

of the patterns of activity in J. H. Conway's famous Game of Life⁷, and even of the frequency of citation of scientific papers⁸, all follow power laws.

Is it possible that the common features of all these disparate phenomena could be explained by a single general theory? Some people, notably the proponents of the theory of self-organized criticality, have claimed that they can, but most scientists agree that power-law distributions are the result of many different processes. The distribution of meteor sizes, for example, is almost certainly the product of a random multiplicative or fragmentation process; the behaviour of the Game of Life is an ordinary critical phenomenon; and the distribution of the number of species per genus can be explained by a simple random-walk model. Other power-law-producing mechanisms include the thermal crossing of random energy barriers, systems driven by coherent noise, and the so-called record dynamics. To this toolkit, Carlson and Doyle have now added another, beautiful, idea, which could explain quite a variety of physical phenomena.

Carlson and Doyle first describe their highly optimized tolerance (HOT) theory in the context of a simple 'forest fire' model. This is an attempt to emphasize the similarities and differences between HOT and self-organized criticality, of which the self-organizing forest fire is one of the best-known examples⁹. Imagine then a forest that is managed by a forester who wants to grow as many trees as possible. The principal bane of this forester's life is fire; fires start in the forest with moderate frequency and can destroy large numbers of trees if left unchecked. So the forester cuts fire-breaks to prevent the spread of fire. What is the best way to place these fire-breaks to minimize the damage? If fires are started by sparks which land uniformly at random everywhere in the forest, then the solution is simple — cut the forest into equally sized chunks. However, if there are more sparks in some areas than others, it turns out that the average damage done by a fire is minimized by cutting the forest into chunks whose sizes vary in inverse proportion to the rate at which sparks land in that area.

Carlson and Doyle show that if you take this result and use it to work out the distribution of the sizes of fires, you get a distribution that follows a power law for a wide variety of choices of the distribution of sparks. Thus a power law is generated by the actions of an external agent (the forester) aiming to optimize the behaviour of a system (the forest).

But the HOT mechanism does more than this. If the forest is placed on a regular grid for simplicity, with trees positioned so as to minimize the average damage done by a fire, then the optimal configuration

is one in which the trees are arranged in blocks with discrete fire-breaks between them. So the model tells you not only what the ideal arrangement of fire-breaks is, but also that the best way to control fires is to build breaks. This 'cellular' structure is one of the characteristic features of HOT systems.

Another feature of HOT systems is their sensitivity to unexpected perturbations and design flaws. For instance, if the distribution of positions at which fires start changes from the one for which the tree configuration is optimized, it can cause catastrophic damage; the average fires can be much larger in this case than if the trees were uniformly clumped. And if one of the fire-breaks has a flaw — a single fallen tree across the break, for example — this can result in much worse damage than such a small perturbation seems to warrant. Carlson and Doyle point out that these phenomena are well known to engineers who design systems for optimal performance. Highly tuned systems are often sensitive to small imperfections, so engineers commonly design them to be slightly suboptimal to avoid such problems.

This last point is crucial to the HOT picture. Carlson and Doyle have pitched HOT not only as a mechanism for generating power-law distributions, but also as a way of quantifying ideas about designed systems which are well known (anecdotally) in engineering, in a way that makes them comprehensible and useful to the scientific

community. In this sense, Carlson and Doyle's paper¹ succeeds very well, constructing a theory of 'robust yet fragile' designs in a language that will be comfortably familiar to many of us. However, their general conceptual approach, and also the presentation of the idea in terms of abstract systems such as forest-fire models, is inevitably going to lead people to ask what real applications HOT has. Is HOT an answer looking for a question?

It seems not, and to prove it Carlson and Doyle have applied their ideas to a variety of real-world systems. In new work, as yet unpublished, they show how HOT can explain data on real forest fires, electrical power failures and Internet traffic. They claim that further examples are easy to find. We won't have to look hard. And if they are right, HOT could be one of the most important additions to the theory of complex systems in recent years. ■

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Neurobiology

Self-regulating synapses

Christine R. Rose and Arthur Konnerth

Information transfer between neurons is achieved mainly through chemical synapses. The presynaptic neuron releases a neurotransmitter into the synaptic cleft, and the transmitter binds to specific receptors on the postsynaptic cell. This generally leads to the opening of ion channels in the postsynaptic membrane and an alteration in the electrical properties of the postsynaptic neuron. The transmission properties of chemical synapses are controlled by neuronal activity. This activity-dependent regulation of synaptic plasticity is thought to represent the cellular basis for the development of neural circuitry and to underlie learning and memory. Hence the importance of the paper on page 454 of this issue¹, in which Liu and Cull-Candy reveal a mechanism for the regulation of synapses in the brain that are responsive to the neurotransmitter glutamate.

