The allure of fragrance

New findings on the sense of smell and its relationship to multimedia

What types of information are difficult to communicate to others? Sound? Visual images? Hardly. Both are ubiquitous in mass media today, to the point of overuse. Is taste difficult to communicate? Smell? Touch? The latter three are likely to become the next additions to the expanding world of multimedia. For this article, we have chosen to focus on the sense of smell, possibly Homo Sapiens' most underdeveloped sense. As we researched the subject, it became clear that our knowledge of smell has advanced dramatically over the last decade and that fragrances could very well become a part of multimedia communications.

An experimental breakthrough
Vacuum Cleaners at the Microscopic Level

Recently, curiosity about our sense of smell has been attracting worldwide attention. To gain insight into the subject we traveled to Aichi Prefecture, western Japan, to tour the National Institute for Physiological Sciences. It was there we interviewed Dr. Takashi Kurahashi, who worked at the institute as a researcher for many years before accepting a position at Osaka University in November 1996. Much of his old research apparatus was still intact and he explained, "We are still busy preparing to move equipment."

Kurahashi, 36, is a leading researcher investigating our sense of smell and recently had an article outlining its basic mechanisms published in the British science magazine *Nature*.

With the notable exception of our sense of sight, most research into understanding the senses is rather primitive. When it comes to smell, in fact, virtually nothing was known until about ten years ago. Until then, people sometimes believed it was connected to wave-like motion, or spiritual phenomenon. About ten years ago there was also a trend toward employing techniques of molecular biology to various kinds of research. At that time, I was graduate student working in biological research, so I was part of this new wave. At first, I had no idea where it was leading and sometimes felt like I was investigating something very exotic, like telekinesis or something.

But ten years ago, the mechanism of how the nose functioned was already well understood.

Yes, it's true we knew there were around 10-million olfactory cells inside the nose. But exactly how they reacted to stimuli as well as the biochemical transmitters involved were still largely unknown. The key to increasing our understanding was finding the right research technique. The diameter of each olfactory cell is only about 10 microns, making it hard to investigate easily.

Let's review how neurological research had been done up to that point. Traditionally, researchers would stimulate neural cells with an electrode to determine their response to various stimuli. Naturally, the smaller the electrode the better. They began with tips approximately 0.1 micron in diameter, and as technology evolved these became even smaller. However, efforts to reduce tip size were all in vain as the experiments

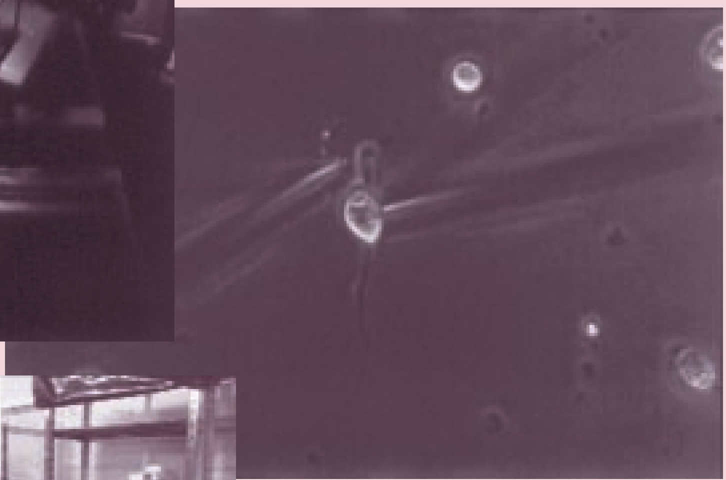
Takashi Kurahashi

Dr. Kurahashi received a bachelor degree in biology from Aichi Education University and a doctorate degree from Tsukuba University, Ibaraki Prefecture. After working for many years at the National Institute for Physiological Sciences, Aichi Prefecture, he accepted a position in November 1996 as an associate professor of physics and biological science at Osaka University. His various awards include the Möet Hennesy-Louis Vitton International Science award and the Leonardo da Vinci award.

