Chapter 1

Interplay of network state and topology in epidemic dynamics

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1.1 Introduction

Throughout history epidemic diseases have been a constant threat to humans (Cartwright, 1972; Oldstone, 1998). There is evidence that even our earliest ancestors suffered from disease-related mortality (Hart, 1983). Many of the old diseases have by now become harmless childhood maladies or have disappeared entirely. However, as humankind prospered and spread out new epidemic diseases continued to arrive in the human population (Karlen, 1995). The extend to which epidemic diseases have shaped our culture and politics can be guessed from religious texts, which contain numerous references to epidemics and rules for their avoidance.

In the 20th century we have witnessed a brief episode in which it seemed that mankind was about to win the struggle and free itself from epidemics. The widespread use of antibiotics drove many infectious diseases back to hiding places in remote locations and animal populations (so-called *disease vectors*). Some sources hold that the second world war was the first major war in history in which far more lives were lost due to fighting than epidemics (Karlen, 1995). But, even when the belief that biomedical progress would conquer epidemics was still widespread, there was evidence to the contrary: In the 1950 new hemorrhagic fevers appeared in several parts of the world (Daubney *et al.*, 1993). The subsequent decades brought Legion-

naires disease (Breiman *et al.*, 1990), Ebola fever (Bowen *et al.*, 1977) and a return of syphilis (Sell and Norris, 1983; Grassly *et al.*, 2005). Nevertheless, the awareness to epidemic diseases remained low until AIDS appeared in the 1980s (Grmek, 1990). Since then new diseases, such as SARS (Omi, 2006) and ESME (Haglund and Günther, 2003), have emerged and old killers, such as Malaria (Pampana and Russel, 1955), Tuberculosis (Bloom and Christopher, 1992) and Influenza (Kilbourne, 1987), have returned; some of them in new forms.

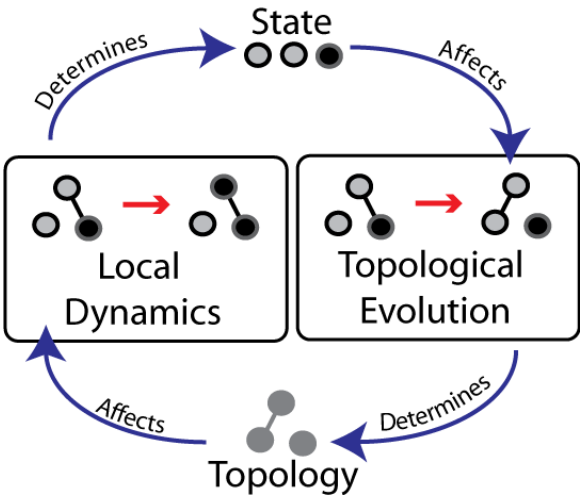

Fig. 1.1 In an adaptive network the evolution of the topology depends on the dynamics of the nodes. Thus a feedback loop is created in which a dynamical exchange of information is possible. Figure reprinted from Gross and Blasius (2008).

At present old and new diseases seem to arrive at a increasing rate. Apart from increased attention in the media, there are several fundamental reasons for this "epidemic of epidemics" (Karlen, 1995). Today the world's population density is higher than ever, which means that epidemics can spread at a higher rate. We also change our environment faster than ever, which promotes epidemics on many scales: Global change drives host populations of pathogens into more densely populated areas; New farming methods and transport of livestock entail an increased probability of the transmission of animal diseases to humans (*zoonoses*); Finally, artificial environments, such as air-conditioning systems and cooling towers provide new ecological niches in which pathogens (in this example Legionella) can

survive.

As we will see below another reason for the emergence and reemergence of diseases lies in the nature of human contact networks. Since neither ecological change, population growth or the contact networks are likely to change significantly over the next decades, more efficient methods to combat epidemics have to be found. In this context networks appear on two levels. On the molecular level, the study of gene regulatory, metabolic or signaling networks can lead to the development of new medicines and pesticides that target pathogens and disease vectors. On the population level the study of contact networks can lead to new insights into the spreading of epidemics across social networks and to the improvement of vaccination schemes. In the present chapter I focus on this latter level.

One idea that has recently attracted considerable attention is to use insights from network research to optimize vaccination campaigns. Previous research has shown that the amount of vaccine that is necessary to stop an epidemic can be significantly reduced by targeted vaccination (Albert *et al.*, 2000; Holme, 2004). However, the success of targeted vaccination schemes depends strongly on certain network properties. Currently, attempts are made to measure these properties in real world social networks (Caldarelli, 2007). But, is it safe to assume that these properties will remain unchanged in the face of a major epidemic? The example of SARS has shown that epidemics can induce behavioral changes that feed back to the contact network (Omi, 2006). Including this feedback in a model gives rise to an adaptive network: a system on which the dynamics of the nodes depends on the network topology, while the evolution of the network topology depends on the state of the nodes (Gross and Blasius, 2008).

While the dynamics OF networks and the dynamics ON networks have been studied for a long time in physics (Albert and Barabasi, 2002; Dorogovtsev and Mendes, 2003; Newman, 2003; Boccaletti *et al.*, 2006; Newman *et al.*, 2006), adaptive networks have only very recently come into focus (Gross and Blasius, 2008). The dynamical interplay between the state and topology has been shown to give rise to several phenomena: In particular adaptive networks have been shown to self-organize robustly to critical states (Bornholdt and Rohlf, 2000) and exhibit the spontaneous emergence of distinct classes of nodes (Ito and Kaneko, 2002) and complex topologies (Holme and Ghoshal, 2006; Rosvall and Sneppen, 2006) based on simple local rules. Moreover, in adaptive networks bifurcations (Gross *et al.*, 2006) and phase transitions (Holme and Newman, 2007) appear that involve local as well as topological degrees of freedom.

