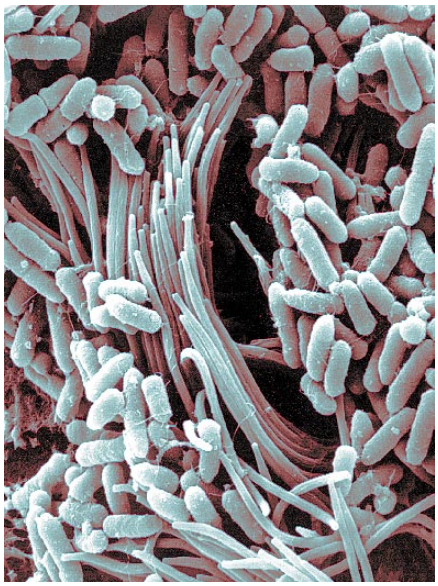

THOMAS MONINGER, UNIV. IOWA

Figure 1 **The rod-shaped *Pseudomonas aeruginosa* on cultured epithelial cells from the human respiratory tract. Each *P. aeruginosa* cell measures about 0.5 by 2–3 μm. The bacterium shows extraordinary nutritional versatility. This might require the large number of genes in its genome (the sequence of which is now published[1]) that are predicted to be involved in regulating gene expression.**

resilient beast. On all counts, the project has met its goals.

Pseudomonas aeruginosa has a large genome, about one-third larger than that of *Escherichia coli*. In fact it has about as many genes as the budding yeast *Saccharomyces cerevisiae*, and about half as many as the fruitfly. The large size of the *P. aeruginosa* genome allows for a wide diversity of genes. Although this is no great surprise, the more detailed annotation of the genome has been quite revealing. Two features that jump out can be summarized as regulation, regulation and more regulation, and pumps, pumps and more pumps.

Stover *et al.* discovered a large number of genes — between 8% and 10% of the predicted total of 5,570 genes — that encode proteins with sequences similar to those of known regulators of gene expression. The authors note a correlation between genome size and the percentage of predicted regulators in sequenced bacterial genomes: the larger the genome, the higher the percentage of regulatory genes. For example, *Helicobacter pylori* — a highly specialized bacterial pathogen that can colonize the acidic environment of the human stomach — has 1,709 predicted genes. Fewer than 20 of these (about 1%) are expected to be regulatory. Smaller genomes have even lower percentages of regulatory genes. The incredible potential for *P. aeruginosa* to turn genes on and off according to the conditions in which it finds itself is consistent with its nutritional versatility.

The *P. aeruginosa* genome also encodes a number of pumps, which may be the key to the bacterium's ability to withstand antibiotics in its human host. It has been suggested that Gram-negative bacteria, a group to which *P. aeruginosa* belongs, can resist the lethal effects of many antibiotics by pumping them out of their cells faster than the chemicals can accumulate. Members of the RND protein family of 'multidrug efflux' pumps can render bacteria impervious to antibiotics[4]. It is not clear how or why these pumps evolved; perhaps they were first needed to eliminate naturally occurring environmental toxins. We already knew of four RND pumps in *P. aeruginosa* (*E. coli* has the same number, whereas *Mycobacterium tuberculosis*, the persistent pathogen that causes tuberculosis, has none). The sequencing project has now revealed six more.

When and where are these pumps active? One idea is that they might be expressed when *P. aeruginosa* exists as a biofilm. These are stationary communities of bacteria that are enclosed by a self-produced extracellular matrix. When bacteria exist as biofilms, they can resist antimicrobial agents. A hypothesis to explain the persistence of *P. aeruginosa* in the lungs of a cystic fibrosis patient is that it may establish a biofilm in this environment[5].

