(for example, the Internet backbone) and some standard models (such as random graphs[6] and preferential attachment models of scale-free networks[7]) lack the self-similarity reported by Song *et al.*, indicating that such scaling is not automatic and, consequently, that it can used as a benchmark for testing models of network structure. Second, it's odd that networks should find themselves configured as fractals. In statistical physics, power laws and self-similarity are associated with phase transitions — with systems teetering on the brink between order and chaos. Why do so many of nature's networks live on a razor's edge? Have they self-organized to reach this critical state[8], perhaps to optimize some aspect of their performance, or have they merely followed one of the manifold paths to power-law scaling[9], full of sound and fury, signifying nothing? ■

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1. Song, C., Havlin, S. & Makse, H. A. *Nature* **433,** 392–395 (2005).
2. Falconer, K. *Fractal Geometry: Mathematical Foundations and Applications* (Wiley, Chichester, 1990).
3. Hartwell, L. H., Hopfield, J. J., Leibler, S. & Murray, A. W. *Nature* **402,** C47–C52 (1999).
4. Girvan, M. & Newman, M. E. J. *Proc. Natl Acad. Sci. USA* **99,** 7821–7826 (2002).
5. Milo, R. *et al. Science* **298,** 824–827 (2002).
6. Erdös, P. & Rényi, A. *Publ. Math. Inst. Hung. Acad. Sci.* **5,** 17–61 (1960).
7. Barabási, A.-L. & Albert, R. *Science* **286,** 509–512 (1999).
8. Bak, P., Tang, C. & Wiesenfeld, K. *Phys. Rev. Lett.* **59,** 381–384 (1987).
9. Newman, M. *Nature* **405,** 412–413 (2000).

Sexually transmitted diseases

Epidemic cycling and immunity

Bryan Grenfell and Ottar Bjørnstad

Are syphilis epidemics caused by external factors such as human sexual behaviour, or are factors intrinsic to the pathogen more important? Comparing the dynamics of syphilis and gonorrhoea provides some clues.

The great Renaissance physician and scholar Girolamo Fracastoro achieved lasting fame for his early observations on the contagion theory of the transmisssion of infectious disease[1]. In 1530, he also coined the name for syphilis — which was then spreading rapidly through Europe — in an extended allegory written in Latin hexameter (epidemiologists were more culturally rounded in those days). In Fracastoro's poem, the god Apollo is angered by a shepherd, Syphilus, and afflicts him with the new disease. On page 417 of this issue, Grassly *et al.*[2] provide a more down-to-earth explanation of the dynamic processes underlying the incidence of syphilis.

Whether fluctuations in epidemics are governed by external drivers (such as behaviour, climate — or the gods), or by intrinsic processes that arise from the dynamic feedback between host and pathogen populations, has been debated since the early 1900s. This controversy parallels long-standing ecological arguments about the relative role of extrinsic (environmental) forces and intrinsic, nonlinear dynamics in driving population fluctuations[3]. Arguably, ecologists are more familiar than epidemiologists with the potential of nonlinear dynamics to drive cycles. This is ironic, because many infectious diseases have excellent historical records of incidence and a simple natural history — an ideal combination for exploring the underpinnings of dynamic fluctuations[4,5].

Comparative approaches, where differences in the dynamics of various infections can be related to biological differences in the underlying host–pathogen interactions, are particularly powerful in studying this problem[6]. Grassly *et al.*[2] use this approach to explore the dynamics of syphilis and gonorrhoea. They base their analysis on disease notification statistics from the United States, where these two sexually transmitted diseases are endemic. The authors use time series of annual disease reports for 68 US cities to demonstrate marked 8–11-year cycles in syphilis incidence from the 1960s to the 1980s. These cycles had previously been attributed to changes in factors extrinsic to the host–pathogen interaction, particularly to changes in human sexual behaviour. If this were the case, however, there should be correlated fluctuations in gonorrhoea because of its similar transmission route and infectious period. Grassly *et al.* demonstrate that there is no such correlation: gonorrhoea shows slow trends rather than cycles during the same period.

The authors use mathematical models to reveal that the distinct behaviours of syphilis and gonorrhoea arise from their different interactions with the human immune system. Thus, the simplest explanation for the periodicity in syphilis incidence is that it results from nonlinear interactions that are fundamental to the host–pathogen transmission process.