Over the past decade, several mecha-

nisms have been described by which neuronal activity alters the transmission properties of synapses that use glutamate (see ref. 2 for a review). Most of these mechanisms are based on an activity-induced alteration in the number and/or functional properties of one type of glutamate receptor — the so-called AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor. AMPA receptors are the main contributors to the excitatory postsynaptic current that can be generated at low frequencies of stimulation. Increased neuronal activity can induce the phosphorylation of AMPA receptors, leading to an increase in the flow of ions through AMPA channels³, or it can induce AMPA-receptor-type activity at synapses that were not previously responsive⁴. The latter process is likely to be mediated by activity-regulated insertion of AMPA receptors at the synapse^{5,6}.

The activity-induced alteration of AMPA-

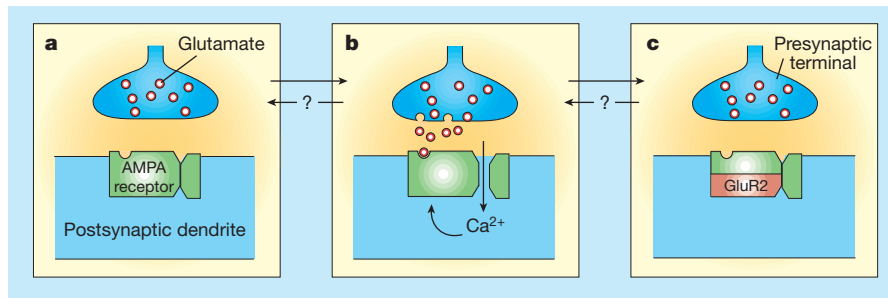


Figure 1 A new way of regulating synaptic activity. Liu and Cull-Candy¹ have found that the composition of AMPA receptors (a subtype of receptors for the neurotransmitter glutamate) in cerebellar stellate interneurons can change in response to neuronal activity. These receptors regulate their own function, perhaps as follows. a, Under control conditions, synapses are characterized by a high proportion of calcium-permeable AMPA receptors that lack the subunit GluR2. b, Release of glutamate from the presynaptic neuron and its binding to AMPA receptors of the postsynaptic neuron leads to calcium influx through the AMPA receptors. The resulting increase in intracellular calcium concentration induces an alteration in the subunit composition of the AMPA receptors themselves (c), resulting in the expression of GluR2-containing receptors with low calcium permeability.

receptor function usually requires an influx of calcium ions into the neurons. How is this increase in intracellular calcium concentration achieved? Many neurons express AMPA receptors that exhibit very low permeability to calcium, because the receptors contain a specific subunit, GluR2 (ref. 7). Calcium influx into these neurons can be achieved by activation of another type of glutamate receptor, the NMDA (*N*-methyl-D-aspartate) receptor, or through voltage-gated calcium channels in the plasma membrane. In contrast, AMPA receptors that lack GluR2 exhibit relatively high calcium permeability. Cells expressing a high proportion of these receptors can use this route for calcium entry.

Liu and Cull-Candy¹ now describe a mechanism of synaptic plasticity based, unusually, on changes in the composition and function of AMPA receptors. They provide evidence that activity regulates the molecular composition of AMPA receptors in postsynaptic stellate interneurons of the cerebellum. The authors use a variety of pharmacological tools to show that these interneurons do not use NMDA receptors. Instead, the synapses are characterized by a high proportion of calcium-permeable, GluR2-lacking AMPA receptors. By contrast, at the cell bodies of the interneurons (that is, at extrasynaptic regions), Liu and Cull-Candy find mainly GluR2-containing AMPA receptors, with low calcium permeability.

What are the mechanisms responsible for the targeting of the different AMPA-receptor subunits to different subcompartments of these neurons? Liu and Cull-Candy tackled this problem by applying high-frequency stimulation to the presynaptic axons. Surprisingly, within just 15 to 30 minutes, the properties of the AMPA-receptor-mediated currents in the postsynaptic interneurons changed strikingly, indicating

the inclusion of GluR2-containing receptors. The results convincingly show the rapid, activity-dependent change in function at these synapses.

