitted 1.43 tonnes of CO_2 per 1000 liters of pure alcohol distilled between 2012-2013; Pernod-Ricard, 2012/2013 Annual Report, p. 112; http://pernod-ricard.com/files/fichiers/Commun/Documents/RA2012_13_VGB_MiseEnLigne_28102013.pdf. That's 1.43 kg CO_2/liter ethanol, the equivalent of 460 gm/bottle in CO_2 emission for an 86-proof fine spirit.

Taking into account the sunk costs for R&D that will be required to develop the first nanofactory, and taking into account the likely productivity, reliability, and productive lifetime of this first nanofactory, estimates for the fully amortized cost of product structures manufactured by the first nanofactory may range from $1000/kg to $10,000/kg, depending upon one's choices among the many assumptions that can be made.

The Fine Spirits Synthesizer appliance would be one such manufactured product of the nanofactory. This implies that the raw fabrication cost for the first Fine Spirit Synthesizer appliance, once the first nanofactory is in hand, might be in the neighborhood of $1,000-$10,000. An additional one-time initial cost for appliance technical design is probably in the $10M-$30M range but would only need to be spent once. After that, with the Fine Spirits Synthesizer appliance in hand, the operating cost of manufacturing fine spirits products should be roughly $0.36/bottle ($0.51/kg) as described elsewhere in this document.

The exemplar Fine Spirits Synthesizer described in Section 5.4 minimizes the cost of synthesis by taking two shortcuts.

First shortcut: **Ethanol**, the second largest fine spirits ingredient by weight, is provided from any one of many possible inexpensive bulk industrial sources, after which the impure ethanol is pumped through molecularly-selective pumps called sorting rotors that extract only the ethyl alcohol molecules and leave all impurities behind. Only the congeners, constituting 0.75% of fine spirits by weight (Table 1), need be synthesized using the more expensive methods of atomically precise manufacturing, e.g., via mechanosynthesis.

Our chosen method for obtaining ethanol will yield the desired ethyl alcohol ingredient at the specified 99.9999997% purity level, thus ensuring that no impurities are added to the replicant fine spirits at a concentration exceeding 1 ppb. However, if for some reason it is deemed desirable to avoid the importation of bulk ethanol with *in situ* purification, then the Fine Spirit Synthesizer can be redesigned to enable the direct synthesis of ethanol at the same 99.9999997% purity level via mechanosynthesis. This change will raise the cost of ethanol from $0.28/bottle ($1.09/kg) in the current system to $3.82/bottle ($15/kg) using the direct synthesis approach (Section 5.3.2). This is vastly less expensive than the crudely-estimated $89,970/kg cost[329] for producing 99.9999997% purity ethanol using standard chemistry laboratory purification techniques (see in-text discussion, Table 4), but is still more than 10 times as expensive as the 99.9% pharmaceutical-grade[330] or medical-grade industrial ethanol that is readily available for $1.45/kg ($0.37/bottle) on international markets (Table 9). An interesting question is whether we really need 99.9999997% ethanol to make indistinguishable-tasting replicant whiskey, or if 99.9% medical-grade ethanol might suffice?

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[329] It seems plausible that this cost can be reduced by at least a few orders of magnitude by developing specialized purification techniques, following a period of well-funded dedicated research to develop these techniques.

[330] http://www.cpichem.com/index.php/ct-menu-item-4/ct-menu-item-8/ethanol-product-summary/gmp-grade-ethyl-alcohol-99-9.

Synthesizing ethanol *in situ* increases the required mass of the Fab Module Block (atomically precise machinery) from 0.2 gm to 20 gm, slightly increasing the appliance build cost. A bigger problem: directly synthesizing ethanol adds 874 W of waste heat generation (Section 5.3.2), increasing the demand on our cryogenic refrigeration system from 19 W for just congeners up to 893 W for ethanol plus congeners. Our refrigeration system must now be ~47 times larger and will draw ~47 times more power (or must use some other method for cryogenic cooling), probably difficult for a desktop appliance-type architecture. The added cost hardly seems worth the trouble, especially given that ingredient purity is not improved.