The abundance of regulatory genes and questions about the regulation of antibiotic pumps in *P. aeruginosa* call for investigators to look into gene expression in this bacterium. To this end, the US Cystic Fibrosis Foundation is again taking a unique approach, by building on its initial investment in *P. aeruginosa* genomics and underwriting the cost of constructing a *P. aeruginosa* gene-expression array. The charity plans to make the array available to interested researchers at a cost consistent with the budgets of academic scientists. It has also created a Cystic Fibrosis Bioinformatics Center, to support scientists using the arrays. One hopes that the genomic information reported by Stover *et al.*[1], and the information to come from the gene-expression analysis, will allow us finally to tame this testy pathogen. ■

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Mathematics

The Lorenz attractor exists

Ian Stewart

For nearly 40 years, one of the classic icons of modern nonlinear dynamics has been the Lorenz attractor. With its intriguing double-lobed shape and chaotic dynamics, the Lorenz attractor has symbolized order within chaos (Fig. 1). The only problem is: does it exist? Mathematicians have lacked a rigorous proof that exact solutions of the Lorenz equations will resemble the shape generated on a computer by numerical approximations, and they also could not prove that its dynamics are genuinely chaotic. Perhaps the calculations showed something that merely looked like chaos — a numerical illusion. The smart money has always been on chaos in the Lorenz system being real, but the rigorous techniques of dynamical mathematics were unable to prove it. Until last year, that is, when Warwick Tucker of the University of Uppsala completed a PhD thesis showing that Lorenz's equations do indeed define a robust chaotic attractor. The proof has since been published (W. Tucker, *C. R. Acad. Sci.* **328,** 1197–1202; 1999), and an excellent summary has been provided by Marcelo Viana (*Math. Intell.* **22,** 6–19; 2000).

Tucker's work is hugely significant, not just because it provides the Lorenz attractor with a solid foundation, but because his techniques will be widely applicable. At last, the embarrassing gap between what we think we know about a nonlinear dynamical system from numerical simulations, and what we actually know in full logical rigour, is starting to close. At the moment the methods are limited to dynamics in three dimensions, but after Tucker's breakthrough that may well change. Dimensions greater than three are of considerable interest because the dimension of a dynamical system is not the dimension of ordinary space, but the number of variables in the equations. For example, the motion of a three-body system consisting of the Earth, Mars and a space probe requires six variables for each body — three of position and three of velocity — and so is an 18-dimensional dynamical system.

Why bother with rigorous proofs? Surely any practical implications of the equations are already embodied in the numerical results — do we need to be obsessed with logical rigour? Yes, we do. There are several reasons for taking numerical solutions of nonlinear differential equations with a pinch of salt. Numerical methods are approxima-

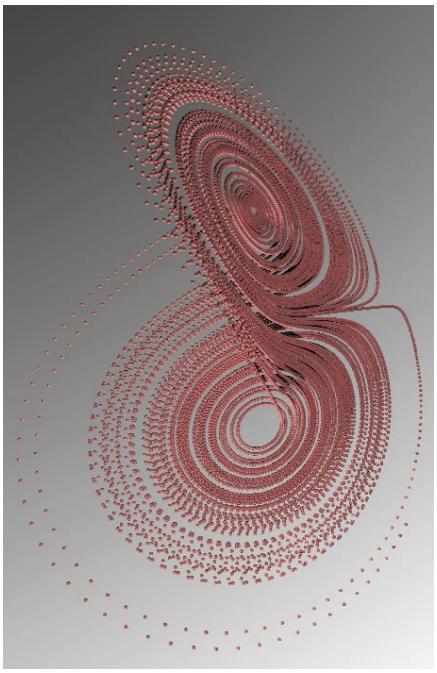
tions, and chaotic systems are highly sensitive to approximations; it is well known that numerics can sometimes give seriously misleading results. But the deepest reason is that until we can prove what our computers seem to be telling us, then we are ignoring a huge gap in our mathematical technique. Often such a gap is a clue that important conceptual ideas are lurking nearby, as is the case here.

The Lorenz attractor dates from 1963, when the meteorologist Edward Lorenz published an analysis of a simple system of three differential equations that he had extracted from a model of atmospheric convection. He pointed out that they possess some surprising features. In particular, the equations are 'sensitive to initial conditions', meaning that tiny differences at the start become amplified exponentially as time passes. This type of unpredictability is a characteristic feature of chaos. Conversely, there is also 'order' in the system: numerical solutions of the equations, plotted in three dimensions, consist of curves winding round and round a curious two-sheeted surface, later named the Lorenz attractor.

The geometry of the attractor is closely related to the 'flow' of the equations — the curves corresponding to solutions of the differential equations. There is an unstable equilibrium, a saddle point, at the origin. The curves repeatedly pass this point, and are pushed away to the left or right, only to circle round to pass back by the saddle. As they loop back, adjacent curves are pulled apart — this is how the unpredictability is created — and can end up on either side of the saddle. The result is an apparently random sequence of loops to the left and right.

