**How do macro-level disease dynamics influence patterns of coinfection and resultant pathogen-pathogen interactions?**

P. Alexander Burnham

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**Introduction:**

In the study and prevention of human disease, the practice of modeling diseases outbreaks using various agent-based and ordinary differential equation-based strategies has been used to great effect for many years. Computational recreation of a disease system affords the scientific community with the opportunity to better understand disease dynamics and increases our ability to predict how an outbreak will behave in a future population, respond to a treatment or be affected by some other abiotic or biotic factor. While these practices have been used to great effect in the epidemiological approach to infectious human disease, disease in other systems could greatly benefit from this under-utilized approach. In addition to enabling us to better understand the dynamics of a multitude of other disease systems in important non-human hosts, modeling non-human disease systems allows the scientific community to parameterize models using relatively more attainable empirical data. An ideal system would be easily manipulated and exhibit diverse pathogen and parasite types. It would have analogues for human spillover events, coinfections, transmission routes and share the dynamical complexity and population structure found in human disease.

One such system is that of the bumble bee (*Bombus Spp.)* and its many taxonomically distinct pathogens and parasites. The documented decline of important pollinators has garnered much attention and concern in recent years. Bumble bees in particular are important native pollinators whose decline has been understudied in light of managed honeybee losses (van Engelsdorp et al., 2008). Around 50% of bumble bee species have decreased in abundance since the 1960s (Colla et al., 2012) and as of 2016, *B. affinis* was the first bumble bee to be federally listed as endangered. In addition to their agricultural value, their eusocial behavior and population structure in conjunction with the rich diversity of pathogens and parasites they host make them an ideal candidate system for studying population level and spatial transmission and dissemination dynamics.

Pathogens and parasites are among the top threats to bumble bee species. Of particular interest, are *Nosema* spp. and several RNA viruses because the prevalence of these pathogens are linked to spillover events from commercial bees (Otterstatter et al., 2005; Fürst et al., 2014). The prevalence of *N. bombi* in declining bumble bee species increased dramatically between 1995 and 2010, coinciding with the importation of commercial bumble bees from Europe. More recently, *N. ceranae*, a pathogen of honey bees (*Apis mellifera*), may be emerging into bumble bee populations from honey bees (reviewed in Brown, 2017). In honey bees, *N. ceranae* outcompetes the honey bee’sunique species of *Nosema*, *N. apis* (A. Bourgeois et al., 2010; M. Natsopoulou et al., 2014).

While both *N. bombi* and *N. ceranae* infect bumble bees, no studies have yet examined how these pathogens interact within the bumble bee host and whether coinfection of both species denotes higher mortality. In addition to *Nosema*, RNA viruses, once considered specific to honey bees, have been detected in bumble bees and evidence is accumulating that these viruses are spilling over from managed honey bees into wild bees (Fürst et al., 2014; Alger & Burnham, unpub. data). Symptoms of RNA viruses include behavioral abnormalities, inefficient foraging behavior, deformities, abnormal queen cells and death (Chen, 2007; Schroeder and Martin, 2012; Graystock et al., 2015).

In honey bees, coinfection of multiple pathogens results in higher mortality and colony losses (Cox-Foster et al., 2007). However, similar studies in bumble bees are severely lacking. Although Nosema and RNA viruses have been detected in bumble bees, no studies have examined interactions between these pathogens within the bumble bee host. Furthermore, while many studies have examined how pathogens fluctuate through time in honey bees, very few studies have examined this in bumble bees (Rigaud et al., 2010). Filling these knowledge gaps is important as varying fluctuations in disease loads between pathogens might result in particular pathogens peaking in abundance simultaneously, increasing the probability of coinfection and synergistically exacerbating their effects (Burnham et al., unpub. data). As coinfections (multiple pathogens in one host) play an important role in honey bee losses (Cox-Foster et al., 2007), documenting these mechanisms in bumble bees is vitally important in understanding and mitigating population declines.

The bee-pathogen system affords epidemiologists with a model system capable of extrapolating model parameters to other complex dynamical disease systems. Bumble bees have been used as a model organism in behavioral ecology and data from bumble bees in the field have informed many of the models used in optimal forging theory. The hierarchical levels of interaction space in the bumble bee system mirror those of humans, making bumble bees an ideal model organism for parametrizing robust general models for disease transmission and dissemination. The individual bee is a stand in for an individual human, the colony as a city populated by individuals, and a field of colonies as a network of interconnected cities. Using this approach, human disease outbreaks as well as emerging infectious disease in other animal systems can be modeled by adjusting parameters accordingly.

Studying spatial dissemination, coinfection and resultant pathogen-pathogen interactions in this bumble bee system, replete with diverse pathogen types, spillover events and human-analogue transmission routes, affords the scientific community with an opportunity to better understand this complex dynamical network helping to push the fields of disease ecology and epidemiology forward. In order to address the above mentioned knowledge gaps, I aim to use a combination of empirical data and epidemiological models to examine **1)** how pathogens disseminate throughout the environment at the individual, colony and colony network levels, **2)** what common coinfections occur innature andwhat are the main drivers behind co-infection in the bumble bee **3)** and finally, testhow pathogens interact with each other and their host environment once coinfected.