Second shortcut: **Water**, the largest ingredient of fine spirits by weight, is provided from filtered tap water.

Our chosen method for obtaining water will **not** yield the ideal 99.9999998% purity level. Tap water typically contains 140-400 ppm of Total Dissolved Solids (TDS), whereas carbon-filtered or mountain spring/aquifer water can be 50-140 ppm TDS, and reverse osmosis, distillation, deionization or microfiltration can produce ideal drinking water at 1-50 ppm TDS.[331] At 10 ppm TDS, the water is 99.999% pure. We can boost the purity to 99.9999998% at an additional cost of only $0.026/bottle ($0.058/kg) (Section 5.3.3). This would require adding 248 gm of extra sorting rotors to the Fine Spirit Synthesizer design and increasing power consumption by 372 W. Sorting rotors operate at room temperature or higher, so this extra waste heat need not be handled by the cryogenic refrigeration system. Water cooling of the sorting rotors should be good enough, but the water sortation module should probably be physically separated from the main appliance to avoid any significant internal heat transfer. A water nanosieving system with a lower mass but a higher power draw (Section 5.3.4) could also be employed.

But do we really need 99.9999998% water to make indistinguishable-tasting replicant whiskey, or will 99.999% water suffice? If we really want the super purity ingredient, we can obtain the missing four "9"s of water purity at a $0.03/bottle higher cost, 372 W more power consumption, and a 141 cm^3 larger water sortation unit that is separate from the main appliance, as described in the previous paragraph.

Industrial production: The scaling analysis for an industrial-sized fine spirits manufacturing plant is beyond the scope of this document. However, even assuming no efficiencies of scale beyond the parameters of the exemplar Fine Spirits Synthesizer appliance described in Section 5.4, the entire ~52 million bottle annual production run of all five Jameson Irish Whiskey product lines[332] could be manufactured at a process cost of only $19M. We surmise that this might be as much as 10 times less expensive than current methods. Since one appliance can fill 8760 bottles/yr, a 52 million bottle plant might require the equivalent capacity of ~5900 appliances having a total mass (including the heavy LN2 refrigeration units) of ~400 metric tonnes and a volume of ~200 m^3 (e.g., a cube ~6 meters or ~19 feet on a side), with a power draw of ~7 MW and a minuscule

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[331] http://www.waterfiltersonline.com/tds-sources.asp.

[332] Pernod-Ricard, 2012/2013 Annual Report, p. 131; http://pernod-ricard.com/files/fichiers/Commun/Documents/RA2012_13_VGB_MiseEnLigne_28102013.pdf.

carbon footprint of ~16 tonnes/yr of CO_2 emission for the entire plant (that can easily be reduced to zero carbon emission[333]).

[333] The carbon emission in the form of (0.3 gm CO_2/bottle)(52 million bottles/yr) = 15.6 tonnes/yr CO_2 can be reduced to zero by permanently sequestering the CO_2 in another form, e.g., solid diamond (9 MJ/kg CO_2), requiring, in the case of diamond, a continuous additional power expenditure of (15.6 tonnes/yr CO_2) (9 MJ/kg CO_2) = 4.5 kW at the plant, costing an extra $2,700 over the entire year (taking 1.94×10^{-8} $/J for electricity) and adding only $0.00005/bottle to the fine spirits production cost – a negligible sum. The solid diamond is produced by mechanosynthetic processes (Section 5.1.1) using CO_2 as a carbon feedstock, in a nanofactory. The 4250 kg/yr of waste diamond thus produced might have considerable resale value, especially if made into laptop supercomputers or other products having a complex nanoscale structure (http://www.molecularassembler.com/Nanofactory/).

