Coevolutionary cycling of host sociality and pathogen virulence in contact networks

Federico Prado, Alyssa Sheih, Jevin D. West, Benjamin Kerr *

Department of Biology, University of Washington, Box 351800, Seattle, WA 98195, USA

ABSTRACT

Infectious diseases may place strong selection on the social organization of animals. Conversely, the structure of social systems can influence the evolutionary trajectories of pathogens. While much attention has focused on the evolution of host sociality or pathogen virulence separately, few studies have looked at their coevolution. Here we use an agent-based simulation to explore host–pathogen coevolution in social contact networks. Our results indicate that under certain conditions, both host sociality and pathogen virulence exhibit continuous cycling. The way pathogens move through the network (e.g., their interhost transmission and probability of superinfection) and the structure of the network can influence the existence and form of cycling.

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1. Introduction

In many animal species, group-living comes with significant advantages to the individuals comprising the group, including protection from predation, increased foraging efficiency, increased information exchange, reduced energy expenditures in movement and thermoregulation, and improved access to mates and helpers for infant rearing (Alexander, 1974; Beauchamp, 2004; Caraco et al., 1980; Hamilton, 1971; Hoogland and Sherman, 1976; Krause and Ruxton, 2002; Lazarus, 1979; Lee, 1994; Pulliam, 1973). However, group-living carries costs for group members as well: a group of animals may attract predators more easily; competition for food, nesting sites and mates among members of a group may be intense; some individuals may suffer from infanticide; there is an increased likelihood of misdirected parental care; and disease transmission may be more prevalent in gregarious species (Alexander, 1974; Andersson and Wiklund, 1978; Brown and Brown, 1986; Brown et al., 2001; Dobson and Meagher, 1996; Ezenwa, 2004; Hoogland, 1979; Hoogland and Sherman, 1976;

Krause and Ruxton, 2002; Rubenstein and Hohmann, 1989). In this article, we focus on this last cost of group-living: enhanced disease transmission.

Transmission of pathogens or parasites may place an upper bound on group size and limit the level of interaction among individuals within a group, i.e., their sociality (Altizer et al., 2003; Anderson and May, 1979; Hart, 1990; Ezenwa, 2004). Social animals possess several strategies to lower the transmission of disease: avoidance or reduced contact with infected individuals, altered behavior of infected individuals such as self-imposed isolation from herds, and reduced chances of mating with or by infected individuals (Hart, 1990). The foregoing suggests that contagious pathogens may influence the evolution of social behavior in animals (Alexander, 1974; Altizer et al., 2003; Brown and Brown, 1986; Hart, 1990; Hoogland, 1979; Hoogland and Sherman, 1976; Loehle, 1995; Rubenstein and Hohmann, 1989).

At the same time, the social behavior of animals is likely to influence the evolution of various pathogen characteristics. For instance, theoretical studies suggest that the average number of sexual or needle-sharing partners and the rate of sexual or needle partner switching can determine the evolution of mutation rate, genetic and antigenic diversity, and virulence in HIV (Ewald, 1994; Ewald et al., 1994; Massad, 1996). Further, experiments have shown that pathogens may evolve different degrees of infectivity

* Corresponding author. Tel.: +1 206 221 3996; fax: +1 206 543 3041.
  E-mail addresses: fprado@u.washington.edu (F. Prado),
asheih@u.washington.edu (A. Sheih), jevinw@u.washington.edu
(J.D. West), kerrb@u.washington.edu (B. Kerr).

(i.e., probability of successfully infecting a susceptible host upon contact) and/or virulence (i.e., how quickly the pathogen kills its host) in response to changes in the way hosts move and contact each other (Boots and Mealor, 2007; Kerr et al., 2006).

Here we focus on pathogen virulence, and how it responds evolutionarily to the social structure of the host population. The so-called "conventional wisdom" is that, all else being equal, virulence should be selected against (for a discussion, see Bull, 1994; Ewald, 1994). A more virulent pathogen kills its host sooner, reducing the period during which it can jump to a new host. However, some of the traits that lead to higher virulence are also thought to provide separate benefits such as enhanced transmission rates and/or superior intra-host competitive ability (May and Anderson, 1979; Massad, 1996; Nowak and May, 1994). Such pathogen traits may simultaneously come with advantages (higher rate of movement to new hosts) and disadvantages (shorter period infecting any one living host). Given that the relative magnitude of these costs and benefits may ultimately depend on host social structure, host sociality may exert selective pressure on virulence.

Many theoretical models have focused on the evolution of pathogen virulence (Boots et al., 2004; Boots and Sasaki, 1999, 2003; Day 2002; Gandon et al., 2002; Nowak and May, 1994; Massad, 1996; van Baalen, 1998, 2002; see Galvani, 2003 for a review). Very few, however, have explored how host sociality and pathogen virulence coevolve. In an elegant study, Bonds et al. (2005) explored the coevolution of sociality and virulence assuming that the populations through which pathogens spread are composed of globally interacting individuals (i.e., every individual has some chance of contacting any other). When social contacts are ephemeral and the host population is highly fluid, their assumption may be reasonable. For many socially transmitted diseases, however, pathogens move through a structured network of hosts and do not have potential access to all hosts at all times.

A modeling approach that explicitly treats the host population as a network is a direct way to capture the constrained movement of pathogens. Such an approach allows for variability among hosts in social connectivity (whether heritable or not) and the formation of social clusters, which can isolate pathogens (Klovdahl, 1985; Read and Keeling, 2003, 2006; Volz and Meyers, 2007). Networks consist of a set of nodes, connected together by links. In this article we use a network approach with nodes representing individual hosts each of which can be infected by a pathogen. Links represent social contacts between hosts as well as conduits for pathogen movement. All else being equal, we assume that "better-connected" hosts (i.e., nodes with more links) have a lower death rate because there are benefits to being "social" (e.g., due to increased predator protection, information exchange, or foraging efficiency). On the other hand, these same nodes are also more likely to become infected as links are pathways of disease transmission. Thus, hosts face a trade-off between the risks and rewards of sociality. Given that pathogen spread is a cost of individual sociality, pathogen virulence may exert strong selection on host sociality. We assume that pathogens face two distinct trade-offs: higher virulence correlates positively with: (a) transmission to new hosts and (b) within-host competitive ability. When more virulent strains possess higher levels of within-host replication, such tradeoffs are possible (e.g., de Roode et al., 2008; Fraser et al. 2007). Given that social connections among hosts determine the routes of pathogen transmission, host sociality may exert selective pressure on pathogen virulence. To the extent that pathogens affect the evolution of host sociality and hosts affect the evolution of pathogen virulence, a coevolutionary antagonism ensues. Whether such interaction leads to coevolutionary stable strategies or to indefinite evolutionary cycling is an open question.