In this chapter I discuss a simple conceptual adaptive network model of epidemic spreading. It is shown that, even in this very simple model, adaptive feedback leads to qualitative changes in the dynamics. The core of the chapter is formed by results that have been previously published in Gross *et al.* (2006). In contrast to the original publication the results are discussed in the context of subsequent works (Zanette, 2007; Shaw and Schwartz, 2008; Gross and Kevrekidis, 2008; Risau-Gusman and Zanette, 2008; Zanette and Risau-Gusman, 2008) which provide a broader perspective.

The chapter starts in Sec. 1.2 with a, necessarily brief, background introduction to epidemics on networks. The subsequent section, Sec. 1.3, introduces a simple model of epidemics on adaptive networks. Furthermore, numerical results are discussed that show the adaptive response of the contact network to the emergence of the disease. Section 1.4 contains a detailed introduction to the moment closure approximation which is then used to study the dynamics of the adaptive network analytically on an emergent level. In the subsequent section, Sec. 1.5, the focus shifts back to the detailed level as we discuss the mechanisms behind the observed dynamics in the context of subsequent investigations. The final section, Sec. 1.6, summarizes the results.

1.2 Epidemics on networks

Traditionally epidemics are modeled in the mean field limit of a well-mixed population or by systems of partial differential equations that account for physical space (Anderson and May, 2005; von Festenberg *et al.*, 2007). However, over the recent years the modeling of epidemics on artificial, i.e. computer generated, contact networks has attracted increasing attention (Pastor-Satorras and Vespignani, 2001; May and Lloyd, 2001).

Previous research has shown that the structure of social networks can have a significant impact on the dynamics of epidemics. A quantity that is of particular interest is the epidemic threshold, which is roughly speaking the the minimum infectiousness that a disease has to have in order to invade and persist on a network (Anderson and May, 2005). This threshold is generally lower on networks that have a broader degree distribution and vanishes in scale-free networks with a scaling exponent between two and three (Pastor-Satorras and Vespignani, 2001; May and Lloyd, 2001). Model epidemics can thus survive on a scale-free contact network even if their

infectiousness is arbitrarily low.

It has been frequently pointed out that real contact networks are not perfectly scale-free. In particular the maximum degree that can be found on in a real populations is finite and hence non-zero epidemic thresholds do exist (May and Lloyd, 2001). In former times also technological constraints on the size of cities and the speed of travel imposed strong limits on disease transmission due to geographic embedding. However, in the present day these constraints have largely been removed by technological progress. Today scale-free-like behavior is observed in many social networks (Caldarelli, 2007). It can be expected that in the mega-cities of the future the social networks will exhibit scale-free behavior over many orders of magnitude.

Scale-free networks, and more generally networks with a broad degree distribution, are very robust against random attacks, but relatively susceptible to targeted attacks (Albert *et al.*, 2000; Holme, 2004). In the context of diseases this means that targeted vaccination which focuses on the most important, i.e., most central, nodes of the network can be much more effective than vaccination of random individuals. Vaccinating the most highly connected nodes can split the network into small disconnected components and thus prevent large outbreaks. A caveat of this approach is that social networks are generally exhibit a assortative degree correlations (Newman, 2002); on these networks nodes of high degree are preferentially linked to other nodes of high degree. Thus the highly connected nodes form a densely connected community. Attacking these nodes by vaccination is therefore unlikely to disconnect large parts of the network unless a large fraction of the highly connected nodes is removed.

In summary the degree distribution and degree correlations are important network properties that can strongly affect both the dynamics of the epidemic and the success of counter-measures. In the subsequent section I argue that these properties can change due to a simple, intuitive mechanism.

1.3 An adaptive SIS model

In order to study the interplay of epidemic spreading and topological evolution we consider a network of N nodes and L links. Each of the nodes represents an individual while each of the links represents a contact over which the disease can potentially spread. In epidemiological models discrete states are generally assigned to the individuals that signify the stage

of the disease. In the simplest case there are only two of these states called S, for susceptible, and I, for infected. Thus the network effectively consists of boolean nodes, and the links can be denoted as SS-links, SI-links, and II-links according to the states of the nodes that they connect.

Susceptible individuals can become infected if they are in contact with an infected individual. The transmission of the disease along a given SI-link is assumed to occur at a rate p. Once an individual has been infected she has a chance to recover, which happens at a rate r and immediately returns the individual to the susceptible state. Together these processes of infection and recovery constitute the dynamical rules for a so-called *SIS-model*, a standard model of epidemiology. In the model proposed in Gross *et al.* (2006) another process is included: If a susceptible individual is connected to an infected individual she may want to break the link and instead establish a new link to another susceptible individual. On a given SI-link this *rewiring* occurs at a rate rate w.

Rewiring, rather than cutting links, captures that the number of social contacts cannot be reduced arbitrarily; If you knew that the owner of your neighborhood bakery has some infectious disease, you might decide to buy your bread somewhere else while stopping to eat entirely is usually not the preferred option.

In the adaptive SIS-model the rewiring process has been introduced 'optimistically': Only susceptible nodes rewire, and they manage unerringly to rewire to a node that is also susceptible. Under these conditions rewiring always reduces the number of links that are accessible for epidemic spreading and therefore the *prevalence* of the disease, i.e., the density of infected, is always reduced by this form of rewiring behavior.