Appendix A. Contemporary Chemical Sensor Technologies

The analysis of the chemical composition of fine spirits is the single biggest cost in the bulk chemical replication of fine spirits. Is there any way to reduce this cost using other contemporary methods? There have been many attempts to combine chemical sensors with electronics and automation (as briefly described below), but unfortunately none of these methods have yet approached the generality, sensitivity, and flexibility of the laboratory methods previously described in Section 4.4.4.

Chemical Field-Effect Transistor (ChemFET). The ChemFET is a type of a field-effect transistor acting as a chemical sensor.[334] It is a structural analog of a MOSFET transistor,[335] but where the charge on the gate electrode is applied by a chemical process. A ChemFET may be used to detect atoms, molecules, and ions in liquids and gases. The ISFET, an ion-sensitive field-effect transistor, is the best known subtype of ChemFET devices. It is used to detect ions in electrolytes. The ENFET is a ChemFET specialized for detection of specific biomolecules using enzymes.

An EOSFET or electrolyte-oxide-semiconductor field effect transistor is a ChemFET, like a MOSFET, but with the metal replaced by electrolyte solution for the detection of neuronal activity. The EOSFET is made of silicon that is doped in such a way that it can sense the electrical activity of the neurons (action potentials) in the above-standing physiological electrolyte solution. It also contains capacitors for the electrical stimulation of the neurons. Using EOSFETs it is possible to cultivate a network of brain cells that reconnect on a silicon chip – like a brain on a microchip – and can monitor brain cell activity at high resolution. Many EOSFETs may be integrated in a neurochip.

Electronic tongue. The electronic tongue is an electrochemical instrument that measures and compares tastes.[336] The electronic tongue uses chemical sensors to receive information from chemicals on the tongue and send it to a pattern recognition system. Each E-tongue sensor has a spectrum of responses different from the others. The information given by each sensor is complementary and the combination of all sensors' results generates a unique taste fingerprint. Most of the detection thresholds of sensors are similar to or better than those of human receptors.

Electronic tongues have applications in the pharmaceutical and food/beverage industries, such as:

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[334] Florinel-Gabriel Banica, *Chemical Sensors and Biosensors: Fundamentals and Applications*, John Wiley and Sons, Chichester, 2012, chapter 11.

[335] http://en.wikipedia.org/wiki/MOSFET.

[336] http://en.wikipedia.org/wiki/Electronic_tongue, http://www.electronictongue.com, http://www.alpha-mos.com/analytical-instruments/astree-electronic-tongue.php. See also: Manel del Valle, "Sensor Arrays and Electronic Tongue Systems: Review Article," *Intl. J. Electrochem.* (2012):1-11, http://www.hindawi.com/journals/ijelc/2012/986025/.

(1) to analyze flavor aging in beverages (e.g., in fruit juice, alcoholic or non-alcoholic drinks, or flavored milks;

(2) to quantify bitterness or "spiciness level" of drinks or of dissolved compounds (e.g., bitterness measurement and prediction of teas);

(3) to quantify taste-masking efficiency of formulations (e.g., tablets, syrups, powders, capsules, or lozenges);

(4) to analyze the taste stability of medicines; and

(5) to benchmark target products.

Electronic Nose. Machine olfaction[337] is the automated simulation of the sense of smell.[338] It is an emerging application of modern engineering where robots or other automated systems are needed to measure the existence of a particular chemical concentration in air. Such an apparatus is often called an electronic nose or e-nose. Machine olfaction is complicated by the fact that e-nose devices to date have had a limited number of elements, whereas each odor is produced by own unique set of (potentially numerous) odorant compounds. There are hopes that advanced technology could do everything from testing perfumes to helping detect cancer or explosives by detecting specific scents, but artificial noses are still problematic because the complex nature of the human nose, especially its ability to detect even the most subtle of scents, is at the present moment difficult to replicate.[339]