Syphilis stimulates significant — albeit

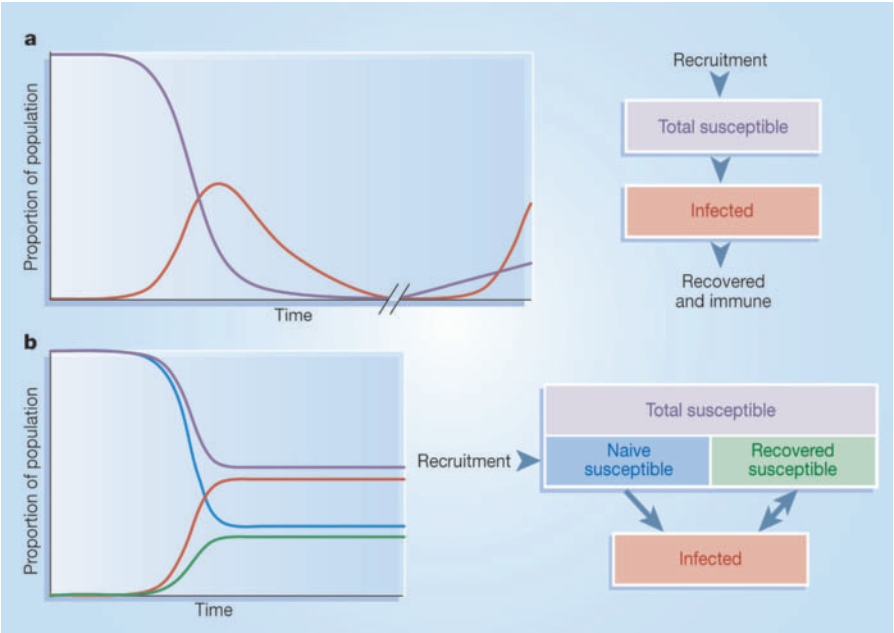

Figure 1 **The impact of immunity on the dynamics of epidemics.** a, **Dynamics of the basic susceptible–infected–recovered (SIR) model, assuming that the infection attacks a naive susceptible population. Because of prolonged immunity following recovery, the supply of susceptible individuals becomes exhausted and the epidemic extinguishes itself. After the epidemic, new recruits augment the susceptible class until a further epidemic is possible (shown schematically here). This is the basis of syphilis dynamics, as shown by Grassly *et al.*[1].** b, **The susceptible–infected–susceptible (SIS) model, where there is no immunity to reinfection (as with gonorrhoea). Unlike the SIR model, total susceptible numbers are replenished by a flow of previously infected individuals, so that the epidemic moves smoothly to an equilibrium level (analogous to the carrying capacity of logistic models in ecology[8]), rather than declining.**

imperfect — immunity following recovery from infection. Consequently, as Grassly *et al.* show, the dynamics of syphilis infection have many features of the well-known 'susceptible–infected–recovered' (SIR) model for microparasitic infections[4,5]. In SIR dynamics, oscillations in disease incidence can be driven by prolonged immunity following infection (combined with a relatively short infection period[4]). Cycles occur because major epidemics extinguish themselves by exhausting their supply of susceptible individuals (Fig. 1a); the numbers of individuals in at-risk groups then build up slowly, eventually providing enough scope for the next major outbreak.

Unlike syphilis, gonorrhoea can evade post-infection immunity by camouflaging itself with different arrays of surface proteins[7]. At the population level, this corresponds to the 'susceptible–infected–susceptible' (SIS) model of infection, in which the same individual can be infected repeatedly[4,8] (Fig. 1b). Thus in SIS dynamics, infection does not decrease the total number of susceptible individuals, preventing the boom-and-bust dynamics seen in acute SIR infections.

By contrast, the prolonged immunity seen in SIR systems causes overcompensatory dynamics and recurrent epidemics, which bear strong analogies to the cycles of many predator–prey systems in ecology. In fact, SIR dynamics are, like the SIS interaction, regulated by an upper population limit on cases and susceptible individuals[4]; the system therefore needs some form of regular or stochastic 'forcing' to drive strong epidemics. A dramatic illustration is given by acute, immunizing childhood infections such as measles, where seasonal variation in contact rates can produce violent biennial epidemics[5]. With its more sedate decadal dynamics, syphilis is unperturbed by seasonal influences. However, Grassly *et al.* show that random 'shocks' provided by demographic stochasticity (arising from the probabilistic nature of individual infection events, for example) are sufficient to excite oscillations in the model that closely resemble the cycles seen in the incidence data. On a longer timescale, external shocks, such as a reduction in sexually transmitted disease associated with control measures against the spread of HIV, further influence the dynamics of both syphilis and gonorrhoea.

