a precise calculation.) The star, and thus presumably its planets, are about three billion years old, and it would be extremely unlikely that the system just happens to be so near to the end of its expected lifetime. What the calculation implies, then, is that the nominal AFOE parameters are unlikely to be correct. Nonetheless, the characteristics of the system could well be within the error bars quoted for the AFOE data.

By contrast, systems using the Lick or combined Lick/AFOE data sets appear to be stable for at least ten million years and possibly much longer. Additional integrations, not shown in Fig. 1, imply that systems with more massive planets (smaller $\sin(i)$) are generally less stable, especially if the orbits are substantially inclined to one another, and that changing the orbital period of the outer planet within the range allowed by the data can have a big effect on the stability of the system.

Neither the star υ Andromedae nor any of its three planets appear in themselves to be particularly unusual, but the system as a whole stands out in the currently known menagerie of extrasolar planets. Its existence shows that several massive planets can orbit far closer to a star than do the gas giants (Jupiter and Saturn) and smaller ice giants (Uranus and Neptune) of our Solar System. So if giant planets all form far enough out in a protoplanetary disk for ice to condense (the conventional, but not exclusive, view of theorists[6]), then the migration or mutual scattering (or both) that brings them in towards their star is not always violent enough to destroy themselves or their brethren.

The υ Andromedae system is just one example of a wide variety of planetary configurations that can be expected to exist in our Galaxy. All of the extrasolar planets thus far discovered orbiting main-sequence stars are more massive than Saturn, and most either orbit very close to their stars or travel on much more eccentric paths than do any of the major planets in our Solar System. The Sun's planets are all either low in mass or travel on distant orbits from their star, and they are therefore more difficult to discover using the Doppler technique. So it could be that most planetary systems will turn out to be like ours.

There is much, much more to come. With the projected advances in detection technology, including schemes to find Earth-like planets[7], we are at the beginning of a Golden Age of extrasolar planetary studies. □

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Biochemical sensors

Adapting to nanoscale events

Daniel Branton and Jene Golovchenko

A hallmark of twentieth-century science has been the continual development of experimental strategies to observe individual atomic-scale 'events'. These strategies ultimately rely on significantly amplifying the consequences of a selective microscopic interaction, for example the chemical development of a silver halide grain in a photographic emulsion, the condensation of a droplet around a single ion in a cloud chamber, or the charge amplification in electron multiplier devices.

New strategies for detecting and characterizing single-molecule events are now emerging in the biochemical sciences. The latest example comes from Gu *et al.* on page 686 of this issue[1]. This group, working in Hagan Bayley's laboratory, show how measurement of ionic transport through a single, atomic-scale pore in an insulating membrane can be used to detect organic molecules of relative molecular mass as low as 100. Coupled with highly sensitive semiconductor electronics, the membrane–pore system can amplify these currents on timescales commensurate with the interaction times between the molecule and the pore. The system thus reveals the presence, nature and interaction of single molecules with the pore. Remarkably, a single protein channel can be adapted for simultaneous analysis of a mixture of organic molecules.

Gu *et al.*[1] assemble the nanoscale chemical and mechanical building blocks of their detector from the toolbox of biochemistry; the key components are shown in Figs 1 and 2 of the paper on page 687. Seven α-haemolysin molecules (a bacterial toxin) self-assemble to form a channel with a 15-Å-diameter aqueous pore through a 50-Å-thick lipid bilayer membrane[2]. The membrane separates two chambers filled with a conducting salt solution. Because the lipid bilayer is a nearly perfect insulator, the d.c. electrical conductance across the membrane is determined by the interaction between ions of the salt and the molecular pore in the α-haemolysin channel. When a bias is applied across the membrane, the current flow is tiny (at the picoampere level), but it can nonetheless be measured with modern room-temperature semiconductor electronics.

