Not a Library**

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I

Combinatorial chemistry evokes conflicting responses—it is a superbly efficient way to discovery, it is unthinking to unsporting, it is the ultimate biomimetic process. All these perspectives capture some aspect of a very hot field. I find especially enlightening Albert Eschenmoser's view:[1]

> *"The essential step in combinatorial chemistry is not the synthesis; rather it is finding a target, based on specific properties. Combinatorial synthetic research is an adaptation to what nature has been doing all the time: synthesis followed by selection, as opposed to synthesis by design. The aim of combinatorial chemistry is primarily discovering a molecule, whereas that of chemical synthesis is constructing a molecule."*

Central to modern combinatorial practice is the generation at some intermediate stage of a large set of molecules. The ways *in* to this set are many and ingenious—the compounds may be pooled all in one vessel, produced separately (and readied to signal their identity) by a set of efficient reactions. The molecules may be as globally diverse as chemistry can make them, or scattered round a structural feature of proven utility. The ways *out* of that set are equally rich—one may sample for activity with respect to what one's heart (or employer) wishes, one may let a biological molecule seek out a partner among the many, to inhibit or accelerate. But whatever one does, if the process is to work, one has to have many.[2]

I admire the ingenuity of combinatorial chemistry, love the way it demystifies normal exploratory synthesis, and ponder the philosophical questions it raises. But there is one aspect of its nomenclature that just rubs me the wrong way. This is the common denomination of the large combinatorial set as a "library".

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[**] I am grateful to Albert Eschenmoser, Sylvie Coyaud, and Henning Hopf for their comments.

It's about as far from a library as one can get in this world! To a secular refugee of World War II who did not own a book until age 13, a library was about as close to a holy place as I could imagine. I remember most of mine—the small refugee camp library in Bindermichl, Austria; the city library in Munich where I put my name on a long waiting list for the next installment of Karl May's adventures of Kara Ben Nemsi or Old Shatterhand; the beautiful public library in Woodside, Queens, decorated with murals by superb artists set to work during the Great Depression.

Now these were *libraries* (Figure 1). They were filled with organized knowledge, with wisdom, with the salacious (to a boy), hidden under the librarian's desk. These true libraries were the work of men and women shaping laughter and tears, defeating entropy. The set of all possible molecules or a finite subset thereof, even if we can "read" it chemically, is no more a library than the set of all books made of random letter arrangements.

II

Neither the lure of combinatorics, nor the critical appreciation of the lack of human meaning in the outcome of the combinatorial process is new. One of the oldest of kabbalistic texts is the *Sefer Yetzirah*, probably originating in the 3rd or 4th century of our era. It is a brief, mysterious, and poetic work, perhaps a guide to Jewish mystical practice. The gate to enlightenment is through permutations of the letters of the Hebrew alphabet:[3]

> *"Twenty-two foundation letters:*
> *He engraved them. He carved them.*
> *He permuted them. He weighed them.*
> *He transformed them.*
> *And with them, He depicted all that was formed*
> *And all that would be formed."*
> *Sefer Yetzirah* does some math:[4]
> *"Two stones build two houses*
> *Three stones build six houses*
> *Four stones build twenty four houses*
> *Five stones build one hundred and twenty houses*
> *Six stones build seven hundred and twenty houses*
> *Seven stones build five thousand and forty houses*
> *From here on go out and calculate*
> *That which the mouth cannot speak*
> *And the ear cannot hear."*

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Figure 1. A view of the library of the University of Salamanca, as an example of a "proper" library. (From *Salamanca—Ciudad patrimonio de la humanidad de España*, Artec Impresiones, Segovia, **1998**.)

As for the intelligibility of what emerges, notwithstanding the entry to the garden of philosophy it provides for the mystic, this is what Cicero has to say (speaking through the stoic Lucilius Balbus) in *De Natura Deorum*, in the context of arguing with the Epicureans:[5]

"Hic ego non mirer esse quemquam, qui sibi persuadeat corpora quaedam solida atque individua vi et gravitate ferri mundumque effici ornatissimum et pulcherrimum ex eorum corporum concursione fortuita? Hoc qui existimat fieri potuisse, non intellego, cur non idem putet, si innumerabiles unius et viginti formae litterarum vel aureae vel qualeslibet aliquo coiciantur, posse ex iis in terram excussis annales Enni, ut deinceps legi possint, effici; quod nescio an ne in uno quidem versu possit tantum valere fortuna."[*]