■ Experimental apparatus that facilitated a breakthrough in olfactory research

● We analyzed the electrical response produced by stimulating cells with various fragrances.

◀ An electrode is used to vacuum the cell and a micropipette injects a fragrance molecule.



▲ Both the micropipette (left), which delivers the fragrance molecule, and the measuring electrode (right) are in intimate contact with an olfactory cell.

While operating a PC, researchers must adjust the frequency and quantity of fragrance to be injected. Response data is then quantified to determine the degree of excitement. ▶

just didn't go as smoothly as hoped. During this rather unproductive time period, though, German researchers developed in 1981 a technique called the "patch clamp."

The German researchers approached the problem from a totally different point of view, using a relatively large electrode tip that was 1 micron in diameter. Instead of penetrating the neural cells, they placed the electrode tip in intimate contact with the surface of the cell. Then they began suctioning the cell through that electrode. As the suction increased, the cell membrane broke leaving the electrode in direct contact with the cell's interior. Using this method, researchers were finally able to fully investigate the electrical response of olfactory cells.

You may recall playing a trick on someone as a child by putting a vacuum hose on their cheek or arm and pulling their skin. The patch clamp is quite similar to this childhood prank. Dr. Kurahashi pioneered adapting the patch clamp to investigate olfactory cells, also adding his own ideas and refinements. The result: a quantum leap forward in our knowledge of how olfactory cells work. The above photograph shows Dr. Kurahashi's experimental apparatus.

A single olfactory cell from lab animals such as newts was used in this experiment. The center photograph shows two needles, one of which is an electrode in intimate contact with the cell, the other a micropipette that chemically stimulates a small area with a fragrance. This apparatus employs a special monitoring system that facilitates adjusting the quantity and frequency of stimulation. Unfortunately, olfactory cells only respond for about 30 minutes. During that time, a researcher must simultaneously control stimulus levels, monitor responses, move the pipette and operate the keyboard. It turns out to be something of a battle against time.

At first I was looking for a part-time position to help defer my expenses as a student who was majoring in education. I was cleaning beakers and other equipment, like a dishwasher. But I was really interested in electronics, so I asked my supervisor if I could play with the computer. I gradually developed an interest in the research going on in that department, and found myself immersed in the field of physiological science.

Dr. Kurahashi is unique within his field in that he is well-versed in computers, something he capitalized on for a significant experimental success in 1985.

It was from that point that my work really started to take off. Last year I published an article in *Nature* on the mechanism of olfactory response, a subject connected to some of those early research projects.

Now let's take a look at why we tend to become desensitized to smells after a given period of time—even strong smells.

A model for information communication
Analyzing a Single Flagellum

When a fragrance molecule comes in contact with an olfactory cell, an electrical response is produced. I checked different locations on a single cell until I found the point of maximum electrical response, which turned out to be the flagellum.

Let's move on now and talk about how an external stimulus is turned into an electrical signal. A researcher from New York's Columbia University discovered in 1991 a likely match between a specific receptor protein and fragrance molecule. There are at least 1,000 different kinds of olfactory receptors, but each recognizes and responds to just one fragrance. Each olfactory cell, however, can only utilize a few of its receptors at once. So if it is not using the receptors for a particular fragrance, it will not respond to it.

How does this electrical response get transmitted? The figure shows a receptor on a flagellum responding to a fragrance molecule, which results in a biochemical change from G (G-protein) to AC (adenyl acid cyclase). Because the AC is in an excited state, it converts ATP within the flagellum to cAMP. Basically, this excited state travels from one cell to another until finally a door opens.

The surface of the flagellum contains a pathway called an ion channel, which is normally closed. But when levels of cAMP within the flagellum increase, the pathway opens, and Natrium and positive Calcium ions are allowed into the cell, which then enters into a state of electrical excitement.

Dr. Kurahashi took this experimental method one step further. He wanted to find out what happens when controlling the level of cAMP, which is the information carrier.

