

Network structure and the biology of populations

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A scientific growth area in recent years has been the study of networks of interacting entities within a population, including species in food webs, human or other animals transmitting infection, proteins in cells, cells in organisms (e.g. neuronal networks), the internet and the World Wide Web. Here, I review some of the differing network patterns that arise in theory and in practice, with an emphasis on their dynamical implications, particularly for resistance to deliberate or accidental disturbance. I offer caveats and opinionated comment about some excesses of enthusiasm and suggest some areas where these network ideas might find further application.

Biological networks and their properties

Back in the early 1970s, one of the few tentative generalisations in ecology texts, based on arguments by Elton [1], was that ‘complex ecosystems are more stable’, in the sense that those with more species and/or a richer network of interactions among them were better able to withstand disturbance, either natural or human created. My accidental introduction to ecological research began with the observation that, as a mathematical generality, this proposition was false [2]. However, real ecosystems are the winnowed product of historical processes rather than randomly constructed networks. But what network structures do we observe in nature (possibly different in different environments) and what do these imply for food-web dynamics? This ‘network agenda’ arrived in ecology relatively early compared with other areas in the life sciences, and subsequent experiments, observations and theoretical studies have taken us a good distance down the road to answering these interesting questions.

More generally, empirical and theoretical work on the structure and dynamical behaviour of networks is burgeoning across the life sciences. Such work derives from advances in instrumentation and in computer power. Here, I sketch some mathematical facts about different kinds of network, listing various areas of current research (including some under the new heading of ‘Systems Biology’), with an emphasis on commonalities and cross-cutting themes. I then summarise some suggested explanations for how these networks have evolved or been constructed, and sound some cautionary notes against excesses of enthusiasm. In particular, I focus on

the interplay between contact networks and the transmission dynamics of infectious diseases, partly because there is a lot of data, theoretical understanding and implications for policy. In conclusion, I offer some opinions about ‘what is next’. This review is necessarily sketchy and idiosyncratic, even in the areas that I have emphasised. **Box 1** indicates some excellent and more detailed reviews of particular aspects of networks in biology.

Kinds of network

The oldest and best-studied network model is the Erdos–Renyi random graph [3], in which n nodes (or vertices) are connected by links (or edges) placed randomly between pairs of nodes. Less interesting is a uniform network, in which each node is linked to exactly m others.

The basic statistic used to characterise the structure of a large network is its ‘degree distribution’, $P(i)$. Here, $P(i)$ is the probability that a randomly chosen node will ‘have degree i ’, that is be linked to i other nodes. For the Erdos–Renyi network, the degree distribution is given exactly by the binomial distribution or, in the limit of large n , by the Poisson distribution: $P(i) = m^i e^{-m} / i!$, where m is the average number of links.

Poisson and binomial distributions are strongly peaked about the average, m , with the probability of finding larger i values diminishing rapidly, as $1/i!$. That real-world networks are more complicated was driven home in 1967 by Milgram [4], who asked 160 people in the western USA to send a letter to someone (unknown to them) in Massachusetts by sending it to an acquaintance who might be able to further its journey to the target; 42 letters arrived, after an average of 5.5 hops; hence, ‘six degrees of separation’. This motivated Watts and Strogatz’s interesting and influential work [5] on ‘small world’ networks, which combine local clusters with occasional ‘long hops’. I think this helped focus attention on degree distributions with ‘fat tails’, which decrease relatively slowly as i increases. One such canonical distribution is the exponential: $P(i) \sim e^{-\alpha i}$.

More recently, guided by data and the models discussed here, much attention has been given to so-called ‘scale-free’ networks [6]. These obey the power-law degree distribution $P(i) \sim i^{-\gamma}$, where γ is a constant (usually $2 < \gamma \leq 3$). Such distributions have very fat tails, and also the peculiar feature that there is no characteristic number of links per node: hence ‘scale-free’ (SF).

Two other interesting statistical properties of large networks are the network ‘diameter’ (d) and the ‘clustering coefficient’ (C) [3,7–9]. The former is calculated

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Box 1. More detailed reviews

Here, I highlight some excellent reviews that provide more details of various aspects of the topics covered here in the main text.

