TALK to any perfumer and you will discover that brewing a top-selling fragrance is mostly art and very little science. These olfactory connoisseurs travel the world roaming markets, gardens, jungles and rivers to sniff out exotic new scents – their brains trained to tease apart complex odours and describe them in words. As finely tuned as these professional "noses" may be, however, there isn't a perfumer in the world who can sniff something and give you any idea what the smelly molecule might look like. Nor can they look at a molecule's structure and tell you what its odour is likely to be. Bridging that gap is one of the toughest challenges facing olfactory neuroscientists today.

For other senses, notably vision and hearing, the link between stimulus and perception is clear. Knowing the wavelength of light will tell you its colour; if you know the frequency of a sound you can be sure of its pitch. When it comes to olfaction, though, the link between a thing's molecular structure and its smell is something scientists just don't know.

That poses a vexing problem for the fragrance industry when it comes to developing new molecules to scent products like candles, foods and shampoos. At the moment the best approach chemists have is to design and synthesise a molecule, bottle it and call in "noses" to assess the concoction. It is a costly and imprecise trial-and-error approach.

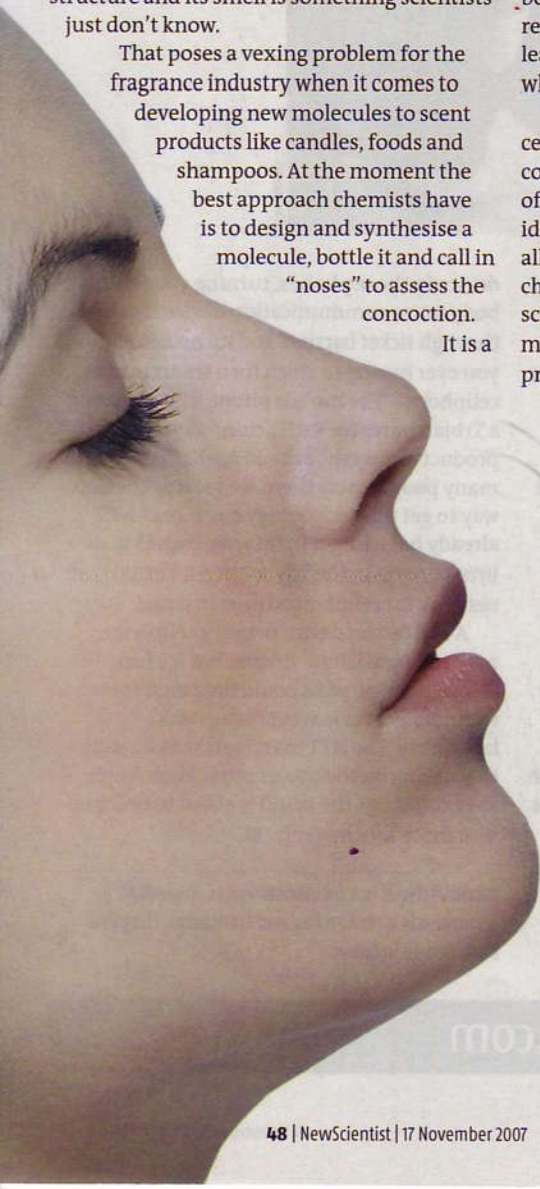
Now a controversial new study published in *The Journal of Neuroscience* (DOI: 10.1523/jneurosci.1158-07.2007) claims to have cracked, at least in part, the scent prediction puzzle. The authors claim they can use chemical structure to predict the "pleasantness" of an odour. "Our study shows that what the nose is doing in sensing pleasantness is detecting a fixed order that's in the world – it's set, it is written into nature," says Noam Sobel, a neuroscientist at the Wiezmann Institute of Science in Rehovot, Israel, a world authority on olfaction and co-author of the study. It's a bold claim, not least because it challenges the received wisdom that cultural conditioning, learning and memory are what determine whether a smell is pleasant or not.