Despite the positive primary effect of rewiring, it has also some adverse consequences, that may limit the benefit from rewiring if the epidemic is already established in the population. Figure 1.2 shows results from simulations that have previously reported in Gross *et al.* (2006). The results were obtained by explicit individual-based simulation of a network with $N = 10^5$ nodes and $L = 10^6$ links. In this case the average degree of a node is $\langle k \rangle = 2L/N = 20$, as every link connects to two nodes. The figure shows in the bottom row the degree distributions of susceptible and infected nodes and, in the top row, the mean degree of the neighbors $\langle k_{\mathrm{nn}} \rangle$ of a node with given degree. Let us first consider the left and center column which correspond to (1) frozen network topology $w = 0$ and (2) frozen epidemic dynamics $p = r = 0$.

In the first case (left column) rewiring is done independently of the epi-

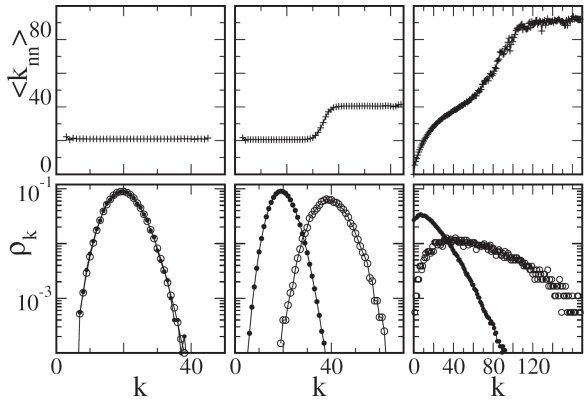

Fig. 1.2 Structure of adaptive networks. Plotted is the mean nearest-neighbor degree $\langle k_{nn} \rangle$ (top) and the degree distribution ρ_k for susceptible nodes (bottom, circles) and infected nodes (bottom, dots) depending on the degree k. (Left) Indiscriminate rewiring: the network is a random graph with Poissonian degree distributions and vanishing degree correlation. (Center) No local dynamics ($p = r = 0$): the infected and the susceptible nodes separate into two unconnected random subgraphs. (Right) Adaptive network with rewiring and local dynamics ($w = 0.3$, $r = 0.002$, $p = 0.008$): the degree distributions are broadened considerably and a strong assortative degree correlation appears. Figure reprinted from Gross *et al.* (2006).

demic state, in this case there is no adaptive topological change and the network becomes a random graph. Although nodes of high degree have a slightly higher probability of being infected, the effect of this asymmetry is hardly visible in the degree distribution; both the infected and the susceptible nodes independently follow almost exactly the Poisson distribution, that would be expected in a random graph. The neighbor-degree is $\langle k_{\rm nn} \rangle = 21$, independently of the degree of the node under consideration, which implies that the degree correlation vanishes.

In the second case (center column) all nodes remain in their initial state, however all SI-links converted into SS-links by rewiring. To investigate this in more detail let us denote the *prevalence* of the disease, i.e. the density of infected nodes by $I = 1 - S$, where S is the density of of susceptible nodes. Likewise, the average density of the links per node is denoted by $[SS]$, $[SI]$, and $[II]$, respectively. So, effectively all quantities are normalized to the total number of nodes N. In the initial random configuration the link densities are approximately $[SS] = \langle k \rangle S^2/2$, $[II] = \langle k \rangle I^2/2$, and $[SI] = \langle k \rangle/2 - [SS] - [II] = \langle k \rangle SI$. Since all links that are initially SI-links end up as SS-links we obtain the final link densities $[SI] = 0$,

$[SS] = \langle k \rangle (1 - I^2)/2$, and $[II] = \langle k \rangle (I^2)/2$. Note that, although the susceptible nodes are isolated from the infected, the links within each of the two subpopulations are still placed randomly, so that the infected nodes as well as the susceptible nodes both follow a Poissonian degree distribution, albeit with different mean. Consequently the degree correlation is still zero within each subpopulation. However, since susceptible individuals have a higher degree and are connected to other susceptible individuals a positive degree correlation appears if the whole population is considered.

An even stronger effect of state-sensitive rewiring can be observed if rewiring and epidemic spreading take place on the same time-scale. The right column of Fig. 1.2 shows that the degree distribution becomes very wide (note the different scale) and a strong positive (assortative) degree correlation appears. To understand this consider the following: In the case of fast rewiring, the degree of susceptible nodes increased because of links that were rewired into the susceptible population. However, this rewiring had to stop once all SI-links had been converted into SS-links effectively limiting the width of the degree distribution. If both epidemic and topological dynamics take place on the same timescale either the disease will go extinct or rewiring will continue indefinitely. In the latter case the degree of a susceptible node growth linearly until it eventually becomes infected, giving rise to a wide degree distribution.

It is interesting to note that there are several parallels between the adaptive SIS model studied here and models of opinion formation on adaptive networks (Do and Gross, 2009). Also in opinion formation the strongest impact of the dynamics on the topology is observed if topological evolution and local dynamics take place on approximately the same time scale (Gil and Zanette, 2006; Holme and Newman, 2007). In this case the appearance of a broad degree distribution could be linked to a single continuous phase transition. In case of the adaptive SIS model one could suspect the corresponding phase transition is actually the epidemic threshold. However, as I will show in the next section the situation is slightly more complex.

Finally, note that the shape of the degree distribution is reminiscent of the one observed by Ito and Kaneko in an adaptive network of coupled oscillators (Ito and Kaneko, 2002). However, while Ito and Kaneko start with a homogeneous population that spontaneously divides into two distinct topological classes, it clear that in the adaptive SIS model these classes correspond to susceptible and infected nodes. Hence the emergence of the bimodal degree distribution is less surprising in the present case.