Since 1982,[340] research has been conducted to develop technologies, commonly referred to as "electronic noses", that could detect and recognize odors and flavors. Most artificial or electronic nose instruments work by combining output from an array of non-specific chemical sensors to produce a finger print of whatever volatile chemicals it is exposed to. They generally comprise: an array of sensors of some type, the electronics to interrogate those sensors and produce the digital signals, and the data processing and user interface software. Most electronic noses need to be "trained" to recognize whatever chemicals are of interest for the application in question before it can be used. The training involves exposure to chemicals with the response being recorded and statistically analyzed, often using multivariate analysis and neural network techniques, to "learn" the chemicals. Many current electronic nose instruments suffer from problems with reproducibility subject to varying ambient temperature and humidity. An example of this type of technology is the colorimetric sensor array, which visualizes odor through color change and creates a "picture" of it.[341]

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[337] http://en.wikipedia.org/wiki/Machine_olfaction.

[338] T.C. Pearce, S.S. Schiffman, H.T. Nagle, J.W. Gardner, eds., *Handbook of Machine Olfaction: Electronic Nose Technology*, Wiley-VCH, Weinheim, 2002, http://www.amazon.com/Handbook-Machine-Olfaction-Electronic-Technology/dp/3527303588

[339] http://en.wikipedia.org/wiki/Odor#Advanced_technology.

[340] Krishna Persaud, George Dodd, "Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose," *Nature* 299(1982):352-5.

[341] N.A. Rakow, K.S. Suslick, "A Colorimetric Sensor Array for Odour Visualization," *Nature* 406(2000):710-714; K.S. Suslick, "An Optoelectronic Nose: Colorimetric Sensor Arrays" *MRS Bulletin* 29(2004):720-725; S.H. Lim, L. Feng, J.W. Kemling, C.J. Musto, K.S. Suslick, "An Optoelectronic Nose

The more commonly used sensors for electronic noses include Metal-Oxide-Semiconductor (MOSFET) devices, conductive organic polymers (e.g., polypyrrole), polymer composites (similar in use to conducting polymers but formulated of non-conducting polymers with the addition of conducting material such as carbon black, tin-oxide gas sensors, quartz crystal microbalances (a way of measuring mass per unit area by measuring the change in frequency of a quartz crystal resonator), and SAW (a class of microelectromechanical systems (MEMS) which relies on the modulation of surface acoustic waves to sense a physical phenomenon.[342]

One example of a commercial system is the Cyranose 320 (above) is a handheld "electronic nose" developed by Cyrano Sciences of Pasadena, California in 2000.[343] Applications researched using the Cyranose 320 include the detection of COPD and other medical conditions, as well as industrial applications generally related to quality control or contamination detection. Electronics noses have also been used to detect tuberculosis,[344] lung cancer,[345] prostate cancer,[346] alcohol,[347] and 10 atmospheric contaminants aboard the space station[348] including methanol, ethanol, formaldehyde, and Freon 218.

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for Detection of Toxic Gases," *Nature Chemistry* 1(2009):562-567; B.A. Suslick, L. Feng, K.S. Suslick, "Discrimination of Complex Mixtures by a Colorimetric Sensor Array: Coffee Aromas," *Anal. Chem.* 82(2010):2067-2073; L. Feng, C.J. Musto, J.W. Kemling, S.H. Lim, K.S. Suslick, "A Colorimetric Sensor Array for Identification of Toxic Gases below Permissible Exposure Limits," *Chem. Commun.* 46(2010):2037-2039; L. Feng, C.J. Musto, K.S. Suslick, "A Simple and Highly Sensitive Colorimetric Detection Method for Gaseous Formaldehyde," *J. Am. Chem. Soc.* 132(2010):4046-4047.

[342] Frank Röck, Nicolae Barsan, Udo Weimar, "Electronic Nose: Current Status and Future Trends," *Chemical Reviews* 108(2008):705-25.

[343] http://spinoff.nasa.gov/spinoff2001/ps4.html, http://www.foodingredientsonline.com/doc/cyrano-sciences-unveils-portable-electronic-n-0002, http://www.smithsdetection.com/biological-agents-detection/43-about-us/169.html.

[344] http://www.theguardian.com/global-development/2011/nov/07/tuberculosis-electronic-nose-device.