And if stable strategies or cycling do occur, how are they affected by the precise structure of the network? Here we explore these topics using simulated social contact networks.

2. Agent-based simulation

To investigate the coevolution of sociality and virulence, we use an agent-based simulation. First we build a virtual network of no more than N nodes, where each node represents a host. Every host is assigned a parameter σ, which defines its sociality. We note that σ is actually the expected number of contacts the host has in the network, which is only a component of sociality; however, for convenience we will use the term "sociality" to refer to this variable. At the beginning of the simulation, sociality for each host is chosen from a narrow range: $\sigma_i \sim Unif(\sigma^*_{min}, \sigma^*_{max})$. The value of σ_i is the genotype of host i. Its phenotype, ϕ_i, is the maximum number of links that node i can have with other nodes. This phenotype is realized once during the lifetime of a host; we assume $\phi_i \sim Poisson(\sigma_i)$, with the constraint that the host phenotype lies between a minimum and a maximum value (ϕ_{min}, ϕ_{max}). Before connections between host nodes are established, we can think of ϕ_i as the number of "stubs" (later to become links in a network graph), belonging to host i. Two hosts with at least one stub each can end up connected. We connect the nodes by randomly choosing, without replacement, two stubs from distinct hosts and forming a link between them. Self-connection is not allowed, but multiple links between two given nodes are permitted. There will be at most one node with stubs remaining at the completion of this random connection. We let the number of actual links made by host i be λ_i, where $\lambda_i \leq \phi_i$. At the beginning of the simulation, we randomly infect one-half of the hosts with pathogens. Initially, each pathogen is assigned a parameter v_i, which defines its virulence $(v_i \sim Unif(v^*_{min}, v^*_{max}))$. The value v_i is the genotype of the pathogen infecting host i.

After the network has been initiated, we update it asynchronously. An update step can take one of three forms: (1) "birth", (2) "death", or (3) "infection". A birth or death occurs when a host is added to or removed from the network. An infection takes place when a host receives a pathogen from an infected node connected to it. To determine which of the above three events takes place, each host i carries three "weights" at time t which can be loosely thought of as rates: A birth rate $\beta_i(t)$, a death rate $\delta_i(t)$, and an infection rate $\iota_i(t)$.

The birth rate, $\beta_i(t)$, is negatively density-dependent:

$$\beta_i(n(t)) = \beta_{max}\left(1 - \frac{n(t)}{N}\right), \tag{1}$$

where $n(t)$ is the number of hosts at time t, $n(t) \leq N$, and β_{max} is the maximum birth rate (at $n=0$). We give all hosts the same birth rate (that is, we assume no fecundity selection). All offspring are born uninfected (i.e., no vertical transmission occurs) and placed randomly in the network (i.e., they often end up unlinked to their parents).

Each host has a unique death rate (that is, we assume viability selection) which depends on the virulence of any infecting pathogen that the host may be carrying, and on how many other hosts are connected to it. The death rate $\delta_i(t)$ of host i is given by

$$\delta_i(t) = \begin{cases} \delta_{un} - b_h\left(\frac{\lambda_i(t) - \lambda_{min}}{\lambda_{max} - \lambda_{min}}\right) & \text{if host } i \text{ is uninfected,} \\ \delta_{in} - b_h\left(\frac{\lambda_i(t) - \lambda_{min}}{\lambda_{max} - \lambda_{min}}\right) + c_p\left(\frac{v_i(t) - v_{min}}{v_{max} - v_{min}}\right) & \text{if host } i \text{ is infected.} \end{cases} \tag{2}$$

The benefit to the host of sociality is given by b_h, which measures how death rate decreases with social connectivity. The cost to the

pathogen of virulence is given by c_p, which measures how death rate of the host increases with the virulence of the infecting pathogen. The parameter δ_{un} is the death rate of a minimally connected uninfected individual, and δ_{in} is the death rate of a minimally connected individual infected with a minimally virulent pathogen. Note $\delta_{in} > \delta_{un}$.

The infection rate $\iota_i(t)$ of host i, which measures how fast host i *becomes* infected, is given by

$$\iota_i(t) = \begin{cases} \sum\limits_{j \in Neighbors(i)} \tau_j(t) & \text{if host } i \text{ is uninfected,} \\ \theta\left(\sum\limits_{j \in Neighbors(i)} \tau_j(t) \right) & \text{if host } i \text{ is infected,} \end{cases} \quad (3)$$

where $\tau_j(t)$ is the transmission rate "through" one of the neighbors connected to focal host i (the indices of all neighbors of host i form the set *Neighbors*(i)). The parameter θ is the probability of superinfection. Such secondary infection leads to a virulence change in the focal node only if the virulence of the transmitting host is higher than that of the infected focal node. Thus, we assume that a superinfecting pathogen displaces a native pathogen only if the former has higher virulence (i.e., we assume a positive relationship between virulence and within-host competitive ability). The transmission rate is

$$\tau_j(t) = \begin{cases} 0 & \text{if host } j \text{ is uninfected,} \\ \tau_{\min} + b_p\left(\dfrac{v_j(t) - v_{\min}}{v_{\max} - v_{\min}} \right) & \text{if host } j \text{ is infected.} \end{cases} \quad (4)$$

The benefit to the pathogen of virulence is given by b_p, which measures how transmission rate increases with virulence. The parameter $\tau_{\min}$ is the transmission rate of the minimally virulent pathogen. For simplicity, we assume transmission rate is a linear function of virulence. Previous studies have shown that with such a relationship, pathogens will evolve toward infinite levels of virulence in unstructured populations, but there can be a finite evolutionarily stable strategy (ESS) with population structure (Haraguchi and Sasaki, 2000; van Baalen, 2002).

