monochromaticism of any faulty colouring. Cosmetic enhancement comes at a price: here, the addition of new colours. So, in a second step, to restore the graph to its original hues of red, green and blue, we call upon error-correcting codes, the redundancy-adding devices invented by coding theorists to make signals immune to noise. This is no coincidence: just as an encoded string with not too many erroneously flipped bits can, through error correction, be restored to its original state, so a PCP proof with not too many errors can be seen to encode a correct proof. Indeed, any error that is not smeared widely enough to be easily spotted is *de facto* inconsequential.

If you think that no one besides children and cartographers has any interest in colouring graphs, think again: the Riemann hypothesis, protein folding, cryptography and most questions in artificial intelligence can be reduced to the three-colourability of some graphs. That universality is another wonder in the computing cosmos.

PCP, and its elementary proof by Dinur[3], is the culmination of 40 years of research in the field of computational reduction. Keep in mind that this is all about verifying proofs, not about understanding them — with only three bits! — let alone discovering them. That must still be done the hard way. In the end, PCP boils down to one revolutionary insight: in the art of persuading others of the truth, the ultimate weapon is a set of dice. ■

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STRUCTURAL BIOLOGY

Dangerous liaisons on neurons

Giampietro Schiavo

Crystal structures show that botulinum toxins bind simultaneously to two sites on neurons. This dual interaction allows them to use a Trojan-horse strategy to enter nerve terminals, with deadly effect.

Botulinum neurotoxins (BoNTs) are some of the most deadly substances known to mankind. By blocking nerve function, they cause botulism, a severe condition that may ultimately lead to muscular and respiratory paralysis. These sophisticated bacterial proteins owe their toxicity to their extraordinary specificity for neurons and to their enzymatic activity. In this issue, papers by Jin *et al.*[1] and Chai *et al.*[2] describe the mechanisms by which BoNT/B — a toxin that causes human botulism — recognizes the surface of neuron junctions (synapses)*. This work provides insight into how other BoNTs may exert their lethal action, and describes a mode of binding that might be used by other biological compounds.

Once inside a neuron, a single molecule of BoNT is, in principle, capable of deactivating the whole synapse. BoNTs consist of two protein segments, known as the heavy and light chains. It is the light chain that deactivates neuromuscular junctions — the synapses that connect muscles to their controlling neurons — by specifically inhibiting members of the SNARE protein family[3]. SNARE proteins are distributed over the membranes of all animal and plant cells and are also found on the membranes of synaptic vesicles, the bubble-shaped organelles that store and release neurotransmitter chemicals at neuron terminals. SNARE proteins are essential for membrane fusion, during which vesicles merge with the cell membrane and release their load. Once the synaptic vesicles have done this, they are recycled by the neuron for further use.

So how do BoNTs enter neurons? The heavy chain is most likely to be responsible. One half of the heavy chain mediates binding to neurons by interacting with lipid molecules (polysialogangliosides, PSGs) in the cell membrane, and with either one of two integral membrane proteins — synaptotagmin I or synaptotagmin II — found in synaptic vesicles. A dual-receptor model for these toxins was proposed long ago[4], but experimental validation of this theory has required a worldwide effort. The model predicts that the interaction of BoNTs with both PSGs and protein receptors is necessary to explain their awesome potency[3], with a different protein receptor being recognized by each BoNT.

Evidence for protein involvement in BoNT binding was scarce until it was discovered[5] that BoNT/B binds to both PSGs and the part of synaptotagmins that lies inside synaptic vesicles, in the area known as the lumen. More recently, the specific regions of synaptotagmins that bind BoNT/B have been identified[6],

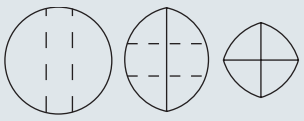
*This article and the papers concerned[1,2] were published online on 13 December 2006.

50 YEARS AGO

The recent passion for the progressive splitting up of genera has spread through most branches of zoology and latterly to botany as well. In fact, the present phase in taxonomy is to lump species and split genera... At present, names are very often proposed on flimsy grounds and the work of proving their validity or otherwise is handed down to future workers. New genera are established using merely the specific characters of the unique species included without any additional evidence. The result is that two species such as *Cypraea tigris* L. and *C. pantherina* Sol. are placed in different genera, whereas they are only just distinct species which actually hybridize. Such absurdities should have no standing in nomenclature.
From *Nature* 22 December 1956.

100 YEARS AGO

"Cutting a Round Cake on Scientific Principles" — Christmas suggests cakes, and with these the wish on my part to describe a method of cutting them that I have recently devised to my own amusement and satisfaction. The problem to be solved was, "given a round tea-cake of some 5 inches across, and two persons of moderate appetite to eat it, in what way should it be cut so as to leave a



minimum of exposed surface to become dry?" The ordinary method of cutting out a wedge is very faulty in this respect... The cuts shown on the figures represent those made with the intention of letting the cake last for three days, each successive operation having removed about one-third of the area of the original disc. A common India-rubber band embraces the whole and keeps its segments together.
From *Nature* 20 December 1906.

50 & 100 YEARS AGO