1.4 Extracting dynamics by moment closure

Let us now study the dynamics of the adaptive SIS model with the tools of nonlinear dynamics. For this purpose we need to derive a low-dimensional emergent-level description of the system. A convenient tool to achieve this is the so-called *moment-closure approximation* which is frequently used in epidemiology (Keeling *et al.*, 1997; Parham *et al.*, 2008; Peyrard *et al.*, 2008).

1.4.1 *Basic moment-expansion of the model*

Based on previous section it is reasonable to assume that the state of the system can be characterized by the density of infected nodes, I; the density of SS-Links per node, $[SS]$; and the density of II-Links per Node, $[II]$. The density of susceptible nodes, S, and the density of SI-Links, $[SI]$, are then given by the conservation relations $S + I = 1$ and $[SS] + [SI] + [II] = \langle k \rangle$. An advantage of this normalization is that we can write all subsequent equations as if we were dealing with a number of individual nodes and links instead of densities.

Lets start by writing a balance equation for the density of infected nodes. Infection events occur at the rate $p[SI]$ increasing the number of infected nodes by one; Recovery events occur at a rate rI and reduce the number of infected nodes by one. This leads to

$$\frac{\mathrm{d}}{\mathrm{dt}} I = p[SI] - rI. \tag{1.1}$$

The equation contains the (presently unknown) variable $[SI]$ and therefore does not yet constitute a closed model. One way to close the model were a mean field approximation, in which the density of SI-Links is approximated by $[SI] \approx \langle k \rangle SI$. However, in the present case this procedure is not feasible: Rewiring does not alter the number of infected and hence does not show up in Eq. (1.1). Thus the mean-field approximation is not able to capture the effect of rewiring. Instead, we will treat $[SI]$, $[SS]$, and $[II]$ as dynamical variables and capture their dynamics by additional balance equations. This approach is often called *moment expanision* as the link densities can be thought of as the first moments of the network.

For the sake of conciseness it is advantageous to write balance equations only for the densities of SS- and II-links and obtain the density of SI-links by the conservation relation stated above. First the II-links: A recovery event can destroys II-links if the recovering node was part of such links.

The expected number of II-links in which a given infected node is involved is $2[II]/I$. (Here, the two appears since a single II-link connects to two infected nodes.) Taking the rate of recovery events into account, the total rate at which II-links are destroyed is simply $2r[II]$.

To derive the rate at which II-links are created is only slightly more involved. In an infection event the infection spreads across a link, converting the respective link into an II-link. Therefore every infection event will create at least one II-link. However, additional II-links may be created if the newly infected node has other infected neighbors in addition to the infecting node. In this case the newly infected node was previously the susceptible node in one or more ISI-triplets. In the following we denote the density of triplets with a given sequence of states A, B, C as $[ABC]$. Using this notation we can write the number of II-links that are created in an infection event as $1 + [ISI]/[SI]$. In this expression the '1' represents the link over which the infection spreads while the second term counts the number of ISI-triplets that run through this link. Given this relation we can write the total rate at which II-links are created as $p[SI](1 + [ISI]/[SI]) = p([SI] + [ISI])$.

Now the SS-links: Following a similar reasoning as above we find that infection destroys SS-links at the rate $p[SSI]$. Likewise SS-links are created by recovery at the rate $r[SI]$. In addition SS-links can also be created by rewiring of SI-links. Since rewiring events occur at a rate $w[SI]$ and every rewiring event gives rise to exactly one SS-link the total rate at which rewiring creates SS-links is simply $w[SI]$.

Summing all the terms, the dynamics of the first moments can be described by the balance equations

$$\frac{\mathrm{d}}{\mathrm{dt}}[SS] = (r + w)[SI] - p[SSI] \tag{1.2}$$

$$\frac{\mathrm{d}}{\mathrm{dt}}[II] = p([SI] + [ISI]) - 2r[II]. \tag{1.3}$$

Again, these equations do not yet constitute a closed model, but depend on the unknown third moments $[SSI]$ and $[ISI]$. However, the first order-moment expansion captures the effect of rewiring. While we will return to the equation above later, a feasible way of closing the system is to approximate the second moments by a mean-field-like approximation: the *moment-closure approximation*.

Let us start by approximating $[ISI]$. One half of the ISI-triplet is actually an SI-link, which we know occurs at the density $[SI]$. In order to approximate the number ISI-triplets running through a gioven link we have to calculate the expectation value of the number of *additional* infected nodes

that are connected to the susceptible node. For this purpose let us assume that the susceptible node of the given SI-link has an expected number of $\langle q \rangle$ links in addition to the one that is already occupied in the SI-link. Every one of these links is an SI-link with probability $[SI]/(\langle k \rangle S)$. (Here, we have neglected the fact that we have already used up one of the total number of SI-links. This assumption is good if the number of SI-links is reasonably large.) Taking the density of SI-links and the probability that they connect to additional SI-link into account we obtain

$$[ISI] = \kappa \frac{[SI]^2}{S} \tag{1.4}$$

where $\kappa = \langle q \rangle / \langle k \rangle$ remains to be determined. The quantity $\langle q \rangle$ that appears in κ is the so-called *mean excess degree*. Precisely speaking it denotes the expected number of additional links that are found by following a random link.

The mean excess degree of a network is governed by two opposing effects (Newman, 2003): One the one hand we are only counting the additional links, so that for a node of given degree k the excess degree is $q = k - 1$. On the other hand, we have reached the node by following a link and therefore have a higher probability to arrive at a node of high degree. Depending on the network topology the $\langle q \rangle$ can therefore be larger or smaller than $\langle k \rangle$. It is a special property of Erdös-Renyi random graphs that both effects cancel, so that $\langle q \rangle = \langle k \rangle$ and $\kappa = 1$. Smaller values of κ are found in homogeneous networks such as regular lattices while networks with a wider degree distribution generally correspond to larger (and in scale-free networks even diverging) values of κ.