Which updating event takes place and which node is updated depends on the size of the birth, death and infection rates of all nodes. Specifically, a higher weight will make that event more likely to occur. Let $W(t) = \sum_{i=1}^{n(t)} (\beta_i(t) + \delta_i(t) + \iota_i(t))$. The probability of node i giving birth is $\beta_i(t)/W(t)$. All nodes are "born" uninfected. Similarly, the probability of node i dying is $\delta_i(t)/W(t)$, and of getting infected is $\iota_i(t)/W(t)$. A death event of host i alters the death rate (and potentially the infection rate) of all its former "neighbors". These variables are recalculated for each neighbor, which now has fewer links (λ) and a potentially diminished infection rate (ι), a result of the inability of the "killed" node to transmit the pathogen to its former neighbors (had it been infected). Finally, if an infection event is chosen, node j is chosen with probability $\tau_j(t)/(\sum_{j \in Neighbors(i)} \tau_j(t))$ as the transmitter. Recall that the infection rate of a focal node is proportional to the sum of the transmission rates of all the nodes that connect to it (Eq. (3)). If transmission occurs, the new infection at the focal node affects its mortality, as well as its transmission rate of the pathogen to all its neighbors. This change in turn affects the infection rate of each neighbor. We therefore update the death rate of the newly infected node and the infection rates of all its neighbors.

A death event potentially makes stubs available in the network. In other words, links of nodes that were connected to the "killed" node become stubs that can now be connected to other living nodes. Equally, births bring to the network uninfected nodes that are initially unconnected (i.e., nodes with stubs that could become links to other nodes). Without regularly forming new links within the network, births and deaths could eventually isolate all nodes from one another. To prevent this, every epoch we randomly connect free stubs within the network leaving all pre-existing connections intact. An epoch is defined as N asynchronous updates (i.e., the number of updates equivalent to the maximum number of hosts in the entire network).

To explore the coevolution of sociality and virulence, we allow σ and v to evolve. Every node carries one or two genotypes (host and, if infected, pathogen). When a new host is born, a mutation can alter its genotype from its parent's genotype. When a pathogen is horizontally transmitted to a new host, a mutation can change its genotype from its parent's genotype in the former host. The genotype of a host would be its sociality ($g=\sigma$), while that of a pathogen would be its virulence ($g=v$). If g_{par} is the genotype of the parent, we assume that the genotype of the offspring g_{off} is

$$g_{off} = \begin{cases} g_{par} + R_g & \text{with prob. } \mu_g, \\ g_{par} & \text{with prob. } (1 - \mu_g), \end{cases} \quad (5)$$

where μ_g is the probability of mutation and R_g is a random variable ($R_g \sim Unif(-\psi_g, \psi_g)$), where ψ_g relates to the amount g can change due to a single mutation. We require g to remain between $g_{\min}$ and $g_{\max}$, to keep the evolving genotypes within boundaries.

In the simulations described above, the network is randomly connected. For comparison, we run additional simulations in which a specific type of network structure is imposed. We divide the network into C clusters (or subpopulations), each composed of no more than N/C nodes. Nodes in each cluster are connected using the same algorithm mentioned above with the exception that no more than a total of s stubs from each cluster are left unconnected, or alternatively, a single node remains with more than s free stubs, whichever occurs first. The free stubs left in each cluster are then randomly linked allowing some connection between clusters. Thus pathogens in each cluster evolve semi-independently, where the few connections between subpopulations restrict pathogen transmission between clusters. The birth rate in each cluster is given by

$$\beta_k(n_k(t)) = \beta_{\max}\left(1 - \frac{Cn_k(t)}{N} \right), \quad (6)$$

where $n_k(t)$ is the number of hosts in cluster k at time t. A new host is born in a cluster different from that of its parent with probability ρ. Deaths and infections occur with the same probabilities as in the random network.

We terminated most of our simulations at 10,000 epochs. At times, we ran longer simulations to check long-term behavior of evolving variables. Typical parameter ranges are shown in Table 1. After exploration with different values of the parameters, these ranges were selected because they kept the pathogen endemic.

3. Results

To gauge how host sociality (σ) influences the evolution of pathogen virulence (v) and vice versa, we initially ran simulations in a random network in which only one was allowed to evolve while the other was kept constant. Fig. 1a shows average evolved sociality at epoch 10,000 for different values of fixed virulence. Low virulence selects for high sociality, which evolves near its maximum. Above a threshold level of virulence, which we refer to as the "social switch", host sociality evolves near its minimum. Thus, the relationship between fixed virulence and evolving sociality resembles a "bang–bang" or step function. Beyond higher values of virulence, the pathogen goes extinct. Fig. 1b shows average evolved virulence at epoch 10,000 for different values of fixed sociality. At low host sociality, virulence evolves close to its minimum. Higher sociality selects for higher pathogen virulence.

Table 1
Parameters and variables used and their values or ranges.

Symbol	Definition	Value or range
β_{max}	Maximum birth rate	1.0
σ_i	Sociality genotype of host i	2.2–7.0
σ^*_{min} (σ^*_{max})	Minimum (maximum) sociality at beginning of simulation	4.0 (5.0)
ϕ_i (λ_i)	Sociality phenotype (number of links) of host i	0–13
v_i	Virulence of pathogen in host i	0.01–0.3
v^*_{min} (v^*_{max})	Minimum (maximum) virulence at beginning of simulation	0.1 (0.2)
δ_{un}	Background death rate of a minimally connected uninfected host	0.22
δ_{in}	Background death rate of a minimally connected host infected with a minimally virulent pathogen	0.25
c_p	Cost to the pathogen from increased virulence	1.0
b_h	Benefit to the host from increased sociality	0.2
τ_{min}	Transmission rate of minimally virulent pathogen	0.5
b_p	Benefit to the pathogen from increased virulence	0.43
θ	Probability of superinfection	0.0–0.1
μ_σ (μ_v)	Probability of mutation of host sociality σ (pathogen virulence v)	0.05
ψ_σ (ψ_v)	Amount σ (v) can change due to a single mutation	0.06 (0.003)
ρ	Probability of a host being born in a different cluster from its parent's	0.01
C	Number of clusters in clustered network	100
N	Maximum number of hosts in the entire network	10,000
$n(t)$	Number of hosts in the network at time t	≤ 10,000
s	Maximum number of stubs left unconnected from each cluster which may later become intercluster links	1–128