The innovative step here[1] is to sensitize the nanopore to specific organic chemical species by using β-cyclodextrin as an adapter. β-cyclodextrin, a doughnut-like molecule made of seven sugar units, diffuses into the α-haemolysin channel, partially obstructing its water-filled pore. The authors show that the cyclodextrin molecule is exquisitely sensitive to different guest molecules. Thus, when bound to cyclodextrin, members of the adamantane family of petroleum derivatives can be distinguished, as can members of the group of tricyclic pharmaceuticals that include imipramine and promethazine. These guest molecules each bind to β-cyclodextrin for milliseconds and make their presence known by altering the electrical conductivity of the α-haemolysin pore in which the β-cyclodextrin resides.

In neurobiology and biophysics, it is routine to measure picoampere ionic currents passing through single protein channels in biological membranes or planar lipid bilayers[3]. Such measurements are usually made to determine the properties and behaviour of the channel, but they can also reveal details about the concentration and other properties of molecules that are able to pass through or into the channel. Very small alterations in the distribution of charges lining the pore can give rise to relatively large changes in the ionic flux, so a membrane channel can serve as an amplifying transducer. Such a transducer allows one to detect extremely small modulations ($< 0.02\ kT$) in the energy barrier to ionic transport[4], and does so at bandwidths that permit high-speed (< 50 μsec) measurements. Thus, membrane channels have been used to effect high-speed molecular counting and sizing[5,6], and show promise for high-speed sequencing of polynucleotides[7]. Channels have also been modified to incorporate design elements that convert them into sensitive, analyte-driven switches[8], or genetically engineered to create selective, divalent metal sensors[9].

Bayley and his colleagues have long puzzled over how to engineer or redesign the α-haemolysin channel as a biosensor that can discriminate between different organic molecules[9]. They reasoned that the sensitivity and extraordinarily rich informational content of single-channel recordings reduce the requirement for the channel to contain a highly selective binding site. By fashioning a single-channel detector, rather than one that integrates signals from numerous sensor molecules, several independent

features can be simultaneously recorded for each analyte-binding event. For example, the current amplitude, voltage-dependence and typical kinetics can, together, produce a distinctive signature for each of several analytes, even though the sensor binding selectivity is minimal. Furthermore, use of an adapter together with an information-rich single-channel recording method may avoid the contradictory requirements of high selectivity (to achieve specificity) but rapid reversibility (to achieve speed in a changing environment). Because fresh adapters can be continuously flushed into the device, even an adapter (or carrier) that binds tightly to the analyte can maintain the system's speed if the adapter association with the channel exhibits rapid reversibility.

Although it will obviously be of great interest to identify the atomic-level changes that account for changes in ionic current flow upon adapter and analyte binding, there remain many questions about the ultimate capabilities of single-channel pores in atomic-scale investigations of individual molecules. What are the fundamental physical processes that limit the sensitivity and speed with which single-molecule measurements can be made? Can electronic currents be used to replace ionic currents? Can robust membrane–pore systems be engineered using advanced materials science and nanolithography techniques, perhaps in conjunction with the methods of biological or chemical engineering? Can sensitive electronic circuitry and photonic sensing capabilities ultimately be integrated directly into a membrane–pore system, as they have for other chemical sensors[8,10]? These questions may not be answerable today. But, in the twenty-first century, exciting new nanoscale tools and molecular machines will surely emerge at this interface of biology, chemistry and physics. □

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Neurobiology

Attraction is relative not absolute

Masataka Watanabe

Suppose you like wine very much, and are faced with the choice of ordinary table wine or Beaujolais Nouveau — the latter is probably very attractive. But if presented with Beaujolais Nouveau and a superior wine, such as Romanée-Conti, the attraction of the Beaujolais Nouveau may subside. A similar phenomenon called 'reinforcement contrast effect' seems to occur in animal-learning studies, and Tremblay and Schultz[1] now show (page 704 of this issue) that a region of the brain called the orbitofrontal cortex may be actively involved in this process.