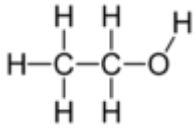
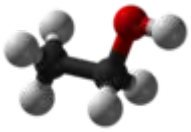
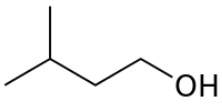
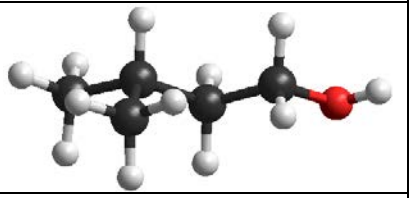
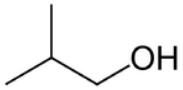
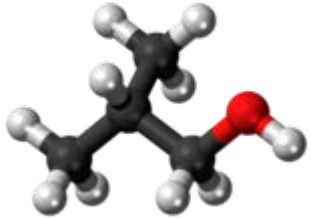
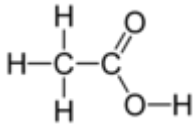
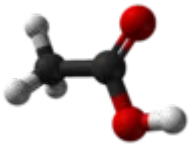
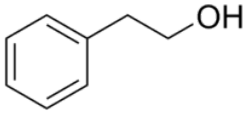
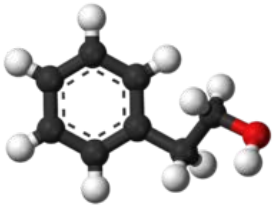
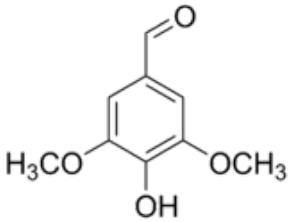
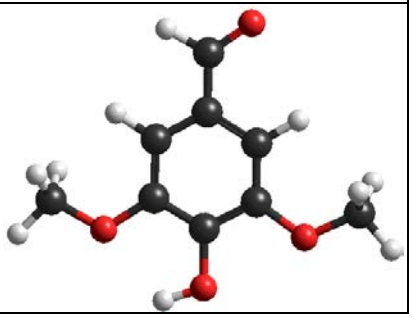
[345] http://www.dailymail.co.uk/health/article-2662627/The-electronic-nose-sniff-lung-cancer-New-breathalyser-test-allow-doctors-detect-disease-early-stages.html.

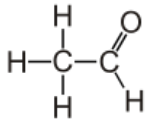
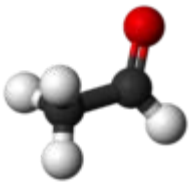
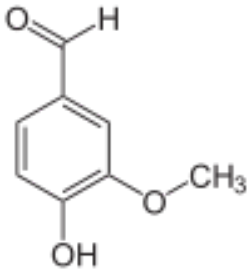
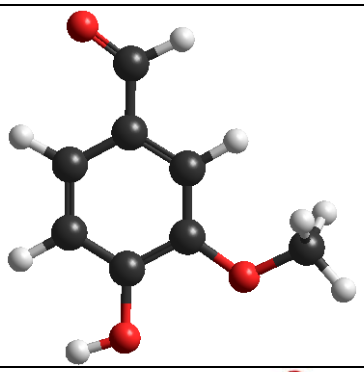
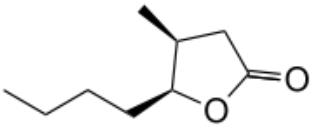
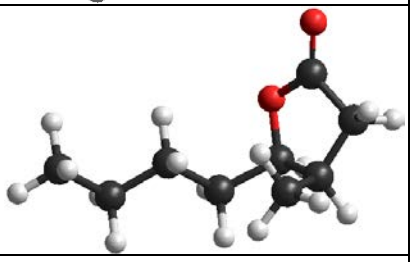
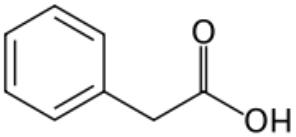
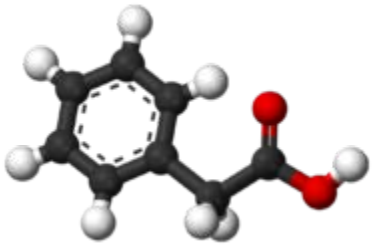
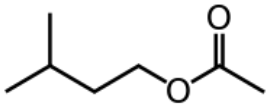
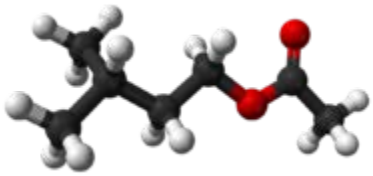
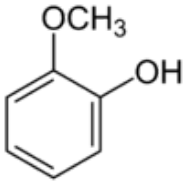
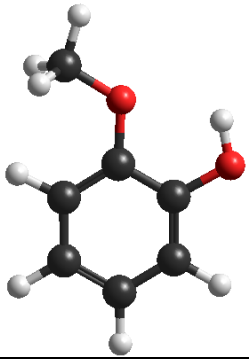
[346] http://www.sciencedaily.com/releases/2014/05/140501165619.htm.

