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Disease Transmission and Networks☆

Dhruba Naug, Colorado State University, Fort Collins, CO, United States
Jae C Choe, Ewha Womans University, Seoul, Korea

Abstract

While epidemiological models have traditionally assumed that diseases spread by the mass action principle, actual contact networks within social groups do not meet this assumption. Theoretical models have shown that disease dynamics could vary considerably under different types of contact networks, but these models face challenges in terms of their evaluation due to the difficulty of collecting empirical data. The honeybee colony with its elaborate social organization and large repertoire of diseases provides an ideal setting to explore how the structure of the contact network contributes to the transmission of a disease.

Keywords

Disease transmission; Honeybees; Social groups; Social insects; Social networks

Introduction

Animals living in large groups are particularly vulnerable to infectious diseases. The close proximity of individuals offers excellent transmission opportunities to a pathogen that is spread by direct contact between hosts. Many studies show a positive relationship between group size and parasitism in terms of prevalence (proportion of infected individuals in a group) and intensity (number of pathogens per individual) (Strassmann, 1981; Côté and Poulinb, 1995; Rifkin *et al.*, 2012). If the host population is homogeneous in exposure and susceptibility to a pathogen, the birth and death rates of the host and the contact rate between susceptible and infected individuals are sufficient to predict the infection dynamics. However, groups are rarely homogeneous and individuals differ among themselves in various respects such as age, sex, physiological state, behavior, and spatial location. This causes individuals to differ in their probability of becoming infected and transmitting the infection, making it more difficult to predict the trajectory of an infection.

The rate at which an infection spreads and whether it persists in the population depend on the magnitude of the key epidemiological parameter, R_0, or the mean number of infections caused by a single infected individual. In order to stop an epidemic outbreak, R_0 must be maintained below 1. According to the mass-action SIR (susceptible-infected-recovered) model, the most basic model of epidemic spread, $R_0=\beta TS$, where β is the transmission coefficient that incorporates both infectiousness and contact rate of the infected individuals, T is the duration of infectiousness, and S is the available number of susceptible individuals (Bjørnstad *et al.*, 2002; Volz and Meyers, 2007). The simple SIR model has provided many important insights into the epidemiology of a wide range of pathogens but its fundamental assumption of homogeneous mixing among individuals is clearly unrealistic. Population-level estimates of R_0 can obscure the considerable variation in contact rate and infectiousness among individuals. Several studies have shown that typically, 80% of the transmission events are contributed by 20% of the host population: a trend that is referred to as the 80/20 rule (Perkins *et al.*, 2003; Paull *et al.*, 2012). This was highlighted during the recent global epidemic of severe acute respiratory syndrome (SARS) when a few infected individuals were responsible for giving rise to an unusually large number of secondary cases (Galvani and May, 2005). Whether or not infected individuals have contact rates that are disproportionately higher than the population average has important implications because public-health programs generally rely on the immunization of only a fraction of the hosts to protect the entire population.

Network Theory

The effects of host heterogeneity on the spread of infectious disease can be most simply modeled by dividing a population into subpopulations with different within-group and between-group transmission rates. A more explicit approach is to use models that incorporate the structure of the actual contact network in the population (Scott, 2017). Unlike the continually changing set of contacts in random mixing models, each individual is assigned a finite set of contacts to who they can transmit infection and from who they can be infected. Predictions from network models can be considerably different from those that use mean-based approaches. Although individuals may have the same number of contacts per unit time in both network and mass action models, the fixed contact structure in networks can lead to rapid, localized spread of an infection followed by a slowing down of the process

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as the number of susceptible individuals depletes locally. This makes disease extinctions more likely than outbreaks though the latter are more explosive if they occur.

The use of network models also has bearing on the evolution of the pathogens themselves. Given their high reproductive rates, pathogens are likely to undergo rapid selection to adapt to the available transmission routes between infected and susceptible individuals (Bishop *et al.*, 2000). Both theoretical and experimental results show that high transmission rates are selected in localized networks where there is intense competition for susceptible hosts while networks that are more global in their connectivity select for lower transmission rates due to lack of such competition. Localized contact structure also selects for a higher diversity in the pathogen population in contrast to a randomly mixed host population where cross-immunity to similar strains structures the pathogen population into discrete, nonoverlapping strains.