Despite this logic, the irrational yet deeply human search for meaning has persisted in seeking inspiration from the combinatorial. The kabbalistic path is a distinguished one. Along it ambles the remarkable Catalan mystic and writer, Ramon Llull (1232 – 1316), who placed around one wheel nine absolute principles, around another nine questions (whether? what? of what? why? and so on), nine subjects, nine relative principles, nine virtues, nine subjects, nine vices. Imagine these arranged as concentric wheels, spun. Llull reasoned that all the elements of a rational universe were contained in this, his *Ars Combinatoria*.[6]

Four hundred years later, two very different people were seduced by the Llull's vision. One was the remarkable polymath (and alchemist) and Jesuit priest Athanasius Kircher (1601 – 1680), the other the great philosopher and coinventor of the calculus Gottfried Wilhelm Leibniz (1646 – 1716). Leibniz wrote a *Dissertatio de Arte Combinatoria*, and in a letter from 1679 he describes the value of his combinatorics:[7]

"Car mon invention contient l'usage de la raison tout entier, un juge des controverses, un interprete des notions, une balance pour les probabilités, une boussole qvi nous gvidera sur l'ocean des experiences, un inventaire des choses, un tableau des pensées, un microscope pour eplucher les choses presentes, un telescope pour deviner les eloignées, un Calcul general, …"[**]

[*] Is it possible for any man to behold these things, and yet imagine that certain solid and individual bodies move by their natural force and gravitation, and that a world so beautifully adorned was made by their fortuitous concourse? He who believes this, may as well believe, that if a great quantity of the one-and-twenty letters, composed either of gold, or any other matter, were thrown upon the ground, they would fall into such order as legibly to form the Annals of Ennius.

[**] My invention contains the application of all reason, a judgment in each controversy, an analysis of all notions, a valuation of probability, a compass for navigating over the ocean of our experiences, an inventory of all things, a table of all thoughts, a microscope with which to prove the phenomena of the present, and a telescope with which to preview those of the future, a general possibility to calculate everything.

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Sounds like one of my theoretical chemistry colleagues… But Leibniz was extravagant only in his claims; he actually made something of them, to our benefit.

Combinatorics was in the air in the 17th century. In 1622 Paul Guldin actually calculated the size of a library that would hold the printed sequences of 23 letters, regardless as to whether they make sense or could be spoken, and in 1636 Marin Mersenne did an analogous computation for musical sequences running over three octaves.[8]

And it is so easy to make fun of the *Ars combinatoria*. So, Jonathan Swift (1667–1745) does the Ciceronian turn; Captain Gulliver comes to the Grand Academy of Lagado, where he spots:[9]

"…a frame… twenty-foot square, placed in the middle of a room. The superficies were composed of several bits of wood, about the bigness of a dye, but some larger than others. They were all linked together by slender wires. These bits of wood were covered on every square with paper pasted on them, and on these papers were written all the words of their language… but without any order. The pupils… took each of them hold of an iron handle… and giving them a sudden turn the whole disposition of the words was entirely changed… The professor shewed me several volumes in large folio already collected, of broken sentences, which he intended to piece together, and out of these rich materials to give the world a compleat body of all arts and sciences; which however might be still improved, and much expedited, if the publick would raise a fund for making and employing five hundred such frames in Lagado."

I cannot pass by the ancient English art of change-ringing of church bells. A complete set of permutations is called a peal; to ring one on twelve bells would take forty years. No claims to deep knowledge in this delightful musical ritual, only a way in to the sublime, in the original sense of the word. Change-ringing has led to an idiom in English, and is central to Dorothy Sayers' entertaining 1934 novel, *The Nine Tailors*.[10]

The line continues into the twentieth century; combinatorics continue to fascinate, and not only chemists. In one of Arthur C. Clarke's striking short stories, *The Nine Billion Names of God*, a Tibetan monastery make a very early use of a computer to list the permuted nine-letter names of God. A small combinatorial set, by today's standard. When it's done… well, you'll have to read the story.[11]

One of Raymond Queneau's inventions is a sonnet where each line may be chosen from among ten variants. Meaning remarkably emerges, like function in a tetradecapeptide.[12]

III

To me there are two possible cultural rationalizations for the word "library" in the context we are looking at. The first is not one combinatorial chemists may like. It is to be found in one of the most remarkable short stories of the great Jorge Luis Borges, *The Library of Babel*. Borges' protagonist is a man who lives in a phantasmagoric setting:[13]

"The universe (which others call the Library) is composed of an indefinite and perhaps infinite number of hexagonal galleries… There are five shelves for each of the hexagon's walls; each shelf contains thirty-five books of uniform format; each book is of four hundred and ten pages; each page, of forty lines, each line, of some eighty letters which are black in color."