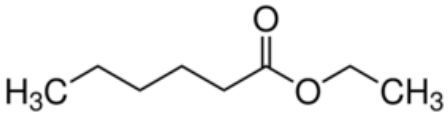
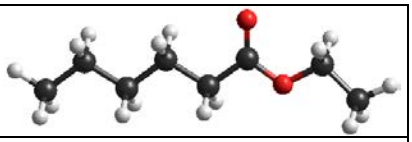
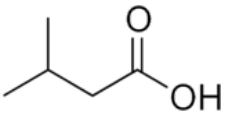
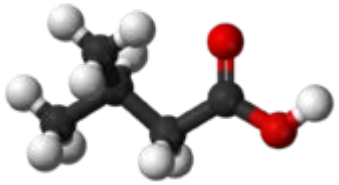
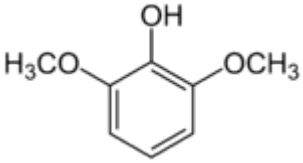
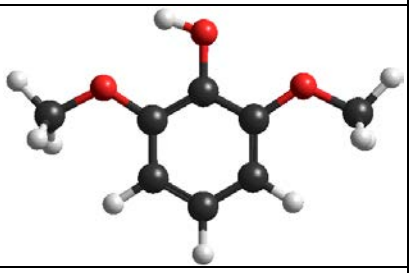
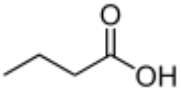
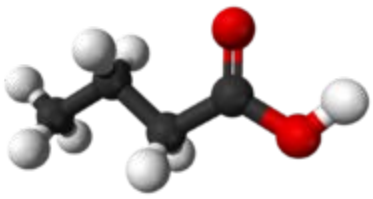
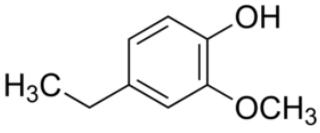
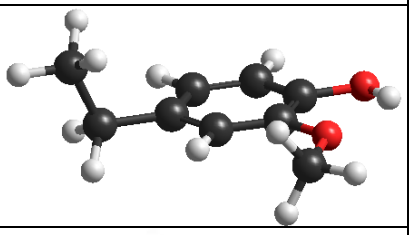
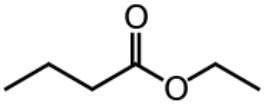
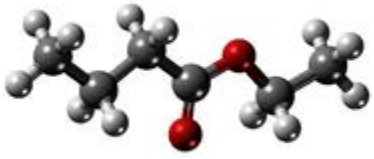
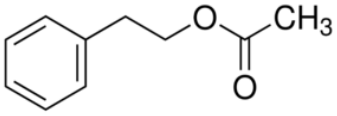
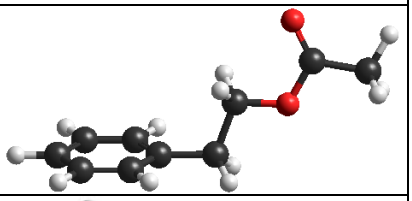
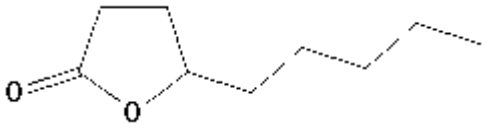
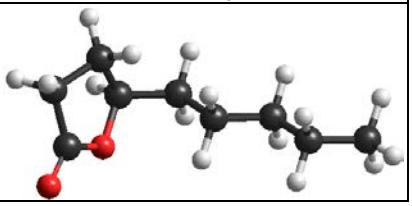
[347] http://www.business-standard.com/article/pti-stories/electronic-nose-could-aid-in-rescue-missions-114072400809_1.html; see also http://en.wikipedia.org/wiki/Breathalyzer.