The mathematics of networks or ‘graphs’ are reviewed extensively and in detail by Bollobas [7] and Newman [3]. Bollobas focuses on the mathematical technicalities, whereas Newman integrates the mathematics with applications in a readable way. A briefer and exceptionally lucid review along these latter lines is by Strogatz [8].

The thoughtful recent review of ‘network thinking in ecology and evolution’ by Proulx *et al.* [9] in *TREE* is, in many ways, complementary to the present one. In particular, Box 1 from the article [9] provides a comprehensive and helpful glossary of technical terms used in mathematical descriptions of networks. For an account of ‘ecological networks’, see the recent collection of papers compiled by Pascual and Dunne [67], especially the chapter by Dunne [60]. Keller [20] gives a constructively critical appraisal of work on the purported ubiquity of scale-free networks; I particularly liked her more general scepticism of grand generalisations.

by first finding the shortest path (smallest number of links) between each pair of nodes; d is then the maximum such shortest path (some biological authors take d to be the overall average shortest path). For an Erdos–Renyi random network with n nodes, d is proportional to $\log n$. Exponential networks have smaller diameters, and SF ones are ultra-small [with diameters scaling as $\log(\log n)$ in the usual case where $2 < \gamma \leq 3$]. C is the average probability that two neighbours of a given node are also neighbours of each other; again, this quantity is well named, giving an intuitive sense of how ‘clumpy’ the network is. Many real-world networks have high C values (≥ 0.5). For the Erdos–Renyi network, $C = m/n$ is, by definition, the same for any node, regardless of its neighbours.

The degree distribution gives important information, but it does not define the structure of a network uniquely. Figure 1 shows two networks with identical $P(i)$, but with significantly different d and C . More generally, Milo *et al.* [10] have propounded a bottom-up approach that concentrates on identifying small patterns (subnets with three, four or even five connected nodes) that are over-represented in the network. These are called ‘network motifs’ and can be used to characterise distinct categories of networks.

Observed networks

This is a rapid gallop across the landscape of examples, with infectious disease deferred for closer attention later.

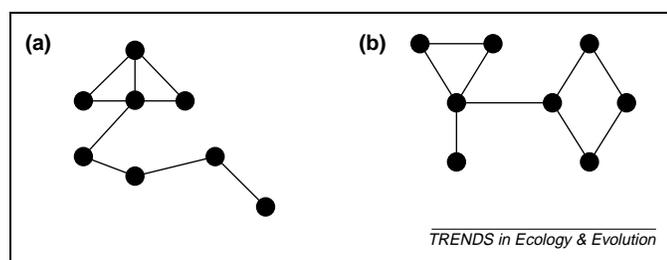


Figure 1. Two eight-node networks with the same degree distribution, but differing in structure (and having different diameters, d , and clustering coefficients, C). Specifically, the degree distribution $\{P(i)\}$ for both (a) and (b) is $P(4)=0.125$, $P(3)=0.125$, $P(2)=0.625$ and $P(1)=0.125$. But for (a), $d=5$ and $C=0.43$, whereas for (b), $d=4$ and $C=0.21$.

Barabasi and Albert [11], beginning with studies of the links among web pages within their University of Notre Dame, have shown that the degree distribution of the world wide web (www) and of the internet seems to be SF (reviewed further in [6]). Others (e.g. [12]) have noted that, although the broad patterns of these IT networks are SF, important details of subcomponents can differ in ways that can have practical implications. Patterns of scholarly publication and, more generally, the ‘mapping of knowledge domains’, generate networks whose properties repay study. Their degree distributions often have SF features (reviewed in [13]).

Introducing a Special Section in *Science* on ‘Networks in biology’, Jasny and Ray [14] write that “Biologists are striving to move beyond a ‘parts list’ to more fully understand the ways in which network components interact with one another to influence complex processes”. An increasing number of papers deal with networks of interacting proteins (linked nodes) that determine how cells function. For example, Kollmann *et al.* [15] study the signalling network of bacterial chemotaxis in *Escherichia coli* and suggest that the observed network structure is the smallest that is sufficiently robust to ensure accurate chemotactic response for the relevant population in its noisy environment. They go on to speculate on the evolutionary implications and the fact that these ‘topological design principles compensating for intercellular variations seem to be highly conserved among bacterial chemosensory systems’.

