

dimension and the walk dimension that determines which of Condamin and colleagues' three cases applies. If the walk dimension is greater than the fractal dimension ($d_w > d_f$) — if the walker is significantly impeded or the lattice is sparse — a compact, local exploration arises. In this case, the authors find a strong, positive dependence of the mean first-passage time on the initial source–target separation, of the form $r^{d_w-d_f}$. They calculate d_w and d_f exactly for the case of a Sierpinski fractal lattice, and find good agreement between the predicted and calculated dependencies of the mean first-passage time on both N and r .

The opposite case, in which the fractal dimension is greater than the walk dimension ($d_f > d_w$), characterizes a non-compact exploration, in which a random walker leaves a region with many sites still unvisited. The Lévy flight is one such case. This is a random walk that

performs jumps of many sizes, making its starting point irrelevant. It has been proposed as an optimal search strategy for, say, animals foraging for sparse resources. Here, the authors' formula for the mean first-passage time also shows a dependence on the source–target separation of the form $r^{d_w-d_f}$. Because the exponent is by definition negative, however, this dependence disappears at large values of r , leaving the mean first-passage time dependent on the number of nodes alone. Finally, in the authors' third case, $d_w = d_f$, they find a weak, logarithmic dependence of the mean first-passage time on the separation.

The authors' methods and calculations¹ cut to the essence of the problem of the mean first-passage time with a simple, general solution in terms of just the number of nodes in the lattice on which the walk takes place, and the separation of target and source. But their work closes a

chapter, not a whole book: many other types of problem involving first-passage times fall outside the terms on which this model was based. This is seen, for example, in the search strategies of some predatory animals, which mix elements of the random-walk model with concentration on seasonal 'hot spots' to find prey. Similarly, in biological cells, peptide binding to transmembrane receptors depends on hydrophobic attraction superimposed on thermodynamic, random brownian motion. Such situations will continue to provide an unlimited number of questions for the mathematician. ■

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1. Condamin, S., Bénichou, O., Tejedor, V., Voituriez, R. & Klafter, J. *Nature* **450**, 77–80 (2007).
2. Montroll, E. W. *J. Math. Phys.* **10**, 753–765 (1969).

PLANT PATHOLOGY

Deadly special deliveries

Nicholas J. Talbot

When attacking a plant, pathogens must deliver proteins into their victim's cells. The causal agent of potato late blight uses a system that is remarkably similar to that used by the malaria parasite in red blood cells.

To infect plants and cause disease, many microorganisms evade or subdue plant defences so that they can proliferate unhindered within the host's tissues¹. For this purpose, pathogenic bacteria have systems to deliver 'effector' proteins directly into plant cells, where they interact with plant proteins and suppress defence mechanisms².

Whisson *et al.* (page 115 of this issue³) describe how the agent of potato late blight, *Phytophthora infestans*, uses a special host-cell-targeting signal⁴ to attack its plant host. This provides the first clue as to how pathogen proteins are delivered into plant cells by a eukaryote — the vast group of organisms that differ from bacteria in having cells with membrane-bound nuclei. Beyond that, it turns out that *P. infestans* uses a signal that closely resembles that used by the malaria parasite, *Plasmodium falciparum*, to deliver parasite proteins into red blood cells^{4–6}.

There has been rapid progress in understanding how bacteria attack both animals and plants using an array of effector proteins^{2,7}. Bacteria deliver effectors mainly by use of a mechanism, called the type III secretion system, that allows proteins to be sent directly into the cytoplasm of host cells⁷. By contrast, we know little about effector proteins in the plant pathogenic fungi and oomycetes such as *P. infestans*. Oomycetes physically resemble fungi, but are in fact closely related to brown algae, and are responsible for some

of the most devastating plant diseases.

Phytophthora infestans attacks potato plants, and was the cause of the Irish potato famine of 1845–49 that resulted in the death of up to a million people and the emigration of as many again⁸. Whisson *et al.*³ investigated how a particular effector protein, Avr3a, is delivered into potato plants. Avr3a is one of many secreted proteins in *P. infestans* that contain a group of amino acids with the sequence (in single-letter code) RXLR-EER — with X being any amino acid, and EER occurring within 25 amino acids of the RXLR motif⁹. This motif (both with and without EER) has been identified in Avr proteins of other oomycete pathogens, such as *Hyaloperonospora parasitica*⁹. It also resembles the RXLXE/Q motif found in the malaria pathogen *P. falciparum*, which belongs to a group of animal parasites known as the Apicomplexa.