In elegant prose Borges explores the deeply melancholy and delusional side of the optimistic longing in *Sefer Yetzira*. In the ultimately meaningless world of all letter combinations, human beings, destined to seek order, put all hope into a random phrase. It's the bleakest of libraries.

The second justification is more positive. The DNA sequence of humans, of any organism, now that's a library, as Eschenmoser reminded me.[14] The genome is a historical record of evolutionary experiments. Of blind alleys and superb improvisations. The greatest biological tragedy of our time—massive species extinction as a result of human actions—can be seen as a betrayal of our intellect, as a violation of what the second Adam in *Genesis 2:15* was instructed to do, as … the ultimate book burning. Species extinction is like going into an ancient library (the DNA of a species) and instead of opening the book, or even shelving it, just consigning it to the flames of our greed.

I have digressed, in anger, but I think with cause. The "library" locution for the trial sets of combinatorial chemistry probably originated in the context of DNA sequences.[15] Not libraries, I would still say.[16] But bearing a hint of legitimacy by association with the genome.

IV

Why the word "library" to describe a cleverly made assortment of molecules about to be interrogated in some way? Why not "warehouse", or "supermarket", or even "lottery"? Could it be for the same reasons scientists gave and still give Greek-origin and Latinate names to concepts, long past the time when Greek and Latin were parts of their education—a reaching for cachet mixed with a soupçon of scholarly pretentiousness? The beauty of human design, wedded to the aleatory wonder of directed free energy, suffices. We don't need this seeming sophistication.

But we do, did need a word. And for some reason just plain "pool", a nice neutral word of much currency in the early combinatorial literature, would not do. Never having to struggle with recalcitrant beads or robots, reactions that should go but don't, I have no right to criticize the choice that was made in the heat of the experimental moment by the protagonists. But it's still fun to think about what might have been. If Anglo-Saxon linguistic dominance is to be combated, in a friendly way, a friend suggests that we might have co-opted "pot-pourri". Or "méli-mélo". Or "olla-podrida". Or, I would add, "Vivoli", to celebrate the best selection of ice cream in this world. You could try the pseudopithy modernese of "combiset", or "diverset", if only the latter were not already a trademark. If you want to hint at the wealth that's a

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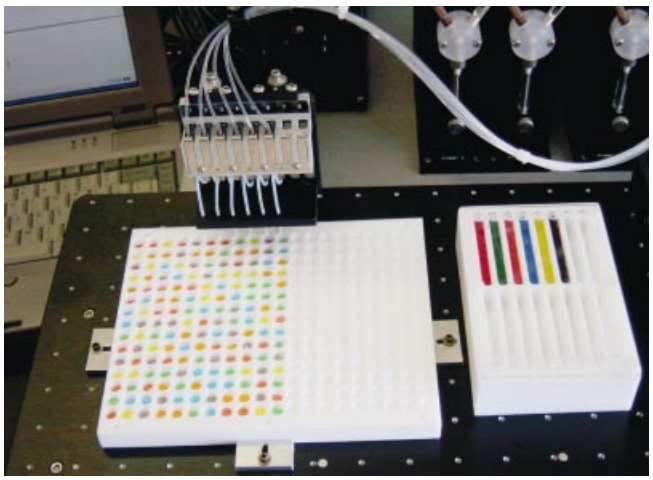

Figure 2. A combinatorial library (with thanks to Professor Selim Senkan, University of California at Los Angeles, for this picture that we found in his review[17]) has certain similarities to a praline sortiment (the picture was supplied by the Confiserie Sprüngli, Switzerland).

twinkle in the eye of some (maybe too many) of those entrepreneurial combinatorial chemists, why not "portfolio"?