At a coarser level in biological systems, increasing attention is being paid to how networks of cells work together in organs, for example in neuronal networks (e.g. [16]). Other active areas of experimental and theoretical work on network structures and dynamics range from how individuals interact in societal and behavioural networks to word-adjacency networks from different languages: for instance, social insects (e.g. [17]), human social systems (e.g. [18]), and other examples listed in [10]. Again, small world, and especially SF, distributions are ubiquitous.

Possible explanations and some caveats

Barabasi and Albert [11] give a plausible way in which a SF network (such as the internet) could assemble itself. If networks arise by the sequential addition of nodes, and if each new node links preferentially to highly connected nodes, then this results in a SF degree distribution. More precisely (although a bit different from the Barabasi–Albert models), suppose new links are added such that each end attaches with probability p to a new node, and with probability $(1-p)$ to an existing node; in the latter case, the attachment is with relative probability i to a node with i connections. The asymptotic result of this process is a SF distribution, $P(i) \sim i^{-\gamma}$, with $\gamma = (2-p)/(1-p)$. As p ranges from 0 to 1, γ goes from 2 to ∞ . More restrictively, if we assume that each link connects a new node to the existing network, we have $p=0.5$ and, thus, $\gamma=3$ (reviewed in [3,7]).

These ideas appeal to me as an explanation for why broad-scale features of IT systems are SF. But for the life sciences (proteins signalling in cells, neuronal networks, behavioural dynamics of social insects, etc.), many,

including myself, see some problems (e.g. [19,20]). Not the least of these is that many of the observed degree distributions for intracellular signalling, although roughly linear on a log-log plot (i.e. a power law) over much of their range, are in fact better fit with an exponential or other degree distribution [20,21].

Another problem, only recently pointed out [22], is that many of these networks are in fact samples (often rather small samples of 10% to 20%) of the full network in question. But samples from SF networks are not SF. Conversely, if the observed sample is SF, then the full network is not. Indeed, a random sample from a network will not have the same degree distribution as the whole, except when the 'parent network' is a binomial or negative binomial network (of which Erdos–Renyi and exponential are special cases) [22].

A different approach to 'superfamilies of evolved and designed networks' was outlined earlier [10]. By using small subnetworks, Milo *et al.* classify 'network motifs' and, on this basis, identify several 'superfamilies' of networks. One distinct superfamily includes protein signalling, developmental genetic networks and neuronal wiring. Others include power grids, protein-structure networks, social networks and linguistic patterns from different languages (Indo-European to Japanese). This work is, as yet, essentially phenomenological.

In seeking models for the self-assembly of networks, essentially all earlier work focussed on growing networks (with preferential attachment to highly connected nodes being the key to generating fat-tailed, SF-like distributions). Salathe *et al.* [23] propose a model that can generate fat-tailed networks, even in the absence of network growth, by not only adding, but also selectively eliminating nodes (with probability inversely related to the sum of their first- and second-order connectivity). Such a generalised birth–death process is arguably closer to the realities of evolutionary processes in biological systems. Other approaches involve mechanisms for duplication or 'rewiring' [24], or various kinds of optimization [25].

Two final caveats: Cassman *et al.* [26] have recently written about 'the use of modelling and simulation, combined with experiment, to explore network behaviour in biological systems – in particular their dynamic nature'. They worry about the innumeracy of many of their well-intentioned colleagues, who have little intuitive grasp of the connections between what goes into the computer and what comes out. They fear that 'During the past 30 years biology has become a discipline for people who want to do science without learning mathematics'. This is strong stuff, but I think there is some legitimacy to these worries [27].

The converse of this worry is the increasing number of physicists involved in Systems Biology, many of whom publish almost exclusively in theoretical physics journals. Much of this work is excellent and solidly grounded on collaborations with biological colleagues, but some seems to be avoiding competent biological review, and quite a bit thinks it sufficient to cite apparently relevant work in theoretical biology without actually reading it. This results in misunderstandings or repetition of earlier work published in biological journals.