I packaged cAMP in such a way that is appeared inactive and injected it into a cell. Then I exposed the cell to light energy. This caused the cAMP to break out of its packaging and became activated, and in direct with the cell for the first time. The beauty of this is that depending on how much light the cell is exposed to, the level of activity changes allowing me to monitor what happens during the information transfer process.

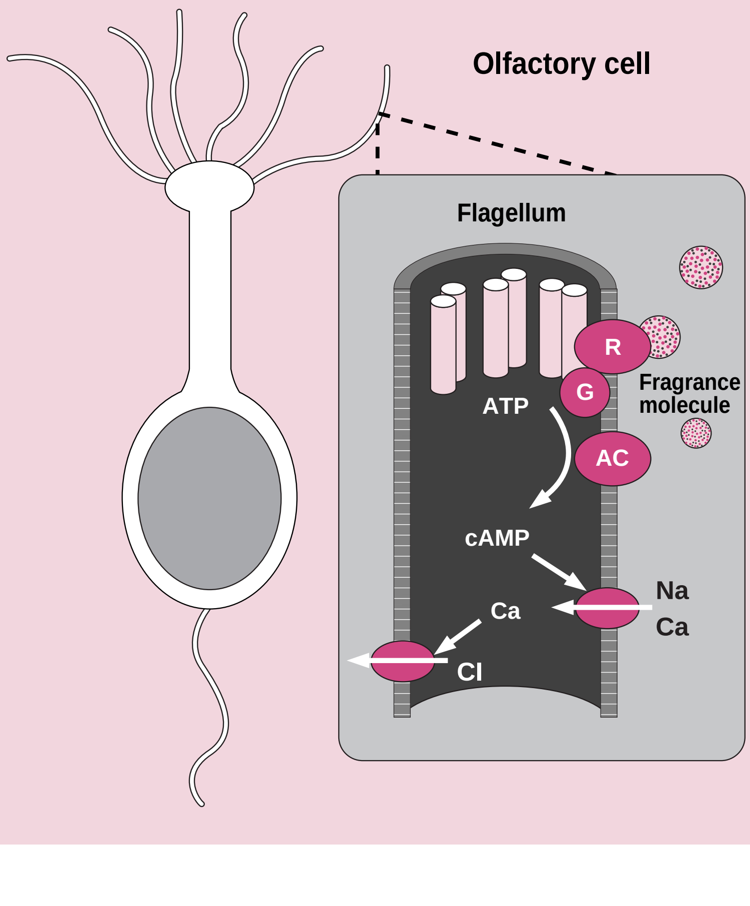
Dr. Kurahashi discovered that a Calcium ion enters the cell and activates cAMP, which acts like a gatekeeper to then close the ion channel, blocking more Calcium ions from entering. This explains why after a certain time we become desensitized to a strong smell. A flagellum having only a 0.2 micron diameter possesses an extremely sophisticated ability to transfer information.

Think of a dog, who begins sniffing something, but then forcefully blows air out his nose, almost like a sneeze. What this does is wash Calcium ions out of the olfactory cells. When people enter a room and smell gas, they begin sniffing, an unconscious attempt to sensitize themselves to the smell.

This means that for wine tasting, from the standpoint of molecular biology, it's better to consciously keep sniffing to keep your nose sensitized. During the past decade, this and almost all other functions of the olfactory cell have been discovered.

■ Experiments revealing the mechanism of olfactory cells

This drawing may appear complicated, but it unveils the mystery of fragrances.



The gate is opened by cAMP, the last runner in a relay race transmitting olfactory cell response. When the gate opens, positive ions of Natrium and Calcium enter the cell and generate an electrical current, just like in a human being.

R: receptor protein
AC: adenyl acid cyclase
G: G-protein

Calcium closes the ion channel gate after entering the cell, which is why we become desensitized to smells after a short time. This gate also affects us through a phenomena called "musking" in which the introduction of a new smell desensitizes us to an old smell.

