and thriving from the excitement of experimentation is my key to being a happy scientist. But for all but the most brilliant scientists, our real influence will come through that most undervalued part of our work – teaching.

What's your next historical work on? I'm thinking about the power of metaphor in science and the way it frames and limits how we think about the natural world. I've already written about 17th and 18th century approaches to heredity, and the history of the genetics of behaviour in the 1950s. In both cases, scientific progress was limited by the metaphors people used. The early modern view that animals were machines could not cope with hereditary phenomena that combined both blending inheritance and particulate inheritance, and so people simply ignored the problem. 250 years later, the ethologists of the 1950s and 1960s seem to have not picked up on the analogies with cybernetics — feedback loops and so on — that were being used with such effect by the molecular biologists. I want to expand this to a more general analysis of the role of metaphor in science.

What's the next Big Thing? In broad terms, the molecular tools that have been developed in a handful of model systems will be applied to a wide range of really interesting organisms that have a known ecology and natural history. More specifically, I think we may start to look at animal behaviour in a novel way. With the genomes of the 12 *Drosophila* species, *Nature* published a think-piece by Leslie Vosshall. She concluded with a suggestion that *Drosophila* could be used to study the neurobiological bases of emotions such as empathy and hatred – "The only a priori limitation to studying any of these traits is the belief that flies can show such emotions and the design of a plausible behavioural paradigm to measure them." At the time, I thought this was hubristic. On reflection, I think she may be right, and I am currently pursuing some of these ideas. In 10 years time, I suspect we will have made some surprising progress using insects to study traits that were previously thought to be restricted to higher animals.

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Quick guide

Ocelli

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What are ocelli? Ocelli (singular *ocellus*) is Latin and means little eye. One to three ocelli can be found in many insects, located at different positions on their heads. Ocelli have evolved as a second visual system, in addition to the compound eyes that insects are famous for.

Which insects have ocelli? Most flying insects have ocelli, while those that never get airborne usually don't have them. There are of course exceptions, but there is a high probability that, if you are a flying insect, you will have ocelli. For example, locusts, dragonflies, cockroaches and most species of flies are all equipped with ocelli. Many studies on ocellar function have been done on these species.

What do we know about how ocelli work? That is a good question. It is only recently that progress has been made towards an answer. Let's start with the way that ocelli are constructed. Ocelli are similar to our own eyes in that they use a single lens to collect light and project it onto a layer of light-sensitive cells, called photoreceptors. As frequently done with our eyes, you can compare an ocellus to a camera — a very bad one, though. By modifying the curvature of the lens, our eyes produce a crisp image more or less independent of the distance from the objects we are looking at. This is called accommodation and is similar to shifting the lens of a camera to focus an object precisely onto a CCD chip or film. The lens of an ocellus, however, cannot accommodate or be moved back and forth. Even worse, the ocellus lens is positioned so that it always under-focuses. As a result, the image at the photoreceptor layer shows hardly any image details. This is similar to what you get if the autofocus of your camera has failed to adjust quickly enough when taking a snapshot, and all you can see on the photograph are some bright and dark blurs.

So what are ocelli good for? Sorry — I didn't quite answer your question on the function of the ocelli, did I? They are obviously not made to provide any image details about the visual surroundings. But, like a photometer, they provide information about light levels. Imagine an insect buzzing around. It is usually much darker in the lower parts of its field of vision than in the upper parts, even under cloudy conditions. We know from studies in flies that there are three ocelli (Figure 1) to sample light levels at different but slightly overlapping patches in the upper visual hemisphere. The left and right lateral ocelli integrate light from extended areas centred about 45 degrees above the horizon in the left and right part of the lateral field of vision, respectively. The medial ocellus monitors the dorso-frontal part of the surroundings.

If the fly is caught by a gust of wind and is rolled to the left, the visual field of the left ocellus is suddenly exposed to the darker ground while the right ocellus, now seeing more of the sky, receives much more light. The neural machinery along the ocellar pathway analyses the change in illumination between the left and right ocellus, which tells the fly that it has been rolling to the left. Of course, this works also for roll movements to the right and, if the medial ocellus with its frontal visual field is included, the ocellar system can also figure out whether the fly encounters a nose-up or nose-down pitch movement. Altogether, the ocellar system informs the fly about changes in attitude, or in other words, body rotations in the horizontal plane.