In *P. falciparum*, the RXLXE/Q motif is necessary for the translocation of proteins into red blood cells^{4–6}. After entering the red blood cell, the parasite occupies a compartment called the parasitophorous vacuole and secretes substances into the vacuole, from where RXLXE/Q-containing proteins are then selectively delivered into the cytoplasm of the red blood cell^{4–6} (Fig. 1a, overleaf). It was known that the RXLR-EER motif from oomycetes can operate as the host-cell-targeting signal in *P. falciparum*, which suggested that there might be a common delivery mechanism for

oomycete and apicomplexan effectors¹⁰. Until now, however, there has been no direct experimental evidence that the RXLR-EER sequence is necessary for protein delivery in plant cells.

The Avr3a effector probably suppresses plant defences. Plants have evolved resistance proteins to counter this sort of intracellular microbial attack, however, and inside a cell these proteins interact (directly or indirectly) with Avr proteins to bring about cell death and thereby prevent further infection¹. Expression of Avr3a inside plant cells showed that the RXLR-EER motif in itself is not necessary for Avr3a to induce a host response^{3,9}. But the motif is necessary for the activity of Avr3a when it is secreted by *P. infestans*, implying that it is essential for host-cell targeting^{9,10}.

To test this idea, Whisson and colleagues³ replaced RXLR-EER with alanine residues or with the sequence KMIK-DDK, both of which maintained the predicted structure of Avr3a but resulted in loss of the potential host-cell-targeting signal. In these cases, the mutations prevented *P. infestans* from provoking a host response, suggesting that delivery of Avr3a to its site of action was not happening.

To investigate matters further, the authors fused the gene encoding Avr3a with a gene encoding β -glucuronidase, an enzyme known to work only inside plant cells¹¹. When this reporter gene was expressed in *P. infestans*, the delivery of Avr3a to plant cells was observed directly using an enzyme assay that leads to a coloured product, which could be seen clearly in plant cells. This experiment provides convincing evidence that RXLR-EER acts as a host-cell-targeting sequence.

Analysis of the *P. infestans* genome shows that it may encode as many as 425 proteins with the RXLR-EER motif, 169 of which are very strong candidates³. These proteins are likely to act as effectors both for modulating the host response and for implementing the structural alterations in host cells necessary for invasion

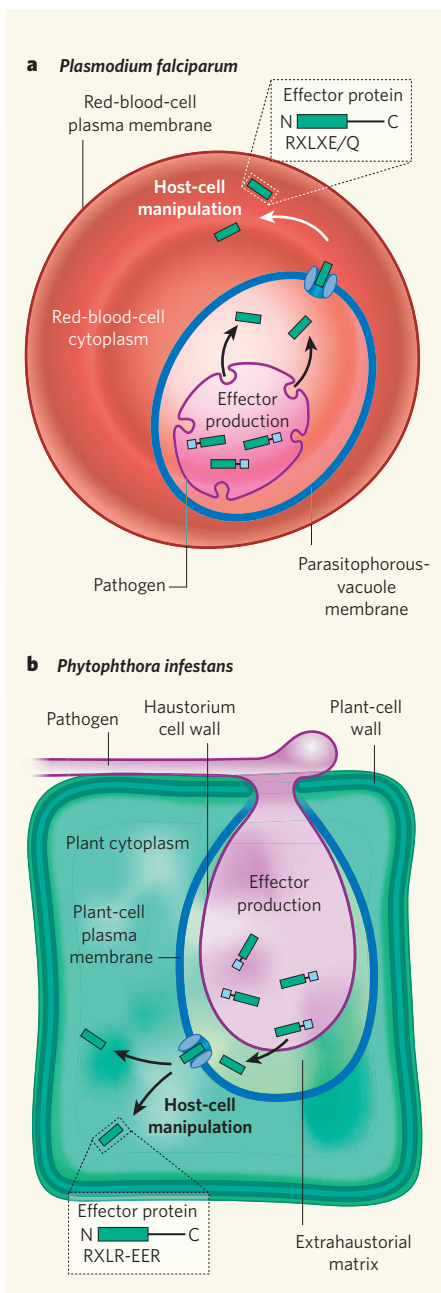


Figure 1 | Effector-protein delivery systems in *Plasmodium falciparum* and *Phytophthora infestans*. **a**, After entry into a red blood cell, *Plasmodium falciparum* delivers host-cell-targeting effector proteins with the RXLXE/Q motif into the parasitophorous vacuole. These are then taken up into the cytoplasm of the red blood cell. **b**, *Phytophthora infestans* forms a specialized feeding structure known as a haustorium, which is the site of effector-protein secretion into the plant cell through the RXLR-EER host-cell-targeting system studied by Whisson and colleagues³. Proteins are delivered into the extrahaustorial matrix and then cross the plant-cell plasma membrane into the cytoplasm of the plant cell. In both cases a putative ATP-dependent translocator protein is shown. The process could, however, also operate through endocytosis. The blue box on the protein at the site of effector production depicts a signal sequence that is cleaved during secretion from the pathogen.

by the feeding structures, known as haustoria, that *P. infestans* produces inside plant cells (Fig. 1b). Identifying these effectors and their targets will provide insight into the processes necessary for the initial spread of the pathogen in plant tissue.