Fifty years ago, in an experiment by Zeaman[2], rats were trained to run to a goal, for which they received a large reward. They were then shifted suddenly to a small reward. A second group of rats was trained the other way round; that is, they were first given a small reward and then shifted to a larger one. The animals that were shifted from a small to a larger reward immediately ran faster than would have been expected if the large reward were used alone. Conversely, those rats shifted from a large to a small reward ran more slowly than would have been expected with the small reward alone. The results indicated that the relative — but not absolute — magnitude of reward determines the attraction, as assessed by the eagerness of the rats to run to the goal.

Where in the brain is the attraction of a reward evaluated? To find out, Tremblay and Schultz[1] trained monkeys in a modified delayed-response task (Fig. 1). When the animal pressed a lever at the bottom of an experimental panel, a picture 'cue' was presented briefly on either the right or left side of the panel. Then there was a delay, after which the animal had to press the lever (right or left) above which the picture had been presented. This meant that, to obtain a reward, the monkey had to retain a memory of where the picture (although not what picture) was presented. Within a block of several tens of trials, the same two pictures were used continuously, and each picture always predicted one kind of reward.

Tremblay and Schultz found that whereas neurons in the lateral part of the prefrontal cortex showed changes in activity during the delay period, according to the position or identity of the picture, neurons in the orbitofrontal cortex were not sensitive to these factors. The orbitofrontal cortex — so called because it is located above the orbit, or eye socket — occupies the ventral surface of the prefrontal cortex (Fig. 2, overleaf). Humans and monkeys with damage to the orbitofrontal cortex often show impaired motivational and emotional behaviour[3], such as altered reward preferences[4]. Consistent with this, the authors found that many orbitofrontal neurons were sensitive to the different rewards. They observed such responses when the picture cue was presented, during the expectation of reward, or after the monkey had received the reward.

Figure 1 shows the activity of such an orbitofrontal neuron. The neuron is more active when the monkey sees a square, which predicts a morsel of apple, than when it is presented with a triangle, which predicts a piece of lettuce (Fig. 1a). But in the next trial block, when a square predicts apple and a plus sign a piece of banana, the same neuron shows higher activity to the cue for banana, because monkeys prefer bananas to apples, and apples to lettuce (Fig. 1b). The attraction of the apple now seems to subside, and the neural activity to the square cue is reduced. In fact, it is similar to the activity for the triangle cue, which predicted the lettuce reward in the previous trial block. So, the activity of orbitofrontal neurons reflects the relative, but not absolute, attraction of the reward.

Once a monkey has had enough of the reward, the orbitofrontal neurons stop responding to the reward and to the cues that predict it[3]. This process is specific to the nature of the reward, indicating that activity of the orbitofrontal neurons is determined by how much the monkey wants the reward[3]. The work of Tremblay

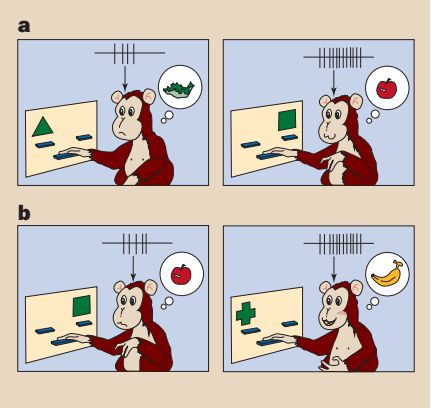

Figure 1 **Activity of an imaginary orbitofrontal neuron reflecting relative reward preference. To gain a reward, the monkey must remember where (right or left side) the cue is presented.** a, **A triangle predicts a lettuce reward, and a square predicts an apple. The monkey prefers apple to lettuce, so activity of the neuron is greater when the animal sees the square.** b, **This time, a square predicts an apple and a plus sign predicts a banana. Because the monkey prefers banana to apple, activity of the neuron is greatest with the plus sign, and much lower than in the previous test with the square. (Figure illustrated by Chiharu Tomita.)**