But can't flies just use their compound eyes to work out orientation in space? That's a very good point. Actually, flies do use their compound eyes as well to work out what their orientation is or how they are moving in space. But there are a couple of reasons why compound eyes alone are not enough to provide information about orientation and self-motion. For one, the neural pathways receiving visual input from the compound eyes consist of a greater number of consecutive processing stages. Each stage is set up by specific types of nerve cells to process the incoming

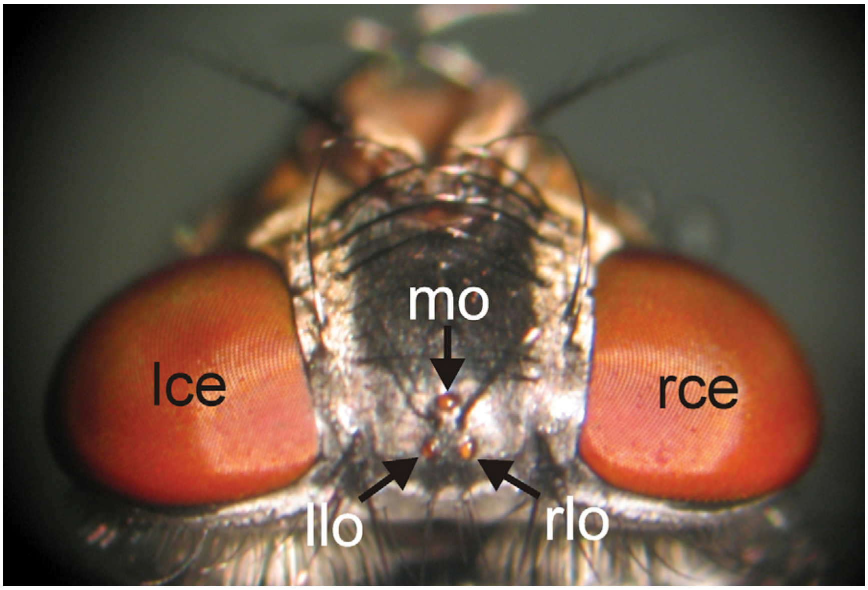

Figure 1. Top view of the blowfly head.

lce and rce mark the left and right compound eye, respectively. The three ocelli of the blowfly are labelled mo, llo, and rlo, which stands for medial, lateral left, and lateral right ocellus. The distance between the left and right margin of the blowfly head is about 3.5 mm.

signals. Processing the signals and transmitting the results to the next stage costs time. For example, one of the compound eye pathways computes how the fly is moving relative to its environment — which is related to the attitude changes signalled by the ocelli. Another one works out whether something the fly might be interested in is moving out there — say a potential mate. In both cases, the fly needs information about the direction of motion, and the analysis of this is more demanding. To work out the direction of motion, the fly needs visual inputs from two different retinal locations. One of these inputs has to be delayed for a certain amount of time before it is correlated with a signal from a neighbouring location. Without going into too much detail, the compound eye pathway has at least twice as many processing stages as the ocellar pathway and — in the context of working out directional motion — involves an additional time delay. Altogether, the compound eye provides the fly with information about its orientation in space and its orientation changes, but the ocelli, which only signal orientation changes, can do it much faster.

What are ocellar signals used for?
Another important question, though one that is not easy to answer for all animals equipped with ocelli. I should probably stay with flies again, because they have been studied in some detail with respect to ocellar function. Ocellar signals are sent to a region of the fly brain called the lateral protocerebrum. There, the signals are transmitted to descending neurons, which connect to motor systems in the thoracic ganglia, such as the flight motor and the neural circuits controlling head and leg movements. There are additional connections to parts of the neck motor system, located in the head, and to other brain regions. The most likely uses to which a fly puts ocellar signals are: to maintain its orientation in space; to stabilize its flight; and to keep its gaze level. All of these tasks can be summarized as stabilization reflexes.

Are signals from the ocelli and compound eyes combined to control stabilization reflexes?
Yes, they certainly are. This is one of the fundamental principles in behavioural control throughout the animal kingdom. Most animals are equipped with more than one sensory system, which they employ in parallel to control reflexes and other behaviour. The reason for this is that biological sensors, as a result of their design, are limited to a certain range of stimulus velocities that they can reliably detect— each sensory system has a limited bandwidth. The behaviour that needs to be controlled, however, can be very slow or very fast and the overall range of possible velocities at which orientation changes of an animal occur may significantly exceed the bandwidth of a single sensory system.

Let me give you an every day example: if you wash your hair while taking a shower and you close your eyes so that the shampoo doesn't burn them, it can be quite difficult to keep balance. Sometimes — in particular when you are distracted because you could not avoid getting shampoo into your eyes — you only realize that you are falling over when it is almost too late. Closing your eyes means that the sensory information about slow changes in your posture mediated by your eyes is suddenly missing. What you are left with is the inner ear organ that indicates changes in orientation — but only at higher velocities. It's only when you start falling over beyond a certain speed that the change reaches the velocity for the inner ear organ to sense it and let you know what's happening. This has something to do with the fact that the inner ear organ uses so-called mechanoreceptors, which are particularly good at sensing fast changes but can hardly pick up on very slow ones. Normally, the eyes and the inner ear organ complement each other to detect both slow and fast changes in orientation.