Note: The asterisk (*) above denotes the minimum or maximum genotype values at the beginning of the simulations. During the runs, both σ_i and v_i may evolve outside of this range, but will still remain within the ranges shown above for σ_i and v_i.
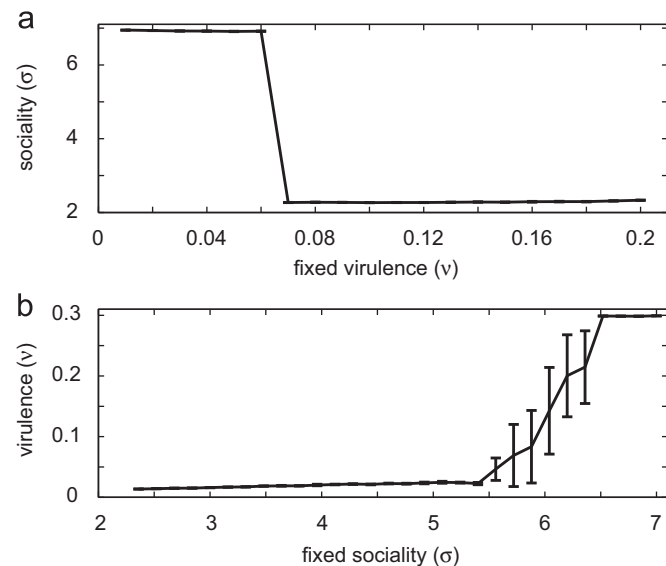

Fig. 1. The evolution of (a) sociality when virulence is fixed and (b) virulence when sociality is fixed. The results shown are the means of each evolved variable (± 1 standard error of the mean from 5 simulations) at epoch 10,000. The parameters used are as in Table 1 with $\theta = 0.02$, $\sigma^*_{min} = \sigma^*_{max} = 4.5$, $v^*_{min} = v^*_{max} = 0.15$. (a) There is a step-like transition from high to low sociality between $0.06 < v < 0.07$. (b) The transition from low to high virulence is gradual and virulence reaches its maximum at $\sigma \geq 6.52$.
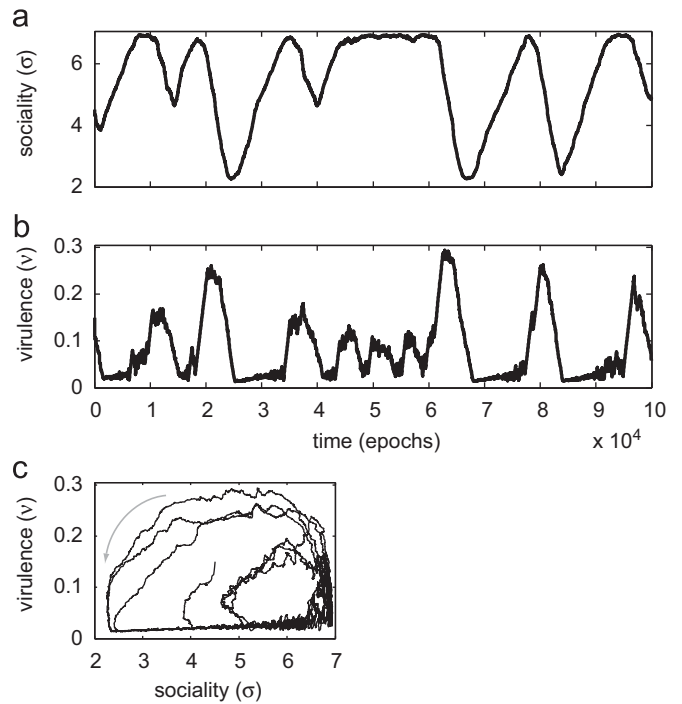

Fig. 2. The coevolution of host sociality and pathogen virulence in a random network. A sample run of (a) average host sociality and (b) average pathogen virulence through time. The parameters used are as in Fig. 1 except for $\sigma^*_{min} = 4.0$, $\sigma^*_{max} = 5.0$, $v^*_{min} = 0.1$, and $v^*_{max} = 0.2$. When virulence is low, hosts evolve high sociality, which selects for high virulence, which in turn leads hosts to evolve lower connectivity, which brings virulence back to low levels. (c) A phase plot of the same sample run with an arrow indicating the direction of rotation. Although irregular, cycling is apparent.

In the next set of simulations, we allowed both genotypes (σ and v) to coevolve in a random network. Under certain parameters, we observe indefinite cycling (Fig. 2). Looking back to Fig. 1, we see that high host sociality selects for high pathogen virulence (Fig. 1b). However, more virulent pathogens select for less social hosts (Fig. 1a). But then low host sociality selects for low pathogen virulence (Fig. 1b). Finally, pathogens with low virulence select for high sociality (Fig. 1a) and the cycle continues. Indeed, because of the aforementioned "social switch" (Fig. 1a), one would expect the evolution of average host sociality to experience directional changes whenever pathogen virulence crossed this threshold ($0.06 \leq \bar{v} \leq 0.07$). Changes in sociality would then promote changes in pathogen virulence and oscillations could ensue. However, one might ask why the oscillations do not dampen with both types reaching an equilibrium.

A closer inspection of Fig. 2 reveals that directional changes in sociality appear to occur at different levels of virulence. For instance, when sociality is high and virulence is increasing, sociality turns downward at a relatively high virulence; however, when sociality is low and virulence is decreasing, sociality turns upward at relatively low virulence. Thus, there does not seem to be a unique "social switch". We note that for the simulations in Fig. 1a, we started the hosts with an intermediate sociality value ($\sigma \approx 4.5$). However, when we repeat these simulations with different initial values of host sociality, the social switch *moves* (Fig. 3a).