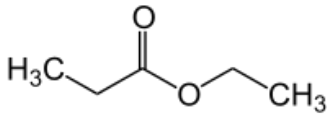
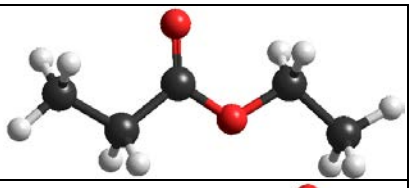
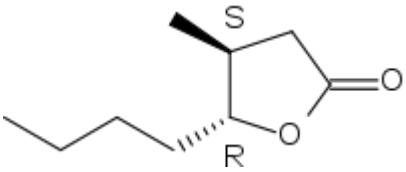
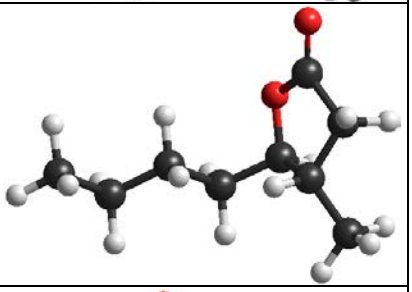
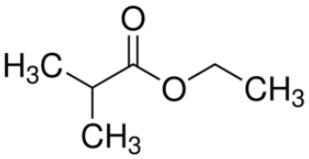
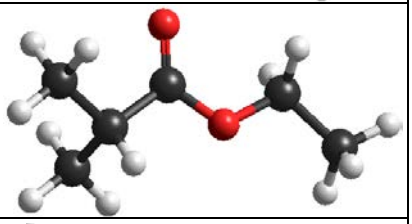
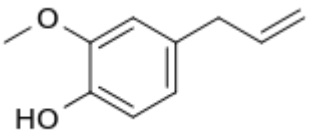
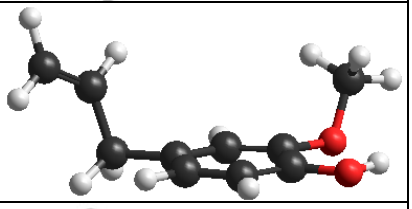
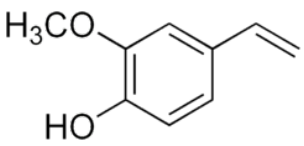
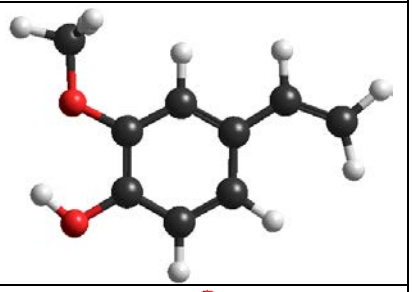
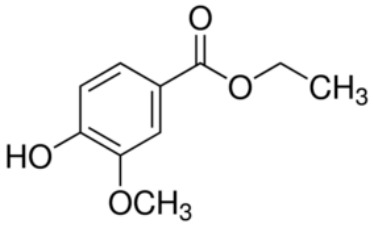
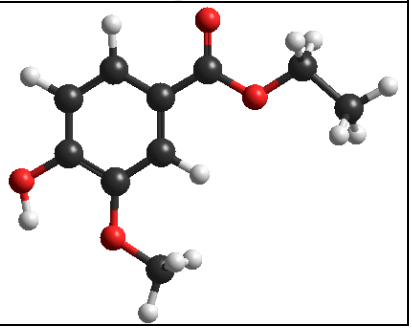
[348] http://www.jpl.nasa.gov/news/news.php?feature=2309.