A transmission network is generally defined by a matrix X that describes the connections among all the individuals within a group. In its simplest form, the matrix is unweighted, with $x_{ij}=1$, if there is one or more interactions that can transmit an infection and $x_{ij}=0$ if there is none. The matrix is also generally undirected, meaning that infection can pass either way across an interaction or $x_{ij}=x_{ji}$. More detailed models can be constructed using weighted, directed networks (Opsahl *et al.*, 2010). The structure of the transmission network can be characterized by a number of parameters that can be quantified from these matrices. The most commonly used ones are (1) degree, the number of connections an individual has; (2) density, the proportion of existing connections out of all possible ones; (3) path length, the average number of links that connect any two individuals; and (4) clustering, the density of the local neighborhood or cliquishness (Boccaletti *et al.*, 2006). Focal measures such as degree can identify high-risk individuals in the population and can be used to inform surveillance and infection control strategies. Network level measures such as average path length and clustering coefficient can make predictions about the spread of the infection in the population. Critical points that reflect order of magnitude shifts in network properties and the consequent propagation of an epidemic can be identified from phase transitions in network parameters.

Network models are difficult and time consuming to build because they require information about the connectivity between every pair of individuals in a group. In this effort, researchers have mainly relied on infection tracing that describes the actual connections through which the infection spreads or contact tracing that looks at all the potential connections from a source individual (Keeling and Eames, 2005). Network models are also complex in terms of their statistical evaluation unlike differential equations based mass-mixing models. Moreover, as different diseases are transmitted via different transmission pathways, network models are disease specific and cannot be easily generalized. In the face of these difficulties, simulating networks with different structures (Fig. 1) and studying the parameters that influence transmission dynamics has been an important and influential research paradigm.

Types of Networks

Random Networks

In these types of networks, each individual has a fixed number of random connections, resulting in a network with no clustering and short path lengths (Barabási and Albert, 1999). The early growth rate of an infectious process and the final epidemic size are lower in these networks compared with the mass-action model, largely because of the quick depletion of the local environment of susceptible individuals around an infected individual.

Regular Networks

In these networks, individuals are connected only to their adjacent neighbors, leading to a homogeneous network with high clustering and long path lengths (Olfati-Saber and Shamma, 2005). This leads to an even stronger depletion of the local environment and thus the growth rate of the infection.

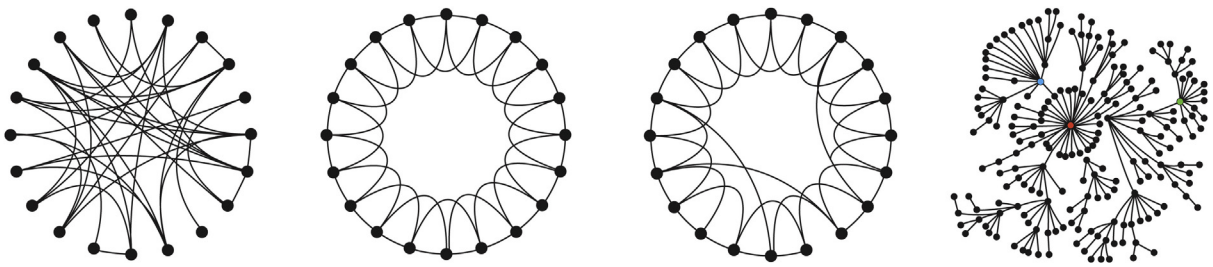

Fig. 1 Four common types of networks, from left to right: random, regular, small-world and scale-free. Adapted from Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393, 440–442 and Strogatz, S.H., 2001. Exploring complex networks. Nature 410, 268–276, with permission from Nature Journals.

Small-World Networks

The transmission properties of small-world networks have generated a lot of interest and are important to understand because many biological networks including human social networks show small-world properties (Watts and Strogatz, 1998; Lago-Fernández *et al.*, 2000). They lie somewhere between regular and random networks, displaying high clustering but small path lengths due to the existence of a few long-range connections. Even though the transmission process is still largely localized, the few long-range links allow the infection to spread relatively quickly and more synchronously over the entire network. Small-world networks may or may not have a scale-free structure.

Scale-Free Networks

These networks are characterized by an extreme heterogeneity in connectivity, the number of contacts per individual being described by a power law distribution (Barabási and Bonabeau, 2003). A few highly connected individuals, called superspreaders in the epidemic context, have a disproportionately high influence on the transmission process (Zhou *et al.*, 2006). Networks of human sexual contacts have been shown to follow such a distribution and the transmission and maintenance of sexually transmitted diseases thus depends mainly on a few promiscuous individuals (Liljeros *et al.*, 2001). In such networks, control measures directed at random individuals are quite ineffective while targeted interventions work really well. By immunizing the superspreaders, the contact network becomes sparser by orders of magnitude and brings about a drastic reduction in the number of transmission events.

