MATHEMATICAL PHYSICS

First encounters

Michael F. Shlesinger

The idea of 'random walks' pops up in areas from biochemical reaction pathways to animals' foraging strategies. A central question — how likely is it that a walker is somewhere for the first time? — now has a simpler answer.

A walker sets out on a random walk, moving between many different sites in no particular order. Formally, knowing the probability of arriving at each of the sites for every possible number of steps provides all the information required to characterize the walk. But it doesn't necessarily give easy answers to some relevant questions: for instance, what is the probability that the walker will reach a certain site for the first time after a given number of steps? This 'first-passage time' problem is notoriously intractable. For that reason, we often settle for the somewhat simpler problem of calculating the average (mean) first-passage time to an arbitrary site.

On page 77 of this issue, Condamin *et al.*[1] revisit the question of the mean first-passage time, and derive some new results of surprising simplicity. The authors consider a finite space made up of a lattice of nodes. This lattice can be arbitrarily regular, disordered or hierarchical, or it can assume some configuration, such as that of a scale-free network. The Internet, and many models of human social interactions, are good examples of the scale-free case. They consist of nodes with many different degrees of connectedness, and the likelihood that a node has a certain number of links declines as a power law with that number: many people (or network nodes) have a small number of connections, but very few have a very large number. First-passage time distributions thus have relevance, for example, for the spread of sexually transmitted diseases in a human social network, or the spread of computer worms through the Internet.

The authors find three cases for the mean first-passage time between an arbitrary source and a designated target at a distance r. To a good approximation, this time always grows linearly with the number of nodes, N, but also depends either on r raised to a certain power or, in a special case, the logarithm of r (we'll return to what these three cases signify in a moment). The linear dependence on N seems to contradict results calculated by Elliott Montroll[2] almost 40 years ago. He was studying the random walk of an exciton (an electron–hole excitation carrying energy) towards a reaction site in a photosynthetic plant cell, and found that, assuming jumps are to nearest-neighbour sites, the mean first-passage time differs according to whether the sites are arrayed in a line, a square lattice or a simple cubic lattice. (The exact formulae are $N^2/6$, $(1/\pi)N/lnN$ and $1.5N$, respectively.)

The reason for the apparent discrepancy is that Montroll averaged over all possible starting points for the walk, thus removing any dependence on r from his problem. Similarly, if every one of the nodes could be visited on any jump with equal probability, the node structure and connections would be irrelevant and the mean first-passage time would be exactly equal to N. It is in fact the node connections that generate the dependence on r. Because Condamin *et al.*[1] explicitly take account of the role of the source–target separation in their formulation of the problem, their results are more fundamental and, when averaged over the possible r values, Montroll's expressions pop out again.

Condamin *et al.* parametrize the mean first-passage time in terms of two characteristic 'dimensions'. These are not dimensions in the usual sense of one, two or three, but are derived from scaling relationships between the variables that are inherent in the problem. First up is the 'fractal dimension', d_f, which characterizes the density of the nodes in the lattice. In a lattice of two dimensions, the meaning of this quantity can be envisaged by drawing a circle enclosing part of the plane of the lattice, and counting the number of nodes it encloses. Then you increase the radius of the circle, and calculate again, repeating this process several times. The number of enclosed modes will scale as some power of the circle's radius; that power is d_f. For a lattice with a constant average density of nodes in the plane, d_f will be 2 — the number of enclosed points scales with area. But for fractal shapes in the plane, such as a Sierpinski gasket (Fig. 1a on page 78) or a so-called percolation cluster, which have a hierarchy of self-similar node groupings that only sparsely fill the plane, d_f will be less than 2.

The second dimension in the authors' formulae[1] is the 'walk dimension', d_w, which characterizes the ease with which the walker can move through the lattice. Mathematically, it enters the expression for the mean-square displacement from the source as a function of the number of moves, n, which is written to scales as n^{2/d_w}. On our regular two-dimensional lattice, d_w would be equal to 2 (meaning that the mean-square displacement grows linearly with the number of moves made, the 'diffusive' case). But on a lattice with many bottlenecks and dead-ends, the walk can be severely impeded, producing a d_w of greater than 2, and a process slower than diffusion.

It is the difference between the fractal

Have I been here before? Condamin and colleagues' mathematical results[1] deal with the likelihood that a walker who has embarked on a random walk is visiting a place for the first time.

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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 calculations[1] 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).
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PLANT PATHOLOGY

Deadly special deliveries

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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 tissues[1]. For this purpose, pathogenic bacteria have systems to deliver 'effector' proteins directly into plant cells, where they interact with plant proteins and suppress defence mechanisms[2].

Whisson *et al.* (page 115 of this issue[3]) describe how the agent of potato late blight, *Phytophthora infestans*, uses a special host-cell-targeting signal[4] 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 cells[7]. 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 again[8]. 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 motif[9]. 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 effectors[10]. 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 infection[1]. 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 colleagues[3] 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 cells[11]. 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 candidates[3]. 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