"Pleasantness is not subjective, it's written into nature"

This isn't the first attempt. For over a century researchers have tried to find a connection between scent and the structure of an odour molecule. While chemists can identify broad groups of chemicals – esters, alkanes, ketones and alcohols – by a characteristic odour, the ability to predict scent without fail has remained elusive. The most recent, and controversial, attempt was proposed in 1996 by Luca Turin, then at University College London. He revived an old idea, first published in 1938, that suggests our brains distinguish scents by sensing the molecular vibrations of the odour (*New Scientist*, 3 January 1998, p 34). The idea gained some backing last year when another group at UCL, led by Marshall Stoneham, suggested a mechanism to explain how the vibration theory might work, but it remains unproven, and as yet no practical system for predicting scents has been derived from it.

Indeed, last year, Charles Sell, a senior scientist at perfume maker Quest International, based in Ashford, UK, published a sobering review in *Angewandte Chemie* stating that despite "recent advances in our understanding of the mechanism of olfaction, our ability to predict odour properties of molecules will not improve significantly in the near future".

And yet people can tell you right away, within a fraction of a second, whether something smells good or bad to them. The question is, how do we do this? "Nobody knows what makes a molecule smell the way it does – there doesn't seem to be any simple general rule," says Rehan Khan, a neuroscientist at the University of California,



Berkeley, and the lead author of the study. "Nobody knows, if you change this single bond to a double bond, whether the scent will go from a flower to smelling like lime."

Khan and his colleagues reasoned that there must be something more than a trivial feeling of pleasure at issue, because this feeling of "pleasantness" appears to dominate our perception of odour. To try to find out what this might be, the team turned to data gathered in the 1980s by the chemist Andrew Dravnieks, then at the Institute of Olfactory Sciences, Park Forest, Illinois, who launched the first systematic effort to quantify odour perception.

Dravnieks asked more than 150 perfumers and olfactory scientists to describe 144 individual odorants using a set of 146 verbal descriptors such as banana, cantaloupe, chocolate, woody, alcoholic, crushed grass, gasoline, resinous, smoky, musky, burnt and seminal. For each of the descriptors the participant was asked to rank the odour from 0 to 5 depending on how chocolatey, musky, woody and so on each one was. This yielded a series of 146 measurements for each odour.

Khan and Sobel wanted to simplify this a little, so they devised a single measure to help them rank each molecule. They settled on a well established statistical technique called principal component analysis (PCA) to condense each of the 146-digit strings down to a single number, which they plotted as points on a line. Odours at one end of the line were very pleasant – fragrant, sweet, perfumy, aromatic and floral. At the other end of the line were odours described as sweaty, sharp, rancid, putrid, foul, decayed and sickening. "When you boil down all the words that people use to describe odours to just one number, the number would correlate with [what they would say] if you asked them to gauge how pleasant it was," says Khan.

Khan and Sobel then tested whether this ranking would stand up to further analysis. If it really did reflect pleasantness, they reasoned, then odours close to each other on the line should smell similar. To test whether this was true, Sobel and Khan chose nine odorants from the 144 and measured the distances from each one to each of the other eight. Then they asked a group of 21 volunteers isolated in separate rooms to sniff each pair of odours and rate them according to how similar or different they smelled. Sure enough, odour pairs that were ranked as similar were also close together on the line. For example, as one might guess, garlic oil and onion oil are close, separated by just nine units out of a possible 183. Vanillin and onion oil, in contrast, are separated by about 80 units. You can play around in this odour space on Sobel's website: www.weizmann.ac.il/neurobiology/worg/

Now the challenge was to see whether any aspects of the smelly substances' molecular structure correlated with pleasantness. Sobel, Khan and their colleagues took 1565 odorant molecules and described their physical structures using 1514 objective measurements, such as the number of atoms and functional groups, numbers of various bond types, molecular weight and so on. Again for each odorant, they used PCA to condense its measurements into a single number. When they plotted these numbers along a single line, a now-familiar correlation became clear. "The amazing thing is if you actually walk down that line and smell them one by one," says Sobel, "they'll go from unpleasant to pleasant."