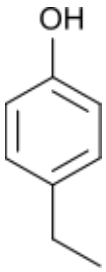
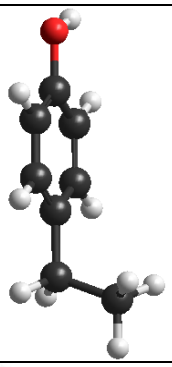
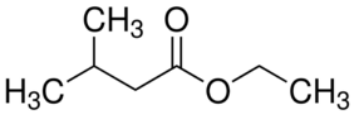
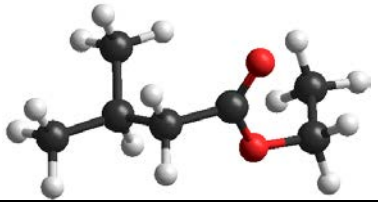
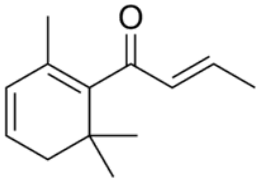
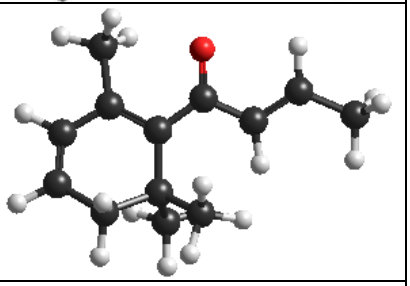
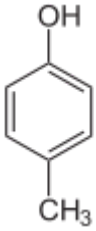
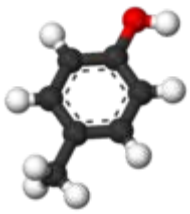
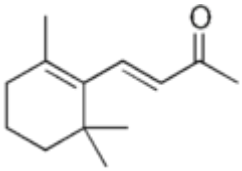
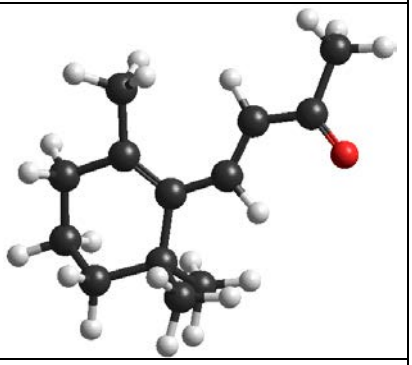
Appendix B. Molecular Structure of Top 31 Congeners in Rye Whiskey

Appendix B. Names and molecular structures for ethanol and all 31 of the "most potent odorants" in rye whiskey, as listed in Table 4.		
ethanol		
3-methyl-1-butanol (isoamyl alcohol)		
2-methyl-1-propanol (isobutanol)		
acetic acid		
2-phenylethanol (phenethyl alcohol)		
syringaldehyde		

acetaldehyde		
vanillin		
cis-whiskeylactone		
phenylacetic acid		
isoamyl acetate		
guaiacol		

ethyl hexanoate (ethyl caproate)		
isovaleric acid		
2,6-dimethoxyphenol (syringol)		
butyric acid		
4-ethyl-2-methoxyphenol (4-ethylguaiacol)		
ethyl butyrate		
2-phenylethyl acetate		
γ-nonalactone		

ethyl propanoate		
trans-whiskeylactone		
ethyl isobutyrate		
eugenol		
p-vinylguaiacol		
ethyl vanillate		

4-ethylphenol		
ethyl isovalerate		
β-damascenone		
p-cresol		
β-ionone		
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