There is actually one more path through which negative Calcium ions can escape. Na ions flow into a cell quite easily in an arid environment, however the flow of Cl ions out of the cell is sparse. In contrast, in a humid environment, Na ions do not flow into the cell as readily, however, it is easy for Cl ions to leave. In both situations the total ion flow is the same. This is why, whether you're in a desert or a sauna, you're still able to recognize smells. Isn't that a neat trick? (This is another discovery made by Dr. Kurahashi.)

For additional information, please refer to the research summary posted on Dr. Kurahashi's homepage (http://venus.bio.sci.osaka-u.ac.jp/kura_pub/kurahasi.html)

People are telling me my work in the field is over, that I have nothing more to do. But to me, this is just the beginning. Now let's take a look at the role of fragrance in our everyday lives.

The analysis and synthesis of fragrance

A Research Center in Full Bloom

If you pinch your nose and close you eyes and drink orange juice, grape juice or lemon juice in a blind test, you probably can't distinguish them. In many cases, people think they are tasting, but are actually smelling. Similarly, consumers sometimes choose soap or detergent based on how nice it smells.

Who creates these smells? In most cases, it's not the cosmetics or food manufacturer, but a company specializing in making ingredients for perfumes. We spoke with a specialist in fragrances, Mr. Michiaki Kawasaki, senior vice president of Takasago International Corporation, one of the top five fragrance companies in the world.

Let's say a cosmetics company wants to launch a new kind of cosmetic soap. For this to happen, they first contact several fragrance makers and brief them on a marketing image, for example, 'a fantasy world.' Then fragrance designers start to work, combining scents to produce a prototype lipstick they present to the client. Fragrances are all about images. In our lab, designers discuss smells as being, for example, red or white—just like visual artists.

On the other hand, fragrance designers for the food industry seem more like chemists, perhaps because they want to recreate fragrances that imitate those found in nature.

Michiami Kawasaki

Michiaki Kawasaki, president of Takasago International Corporation, is also its senior academic director and an honorary board member. He received his undergraduate degree in agricultural chemistry from Tohoku University's Department of Agriculture.

Other positions he has held include: Director, Japanese Cosmetic Science Society; Director, Food Hygiene Society of Japan; Editor, Japan Perfumery and Flavoring Association; Director, Odor Research and Engineering Association of Japan.

Even a fruit juice that claims to be 100% pure, contains a fragrance. When you sterilize juice by applying heat, its natural fragrance evaporates. For the case of orange juice, an orange peel fragrance is added, though the juice is still classified as 100% pure. And sometimes it costs too much to use only natural ingredients, and that's where synthetic fragrances come in. A recent example in our labs is matsutake mushrooms (extremely expensive). We analyzed these mushrooms to create two fragrances, which enabled us to recreate 80% of the natural matsutake mushroom aroma.

Lab researchers are also trying to create totally new fragrances by altering the chemical composition of fragrances found in nature. They can sometimes identify a smell just by seeing its chemical formula.

While in some cases this may be true, in reality there is just no fixed relationship between fragrance and chemical composition. For example, the musk fragrance comes from a complex chemical compound that would be prohibitively expensive to synthesize. But you can recreate this complex scent with a simple chemical compound that is nothing at all like what is found in nature.

There is so much to learn about the field of fragrance.

Some world-famous fashion designers sell soap that contains decomposing organic matter, a smell we identify in our labs as sea cucumber. The aroma of organic matter creates the impression of a high-quality fragrance.

Mr. Kawasaki is engaged in studying the raw materials that make up fragrances. If he were to meet with Dr. Kurahashi, an expert in the biochemistry of smell, what would he ask him about?

Based on an understanding of the olfactory response mechanism, perhaps someone could synthesize a fragrance that humans do not become desensitized to so easily. We are doing research on fragrance materials, but we would like to create a perfume, for example, that a person could enjoy all day long.