In general, the "molecular compactness" of an odorant correlated with its pleasantness; heavier and more compact molecules tended to smell better, and the lighter and more spindly molecules tended to smell worse. That meant that the researchers could use the structure of a molecule to predict whether it would smell good or bad – and they would be correct much of the time.

Sobel and Khan reasoned that if their model was good they should be able to predict the pleasantness of a molecule from its structure alone. To test this they picked about two dozen odorants that they had never smelled before from a bank of chemicals used in olfaction experiments. They predicted each one's pleasantness using the new system, then asked 20 volunteers to smell and rate them. The volunteers' assessments were a good match for the team's predictions.

"That's kind of freakish because we all tend to think of pleasantness as something reflecting our inner structures and desires, and history and cultures," says Sobel. "What we are saying is no. A large part of it is written into the structure of molecules. Just like colour is linked to the structure of light and pitch is linked to the structure of sound, pleasantness is fundamentally linked to the structure of odour." ▶

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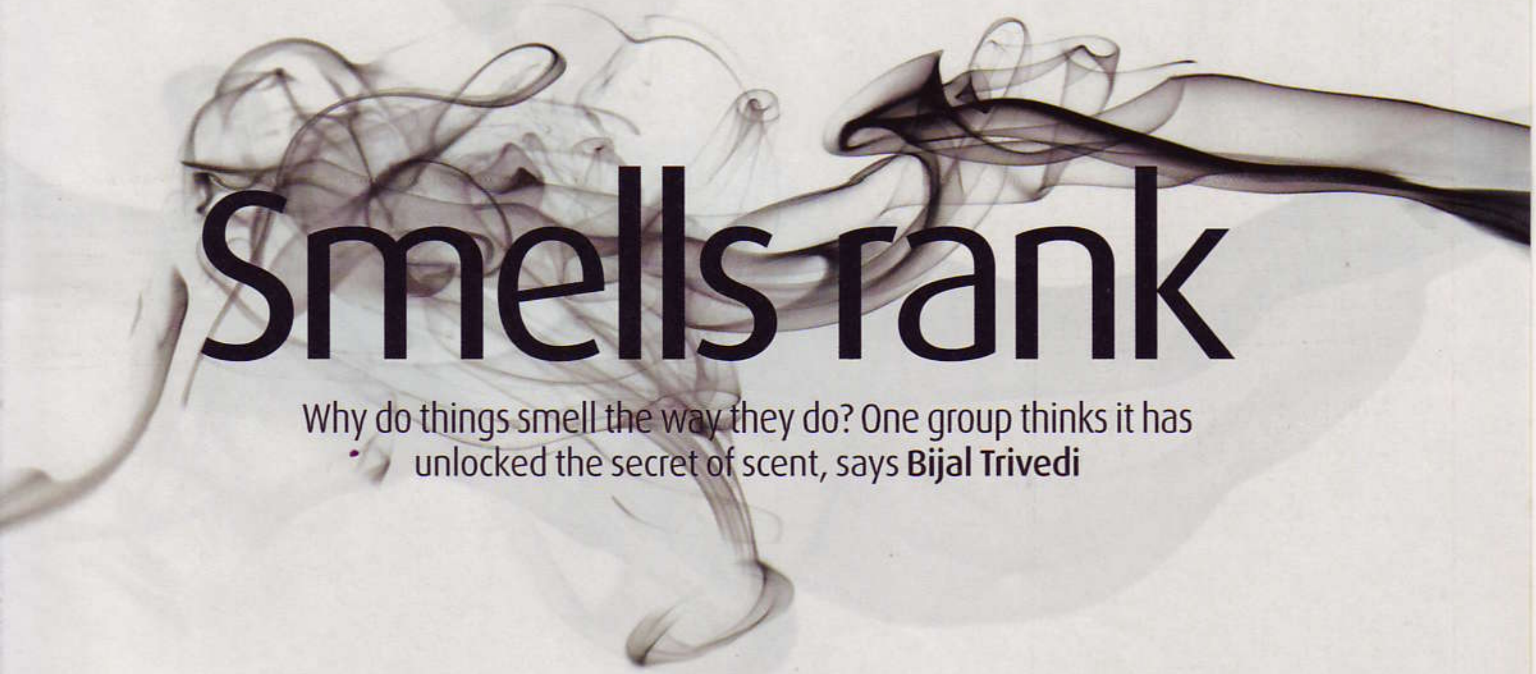