In the present example the network topology changes dynamically in time. For the sake of simplicity I will assume that $\kappa \approx 1$. Note, that this could be called a random-graph-like approximation. It is *not* a high-degree approximation as is sometimes held in the literature and therefore holds also in sparse networks.

Setting $\kappa = 1$ we can approximate the density of triplets by $[ISI] = [SI]^2/S$, and following a similar reasoning $[SSI] = 2[SS][SI]/S$. Substituting these relations into the balance equations we obtain a closed system of differential equations

$$\frac{\mathrm{d}}{\mathrm{dt}} I = p[SI] - rI \tag{1.5}$$

$$\frac{\mathrm{d}}{\mathrm{dt}} [SS] = (r + w)[SI] - 2p[SI] \frac{[SS]}{S} \tag{1.6}$$

$$\frac{\mathrm{d}}{\mathrm{dt}} [II] = p[SI](1 + \frac{[SI]}{S}) - 2r[II] \tag{1.7}$$

1.4.2 *Dynamics of the adaptive SIS model*

Systems of ordinary differential equations (ODEs) can be studied by the standard tools of dynamical systems theory. In Gross *et al.* (2006) the stationary solutions of these equations and there stability are computed analytically. This analysis reveals several transitions in which the dynamics changes qualitatively. In the context of the low-dimension emergent-level ODEs these transitions appear as bifurcations, while in the context of the individual-based detailed-level simulations they correspond to phase transitions. Note, that even the equilibrium solutions of the ODE system correspond in general to highly dynamic states on the detailed level, in which individual nodes undergo infection and recovery and links are continuously rewired.

In Fig. 1.3 results of the analytical investigation of the system of ODEs are shown in comparison to results from individual-based simulation of the full network. Without rewiring, there is only a single, continuous dynamical transition, which occurs at the epidemic threshold and corresponds to a transcritical bifurcation. As the rewiring is switched on, this threshold increases. The epidemic threshold still marks the critical value of infectiousness, p, for the invasion of the disease. However, another lower threshold, marked by a fold bifurcation point, appears. Above this threshold an epidemic that is already established in the network can persist (endemic state). In the following we distinguish between the invasion threshold and the persistence threshold for epidemics. In contrast to the case without rewiring the two thresholds are discontinuous (first order) transitions. Between them a region of bistability is located, in which both the healthy and the endemic state are stable. Thus, a hysteresis loop is formed. First order transitions, bistability, and hysteresis are generic features of the model that can be observed at all finite rewiring rates.

Increasing the rewiring rate further hardly reduces the size of the epidemic in the endemic state, however both thresholds are shifted toward higher infection rates. At higher rewiring rates the the nature of the persistence threshold changes. First, a subcritical Hopf bifurcation emerges. In this bifurcation the stability of a stationary solution is lost by the interaction with an unstable limit cycle. Although the fold bifurcation still occurs it no longer marks the persistence threshold as the stability of the endemic state is lost in the Hopf bifurcation, before the saddle-node bifurcation is reached.

At higher rewiring the Hopf bifurcation becomes supercritical. While

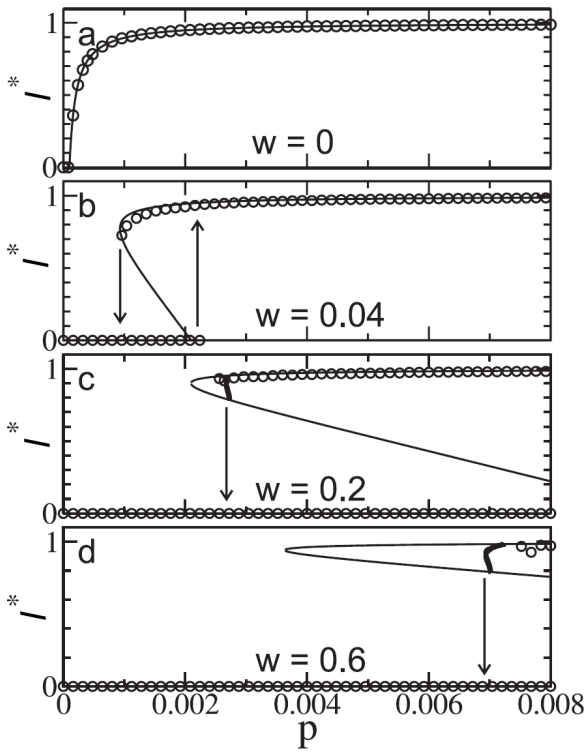

Fig. 1.3 Bifurcation diagram of the stationary density of the infected I^* as a function of the infection probability p for different values of the rewiring rate w. In each diagram $I*$ has been computed analytically from the ODE system (thin lines). Along the stable branches these results have been confirmed by the explicit simulation of the full network (circles). Without rewiring only a single continuous transition occurs at p=0.0001 (a). By contrast, with rewiring a number of discontinuous transitions, bistability, and hysteresis loops (indicated by arrows) are observed (b), (c), (d). Fast rewiring (c), (d) leads to the emergence of limit cycles (thick lines indicate the lower turning point of the cycles), which have been computed numerically with the bifurcation software AUTO. Parameter: $r = 0.002$. Figure reprinted from Gross *et al.* (2006).

this bifurcation still marks the threshold for stationary persistence of the disease, it gives rise to a stable limit cycle on which non-stationary persistence is possible at lower infectiousness. However, the oscillatory parameter region is very narrow. Toward lower infection rates it is bounded by a fold bifurcation of cycles, which leads to the extinction of the disease.