Network structure and infectious disease dynamics

The transmission and control of infectious disease provides good examples where data on, and theoretical understanding of, network dynamics have been put to practical use. Specific instances include HIV/AIDS [28,29], the foot-and-mouth epidemic among livestock in the UK [30], SARS [31] and current planning against a possible avian flu pandemic [32–34].

The first question any ecologist asks of an invasive species is: what is its basic reproductive number, R_0 , as measured by the average number of offspring per capita that survive to reproductive age? For a directly transmitted infectious disease, be it HIV, SARS, or some newly emerging menace, R_0 is the average number of infections produced by an infected individual in a susceptible population (e.g. in the early stage of an epidemic) [28]. If $R_0 < 1$, a self-sustaining epidemic is not possible (at least without further evolution). If $R_0 > 1$, then although early stochastic fluctuations might extinguish the invader, an epidemic is possible. If R_0 is large, an epidemic is certain.

Most early work in this area, before the advent of big computers, treated populations as homogeneous (everyone is average) and also ignored stochastic fluctuations. However, studies of gonorrhoea [35] and of AIDS in its early days [36] found it impossible to explain epidemiological patterns without acknowledging that networks of sexual partnerships [degree distributions of numbers of links (partners) per node (individual)] showed significant heterogeneity, with 'superspreaders' being disproportionately influential. More recently, Lloyd-Smith *et al.* [37,38] have demonstrated another source of marked heterogeneity in contact networks, caused by some individuals being more infectious than others. Analysis of such nonuniform degree distributions for contact networks shows that they can seriously affect both how R_0 is calculated and the importance of stochastic effects.

In deliberately oversimplified terms, we might write $R_0 = \beta Dc$, where β is the transmission probability (measuring the infectiousness of an infected individual), D the duration of infectiousness, and c the average rate at which new contacts are made (e.g. new sexual partners acquired). If we think more carefully about the epidemiological significance of the contact network, however, we see that its degree distribution enters in a nonlinear way: those with more contacts are more likely to acquire infection by virtue of their higher activity level, and are also more likely to transmit infection. This shows up when we turn the handle of the mathematical machinery, finding that the epidemiologically appropriate 'average contact rate', c , is not the mean of the degree distribution of the network, but rather the mean-square divided by the mean [i.e. $c = \langle i^2 \rangle / \langle i \rangle$, where the sharp brackets indicate averages over the degree distribution, $P(i)$] [28]. R_0 can thus be rewritten as Equation I:

$$R_0 = \rho_0 [1 + (CV)^2] \quad [\text{Eqn I}]$$

Here, $CV = \langle i^2 \rangle^{1/2} / \langle i \rangle$ is the coefficient of variation of the degree distribution of the network, and $\rho_0 = \beta D \langle i \rangle$ is the incorrect estimate that we would make for R_0 by treating

the network as homogeneous (unless, of course, $CV=0$, when $R_0=\rho_0$). This observation helps explain how large differences in the incidence of HIV/AIDS in different places can arise from differences (which are not easily measured) in the tails of such contact distributions [28].

Earlier studies of the epidemiological consequences of nonuniform degree distributions in contact networks have also led to an important and rather general theorem (pp. 305–315 and 318 of [28], and [39]). For contact networks with a uniform degree distribution ($CV=0$), we can estimate the proportion, p^* , of individuals ('nodes') to be vaccinated or otherwise treated to eradicate infection: $p^*=1-1/\rho_0$. But if in truth, the degree distribution of the contact network is nonuniform, then if we treat nodes at random we will find that for successful control we have to treat more, possibly much more, than the proportion, p^* , that we estimated. However, if we take advantage of the heterogeneity, and treat in a way that targets the more highly connected nodes, then we can achieve our aim by treating a smaller, possibly much smaller, proportion than estimated by p^* . The greater the heterogeneity (the larger the CV of the degree distribution of the network), the more pronounced these effects will be [28]. This general result, first emphasised in the epidemiological literature in the mid-1980s, has more recently been independently discovered, with interesting and important implications, by Albert *et al.* [40] and others, in the context of the structure of IT networks in relation to targeted versus random attacks.