Actually, I've been working for about ten years in the field of biological psychology. But Dr. Kurahashi is studying information transfer in the human body, while I'm investigating the effects of fragrance on human beings.

In brain wave studies, it's been found that jasmine makes people more alert, while lavender makes them relax. Some people asked Mr. Kawasaki, a chemist, why he needed equipment for measuring brain waves.

Once I was involved in product safety testing of various scents. Up until about ten years ago, testing for skin rashes and other adverse affects were the only kinds of tests getting much attention. I thought to myself, I would also like to do research on the positive effects of scents, and that's why shifted my career path.

During a tour of his lab, Mr. Kawasaki told us that each floor has been dedicated to a specific purpose, with separate levels for cosmetics, food products, fragrance synthesis and fragrance analysis. I was greeted with a new aroma on each floor. On one they were extracting fragrance ingredients from natural materials, and he said, "In the springtime this hallway is filled with many different kinds of flowers." Indeed, when this article is published, that very corridor will be filled with many different smells.

The use of fragrance in mass media and its relationship to brain research

Following the Instincts of the Heart

One of the questions you asked me was whether fragrances could be used in mass media. I remember reading a science magazine when I was in elementary school about a 21st-century TV set that would let you smell what was on the screen.

Dr. Kurahashi's answer was much more thoughtful than we had expected.

In fact, my response to your question is closely connected to how fragrance could be used in mass media. My future projects involve developing scientific formulas that predict or model the behavior of an olfactory cell. It's been shown that the intensity of a smell is directly related to the electrical response of an olfactory cell.

In short, the cell itself is able to recognize the strength of a particular smell. As mentioned earlier, olfactory cells use only a small fraction of their 1,000 receptors, which means the cell is already recognizing a particular scent by selecting which receptors will respond. This means that even if cells encounter a complex fragrance containing many types of fragrance molecules, one can scientifically model the cell's response. By observing which cells react, one can distinguish between a melon and a banana smell, almost like the RGB (red-green-blue) principle governing our sense of sight. This kind of concrete evidence helps create the feeling that one day fragrance could be used in mass communication.

At least we are much further along than we were ten years ago. We now know what needs to happen to allow us to use fragrance in multimedia. In contrast to the sense of sight with its three primary colors, the olfactory cell has some 1,000 different receptors. But each receptor could be modeled using a 16-bit analysis function. The amount of information required to transmit a particular smell would be far less than for sight. So the problem is converting data sent to a TV screen into an actual fragrance.

Mr. Kawasaki, whom we talked with earlier, told me he was once asked by a home appliance manufacturer whether it was possible to make a TV set that would allow the audience to smell what was on the screen. His reply was that both fragrance and taste come from the same material elements, so such a TV set could recreate the experience of actual food items, like tempura. While the use of fragrance in mass media is one possibility for the future, Dr. Kurahashi is thinking on a much larger scale, namely to use fragrance as a tool to learn more about the human body.

For example, a melon fragrance involves some 100 different receptors. But no one has proposed a model about how this information results in the awareness of a melon. Right now our research is limited to investigating the behavior of cells at nerve endings, but I'm hoping we can get closer and closer to investigating the brain itself. If you consider our sense of sight, for example, there is a theory that in the core of the brain exist 'grandmother cells' that only recognize your grandmother's face.

Come to think of it, some smells can trigger very old memories.

The sense of smell affects our perception more than we realize. I personally believe that when people understand our sense of smell, we will have a theory for emotions, memory and learning styles. Some people believe whatever approach is successful with olfactory cells can be applied to brain research because of their similarity with nerve cells. And if we could adapt such techniques to brain research, our understanding of memory would advance dramatically. It's been said the human body cannot be fully explained by science, but some scientists still believe it can, and are studying the brain. I share their sentiments, though I'm not approaching it from the brain standpoint, but rather from molecular biology.

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There is a single clue in a room where we expected no clues at all. The one clue we had was the phenomenon of fragrance. Using it as a starting point, perhaps we can unravel the mystery of the human body.