The findings from the bifurcation analysis are summarized in a two-parameter bifurcation diagram shown in Fig. 1.4. A more detailed understanding can be gained if one considers what happens on the network level.

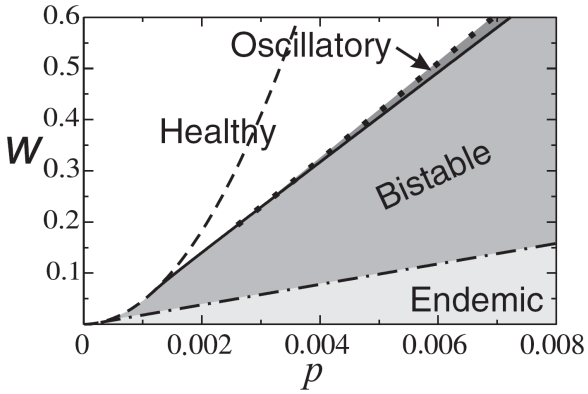

Fig. 1.4 Two parameter bifurcation diagram showing the dependence on the rewiring rate w and the infection probability p. In the white and light gray regions there is only a single attractor, which is a healthy state in the white region and an endemic state in the light gray region. In the medium gray region both of these states are stable. Another smaller region of bistability is shown in dark gray. Here, a stable healthy state coexists with a stable epidemic cycle. The transition lines between these regions correspond to transcritical (dash-dotted), saddle-node (dashed), Hopf (continuous), and cycle fold (dotted) bifurcations. Note that the saddle-node and transcritical bifurcation lines emerge from a cusp bifurcation at $p = 0.0001$, $w = 0$ The rewiring rate is $r = 0.0002$ Figure reprinted from Gross *et al.* (2006).

Indeed I will come back to this point in the subsequent section. B, before let us discuss some possible extensions of the moment closure approximation.

1.4.3 *Accuracy and extensions of the Moment Closure Approximation*

The derivation of the Eqs. (1.5–1.7) has involved approximations at various stages. Nevertheless the predicted bifurcation diagrams are in very good agreement with the numerical results. In the literature much attention has been paid to inaccuracies in the factor κ. However, the results presented here show that the approximation $\kappa = 1$ yields good results even for networks with a relatively wide degree distribution.

One reason for the good agreement between theory and simulation is that adaptive networks are particularly well suited to be treated by the moment-closure approximation; The ongoing topological evolution of an adaptive network means that there is a constant mixing of the topology. One could say that, over time, the adaptive network is an ensemble of itself. It is therefore more accessible to mean-field-like approximations. In

addition the mixing reduces spatial correlations. This may explain why moment closure seems to yield better results on adaptive networks than on static ones.

In my experience ODEs found by moment closure are in good agreement with the explicit numerical simulation of adaptive networks as long as the network under consideration is sufficiently large ($N \approx 10^5$). In small networks deviations can appear because of stochastic fluctuations, which for instance in the SIS model can lead to premature extinction of the disease. However, as real world networks are mostly large this deviation can be seen as a shortcoming of the simulation rather than the moment-closure approximation. Nevertheless, in large networks the closure approximation (rather than the moment expansion itself) is the main source of inaccuracy in the derivation of the ODE system. Let us therefore discuss three approaches which avoid or amend this approximation. The starting point for this discussion are the Eqs. (1.2,1.3) and Eq. (1.1).

One way to avoid the approximation of the second moments is to treat them also as dynamical variables. In this case their dynamics have to be captured by balance equations which will in turn depend on the on the third moments. While this only shifts the problem of closure up by one level. It is reasonable to assume that closure at the level of third moments will yield a more precise approximation than closure at the level of second moments. Apart from the gained accuracy, closure at the third level would allows include processes that act on triplets or triangles rather than on nodes or links. However, apart from a discussion in Peyrard *et al.* (2008) moment closure at higher moments has so far received little attention because of the difficulties involved. In particular the number of equations in the model grows combinatorially with the order of the expansion and the number of states in the model.

Instead of extending the moment expansion to higher orders one can also try to increase the accuracy of the approximation at the second order. In this case the challenge is to find a way to accurately compute the expected density of certain triplets (e.g. $[SSI]$ and $[ISI]$) from a given density of nodes and links(e.g. I, $[SS]$, $[II]$). This may be done for instance by a hybrid analytical/numerical approach proposed in Gross and Kevrekidis (2008). In this case the bifurcations are computed numerically on the level of ODEs. But, whenever the bifurcation software needs to evaluate the system-level equations, it starts a series of a few, very short, individual-based detailed-level simulations. From appropriately initialized simulations good approximations of the true triplet densities are then extracted. While

this procedure provides more accurate results than analytical closure it is faster than full simulation of the system and yields information that would be difficult to extract by simulation alone.

Yet another approach would be to treat the second moments as unknown functions of the link and node densities. Even in this general case the methods of dynamical system theory could be applied to extract many dynamical properties of the system. For instance the approach of generalized models can be used to investigate the stability of stationary solutions, find transitions to oscillatory behavior, and provide evidence for chaotic dynamics without the need to restrict the unknown functions in the model to specific functional forms (Gross and Feudel, 2006).

1.5 Interpretation and extensions of the model

The adaptive SIS model which we have considered so far is clearly conceptual in nature. In order to facilitate the mathematical analysis we have focused on the simplest framework at hand in which epidemic dynamics and topological evolution can be combined. The purpose of these investigations was to demonstrate that the adaptive interplay between local dynamics and topological evolution can give rise to certain phenomena that can not be observed in static networks. The analysis has revealed three such phenomena: (1) a significant shift of the invasion threshold toward higher infection rates; (2) the appearance of a persistence threshold below the invasion threshold, giving rise to bistability and hysteresis; and (3) the emergence of an oscillatory phase.