Smells rank

Why do things smell the way they do? One group thinks it has unlocked the secret of scent, says **Bijal Trivedi**

Sobel's finding that pleasantness seems to be at least partly innate, and thus genetically determined, agrees with another recent study. In September, Hiroaki Matsunami, a neurobiologist and geneticist at Duke University Medical Center in Durham, North Carolina, published a report in *Nature* (vol 449, p 468) showing how perception of the testosterone-derived steroid androstenone could be perceived as sweaty, or sweet and floral, or odourless, depending on the gene variants a person carried. For example, people with two copies of the most common form of the *OR7D4* receptor gene were more likely to find androstenone offensive. People with another variant of the same gene were less sensitive to the odour and found it pleasant. The results are the first to link the function of an odour receptor with human perception.

So what are we to make of evidence that points to odour perception being culturally variable? Consider the sweet Asian fruit durian, which many people say smells of rotting flesh and as a result is banned in many taxis, hotels and airlines throughout south-east Asia. Then there are those fine French cheeses that to some smell like vomit or dirty socks.

To probe this phenomenon Sobel and Khan's team chose 27 odorants rarely used in olfaction experiments and tested them on three groups: Americans in California, Jewish Israelis and Muslim-Arab Israelis. The team also asked the volunteers to rate not only the pleasantness but also the "edibility" of the smells. Each group's preferences proved to be quite similar, and closely matched the team's predictions, suggesting that culture has little to do with how we perceive smells.

That's a conclusion that runs counter to current thought, and it is not shared by Rachel Herz, a neuropsychologist at Brown University's Alpert Medical School in Providence, Rhode Island. There's no such thing as a universally pleasant aroma, insists Herz, who points out that the choice of Californians and Israelis could not be expected to reveal cultural preferences because all the groups are fairly westernised. "If I were doing the experiment, I would have chosen groups from Japan, Italy, South America and Africa, for example."

Sobel points out that it's only our response to food smells that seem to vary from culture to culture. "People confuse pleasantness and appetitiveness," he says. "French people learn to associate certain qualities with the odours of cheese – that does not mean they find it pleasant. My winning argument on this is that you will not find a perfume in the odour of cheese... the same thing is true of the durian."

"To me it is clear that some chemicals are bad for all the population, like sulphurous ones," says Matsunami. "I've never met anyone who liked skunk. There is an innate repulsion to this scent, and there are a number of others that we just seem to love or hate."

Khan and Sobel's study has kicked off a lively debate among olfactory scientists. "People either loved it or hated it," says Sobel. Some say that the team may have developed a unique tool for probing brain functions and provided a foundation for showing how odours might be encoded in the brain. Others doubt every aspect of the study from the methodology to the primary finding to its practical applications.

Khan and his colleagues are not the first to search for a way of chemically classifying odorants. What distinguishes the new work, according to Michael Leon, a neurobiologist who studies learning at the University of California, Irvine, is that no one has extracted a common element from a range of odorants that relates all of them on a single dimension. Khan and his colleagues have come up with "a very important finding", he says.

"I've never met anyone who liked skunk. There is an innate repulsion to this scent"