

Innovations

In the Fragrance Business, the Right Molecule Smells like Money

Luca Turin's unconventional theories on olfactory reception and prediction of odor character have raised a bit of a stink. "I loved perfume," says Turin, CTO of Flexital, Inc., a privately funded company that uses rational design to develop fragrance molecules. "I was very interested in biology. The more I read I thought things didn't add up. I came across a crazy vibration theory." According to this theory, the receptors in the nose distinguish between different odor molecules primarily by probing their vibrational spectra, not their shape. Recently, he has modified his theory to include shape as well.

Luca Turin holds a Ph.D. in biophysics and physiology from the University of London. He was a biophysicist on the staff of the French Centre National de la Recherche Scientifique (CNRS). His passion for fragrance is profiled in Chandler Burr's 2003 book "The Emperor of Scent: A Story of Perfume, Obsession and the Last Mystery of the Senses" and in a BBC documentary called "A Code in the Nose." His blog, at <http://lucaturin.typepad.com>, wittily comments on the evanescent world of fragrance, a fascination that has shaped his life.

In 2001, CEO Jacquelin Grant founded Flexital, based in Chantilly, VA, and hired Turin as its CTO. One of the company's goals is to intelligently develop molecules to replace odorant ones deemed allergenic or environmentally unfriendly. The company holds 27 broad patents on molecules such as Lioral, a synthetic lily-of-the-valley fragrance substitute. Turin says that each substance was a result of hundreds of computations but fewer than ten syntheses. "All the computations are based on my theory," Turin says. "The industry standard for iterations is somewhere between 1000 and 2000," Turin estimates, but he adds that it is a very hard figure to access.

The global fragrance and flavor market is estimated to be between

\$12 billion and \$15 billion, with perfumes making up about \$3 billion of the total. The rest are prosaic shampoos and detergents. Five out of the six biggest fragrance companies are working with Flexital, and the company is "on friendly terms" with the sixth, Turin says.

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Flexital's business strategy is to charge for licensing the scent molecule not for developing the product, even if it was specifically ordered. The R&D work itself is outsourced to laboratories in Germany, England, and Russia. The company's only employees are Turin and Grant. They declined to release the company's financial information. The target markets for the scent molecules developed by Flexital are not only the companies that produce fragrance molecules but also the everyday soap and detergent manufacturers that may be interested in buying "captive molecules" for exclusive use.

The Challenge

Much is unknown about the link between molecular properties and smell. We do not know why there are thousands of odors yet limited receptors, why two very different molecules can smell the same, or what causes some odors to be stronger than others.

The generally accepted stereochemical theory advanced by John Amoore in the 1960s posits that the structures of odor molecules fit into

active sites of nasal receptors like a key to a lock. Turin, however, supports the vibrational theory of olfactory transduction first proposed by G.M. Dyson in 1938 and revived by Robert H. Wright in the mid 1950s. The theory says that receptor proteins in our nose respond to the vibrational spectrum of molecules to discern odor character and that the shape governs the intensity of the smell, i.e., a weak rose versus a strong rose.

A molecule's vibrations are probed by receptors that act as biological spectrometers by using a solid-state mechanism called "inelastic electron tunneling." Odor receptor proteins serve as electron tunnelers, transferring information about smell to the olfactory bulb. The algorithm that Flexital uses to design its fragrance molecules is based on this theory.

Putting the Theory to the Test

Dr. Leslie Vossahl, head of the Laboratory of Neurogenetics and Behavior at Rockefeller University, and her colleague Andreas Keller tested Turin's theory in a double-blind experiment. Their results appeared in the April 2004 issue of *Nature Neuroscience*. "Turin has spent a large part of his career making hypotheses, but in my opinion, he had never put hypotheses to a double-blind test," says Vossahl. "We thought it was only fair that we attempt to put the theory to a reasonable double-blind test before we reject it. It is more difficult to do experiments that are not based on one's own theory. We were guided by what was available in the literature. The upshot of the work is that given the predictions outlined by Luca Turin, we found no experimental evidence in favor of them. While all theories have an inherent appeal to them, this theory cannot perfectly explain the relationship between an odor and how it is perceived by human subjects, which leaves us in a bit of a bind."