Why should the initial value of sociality move the switch? Part of the answer comes in Fig. 3c, where we see that disease prevalence (fraction of infected hosts) increases with sociality for a fixed value of pathogen virulence. (Note that in Fig. 3c, neither hosts nor pathogens evolve.) When disease prevalence is high, the cost of reducing sociality (loss of valuable social contacts) may
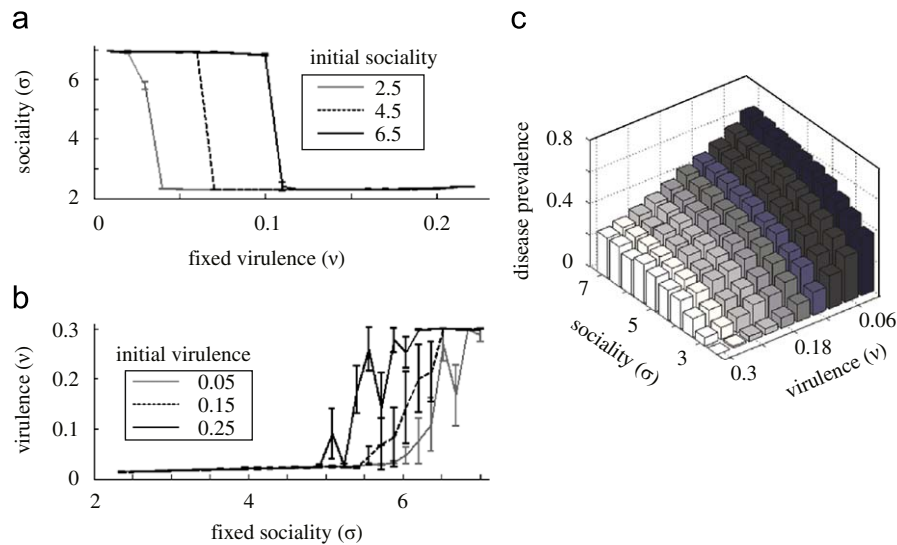
Fig. 3. The evolution of (a) sociality when virulence is fixed and (b) virulence when sociality is fixed for different starting values of sociality and virulence, respectively. In (a), each line was obtained by setting σ^*_{min} and σ^*_{max} equal to the initial value of sociality shown in the box. In (b), each line was obtained by setting v^*_{min} and v^*_{max} equal to the initial value of virulence shown in the box. The results shown are the means of each evolved variable (± 1 standard error of the mean from 5 simulations) at epoch 10,000. The parameters used are as in Fig. 1. (a) The social switch moves from low (when initial sociality is low) to high (when initial sociality is high). (b) Lower levels of initial virulence require a higher sociality before virulence can evolve to its maximum. (c) Disease prevalence (fraction of infected hosts) as a function of host sociality and pathogen virulence. In part (c), neither hosts nor pathogens evolve.

outweigh the benefit (disease avoidance) because the chance of infection is high (see Bonds et al., 2005 for a full discussion of this effect). Conversely, when prevalence is lower, the benefit of reducing sociality may exceed the cost, because the chance of infection is lower. These cost/benefit differences may mean that for certain values of virulence, a network starting with high sociality (and high prevalence) may evolutionarily maintain its high sociality, whereas a network starting with low sociality (and low prevalence) may evolutionarily keep its low sociality. This contributes to a shift in the threshold level of virulence, where the social switch is higher when the network is highly social.

Similarly, we note that the initial value of pathogen virulence also seems to affect the evolution of virulence when sociality is fixed (Fig. 3b). As initial values of pathogen virulence increase, the gradual transition from low to high virulence shifts to the left. Again, part of the reason is found in Fig. 3c where we see that disease prevalence decreases with virulence for a fixed value of host sociality. When disease prevalence is high, susceptible hosts are in short supply and it may be more beneficial for pathogens to keep virulence low as the benefits (host persistence) exceed the costs (lower transmission ability). Conversely, when disease prevalence is low, susceptible hosts are more accessible and it may be beneficial for pathogens to maintain higher virulence. Thus, a network starting with low virulence (and high prevalence) may evolutionarily maintain its low virulence, whereas a network starting with high virulence (and low prevalence) may evolutionarily keep its high virulence. This difference contributes to the shift in the threshold level of sociality, where the virulence transition is lower when the pathogen is highly virulent.

These moving switches (social and virulence) play a role in the sustained cycling of virulence and sociality. To understand this better, we analyze one complete cycle (Fig. 4a). We focus on the role played by the social switch. We start at a time when sociality is high, while virulence is low (t_1 in Fig. 4a). At this time, the social switch is high (Fig. 4b). High sociality exerts selection on virulence to increase (Fig. 4b). As virulence climbs beyond the social switch (t_2 in Fig. 4a), sociality starts to decrease (Fig. 4c). As sociality decreases, the social switch moves to lower values. Meanwhile, virulence hovers at high values, as there is a delay from the time when sociality starts declining to the time when virulence follows

suit (from t_2 to t_3 in Fig. 4a). Once sociality is sufficiently low, virulence starts to decline (at t_3 in Fig. 4a; see Fig. 4d). As virulence starts declining, sociality continues to do the same. Since the social switch is now lower (due to lower levels of sociality) it takes the decreasing virulence some period of time to reach the switch value (from t_3 to t_4 in Fig. 4a). This fixed period contributes to the sustained cycling. Once virulence crosses this lower threshold (t_4 in Fig. 4a), there is selection for higher host sociality. Climbing sociality now leads to an increase in the social switch value, again increasing the difference between the current virulence and the switch. This forces another fixed period before virulence can "catch" the moving switch. Again, these periods contribute to the cycles. Finally, sociality approaches its maximum and the cycle repeats. The shift of the virulence threshold contributes in a similar manner to the sustained cycling.

There is another way to understand the oscillatory behavior in this model. When virulence is fixed at intermediate values, host sociality exhibits bistable behavior (see Fig. 3a for $0.05 < v < 0.1$). Specifically, host sociality evolves to a high-valued equilibrium if it starts high and evolves to a low-valued equilibrium if it starts low. Consider a host population with high sociality where the pathogen has low virulence. If the virulence value is slowly increased (exogenously), sociality remains high until a value above $v=0.1$ (see black line in Fig. 3a), at which point sociality evolves to a low value. After this change in sociality, imagine that the virulence value is slowly decreased. Host sociality does not change back to its high value at the same point, rather virulence needs to be decreased below $v=0.05$ before sociality evolves back to its original high value (see gray line in Fig. 3a). A system with such path-dependent behavior displays *hysteresis* (Murray, 1993). We see that virulence also exhibits a hysteresis loop as sociality is exogenously varied (Fig. 3b). It has been shown that hysteresis can play an important role in oscillatory behavior in multi-variable systems (Murray, 1993; Chen et al., 2000; Han et al., 2005).

