between two hydrophilic stripes. Such surfaces mimic lipid bilayers and allow lipids to invade the proteolipid ring without leaving their bilayer configuration. This model is attractive because it explains fusion without invoking temporary lipid intermediates.

Do the proteolipid complexes dimerize directly, or indirectly through their associated subunits (Fig. 1a)? If the former, how are these subunits accommodated in the complex? Do proteolipids indeed separate laterally to form an aqueous channel? And what ultimately causes the proteolipids to separate vertically. One problem with this model, however, is that the faces of the cavity in a end up facing lipid. This would be energetically unfavourable if the cavity were hydrophobic, as expected.

The presence of a ring of proteolipids at the fusion site may also make it easier for a vesicle to close its fusion pore soon after releasing its contents, preventing the membrane constituents from mixing with the target membrane. Closing fusion pores have been observed during most kinds of secretion. After closing its fusion pore, the vesicle would be free to disconnect from the plasma membrane and prepare for re-use elsewhere. A proteolipid-based ring may also allow the flux of contents through fusion pores to be controlled, as proposed for hippocampal neurons. And it may add an element of safety: fusion intermediates lacking sufficient protein lead to hemifusion, an unproductive association between membranes that fails to allow the release of cargo.

It will be interesting to see further work on the role of proteolipids in fusion, and in particular whether proteolipids are also involved in the fusion of secretory vesicles with the plasma membrane. Many years ago, Israel and colleagues proposed that neurotransmitter is released not from vesicles but through a V0 proteolipid complex, which they called the mediatrix. It would be poetic if they were now proven partially correct.

Wolfhard Almers is at the Vollum Institute, 3181 Southwest Sam Jackson Park Road, Portland, Oregon 97201-3098, USA.

e-mail: almersw@ohsu.edu


That sinking feeling

Michael P. Brenner and Peter J. Mucha

The physics of slowly falling particles in a fluid remains surprisingly enigmatic. Luckily, laws that work for dilute suspensions also appear to apply to higher — and more useful — particle concentrations.

Particles moving through a viscous fluid interact with each other, because each individual particle drags fluid along with it, which then drags on other particles. These hydrodynamic interactions are important in many processes, from the deposition of silt in a river to the motion of dust in the air and the centrifugation of proteins. But despite a century of research, the character of these motions is still hotly debated, even for dilute suspensions in which the particles are well separated.

On page 594 of this issue, Segre et al. provide experimental evidence that the laws governing particle settling under gravity at high particle positions are sufficiently random. Experiments have generally shown that Batchelor’s prediction of Batchelor is valid even for very high particle concentrations, and assumes that the particle positions are sufficiently random. Experiments have generally shown that Batchelor’s prediction

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Fluid dynamics


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On page 594 of this issue, Segre et al. provide experimental evidence that the laws governing particle settling under gravity at high concentrations are quantitatively similar to those at very low concentrations. This result is unexpected, because it has long been assumed that particle motion in a dense suspension is qualitatively different from the dilute case.

Smoluchowski carried out an early study of particle interactions in viscous fluids, described in a 1912 paper, “On the practical applicability of Stokes’ law”. Smoluchowski wanted to calculate the average sedimentation velocity of identical solid particles, each of which is heavier than the underlying fluid, as they slowly sink through the fluid. The calculation of the average velocity has been revised every 30 years since — by Burgers in 1942 and Batchelor in 1972. Batchelor’s calculation works at low particle concentrations, and assumes that the particle positions are sufficiently random. Experiments have generally shown that Batchelor’s prediction
velocity fluctuations, has generated a lot of interest to all who are devoted to the canine race. It describes Dr. Copeman's successful endeavours to isolate the micro-organism responsible for distemper in dogs… Dr. Copeman has now isolated a small coccus bacillus, growing readily on most of the ordinary culture media at the body temperature, from the exudations from the lungs, the tracheal mucus, and from the nasal secretion of dogs suffering from distemper. A cubic centimetre of a broth-culture of this microbe, injected beneath the skin of the abdomen in a dog weighing 7 kilograms, is sufficient to induce an attack of distemper terminating fatally in about a week from the date of inoculation. A vaccine has also been prepared which Dr. Copeman states can protect dogs against attacks of distemper… An injection of 2 cubic centimetres of such vaccine was apparently sufficient to protect fox-terrier pups weighing about 1/2 kilograms when exposed to distemper infection.