"We currently cannot look at the structure of an odor and predict what it would smell like," Vosshall says. "If we could do that, it would be an enormous benefit, both to experimentalists and to people in the flavors and fragrance industry."

Industry Feedback

"Most of the R&D in industry is about making the molecule," says Dr. Avery Gilbert, founder, Synesthetics, Inc. "It is a highly empirical seat-of-the-pants process; more of inspired tinkering. Companies want to know if a molecule is attractive. Is it different from current molecules? What does it cost? The industry always wants substitutes. It boils down to the sense of buying [Turin's] program or buying his molecule. A good molecule they will take from anybody."

"The industry is interested in forecasting of olfactory properties and targeted design of new odorants," says Dr. Christian Margot, Research Chemist, Corporate Research Division of the Swiss company Firmenich. "There is a strong drive to find new odor molecules. Beyond the thrill of discovering new smells, three reasons fuel the research for substitutes of existing materials. First, a lot of natural materials become rare or are not available for worldwide use. Second, other popular chemicals have to be replaced because they tend to bioaccumulate, although they have no proven toxicity. Last, some chemicals, mostly of natural origin like selected terpenes, are suspected to be allergens."

Each company develops what are called "captive molecules," patented novel molecules. Because every fragrance or flavor is a complex mixture of dozens or hundreds of molecules, companies have to build and maintain vast libraries of compounds. Fragrance molecules are obtained by a variety of methods, including the analysis and identification of natural food and flavor constituents. New smell molecules may also be discovered by rational design based on the shape, functional group, and stereoelectronic features of lead molecules. That approach becomes especially useful when the smell is characterized by psychophysical measure-

ments, which allows the development of a structure-activity model.

How were Turin's theories received by the Swiss fragrance specialist? "We are always curious," Margot says. "But so far, there is nothing really exciting."

You Smell with Your Brain

Scent is like an image the brain creates from the signals that come from the olfactory receptors in the nasal cavity. It is assumed that the odor molecule interacts noncovalently with the receptor. Odorant recognition by a cognate receptor (or receptors) appears to be determined by a set of molecular features such as individual functional groups or lipophilic surfaces that must obey precise geometric relationships. Smells such as woody, musky, or smoky can be related to a particular chemical structure. Random chemical modification of a lead molecule often yields surprising results. Sometimes completely different molecules are barely discriminated. "With a model at hand, we can sort of predict specific smells," Margot says.

"Humans seem to have between 350 to 380 different receptors," says Margot, "the evidence gathered so far shows that any chemical will activate a set of receptors. And conversely, any receptor seems to be activated by its characteristic range of chemicals. With these many receptors, you can encode and discriminate hundreds of millions of molecules."

The chemical detection process is just part of the process of smell. The human olfactory pathway is still unknown. The brain converts signals from the nose into an image of a smell. "The long part of that work is the psychophysical characterizations of odor," Margot says. A shared perceptual pathway could explain why molecules that are structurally different from each other smell the same.

Smell is also modulated by adaptation, which may be the reason some people wear too much aftershave. "When you smell a scent at first sniff, it can be quite intense," Margot said. "If you are continuously exposed to that same scent, your sensitivity decreases. That is adaptation. It seems that when two

chemicals are perceived by similar perceptual channels, they cross-adapt. One chemical will decrease sensitivity to the other."

The bottom line is that synthesizing a scent molecule on demand is extremely complicated and requires many empirical inputs. "When you synthesize a chemical that has a good smell, you submit it to perfumers, and if they appreciate it too, they study it in different fragrance blends because everything in perfumery depends on mixtures," Margot says. "Once in the mixture, it often disappears; that means it has no influence on the perceived fragrance. And you don't know why. It hints to the fact that brain processes could refine the olfactory input at a higher level. All the contributions from the olfactory receptors will be processed in a new message by the brain, and we don't know how it happens. Amazingly, there are also lucky chemists [who] without knowing about structure-odor relationships, discover something that smells nice by serendipity."

Despite industrial combinatorial chemistry, developing fragrance remains a bit of a black art. "Perfumers have a combination of tremendous memory, skill, and a willingness to experiment." Turin says, "It took eleven hundred iterations to arrive at the fragrance 'Tommygirl.'"

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