The central technical issue in proving that the Lorenz system is a chaotic attractor is translating these statements into suitably precise mathematics. Tucker's proof combines two main ideas. One is a conceptual characterization of chaotic attractors in terms of 'singular hyperbolicity', introduced by C. Morales, M. J. Pacifico and E. Pujals (*C. R. Acad. Sci.* **326,** 81–86; 1998). Previous work on dynamical systems had concentrated on 'hyperbolic' systems, where the flow of the equations can always be split into a set of contracting directions and a complementary set of expanding ones. But the Lorenz system is not hyperbolic. Singular hyperbolicity replaces the idea of expanding directions in the flow by the condition that part of the flow should expand in volume. If some sides of a box expand and others contract, the volume may nonetheless expand if the amount of expansion beats the amount of contraction. So singular hyperbolicity is less restrictive than hyperbolicity.

Tucker's other important idea is using computer calculations in a rigorous way to establish certain features of the geometry of the solutions of differential equations — normal numerics plus precise error estimates. Tucker obtains a rigorous approximation to the way curves loop back towards the origin by following the time evolution of lots of tiny boxes (up to 10,000). But numerical solutions of differential equations encounter problems near saddle points, because the flow slows down exponentially fast. To get round this difficulty, Tucker uses the well-established technique of a 'normal form'. Near an equilibrium, any differential equation can be transformed into an equation that can be solved by an exact formula, to a high degree of approximation. This formula can be used instead of the numerical procedure whenever the flow gets too close to the equilibrium.



PAUL BOURKE, SWINBURNE UNIV. TECHNOL.

Figure 1 **The Lorenz attractor was first derived from a simple model of convection in the Earth's atmosphere. Previously, the Lorenz attractor could be generated only by numerical approximations on a computer, as shown here. Now we have a rigorous proof that confirms its existence.**

The task then reduces to finding a set of boxes such that curves starting within one box eventually return to a box (usually a different one), which in effect says that the collection of boxes forms an attractor. Some further technical conditions, related to singular hyperbolicity, are required to establish that the flow is chaotic. The search for suitable boxes begins with an informed guess based on raw numerics; any boxes that cause trouble by growing too fast are subdivided until they cease to cause trouble. When the subdivision process of all boxes stops, the proof is complete. Finding a suitable collection of boxes took about 30 hours on a fast computer.

Technicalities aside, the main idea here is that, with care, naive numerics can be used with precise error estimates to establish significant features of the flow of a nonlinear differential equation. When these features are combined with appropriate conceptual insights, the existence of chaotic attractors becomes irrefutable. So, thanks to Tucker, dynamical systems theorists can at last stop worrying about whether their most potent icon might suddenly fall apart. And Lorenz's original insight, that the strange behaviour of his equations was not a numerical artefact, can no longer be disputed. ■

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Malaria

Channelling nutrients

Kiaran Kirk

Malaria, an infectious disease responsible for an estimated 300 million to 500 million clinical cases and 1.5 million to 2.7 million human deaths each year[1], is caused by a single-celled parasite that invades the red blood cells of its host. In the 48 hours after it invades a red blood cell, the parasite grows to many times its original size, and then divides to produce 20–30 new parasites. To fuel this high rate of growth and multiplication, the malaria parasite needs nutrients from outside the infected cell. However, a normal red blood cell is unable to take up at least some nutrients fast enough to satisfy the parasite's voracious appetite. On page 1001 of this issue[2], Desai and colleagues provide new insights into how this problem is solved. They describe a versatile channel that is found in the outer membrane of infected (but not uninfected) red blood cells, and which helps to supply nutrients to the hungry parasite.

It has long been known that following the invasion of a human red blood cell by *Plasmodium falciparum* — the most virulent of the four malaria parasites that are infectious to humans — the membrane of the infected cell undergoes a dramatic increase in its permeability to a range of small solutes, both charged and uncharged[3–6]. The pathways responsible for the increased permeability have previously been shown to have a strong preference for negatively charged ions (anions) over positively charged ions (cations), and to be blocked by drugs known to inhibit anion-selective channels[6]