Liu and Cull-Candy next went on to show that an increase in the level of intracellular calcium was necessary for the alteration in receptor composition. They then analysed the different routes of calcium entry into the cell. They discovered that calcium influx through the synaptic AMPA receptors themselves was sufficient to produce a rise in intracellular calcium that resulted in alteration of the function of these receptors. By contrast, the function of extrasynaptic receptors on the cell bodies was determined mostly by calcium influx through *N*-type calcium channels during action potentials. So, at some synapses in the brain, receptor-mediated calcium influx can regulate the subunit composition — and thereby the calcium permeability and the electrical properties — of the very same receptors. This provides an activity-dependent feedback mechanism controlling the properties of synaptic transmission.

What might be the physiological function of this self-regulating mechanism? At present, this question is difficult to answer. Perhaps these synapses function in two ways

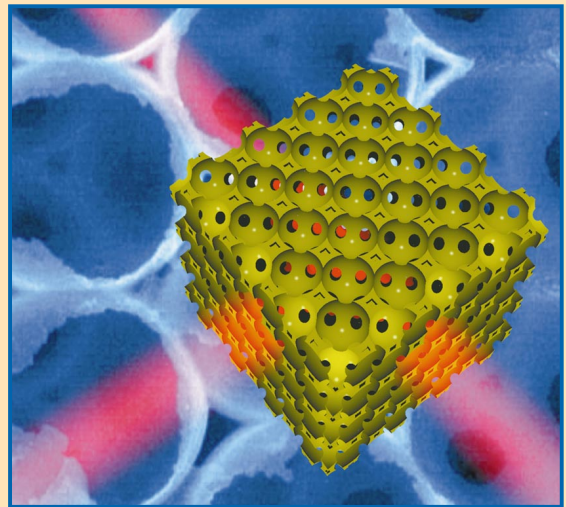
Photonics

Opal appeal

Photons are the best messengers for really quick information transmission. But creating circuitry that can process light with the versatility of electronic silicon chips is a big technological challenge. The most promising approach relies on fabricated structures known as 'photonic crystals'. These materials have carefully tailored properties that make them opaque to selected wavelengths — providing a means to control the routing and transmission of optical signals.

Elsewhere in this issue, Alvaro Blanco and colleagues (*Nature* **405**, 437–440; 2000) describe a simple and cheap method for the large-scale manufacture of three-dimensional silicon photonic crystals. The picture here shows a computer representation of the structures, superimposed on a real image from a scanning electron microscope. Because the crystals are made of silicon, they should be easy to integrate with conventional electronic circuitry.

How is this complex



structure produced? The first step is to construct a three-dimensional template that will ultimately be discarded. It consists of a form of artificial opal: uniformly sized silica spheres, up to a micrometre in diameter, grown from seed particles. Application of heat causes small bridges to develop between the spheres, resulting in a connected structure. Next, gases containing silicon are allowed to infiltrate the template. The voids in between the spheres are gradually filled up as the silicon crystallizes. The final step is to dissolve

away the silica sphere-and-bridge template using an acid etching process.

Theoretical calculations predict that the resulting structure should block wavelengths around 1.5 μm — perfect for manipulating the infrared signals used in fibre-optic communications. The measured reflectance and transmission spectra of the photonic crystals confirmed this behaviour. Equally importantly, the crystals are unlikely to absorb valuable signal power, as bulk silicon only soaks up higher energies. **Karen Southwell**

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(Fig. 1). In control conditions, the complex synaptic response would consist of both the electrical response and a transient calcium signal. Activity-induced insertion of GluR2-containing AMPA receptors into the postsynaptic membrane would switch the synapse to a second mode, in which the calcium signal is suppressed because of the reduced calcium entry. Another plausible, but equally speculative, role for the switch in subunit composition is that it serves as a mechanism to scale transient changes in postsynaptic calcium levels⁸. Or it could have a purely neuroprotective function; calcium entry through AMPA receptors has been implicated in the neurodegeneration associated with ischaemia (reduced blood flow) in the brain and epilepsy.

Before we can completely understand this process and its implications, it will be important to determine the calcium-dependent events that lead to the insertion of a GluR2-containing receptor complex into the postsynaptic membrane. Also interesting is how GluR2 might be removed to reset the system and to re-establish the functional properties found in control conditions. The

answers to these questions may come with analysis of the amplitude and kinetics of the transient changes in intracellular calcium that induce these effects. In fact, different patterns of such calcium transients may either upregulate or downregulate synaptic function through activation of calcium-permeable AMPA receptors in other neurons^{9,10}. The self-regulation of AMPA receptors revealed by Liu and Cull-Candy¹ has added yet another piece to the puzzle of synaptic plasticity. ■

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DNA repair

The bases for Cockayne syndrome

Philip C. Hanawalt

Cockayne syndrome is a rare human hereditary disease, characterized by growth failure, deficient neurological development and severe sensitivity to sunlight. It can arise from mutations in any one of five genes. The protein products of these genes are involved in different aspects of the repair of damaged DNA, and it has been far from clear how all these different mutations result in the same syndrome. Le Page and colleagues¹, writing in *Cell*, now provide important clues to the answer. It seems that the common problem in cells from patients with Cockayne syndrome is a failure to repair oxidation-induced damage to DNA bases, specifically in the strands of DNA that are being transcribed into RNA.