Changes in the probability of superinfection (θ) result in different types of oscillations (Fig. 5). For lower values of θ, sociality evolves close to its maximum while virulence evolves near its minimum without pronounced cycling. For higher values of θ, cycling ensues. As θ continues to increase, the amplitude and positioning of the cycles shift. Generally, average sociality
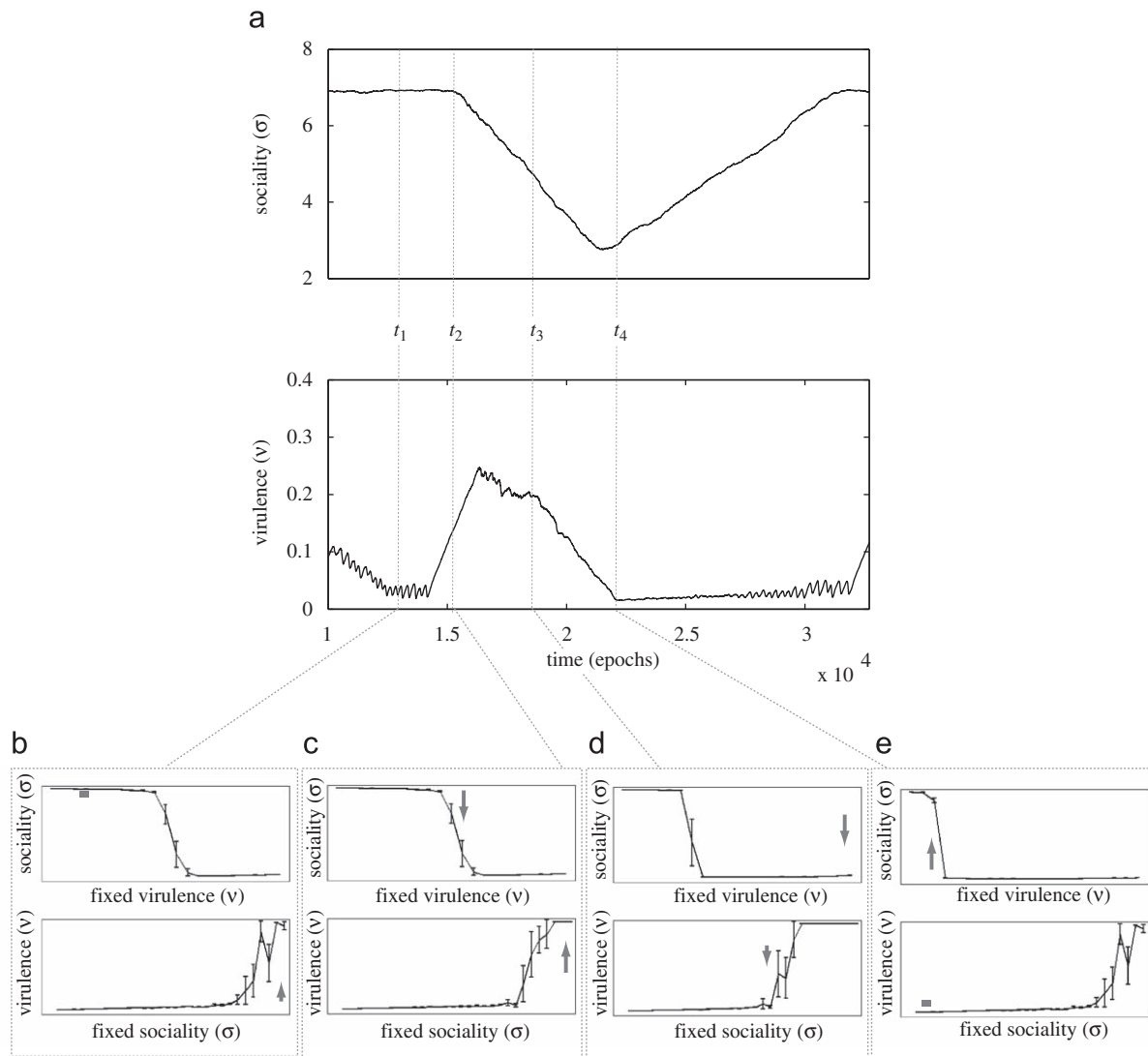
Fig. 4. (a) A typical cycle in host sociality and pathogen virulence. The vertical lines refer to particular times in the cycle. (b–e) The equivalent graphs to Fig. 1 at times (b) t_1, (c) t_2, (d) t_3, and (e) t_4. The axes and the parameters used are as in Fig. 1. Arrows illustrate the approximate location of sociality and virulence at the indicated times and the direction in which they tend to evolve. Rectangles show the lack of directional tendency for the respective variable at that particular time. The shifting of sociality and virulence thresholds, contributing to the sustained cycling, is apparent.

decreases as θ increases, whereas average virulence at first increases and then decreases with θ. When θ becomes too high the pathogen goes extinct (not shown). Gradual changes in the transmission rate of a minimally virulent pathogen (τ_{min}) give similar results (not shown).

The structure of the network influences the way pathogens move through it. To investigate the role of network structure on the coevolutionary dynamics of host sociality and pathogen virulence, we compared a random network to a clustered network. Fig. 6 illustrates a snapshot of a clustered network. Each circle represents a "supernode" (e.g., a cluster comprised of nodes) and the lines connecting the circles are inter-cluster links. The size of each circle is proportional to the average host sociality within the cluster, while its shading is a measure of its mean pathogen virulence (e.g., lighter clusters harbor higher virulence). We allowed the average number of links (s) connecting clusters to vary from 1 to 128 (Fig. 6). For low values of s we observe sustained cycling and the amplitude of oscillations in pathogen virulence appears to be dampened when compared to oscillations of virulence in a random network. For intermediate values of s, cycling ceases. As s increases, cycling reemerges. As s gets very

large, the form of cycling becomes indistinguishable from that of a random network (Fig. 2).