Another task will be to work out the RXLR-EER-mediated mechanism of host-cell targeting; it is likewise not yet clear how the RXLXE/Q signal operates to allow *P. falciparum* proteins to cross the membrane of the parasitophorous vacuole. Exploiting the power of plant genetics — especially in the model plant *Arabidopsis thaliana*, which is the host of *H. parasitica* — may allow rapid progress to be made in tackling this problem.

Finally, the presence of such a similar effector-delivery system in such different organisms as an apicomplexan and an oomycete prompts evolutionary questions. What is the likely origin of this system, and how widespread is

it? Does it exist in relatives of the oomycetes, which include the human parasite *Blastocystis*, or in even more disparate groups of eukaryote pathogens? ■

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1. Jones, J. D. G. & Dangl, J. L. *Nature* **444**, 323–329 (2006).
2. Grant, S. R., Fisher, E. J., Chang, J. H., Mole, B. M. & Dangl, J. L. *Annu. Rev. Microbiol.* **60**, 425–449 (2006).
3. Whisson, S. C. *et al.* *Nature* **450**, 115–118 (2007).
4. Przyborski, J. & Lanzer, M. *Science* **306**, 1897–1898 (2004).
5. Hiller, N. L. *et al.* *Science* **306**, 1934–1937 (2004).
6. Marti, M., Good, R. T., Rug, M., Knuepfer, E. & Cowman, A. F. *Science* **306**, 1930–1933 (2004).
7. Galán, J. E. & Wolf-Watz, H. *Nature* **444**, 567–573 (2006).
8. Boyle, P. P. & Ó Gráda, C. *Demography* **23**, 543–562 (1986).
9. Birch, P. R. J., Rehmany, A. P., Pritchard, L., Kamoun, S. & Beynon, J. L. *Trends Microbiol.* **14**, 8–11 (2006).
10. Bhattacharjee, S. *et al.* *PLoS Pathogens* **2**, e50 (2006).
11. Denecke, J., Botterman, J. & Deblaere, R. *Plant Cell* **2**, 51–59 (1990).

HEARING

A fantasia on Kölliker's organ

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In the silence that precedes the onset of hearing in the developing auditory system, it seems that the cells of a transient structure known as Kölliker's organ are capable of generating their own 'virtual' music.

From a physiological perspective, a developing organ requires a programme that allows it to grow and adapt to internal and environmental constraints. In sensory systems such as those involved in sight and hearing, the adaptable growth of afferent (incoming) nerve fibres is involved in connecting the peripheral sensory organ to the neurons of the central nervous system. Information from the sense organ passes along the afferent nerve fibres in the form of electrical action potentials.

Sperry's chemoaffinity hypothesis¹ proposes that nerve path-finding requires the presence of guidance molecules on the target cells and the growing nerves, and this implies that an internal, or genetic, programme is the main determinant of development. But it is becoming increasingly apparent that sensory information in the form of electrical activity provides complementary, experience-related influences². Thus, the growth of the afferent nerves from the developing sense organs to their targets in the brain begins with genetically encoded guidance, but over time is increasingly affected by experience-dependent processes. In a paper published in this issue (page 50), looking at the auditory system, Tritsch *et al.*³ extend the debate on the importance of experience-dependent development to times before the ear can hear. And they identify a new, sound-independent means of generating neuronal activity.

The ear is a complex organ consisting of outer, middle and inner parts (Fig. 1a, overleaf). After passing through the outer and middle ear, sound reaches the base of the cochlea, a conical-shaped structure in the inner ear. The sound energy induces a travelling wave that propagates along the length of the cochlea, causing the overlying organ of Corti to vibrate at different longitudinal positions depending on the frequencies contained in the sound (low-frequency sounds resonate near the apex of the cochlea and high-frequency sounds resonate at the base). This amplified resonance flexes microscopic hairs (stereocilia) on adjacent inner hair cells (IHCs) and is converted into electrical potentials. Thus, the position along the cochlea predicts the frequency of sound that will stimulate each IHC. This 'place map' is referred to as tonotopy.

The neurotransmitter glutamate is then released from the IHCs through a calcium-dependent secretory pathway, and activates receptors on the afferent nerve fibres that innervate IHCs. This activation produces action potentials (with peak sound-evoked firing rates of more than 300 hertz) that are conducted along the eighth cranial nerve to the brain⁴. So one might imagine a symphony (or organ recital) encoded by the cochlea, with harmonies of waxing and waning action potentials in a parallel array of 40,000 afferent nerve fibres — the high notes augmenting activity in