A Model Network for Experimental Epidemiology

Complex network models being hard to parameterize can lead to predictions that are no more reliable or maybe even worse than those from simpler frameworks. However, with the relative dearth of suitable experimental systems with sufficient social complexity, opportunistically obtained data about the course of natural epidemics in humans have been the only major recourse for testing network models. In this context, the honeybee colony can prove to be an ideal model system. Honeybees not only provide the setting of a crowded social group that is susceptible to a vast array of infectious diseases but they are also extremely amenable to a variety of experimental paradigms at both the individual and the social level. The long association of honeybees and their pathogens over evolutionary time provides a backdrop to test how the network of social interactions in the colony could serve as the central arena for host–pathogen dynamics (Nazzi *et al.*, 2012). The pathogens can exploit the network to rapidly spread across the colony, while the host can use its structural properties as a mechanism to resist the spread. The recent finding that honeybees possess only one-third as many genes for immunity as other insects strongly suggests that the structure of social organization is an important mechanism that compensates for a lower physiological immunocompetence (Evans *et al.*, 2006).

Interaction networks in a social insect colony could be organized according to one of the following designs: (1) work-chains with each individual performing all the required parts of a given task, (2) work-chains with each individual performing one and only one part of a task with one or more other individuals completing the rest, and (3) work-chains with each individual performing only one part of a task at any given time but performing all the parts equally frequently. The efficiency and the reliability of material and information flow are substantially incremented in each successive type of network, which is adaptive for ergonomic purposes. It is however less recognized that the same design features will also promote the transmission efficiency of pathogens, increasing the vulnerability of the colony to an infectious disease.

Food, information, as well as pathogens primarily enter a honeybee colony from the environment through the foragers. Nearest-neighbor based interactions drive the subsequent transfer process, spreading these across the colony. With the individuals spatially distributed within the colony according to their ages, this results in a centripetal flow from the oldest individuals at the outer edge of the colony to the youngest ones residing at the center (Tilman, 1982). This flow pattern imparts some amount of protection to the most valuable youngest members from invading pathogens: a phenomenon that can be termed 'organizational immunity'. (Ping and Yihua, 2008). This social contact network in the colony is therefore highly structured and nonrandom, leading to a pool of individuals that is heterogeneous with respect to its probability of contacting, manifesting, and transmitting an infection, presenting an invading pathogen with the challenge of negotiating this complex landscape (**Fig. 2**).

Superimposed on this general age-based interaction pattern, one also sees that only a minority of the individuals in the colony are the primary drivers of the majority of the transfer process. This gives the interaction network an appearance of a scale-free structure. In contrast to such heterogeneous connectivity observed in the large honeybee colonies, individuals are more uniformly connected to each other in social insect species with smaller colony sizes. Within-species comparisons suggest that colony size is a primary driver of network structure and complete mixing becomes more and more improbable with increasing number of individuals. There is considerable variation in network structure even among colonies of similar sizes and it has been shown that the density of contact network in the colony determines the spread of a contagious pathogen within it.

Small perturbations in the structure of social organization can bring about large changes in transmission dynamics. Many honeybee diseases, which remain in the background at a low level in the colony, can rapidly turn lethal and erupt into an epidemic under certain conditions generally referred to as 'stress'. Investigation of these so-called 'stress' conditions suggest that they translate

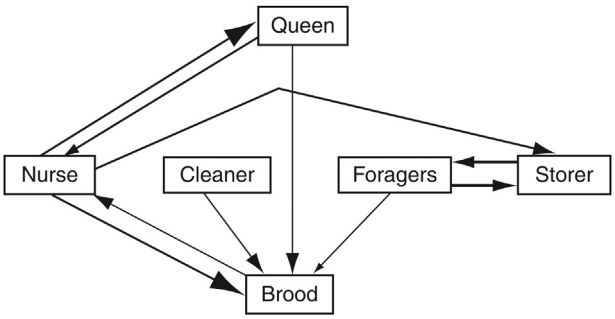

Fig. 2 Idealized social network within a honeybee colony with arrow widths indicating interaction frequency.

into disruption of the normal social organization in the colony in the face of contingencies such as a nectar flow in the environment, high demand for a certain task, or a rapid increase in colony population size (Martin, 2001; Guzmán-Novoa *et al.*, 2010). The resulting higher activity level and more generalization of labor profiles can lead to higher contact rates or other changes in social network structure.