4. Discussion

Our simulations show that while pathogen virulence and/or host sociality evolve to a set level when the other genotype is fixed (Fig. 1), sustained cycling can occur when the genotypes coevolve (Fig. 2). The frequency and amplitude of these oscillations are sensitive to changes in parameters that affect pathogen transmission, such as superinfection (θ) and base transmission rates (τ_{min}) (Fig. 5). For parameter values that lower transmission rate, there is convergence to low virulence and high host sociality. Since limited access to hosts favors lower virulence, the costs of becoming infected are lower (because virulence is lower), and the chance of getting infected may be higher (due to increased prevalence, see Fig. 3c). This maintains sociality at high levels and virulence at low levels. At intermediate transmission rates, access to hosts is less limited and more virulent pathogens are favored. In this situation, the costs of becoming infected are higher, and the
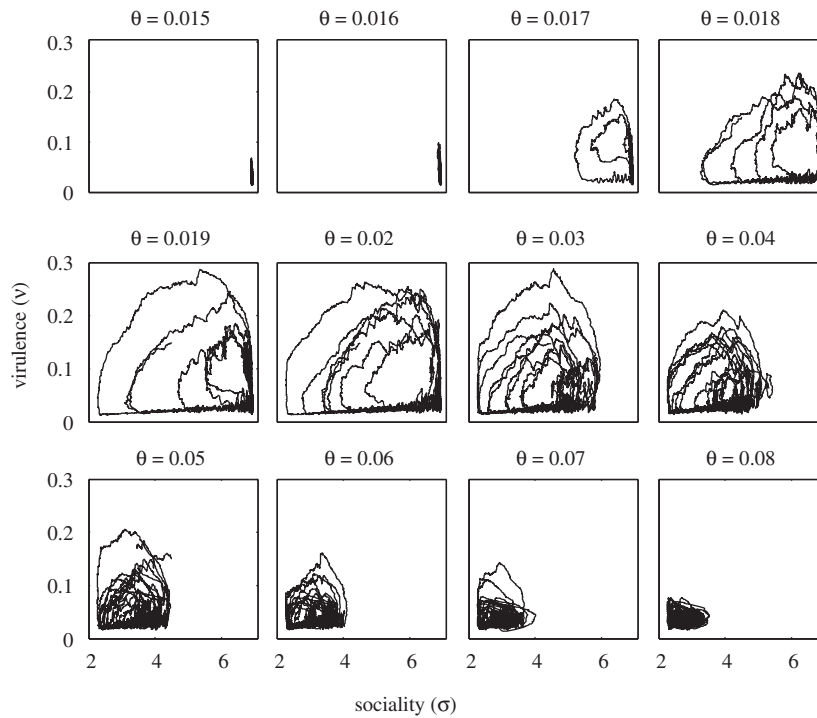
Fig. 5. Phase plots showing the effect of superinfection (θ) on the coevolutionary dynamics of host sociality (σ) and pathogen virulence (v). Only the last 80,000 epochs from a 100,000 epoch run are shown. The parameters used are as in Fig. 2, except for θ. For small values of θ (including $\theta=0$), there is convergence to high sociality and low virulence. For intermediate values of θ, oscillations of different magnitudes and frequencies ensue, the largest dynamical range observed at around $\theta=0.02$. For $\theta > 0.08$, the pathogen goes extinct (not shown).
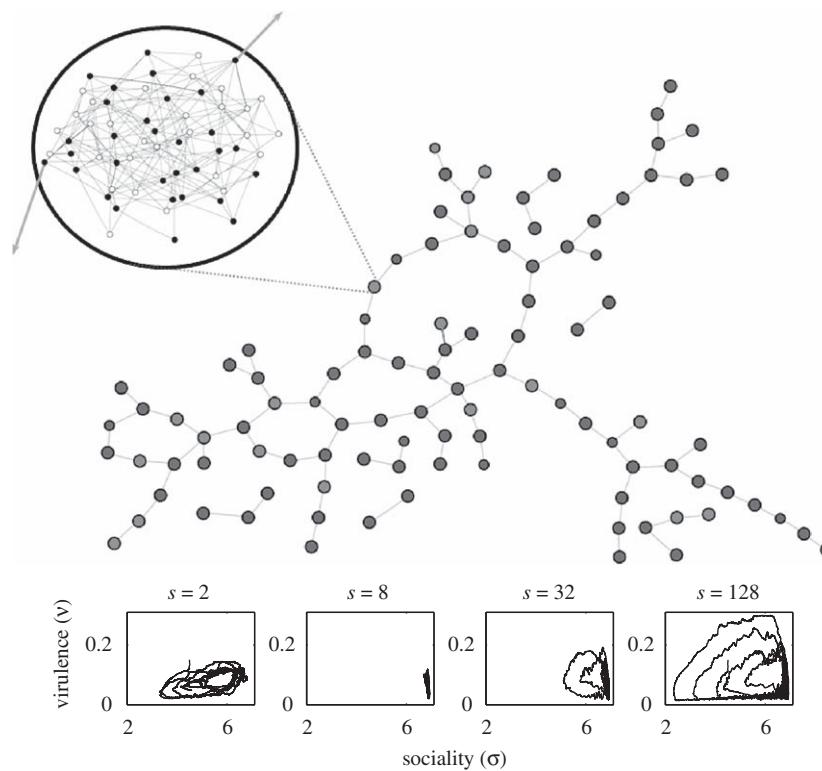

Fig. 6. Top: A snapshot of a clustered network at epoch 10,000. Each gray circle represents a cluster (or "supernode") in which the size is proportional to the cluster's average host sociality, while the shading is a measure of its average pathogen virulence (lighter shading represents higher virulence). The enlargement shows the internal structure of a cluster with infected hosts in white and susceptible hosts in black. Bottom: Phase plots showing coevolutionary cycling (or lack thereof) in clustered networks for different values of s. Only the last 80,000 epochs from a 100,000 epoch simulation are shown.

chance of getting infected lower (because of lower disease prevalence, see Fig. 3c). Thus, highly social hosts lower their sociality and cycling can ensue (see Fig. 5). As transmission parameters increase further, the cycles shift to lower mean sociality and lower mean virulence. With greater access to hosts, it takes a lower number of social contacts to favor higher virulence and a lower virulence to favor lower sociality. In general, this pushes the cycles to the corner of the phase plane where sociality and virulence are low (see Fig. 5).