Different DNA-repair pathways operate on different types of DNA lesions. Nucleotide-excision repair (NER), for example, is a ubiquitous cellular process by which short, single-stranded DNA segments, containing damaged nucleotides, are removed from duplex DNA. The gaps are then filled in by repair DNA synthesis, using the intact strand as a template (see ref. 2 for a review). Defects in NER underlie the hereditary disease xeroderma pigmentosum. This disease — like Cockayne syndrome — is characterized by severe sensitivity to sunlight. However, patients with xeroderma pigmentosum

are several thousand times more likely than Cockayne syndrome patients to develop cancer in exposed areas of skin. Otherwise, mutations in most of the seven *XP* (xeroderma pigmentosum) genes needed for NER of photoproducts in DNA do not usually pose serious health problems. Another pathway, termed base-excision repair (BER), operates on the damage to bases produced by reactive oxygen species, ionizing radiation and some alkylating agents, as well as certain inappropriate bases (such as uracil) in DNA.

Yet another process, transcription-coupled repair (TCR), deals with a variety of DNA lesions that are thought to arrest the transcription of genes³. This process has been considered for some time to be a type of NER. If the ultraviolet wavelengths of sunlight cause damage to the strand of a DNA duplex that is being transcribed into RNA, TCR solves the problem. By contrast, lesions throughout the genome — including ultraviolet-light-induced damage to the non-transcribed strands of expressed genes — are repaired by global genomic NER.

Mutations in either of two non-essential genes — *CSA* or *CSB* — result in defective TCR, and are the genetic defect in over 90% of Cockayne syndrome patients. Certain mutations in *XP* genes also underlie a small number of Cockayne syndrome cases. Two

of these genes, *XPB* and *XPD*, encode components of the general transcription factor TFIIH. This complex is needed to open up the DNA strands in preparation for the enzyme RNA polymerase II to begin transcription. It also opens up regions that include a DNA lesion, allowing NER to take place. The third *XP* gene so involved is *XPG*, which encodes a protein required to make the first of the two incisions in the DNA strand needed for NER.

Thus all the mutations that cause Cockayne syndrome have in common the property that they eliminate TCR of ultraviolet-damaged DNA. This explains the sensitivity to sunlight, but what about the developmental defects, which are unlikely to result from ultraviolet damage to DNA? Might the basis for these defects lie in the defective NER of similar damage caused by other agents? This seems unlikely, as mutations in the *XPA* gene (which is involved in lesion recognition) that totally eliminate both global genomic NER and the TCR of such damage do not result in Cockayne syndrome. A second hypothesis is that the disease is a ‘transcription syndrome’, in which certain groups of genes are deficiently expressed⁴. In this model, the mutations in *CSA* and *CSB*, like those in *XPB* and *XPD*, are envisaged to have direct effects on transcription itself. But it is hard to explain how the mutations in *XPG* affect transcription.

So what is the basis for Cockayne syndrome? Getting to the answer requires rethinking the relationship between TCR and NER. It seems that, far from being a subpathway of NER, TCR may in fact act upstream of both nucleotide- and base-excision repair.

A first step along the way to this answer was provided by the report⁵ that DNA damage produced by ionizing radiation (not ultraviolet radiation) is subject to TCR in normal human cells and in *XPA* mutant cells, but not in *CSB* mutant cells. DNA damage produced by ionizing radiation is generally thought to be remedied by BER, not NER. In addition, TCR of an oxidized base, thymine glycol, has been shown to be defective as a result of *XPG* mutations that result in Cockayne syndrome⁶, but not of other *XPG* mutations that result only in the symptoms of xeroderma pigmentosum⁷. Repair of thymine glycol is also achieved by BER. So, TCR can be linked to BER as well as to NER. These results are further evidence that Cockayne syndrome might result from defective TCR of oxidative lesions.

Le Page *et al.*¹ have now finished testing the hypothesis that all patients with Cockayne syndrome — no matter which gene is mutated — should be deficient in the TCR of oxidative lesions, whatever their nature. Their results firmly establish that both the *XPG* protein and TFIIH have