The next logical step is to search for these phenomena in more realistic models. Indeed, since the original publication of the adaptive SIS-model in Gross *et al.* (2006) subsequent works have appeared that add realism by extending the model in several ways (Zanette, 2007; Shaw and Schwartz, 2008; Gross and Kevrekidis, 2008; Risau-Gusman and Zanette, 2008; Zanette and Risau-Gusman, 2008). In order to understand the common themes and differences between these works and to extrapolate to real world situations, it is conductive to revisit the phenomena listed above and consider them from an individual-based perspective.

As we have seen in Sec. 1.3 rewiring affects epidemic spreading in two opposing ways. The primary effect of rewiring is two reduce the number of links through which the epidemic can spread. But, in time rewiring can lead to the formation of a large densely-linked cluster of susceptible nodes

in which the infection can spread rapidly once it has been invaded.

For the phenomenon (1), the increase of the invasion threshold, only the primary effect of rewiring is of importance. By definition, only dynamics that take place at a low density of infected nodes are relevant for invasion. However, in this limit the number of links that are rewired is also low and hence cannot lead to a significant build-up of connectivity in the susceptible subpopulation. At least under our optimistic assumptions the epidemic threshold is therefore always increased by rewiring.

In more realistic scenarios the epidemic threshold could in principle be decreased by rewiring if rewiring led to an increased density of SI-links. In reality this can happen in several ways. Susceptible nodes may erroneously rewire SS-links to infected nodes. Also, infected nodes may want to avoid contact with other infected nodes and therefore rewire II-links to susceptible nodes. More relevant is probably, the existence of additional disease states. While there are many infectious diseases that follow SIS-dynamics, these are mostly too harmless or too easily controlled to trigger a strong rewiring response in the population. Real world diseases that trigger a stronger behavioral response often have pronounced exposed (E) or asymptomatic (A) phases. Nodes in these phases appear to be susceptible, but have already been in contact with the infectious agent, and will eventually progress to the infected phase. While they are still in the E or A phase they act like susceptible nodes, i.e., they rewire their links to other susceptible nodes, whom they can subsequently (E-phase) or immediately (A-phase) infect.

Another phase that often appears in epidemic models is the R-phase, which denotes either recovered individuals that have acquired (possibly temporary) immunity or removed nodes that have died from the disease. However, in either case R-nodes should not affect the invasion threshold, as their density vanishes in the relevant limit.

The impact of additional epidemic states and rewiring rules was investigated in Shaw and Schwartz (2008); Risau-Gusman and Zanette (2008); Zanette and Risau-Gusman (2008). While it was found that rewiring can have detrimental effects under certain conditions these were relatively mild.

Phenomenon (2), the emergence of the persistence threshold is clearly related to the appearance of highly connected susceptible nodes; Below the invasion threshold an infectious disease can persist on the networks if a large fraction of the population is already infected. In this case SI-links are rewired into a relatively small population of susceptible nodes. The number of SS-links per susceptible node increases correspondingly. Therefore many

SI-links are created in every infection event, which almost compensates the SI-links lost due to rewiring. One could say that, if the susceptible subpopulation is too small, rewiring becomes ineffective as it is unlikely that the rewired link will remain out of reach of the disease for a significant time.

The mechanism described above is robust as long as links are rewired and not just cut. One could argue that few real world diseases reach sufficiently high prevalence for the effect to be of relevance. However, in particular the new emerging diseases on which our main focus lies are known to reach locally high densities of infected (Karlen, 1995).

The third phenomenon, the existence of an oscillatory phase, is caused by the interplay of the two opposing effects of rewiring; First, the number of SI-links are reduced by rewiring. However, even as the density of infected nodes decreases a densely linked cluster of susceptible nodes is build up. Eventually the epidemic invades this cluster which causes a sharp increase in the density of infected nodes, thus completing the cycle. What appears as a smooth oscillation on the level of the ODE is therefore really a series of outbreaks and avalanches if considered on the detailed level.

At first glance it seems surprising that in the oscillatory phase the primary epidemic-suppressing effect of rewiring governs the dynamics when the density of infected is high, while the secondary epidemic-promoting effect rules the increase that sets in at the low point. However, as it is often the case in autonomous oscillations, the cyclic behavior becomes possible due to the differences in the time scales on which the two effects act; The primary reduction of SI-links is immediately effective, but the build-up of links in the susceptible subpopulation requires some time before it can affect the dynamics. Nevertheless the mechanism that causes the oscillatory behavior is relatively fragile. If the density of infected at the low point of the cycle becomes too low the epidemic-promoting effect of rewiring is too weak to launch the epidemic into the growth phase and the disease goes extinct. Hence only cycles of relatively small amplitude at high disease prevalence were observed in the present model.