Although there is considerable advantage in targeting epidemiological control measures, it requires that highly connected individuals be identified, which is easier said than done. Cohen *et al.* [41] have, however, formulated a seemingly paradoxical method for achieving this, without directly identifying the hyperactive nodes. First, pick a node at random; then select randomly among nodes connected to it. On average, this automatically identifies the more highly connected nodes (giving the same kind of mean-square/mean effect seen in Equation I).

Epidemiological contact networks with fat-tailed degree distributions also have implications for stochastic effects in the initial stages of a potential epidemic. For a given value of $R_0>1$, a fat-tailed $P(i)$ implies that relatively few individuals are responsible for most of the transmission or, conversely, that many individuals do not transmit at all. In turn, such relatively small numbers tend to generate relatively large stochastic fluctuations in the initial stages of the epidemic. Consequently, an emerging disease with such a contact network will be less likely to generate an epidemic; however, if an epidemic is sustained, that epidemic is more likely to be explosive. Thus, it can be dangerous to underestimate a disease on the basis of frequent 'failed' attempts. These and other epidemiological implications of nonuniform contact networks are currently receiving much attention, in the light of worries about newly emerging or re-emerging infections [30,31,42,43].

One alarming misunderstanding about the epidemiology of HIV/AIDS that has emerged from some SF enthusiasts should be put to rest. The worry goes as follows. First, it has been argued that observed degree

distributions for networks of sexual contacts are SF [44]. Second, using a simple susceptible–infectious–susceptible (SIS) model, Pastor-Satorras and Vespignani (PSV) [45] note that, for a SF distribution with γ between 2 and 3, there is no epidemiological threshold: no matter how small the transmission parameter, β , an epidemic is possible. The same also holds for the more realistic susceptible–infectious–recovered (SIR) model [46,47]. Barabasi [6] highlights this finding, concluding that HIV/AIDS might present effectively insuperable problems. This conclusion has been singled out for emphasis in reviews of his book [18,48].

But there are several problems with all of this. First, the evidence that sexual contact networks are SF is shaky (e.g. [49]). Second, the reason for the seemingly surprising 'no threshold with a SF distribution' is clear from the epidemiologically correct Equation I for R_0 (PSV implicitly assume $R_0=\rho_0$ even for nonuniform distributions): if $P(i)\sim i^{-\gamma}$ with γ between 2 and 3, then $\langle i^2 \rangle = \infty$ (in the infinitely large population assumed by PSV), whence CV , and consequently R_0 , are infinite, no matter how small ρ_0 is [46]. Third, real populations are finite, whence R_0 is finite and a threshold is restored [47]. Fourth, and more important, even if we have R_0 infinite, the fraction of the population to become infected is very small once ρ_0 is small [being of the order $\exp(-2/\rho_0)$] (Figure 2 [46,47]). Finally, overriding all this, recall the theorem sketched earlier: for a fat-tailed contact distribution, if we take advantage of the heterogeneity then the epidemic is easier to eradicate than for a uniform contact distribution. In short, these rather overheated worries about HIV/AIDS are chimerical (for further discussion, see [46,47]).

What next?

Here, I have only scratched the surface of a large and growing area of activity. Many topics that fall under the heading of networks and their dynamics have not even