For flies, the situation is very similar. The compound eyes detect slower changes in attitude, while the ocelli cover a higher range of velocities. Some flies employ an additional sensory system that functions in a similar way to our inner ear organ. This is a mechanosensory system known as the halteres, which work like little gyroscopes and sense very high angular velocities up to thousands of degrees per second. So the compound eyes, ocelli and the halteres together cover the entire range of orientation changes the fly encounters during walking and flying. The signals all combine to control stabilization reflexes. How the signals from these different sensory systems are weighted and at which stage the combination takes place is still under investigation. But it seems that, at least in the fly, such integration occurs quite early on in the visuo-motor pathways, which helps the animal to keep its gaze level and remain stable in the air during rapid movements but also when slowly drifting.

What is the point in studying the ocelli and other insect sensory systems? There are two answers to that question. For one, using sensory information to control balance and gaze, or to produce other meaningful behaviour, is a common theme amongst all animals, including humans. As I just mentioned, the control of balance and gaze has to work at different speeds — which is true for flies and humans. For instance, flies and humans keep their gaze aligned with the external horizon, which tremendously simplifies the processing of visual information. This is because the connections in the visual system are wired up in a way that assumes a certain orientation of the world when it is projected onto our eyes. Deciphering text when all the words are printed upside-down takes considerably longer than reading upside-up. Although this is an extreme example, it nicely illustrates how important it is to keep the visual environment in its natural upside-up orientation. We do it by moving our head and our eyes relative to our body, while flies can move only their heads to solve the same task. And yet, there are general functional principles that are similar in flies and humans. For slow gaze stabilization, we both use visual information; and for fast stabilization we exploit mechanosensory signals. The big advantage of studying comparatively simple animals such as flies is that we already know a lot about the neural circuits supporting gaze stabilization. We even know the individual neurons that combine ocellar and compound eye signals by name; these play a cardinal role in stabilization reflexes, in general. So, studying the neural mechanisms underlying stabilization reflexes in flies, where both the behavioural and neuronal performance can be quantified, may well help our understanding of how the same task is solved in more complicated animals, such as humans.

The other reason why it is interesting to study ocelli and other sensory systems in insects is because biological systems control gaze and flight in a fundamentally different way from man-made technical systems designed to achieve the same goal. Technical systems, say in aircraft control, use only a small number of highly accurate sensor measurements in combination with heavy supercomputing to come up with command signals to ensure flight stability. Biological systems follow an entirely different approach: they take thousands of local, often noisy, signals and combine the information in a task-specific way, so that the combined outcome can be used immediately for control purposes. They replace the heavy supercomputing stage with clever signal integration. A detailed understanding of exactly how the nervous systems of insects do this may inspire the future design of control engineering architectures.

Where can I find out more about ocelli?

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Primer

The natural history of antibiotics

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Selman Waksman first used the word *antibiotic* as a noun in 1941 to describe any small molecule made by a microbe that antagonizes the growth of other microbes. From 1945–1955 the development of penicillin, produced by a fungus, along with streptomycin, chloramphenicol, and tetracycline, produced by soil bacteria, ushered in the antibiotic age (Figure 1). Today, the evolution of antibiotic resistance by important human pathogens has rendered these original antibiotics and most of their successors largely ineffective, and if replacements are not found, the golden age of antibiotics will soon come to an end.

Understanding the success and failure of antibiotics requires understanding their natural history — the origins, evolution, and functions of the molecular medley that has played such an important role in human health. Studying their natural history could also result in new strategies to find novel antibiotics and delay resistance to existing ones.

Assembly from readily available parts

Antibiotics do not look like the familiar molecules in beginning biochemistry texts; they usually do not even resemble each other. In spite of these apparent differences, they are assembled from the same types of building block through enzyme catalysed reactions that closely resemble those used in making proteins, fatty acids, and polysaccharides. For example, penicillin is derived from a tripeptide of three amino acids, two of which are proteinogenic (cysteine and valine) and one of which is an intermediate in lysine metabolism (α-aminoadipate) (Figure 1). In conventional polypeptide biosynthesis, tRNAs bring the correct amino acid building block to a mRNA template and peptide bonds are formed to generate an amino-acid chain with the mRNA-encoded sequence. Some peptide precursors to antibiotics are biosynthesized this way,