4.1. Coevolution and superinfection

A complimentary explanation for the variable cycling observed in Fig. 5 involves a shift in the "virulence threshold" (Figs. 1b and 3b) with the level of superinfection. For small values of super-infection (θ), the virulence threshold completely disappears; that is, minimal virulence is selected at all fixed values of sociality (not shown). Sociality thus evolves to high levels without favoring increased virulence and the system reaches an equilibrium at high sociality and low virulence. Intermediate values of superinfection (θ) produce a virulence threshold which is high in terms of sociality (as in Fig. 1b). This allows virulence to evolve to high values once sociality is close to its maximum. As explained in the previous section, the delays inherent in chasing moving thresholds promote cycling (Fig. 4). Higher values of superinfection (θ) shift the virulence threshold to low values of sociality. In this case, virulence increases at lower levels of sociality and the cycles hover around low sociality and low virulence.

4.2. Coevolution and network structure

The structure of the network can also affect pathogen transmission and influence the nature of oscillations. What is puzzling, however, is the lack of sustained cycling at intermediate levels of intercluster connectivity (intermediate values of s) and the presence of cycling at both ends of the s spectrum. For a given level of sociality and virulence, all else being equal, a highly clustered network (low s) harbors relatively lower disease prevalence than a less clustered network (higher s) because the pathogen has greater access to the network in the latter. This is consistent with pair-approximation models which have shown that clustering of hosts reduces disease prevalence (Caraco et al., 2001).

Imagine a network with high sociality and increasing virulence (and concomitant declining disease prevalence, see Fig. 3c). In a highly clustered network (with relatively lower disease prevalence), the benefits of disease avoidance may exceed the costs of losing valuable social contacts and as a result, hosts lower their sociality. As sociality decreases, so does disease prevalence followed later by pathogen virulence. Eventually, when virulence is low enough, sociality starts increasing and cycles ensue (Fig. 6, $s=2$). Notice that these cycles are flattened in the virulence axis compared to cycling in a random network.

On a clustered network with intermediate intercluster connectivity, given the same scenario as above, disease prevalence is relatively higher than in the highly clustered network. In this case, the costs to the host of losing valuable connections remain the same but the benefits of disease avoidance shrink as the probability of infection is larger. As a result, hosts remain highly social and cycling ceases (Fig. 6, $s=8, 32$).

As clusters become more coupled, the probability of disease transmission between clusters increases. Pathogens have more access to susceptible hosts and are selected for higher virulence. As virulence increases beyond a certain level, unattainable in more clustered networks, hosts are selected for lower sociality, and again, cycling ensues (Fig. 6, $s=128$).

The topological features inherent in a clustered network may lead to lower levels of virulence as transmission is traded for persistence. This is consistent with the results from several models demonstrating that spatial structure favors lower virulence (Boots and Sasaki, 1999; Caraco et al., 2006; Haraguchi and Sasaki, 2000; van Baalen, 2002). Thus, a clustered structure selects for more "prudent" pathogens, e.g., types do not evolve to maximize their local competitive ability and instead exhibit restraint. The importance of spatial structure for the evolution of restraint has been demonstrated empirically in host–pathogen systems (Boots and Mealor, 2007; Kerr et al., 2006) and theoretically in a few different contexts (Keeling, 1999; Johnson and Seinen, 2002; Prado and Kerr, 2008).

4.3. Trade-offs

Our model is predicated on the existence of trade-offs. High host sociality brings intrinsic benefits in the form of lower death rates, but also increases the probability that a host becomes infected. High pathogen virulence facilitates transmission but increases the probability of host death before the pathogen successfully infects a new susceptible individual. There is some empirical support for pathogen trade-offs (de Roode et al., 2008; Ebert, 1994; Fraser et al., 2007; Kerr et al., 2006; Messenger et al., 1999). However, costs and benefits of pathogen virulence are more often assumed than empirically verified (Ebert and Bull, 2003). Thus, there is great need for more empirical data to confirm the validity of these assumed host and pathogen trade-offs.

4.4. Extensions and conclusions

We assume that social links remain static for the duration of an individual's lifetime. In natural social or sexual networks, links are dynamic and may form and break often during an individual's lifetime (Volz and Meyers, 2007). This issue can be modeled by probabilistically unlinking and relinking hosts at defined intervals of time. Such relinking could be dependent on the states of the nodes; in epidemiological models with such "adaptive rewiring", oscillations in disease prevalence have been observed (Gross et al., 2006). When we unlinked and randomly relinked the entire network at every epoch, we found that sustained cycling in our evolutionary parameters still occurred. However, if in addition to the above changes, we also reduced the variance in the genotype-phenotype map of host sociality (to approach the Bonds et al., 2005 model), cycling still occurred, but under a much narrower range of parameters.

Our model assumes only one type of node and one type of link. It would be interesting to consider networks with different types of nodes, with each node representing a different species (e.g., birds and humans with avian flu as the pathogen). In a way, this would bring together two completely separate networks (e.g., a bird and a human network), each with its own contact structure and disease parameters. Another interesting expansion to our model would be to consider networks with different types of links. For instance, in humans, we could specify cultural links and disease transmission links. Cultural links are particularly interesting because news and information can move much faster and further than disease and often brings about behavioral changes that modify the structure of the social network itself. Indeed, through horizontal cultural transmission, host sociality may change quickly without underlying genetic change. Such culturally mediated shifts in network topology and the consequences

for disease ecology and evolution are particularly interesting in the context of human disease.

Beyond the above extensions, our main message is that the fundamental antagonism that drives ecological oscillations (e.g., predator–prey dynamics) also seems to play a role in sustained evolutionary cycles. Thus, continual shifts in sociality and virulence may not require a changing environment, but can in principle drive each other through a form of negative feedback. In our system, genotypes promote conditions unsuitable for themselves, a phenomenon known as negative niche construction (Laland et al., 1996; Odling-Smee et al., 2003). One of the key features of this niche construction is the tight interplay between ecology (changes in disease prevalence) and evolution (genotypic changes in host sociality and pathogen virulence). Evolutionary changes in hosts and pathogens affect disease prevalence, which can feed back to generate further evolutionary change. In this way, reciprocal negative niche construction is the motor driving continuous coevolutionary cycling between hosts and their pathogens.

Acknowledgments

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