In many subsequent works no cyclic regime was found for two reasons: First, the basin of attraction of the limit cycle is relatively small. Therefore in simulations stochastic fluctuations can cause the system to depart from the cycle unless the number of simulated nodes is relatively high (e.g., $N \approx 10^6$). Moreover, in some model variants the SI-links are rewired to random targets and not just to susceptible nodes. As the density of infected nodes increases, so does the quota of unsuccessful rewiring, in which a susceptible

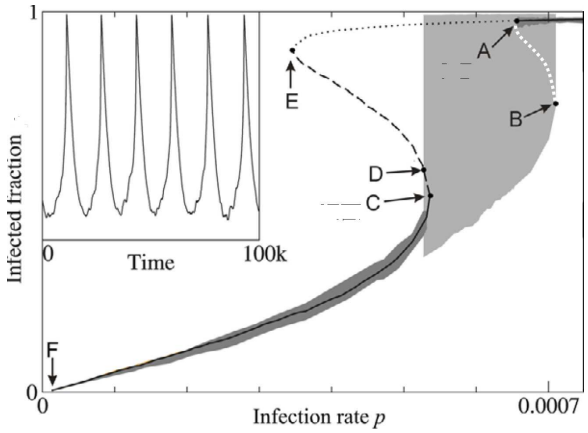

Fig. 1.5 Bifurcation diagram showing that awareness-depended rewiring gives rise to a large oscillatory region. The rewiring rate is assume to change proportional to the prevalence so that $w = w_0 I$. Lines mark pranches of stable steady states (solid) and saddle points (dashed/dotted). The white line tentatively marks a branch of saddle limit cycles. Shaded regions indicate ranges of I observed during long individual-based simulations in the neighborhood of the attractive limit cycle (light gray) and of stable stationary solutions (dark gray). Computation of the Jacobian eigenvalues reveal a subcritical Hopf bifurcation (A), two fold bifurcations (C,E) and a transcritical bifurcation (F). In one can suspect the presence of a fold bifurcation of cycles (B) and a homoclinic bifurcation (D). Inset: time series on the limit cycle attractor at $p = 0.0006$. Other parameters: $w_0 = 0.06$, $r = 0.0002$ Figure reprinted from Gross and Kevrekidis (2008).

node rewires an SI-link link from one infected node to another. Therefore, the epidemic-suppressing effect of rewiring becomes weaker with increasing density of infected. Rewiring can in this case no longer control the epidemic at the high point of the cycle and hence oscillations are avoided at the cost of higher prevalence. By contrast if there is an effect that increases the efficiency of rewiring with increasing density of infected then cyclic behavior is promoted. For instance in Gross and Kevrekidis (2008) it was assumed that the awareness of the population is increased if the density of infected is high and thus rewiring activity is increased. In this case the authors find robust large-amplitude oscillations over a considerable parameter range (see Fig. 1.5). Some evidence suggests that such for awareness-driven cycles occur in nature (Grassly *et al.*, 2005).

It is well known that cycles can also appear in models that involve an R-stage of the epidemic, such as SIRS models. It appears likely that in an adaptive SIRS model the interaction of rewiring-induced oscillations and recovery-induced oscillations can give rise to more complex, i.e., chaotic or

quasiperiodic, dynamics.

1.6 Summary and Conclusions

In this chapter we have investigated a simple conceptual model of the topological response of contact networks to the emergence of an infectious disease and the feedback of topological change on the epidemic. The analysis of this model has revealed that state-dependent rewiring is likely to increase the invasion threshold for diseases but at the same time introduces a persistence threshold below the invasion threshold. The consequence are discontinuous transitions, bistability, hysteresis and the existence of an oscillatory phase.

From an abstract point of view rewiring is certainly beneficial as it generally reduces the number of infected and can potentially drive the disease to extinction. However, from another perspective a word of caution is in order. If we observe small sub-threshold outbreaks of an epidemic in the real world we should ask whether the low prevalence is maybe a result of rewiring and not of low infectiousness of the disease as such. If rewiring plays a significant role in keeping the epidemic below threshold then a discontinuous transition can be expected if the threshold is eventually crossed. This may result in a large outbreak which can be difficult to combat because of hysteresis.

Also, if network properties are taken into account in the planning of vaccination campaigns on should consider that these properties can change in response to emergence of a major epidemic. In particular the widening of the degree distribution and the appearance of strong degree correlations are detrimental for targeted vaccination.

Let me emphasize that the concerns stated above are based on the analysis of very simple models and may therefore prove to be unfounded. To assess the role of state-topology interplay in epidemic dynamics in the real world, more research is certainly necessary. The structure of real contact networks is shaped by many social processes and constraints not related to epidemics. For minor epidemics disease-induced changes in the contact network are therefore probably negligible. However, if a disease is perceived as a major threat it could induce risk-avoidance behavior that has a strong impact on the contact network.

The moment closure approximation that has been discussed here in detail, appears to be a powerful tool for future investigations. It is interesting

to note that this tool is also applicable to certain simple models of social processes which could therefore be included in models of epidemics. A discussion of the differences and similarities between epidemic and social contact processes on adaptive networks is presented in Do and Gross (2009). Constraints that cannot be captured easily by the moment closure approach arise from the physical space in which personal contact networks are necessarily embedded. To clarify the impact of this will probably require explicit spatial simulations. Another factor that is not captured by moment closure is the role of stochastic fluctuations. An informative investigation of fluctuations in epidemics on adaptive networks is presented in Shaw and Schwartz (2008, 2009).

The detrimental effects of rewiring discussed here is absent if links are cut instead of rewired. Whether cutting or rewiring links is the main response to a real world disease depends strongly on its epidemiology as well as on choices made by the individuals. Two prominent responses to SARS, wearing face masks and leaving the affected region, correspond to cutting and rewiring links respectively. Also in the case of AIDS links can be rewired, say, by finding a new partner, or cut, say, by the use of condoms.

In summary epidemics on adaptive networks still pose many open questions. To answer these questions will require further work in the physics of adaptive networks, but also in field epidemiology and the sociology of contact networks. The results that have been obtained so far suggest that future interdisciplinary work could shed light on the physics of the adaptive interplay between state and topology, on the evolution of social networks, and on the dynamics of real world diseases.

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