A disease can also bring about some restructuring of the social organization in the colony. Disease at an individual level is defined as a disruption of homeostatic mechanisms, leading to an alteration in the normal set point of an organism and its symptoms are the physiological mechanisms that restore it. This definition can be extended to an epidemic being a process that disrupts the social organization critical to the functioning of a group and its symptoms are mechanisms that, via collective action of its members, attempt to restore the social structure. It has been speculated that a disease symptom such as bees starting to forage at a younger age is an adaptive response on the part of the host that serves to reduce within-colony transmission of the disease by keeping infected bees outside (Naug, 2008). However, it is equally plausible that such a response can in fact increase transmission rates by contaminating the food they collect. Behavioral fever in response to an infection, which can inhibit the development of a pathogen, requires bees to cluster more tightly that can in turn increase the contact rate among them (Mayack and Naug, 2010). Bees infected with a pathogen have also been shown to incur an energetic stress that increases their hunger level, leading them to be more eager solicitors but more reluctant donors of food. This could lead uninfected and infected bees to occupy different positions in the contact network in terms of sources and sinks in the transmission chain. It is important to note here that the structure of the social network in the colony is an emergent property that arises from individual behavior, which can be altered by simple pathophysiological mechanisms arising from a disease.

Areas for Future Research

For disease ecologists interested in using network theory, the development of network statistics remains a major research focus. A second area of rapidly developing interest is dynamic networks which account for the possibility that the structure of the contact networks might not remain constant over time, maybe partly as a consequence of the disease outbreak itself. More importantly, empirical research has lagged behind the pace of theoretical work made possible by increased computational power. Matching efforts to develop laboratory experimental systems are urgently needed to explore the interaction between network structure and disease dynamics. Integration of behavioral biology and physiology to the already existing framework of ecology, evolution, and mathematical modeling would also be critical to our understanding of the structural and functional properties of biological networks.

Research on the proximate basis underlying the behavioral interactions among individuals will give insights into the role of demographic and environmental factors on disease dynamics via their effects on social structure. It will also help answer the important questions of how the pathophysiology of a disease can alter the structure of the contact network and whether such symptomatic restructuring benefits the host or the pathogen. In social insect groups where the colony social network is considered to be primarily a product of ergonomic considerations, it is important to explore whether pathogens have played any selective role in its design. This addresses the broad issue of how any group of interconnected units, whether a bee colony or a computer cluster, deals with the challenge of shielding its network from attacks without seriously compromising its performance.

Conclusion

It is being increasingly recognized that excessive use of antimicrobials to treat diseases selects for resistant strains of pathogens that can no longer be eliminated by the same drugs. Intervention measures that have short-term epidemiological benefits but long-term

evolutionary repercussions have led to the recent resurgence of many diseases and the heightened virulence of pathogen populations. This has led to the suggestion that understanding the natural dynamics of a disease from an evolutionary, ecological, and behavioral perspective might provide pointers to preventive and curative methods that are more sustainable. There are plenty of accounts concerning behavior and customs in humans that affect the transmission of infectious diseases. Agricultural practices such as the clearing of land and irrigation have brought increased contact between human populations and animal reservoirs of diseases such as schistosomiasis and malaria (Steinmann *et al.*, 2006). Urbanization has brought about increased transmission of lyme disease, cholera, dengue, and leishmaniasis (Kendall *et al.*, 1991; Desjeux, 2001; Bradley and Altizer, 2007; Chowdhury *et al.*, 2011). Changes in sexual behavior have had a large influence on the spread of human immunodeficiency virus (HIV), human papillomavirus (HPV), chlamydia, gonorrhea, and other sexually transmitted diseases (Bunnell *et al.*, 2006; Satterwhite *et al.*, 2007). With the current threat of these numerous emerging diseases, it has become extremely important to understand the dynamics of infectious processes in the context of crowded living conditions that characterize many animal groups and humans. An understanding of the behavioral processes that define the structure of a social group will help identify the transmission pathways used by pathogens to spread and suggest possible ways to manage the social structure as a counteractive measure to both prevent and control the spread of a likely epidemic.

See also: **Communication:** Analysis of Animal Communication: Communication Networks. **Host-Parasite Interactions:** Avoidance of Parasite; Social Behavior and Parasites; Social Immunity. **Social Behavior:** Parasites and Insects: Aspects of Social Behavior; Social Behavior and Infectious Disease.

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