From Nature 31 January 1901.

100 YEARS AGO

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From Nature 31 January 1901.
Batchelor’s calculations, we can hope for a new theory in 2001.

Michael P. Brenner and Peter J. Mucha are in the Department of Mathematics, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139-4307, USA. e-mails: brener@math.mit.edu
mucha@math.mit.edu

Silent genes given voice

Many genes have little apparent influence on growth rates or metabolic fluxes in an organism. But their roles can be revealed by comparing the effects of mutations on two or more metabolite concentrations.

Most mutations have no noticeable impact on an organism. This implies that changing the activity of some enzyme or other by a substantial factor has little effect; even complete deletion of a gene may not be easily detectable if there are appropriate fail-safe features in the design of the organism. Many genes, up to 85% of those in yeast, do not appear to be required for survival, and a high proportion of these seem to have no detectable effects on metabolic fluxes — the chemical processes that result in energy production or growth. This presents a major barrier to functional studies of a genome. How can we hope to deduce the function of a gene that has no apparent effect?

Writing in Nature Biotechnology, Léonie Raamsdonk and colleagues argue that examining metabolite concentrations, which in total are known as the ‘metabolome’, rather than fluxes, is much more likely to reveal such ‘silent’ genes (Nature Biotechnol. 19, 45–50; 2001). The authors call their method FANCY, which comes from ‘functional analysis by co-response analysis’ (in this case brewer’s yeast, Saccharomyces cerevisiae). It uses the fact, long known but often ignored, that typical effects of changes in enzyme activity on metabolite concentrations are much larger than their effects on metabolic fluxes. The authors looked at two mutations affecting 6-phosphofructo-2-kinase, an enzyme whose product fructose 2,6-bisphosphate acts as a signal to regulate energy production; two mutations in the cytochrome oxidase complex, which catalyses a different energy-related process; and a mutation not related to energy metabolism that was used as a control.

Why, though, should changes in enzyme activity have a larger effect on metabolite concentrations than on fluxes? The reason can be seen by looking at what happens when a rock falls into a river. Any transient interruption of the flow of water is rapidly nullified by the increasing level of water just above the rock and the decreasing level just below: as soon as the required pressure is reached, the flow returns to just what it was before. So the rock has no steady-state effect on the flow, although it does have a long-term effect on the water levels, which remain different from their original values as long as the obstacle remains in place. An observer with access only to the steady-state value of the flow can learn nothing about the existence of an obstacle, let alone its location. But an observer with access to the water levels in different places can both detect that an obstacle is present and find out where it is by comparing its effects on the levels above and below it.

As with rivers, so with the genome of an organism such as yeast. Gross properties such as growth rate that depend on fluxes may suggest that most genes are silent. For instance, chemostat culture allows microorganisms to be maintained indefinitely in a phase of exponential growth in a medium of constant composition, the slower-growing strains gradually being eliminated by dilution. Although this approach can in principle reveal very slight differences in growth rates, Raamsdonk et al. found that it failed to reveal the deletion of one or other of the two yeast genes that code for 6-phosphofructo-2-kinase. The mutants achieve growth rates equal to those of the wild type by increasing the concentrations of metabolites upstream from the impediment and decreasing those of downstream metabolites (just as for the rock in the river). The effects on a metabolite such as fructose 6-phosphate are not only easily measurable but also detectably different for the two mutants.

Measurements of relatively few metabolite concentrations can thus give voice to apparently silent genes. But individual concentrations are often less informative than one might wish, because quite different mutations may affect the same concentration to a similar extent; in any case, with a completely unknown gene there is no prior knowledge of which concentrations to examine. What is needed is a comprehensive way of studying many metabolites together. The FANCY method provides this, and can reveal quite subtle effects of changes in genotype. The C in FANCY stands for ‘co-response analysis’ (Hofmeyr, J.-H. S. & Cornish-Bowden, A. J. Theor. Biol. 182, 371–