I've saved my favorites for last. First the simple and lovely international word we owe the French language, and suggested to me by Sylvie Coyaud, "bouquet". It mixes flowers with a hint of books (bouquins). And finally, the German "Sortiment", derived from the Italian "sortimento", and made English by decapitalizing it. A plain word, sortiment, which the Duden dictionary actually defines by a reference to the choice of books in a bookstore! To me the word is hardly prosaic—I think of what is offered to all my chemical senses when I walk into the Confiserie Sprüngli on the Paradeplatz in Zürich. The most luscious of sweet worlds, made by ingenious human beings. A sortiment—waiting to be sampled (Figure 2).

[1] A. Eschenmoser, in an interview with I. Hargittai, *Chem. Intell.* **2000**, *6*(3), 6.

[2] See, among others: P. Seneci, *Solid-Phase Synthesis and Combinatorial Technologies*, Wiley-Interscience, New York, NY, **2000**; *Molecular Diversity and Combinatorial Chemistry* (Eds.: I. M. Chaiken, K. D. Janda), American Chemical Society, Washington, DC, **1996**; *Combinatorial Chemistry* (Eds.: S. R. Wilson, A. W. Czarnik), Wiley, New York, NY, **1997**.

[3] *Sefer Yetzirah* (Tr.: A. Kaplan), Samuel Weiser, York Beach, ME, **1997**, 2:2, p. 100.

[4] *Sefer Yetzirah* (Tr.: A. Kaplan), Samuel Weiser, York Beach, ME, **1997**, 4:16, p. 190.

[5] M. T. Cicero in *De Natura Deorum/Of the Nature of Gods* (Tr.: C. D. Yonge), Prometheus, Amherst, NY, **1997**, II:37, p. 78.

[6] See for example: U. Eco, *The Search for a Perfect Language*, Blackwell, Oxford, **1995**, pp. 140–141; R. Llull in *Selected Works of Ramon Llull* (Ed. and Tr.: A. Bonner), Princeton University Press, Princeton, NJ, **1985**. My source here is a paper by Werner Künzel, *The Birth of the Machine: Raymundus Lullus and His Invention*, www.c3.hu/scca/butterfly/Kunzel/synopsis.html.

[7] G. W. Leibniz, April 1679 letter to Johann Friedrich, the Duke of Hanover, in *Sämtliche Schriften und Briefe*, Akademie-Verlag, Berlin, **1970**, 1st collection (general political and historical exchanges), 2nd vol. (1676–1679), p. 168.

[8] My source here is secondary, from a remarkable book: U. Eco, *The Search for a Perfect Language*, Blackwell, Oxford, **1995**, pp. 140–141.

[9] J. Swift, *Gulliver's Travels into Several Remote Nations of the World, Part III. A Voyage to Laputa, Balnibarbi, Luggnagg, Glubbdubdrib and Japan*, Benjamin Motte, London, **1726**.

[10] D. L. Sayers, *The Nine Tailors*, Harcourt Brace, New York, NY, **1934**.

[11] A. C. Clarke, *The Nine Billion Names of God: The Best Short Stories of Arthur C. Clarke*, Harcourt Brace & World, New York, NY, **1967**, pp. 3–11.

[12] R. Queneau, *Cent mille milliards de poèmes*, Gallimard, Paris, **1963**. A search of websites devoted to this poem reveals some interesting commentary on intellectual property rights—are all of Queneau's sonnets copyright?

[13] "The Library of Babel": J. L. Borges in *Labyrinths: Selected Stories and Other Writing* (Tr.: J. B. Irby), New Directions, New York, NY, **1964**, p. 52.

[14] A. Eschenmoser, personal communication.

[15] I would appreciate the readers' direction to the earliest appearance of the word "library" in the current chemical or biological context.

[16] This is not the place to trace the roots of the word "library" or "Bibliothek". A full account would surely fill one, and certainly feature the definitive novel of bibliomania, which happens to be written by a Chemistry Ph.D.: E. Canetti, *Auto-da-Fé* (Tr.: C. V. Wedgwood), Seabury, New York, NY, **1979**; *Die Blendung*, Hauser, München, **1963**.

[17] S. Senkan, *Angew. Chem.* **2001**, *113*, 322–341; *Angew. Chem. Int. Ed.* **2001**, *40*, 312–329.

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