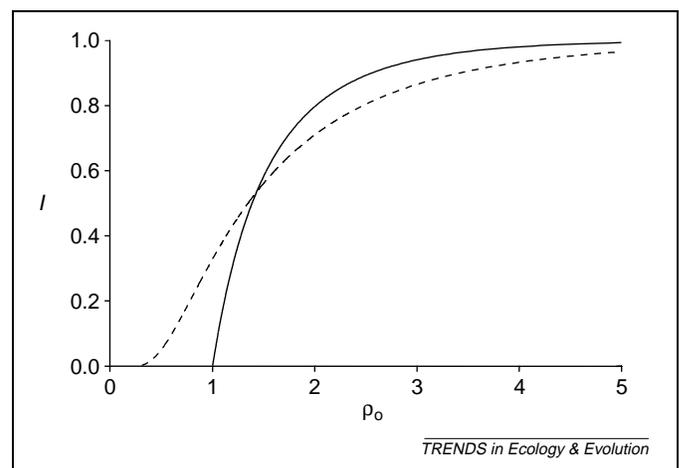


Figure 2. Contact networks and epidemics. The fraction of a population, I , infected in an epidemic is shown as a function of ρ_0 , which (as discussed more fully in the main text) would be the basic reproductive number (R_0) of the infection if the contact network had a uniform degree distribution, but not otherwise, to the contrary of some misunderstandings. The solid curve represents a homogeneous population with a uniform degree distribution, and the dashed curve a scale-free distribution with exponent 3 [i.e. $P(i)\sim i^{-3}$]. Although an epidemic can propagate in a population with a scale-free contact distribution if $\rho_0<1$, the resulting curve is not strikingly different from the conventional one for a homogeneous population; the fraction infected becomes very, very small once ρ_0 is substantially <1 .

been mentioned. One major evolutionary problem, many aspects of which are as puzzling today as they were to Darwin, is the evolution of cooperation. How did our own social systems originate and maintain themselves in the teeth of the evolutionary advantage apparently gained by 'cheats', who take the group benefit without paying the accompanying individual cost? Studies of metaphors for this problem, such as the Prisoner's Dilemma (PD), seem to me mostly to give useful answers only under implausibly restrictive assumptions (reviewed in [50]). A blend of network dynamics with PD metaphors might provide more robust answers to this question [51,52].

I end as I began, with the network structure of species interacting in food webs and ecosystems. As emphasised over 30 years ago [2], real food webs are not randomly assembled, and so the first question is: what patterns, if any, are there in the degree distributions, diameters and clustering coefficients of interacting species in ecosystems? Two recent analyses [53,54] of 16 high-resolution food webs from aquatic and terrestrial ecosystems (with total nodes from 25 to 172) strongly suggest 'two degrees of separation', in the sense that more than '95% of species [are] typically within three links of each other' [54]. These degree distributions are not random Erdos–Renyi ones, although whether they are exponential, scale-free, or something else is the subject of debate [9,20]. One major problem lies in the extent to which constituent species are 'lumped' into functional groups, in ways that can bias analysis [55]. Interestingly, Stouffer *et al.* [56] have shown that approximately exponential degree distributions similar to those observed can be derived from at least two apparently different models proposed earlier [57,58]; this finding is reminiscent of much earlier observations that significantly different mechanisms could result in identical distributions of the relative abundance of species.

Another long-standing question is whether there are significant differences between terrestrial versus aquatic ecological networks. The above analyses [53,54] would suggest not, and this view is supported by recent studies of three different marine ecosystems, which 'substantiate previously reported results for estuarine, fresh-water and terrestrial datasets, [suggesting] that food webs from different types of ecosystems with variable diversity and complexity share fundamental structural and ordering characteristics' [59].

Other studies ask how the network structure of a food web influences what happens when species are added or removed. Not surprisingly, most such studies (reviewed in [9,60]) tend to show that removing the most highly connected species causes more 'knock-on' extinctions than does random removal. Berlow *et al.* [61], however, have shown that removal of low-connectivity species can have large effects, demonstrating that 'keystone species' are not necessarily highly connected ones.

Ultimately, the response to disturbance must depend not only on network structure, but also on the strength of interactions. McCann's [62] excellent review of the existing data and experiments argues that distributions of interaction strengths are strongly biased toward weak interactions. He also observes that weak average

interaction strength tends to be correlated with high variability in the strength. McCann makes it plain that, although most species' invasions have a weak impact on ecosystems, removal of or invasion by a single species (not necessarily a strongly interacting one) can have huge effects on an ecosystem [63–65].

Conclusion

In short, ecologists have made much progress on understanding 'stability and complexity', partly by redefining the questions being asked. There are some tentative generalisations, such as those sketched above, along with Tilman's [66] 'increases in diversity [number of species] cause community stability to increase, but population stability to decrease'. But I suspect finer-grained analyses of food webs might find structural differences shaped by different environmental settings, present indications notwithstanding. It will certainly be interesting to read *TREE's* 40th Anniversary Issue.

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