Nonlinear overcompensatory interactions, as seen in syphilis, can lead to the emergence of space–time dynamics, such as sychronization of disease incidence across different locations, or waves of infection across geographical areas. Indeed, Grassly *et al.* document increasing synchronization of syphilis epidemics across US cities during the 1960s and 1970s. The authors argue convincingly that this is because the underlying network of sexual contacts is becoming increasingly interconnected. However, previous comparative analyses of the spatio-temporal dynamics of measles and whooping cough show that dynamic inference from such systems is not straightforward[6]. In these cases, spatial dynamics emerge through the interaction between local dynamics and spatial coupling between different local systems — sometimes coupling leads to enhanced synchrony, but sometimes synchrony can decay with time if increases in coupling accompany changes in local dynamics.

A challenge in the spatio-temporal dynamics of syphilis is to combine models for local transmission with models of spread across spatial networks[9]. As Grassly *et al.* point out, we must be very cautious in applying simple models to explain the spatial dynamics of human pathogens: basic distance-based networks fail to capture the complex nature of human population mixing. Such contact patterns are often hard to measure directly, and an intriguing task for future models will be to infer spatial patterns and temporal trends of mixing from the analysis of epidemic synchronicity.

Grassly and colleagues' dissection of cyclic versus non-cyclic behaviour is a valuable addition to the taxonomy of comparative disease dynamics. Using comparative studies to tease out the relative role of intrinsic dynamics and extrinsic shocks is an important process for understanding and predicting the dynamics and evolution of established and emerging infections. In the nonlinear, behaviourally and environmentally driven world of epidemics, though, we should always expect the unexpected. ■

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1. Gould, S. J. *Nat. Hist.* **109,** 38–47 (2000).
2. Grassly, N. C., Fraser, C. & Garnett, G. P. *Nature* **433,** 417–421 (2005).
3. Bjørnstad, O. N. & Grenfell, B. T. *Science* **293,** 638–643 (2001).
4. Anderson, R. M. & May, R. M. *Infectious Diseases of Humans: Dynamics and Control* (Oxford Univ. Press, 1992).
5. Grenfell, B. T., Bjørnstad, O. N. & Kappey, J. *Nature* **414,** 716–723 (2001).
6. Rohani, P., Earn, D. J. D. & Grenfell, B. T. *Science* **286,** 968–971 (1999).
7. Snyder, L. A. S., Butcher, S. A. & Saunders, N. J. *Microbiology* **147,** 2321–2332 (2001).
8. Hethcote, H. W., Yorke, J. A. & Nold, A. *Math. Biosci.* **58,** 93–109 (1982).
9. Xia, Y. C., Bjørnstad, O. N. & Grenfell, B. T. *Am. Nat.* **164,** 267–281 (2004).

Cell biology

Border crossing

James U. Bowie

The 'translocon' complex, which determines whether a protein segment will be inserted into or pushed through the cell membrane, seems to make the decision by performing a thermodynamic measurement.

Cells have a border security system that would put any nation to shame. They need to decide millions of times every nanosecond whether to allow something in or out, and a mistake could mean death. The sentries entrusted with these life-or-death decisions are specialized proteins that reside in the cell membrane. Not just any 'wannabe' gets to be a membrane protein, however; it requires a special constitution and careful nurturing. A paper by von Heijne and colleagues in this issue (Hessa *et al.*[1], page 377) tells us a lot more about what it takes to get into the membrane.

Membrane proteins are usually not soluble in the aqueous cytoplasm inside the cell. So cells have developed specialized machinery for injecting them into the membrane as they emerge from the complex in which they are synthesized. Hessa *et al.*[1] focused on the ubiquitous and best-studied insertion machine, known as the Sec translocon[2,3].

The Sec translocon must make several tricky decisions as the protein is being made; based on the emerging protein's amino-acid sequence, the translocon must choose whether to pump the segment into the exoplasm outside the cell, push it sideways into the membrane, or flip it before releasing it into the membrane. Making the correct decision is essential if the protein is to fold properly, so the emerging peptide and the translocon must work in concert. Thus, to predict protein structure from amino-acid sequence, we need to understand how the translocon works with the nascent polypeptide to generate the final fold. The paper by Hessa *et al.*[1] helps to define how one of the decisions is made — how the translocon 'decides' whether to move a segment into the membrane or the exoplasm.

The cell membrane is a complex environment, and only specialized polypeptides, with equally complex and variable surface properties, reside there[4,5]. For simplicity, we can divide the membrane into three regions (Fig. 1, overleaf): the central core of lipid hydrocarbon chains (about 30 Å thick); the interfacial region near the lipid head groups (about 15 Å thick); and the aqueous region. These environments are dramatically different, and so the structure of a membrane