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Five challenges in evolution and infectious diseases

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ABSTRACT

Evolution is a key aspect of the biology of many pathogens, driving processes ranging from immune escape to changes in virulence. Because evolution is inherently subject to feedbacks, and because pathogen evolution plays out at scales ranging from within-host to between-host and beyond, evolutionary questions provide special challenges to the modelling community. In this article, we provide an overview of five challenges in modelling the evolution of pathogens and their hosts, and point to areas for development, focussing in particular on the issue of linking theory and data.

Introduction

Evolution is the change in gene frequencies resulting from selection (where genes with greater reproductive contributions to future generations spread within populations), mutation, recombination or re-assortment (where genetic material is exchanged between chromosomes), or drift. Evolution plays an important role in the dynamics of many infectious diseases. Vaccine escape in influenza, drug-resistance in HIV, and virulence evolution in Marek's disease are all examples of evolutionary processes. Developing models that accurately describe pathogen evolution is inherently challenging because of the complexity of pathogen life cycles and the difficulty in characterizing the (dynamic) fitness landscapes driving pathogen evolution. Ultimately, the pathogen's genotype, together with the characteristics of the host, determines both how disease is caused and how much of the pathogen is emitted by the host. Once emitted, pathogens must infect new hosts. How much transmission is realized also depends on the physical environment, the host's behaviour and population structure, as well as the distribution of the disease in the population. To understand pathogen evolution we need to integrate from the genotype, and span these levels, encompassing stochastic processes such as transmission bottlenecks (see Gog et al., 2015). This requires the integration of knowledge from various fields: molecular biology, microbiology, medicine and epidemiology to name a few (Fig. 1).

Here, we outline five challenges of modelling evolution that reflect this interaction across scales. We start by detailing the most basic and general challenge of all, that of characterizing fitness. Next, we address challenges for modelling how pathogens shape each other's evolution (coinfection) and the related topic of how pathogens shape host immune diversity; and the classic evolutionary problem of what forces allow maintenance of pathogen diversity (coexistence). Finally, we discuss how modelling can help us understand how mechanisms of pathogen replication influence the generation of genetic variation, upon which selection acts.

1. Defining and measuring fitness for pathogens across scales

If we know how fitness changes with changes in the genes in the pathogen, and how it does so across scales (Fig. 1), we can make informed statements about selection and adaptation. Fitness is generally defined as the reproductive contribution of an individual to the next generation, in a particular environment. Pathogens will experience different such environments over the course of an infection: for instance, they will have to overcome the host's

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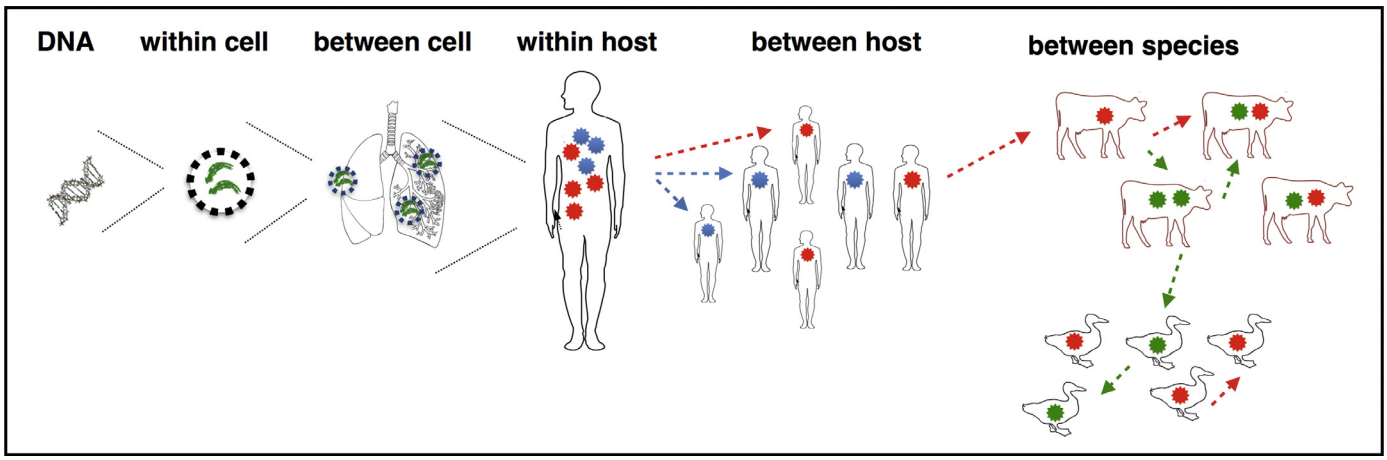

Fig. 1. The scales of infectious disease dynamics and evolution. Diverse research fields address overlapping levels of this hierarchy. Genetics, cell biology, microbiology occur at the smallest scales, but have projections to larger scales; e.g. genetics also contributes to interpreting population level outcomes. Pharmacology, immunology and physiology occur primarily at the whole organism level, but comprise processes at smaller scales and often have impacts at larger scales (e.g. herd immunity). Community ecology and epidemiology arguably are relevant at each scale, with community ecology relevant both for understanding multiple host species but also gut microbiota dynamics, and epidemiological principles describing dynamics in populations from cells to hosts.

defences, colonize the host, withstand attacks of the immune system, and accomplish transmission and infection. The components of fitness can vary over such a cycle (and indeed the cycle often involves numerous pathogen generations), and to calculate fitness, an appropriate average has to be taken over this path, integrating information across various scales.

Although defining fitness of pathogens is straightforward in principle, linking this definition to attainable data in order to quantify fitness is not. Researchers have typically broken the evolutionary cycle apart to focus on particular levels of selection – for example, distinguishing within-host fitness (describing the growth of the pathogen population within an infected individual) and between-host fitness (describing transmission of infection to new host individuals). This has the benefit of corresponding to clear biological differences, as well as quantities that can be measured (although the path to linking processes across scales to fitness is not obvious). However, even with the process broken down into more manageable parts, there are still considerable barriers to defining scale-specific fitness components (see Challenge 2 in Gog et al., 2015) for more complexities related to within-host fitness), and there is no general relationship between fitness at the within-host scale and the number of new hosts infected (Park et al., 2013).

The challenges inherent to even the (apparently contained) problem of measurement of the reproduction of individual pathogens within-host have led to the development of a range of in vitro systems designed to quantify variation in rates of pathogen replication in different contexts. Inevitably, these estimated pathogen replication rates reflect only one aspect of fitness at an in vivo scale. Key modelling challenges include providing further innovations in linking in vitro data-streams to in vivo measurements of aspects of fitness, such as viral titre kinetics or the outcome of competition assays (Huijben et al., 2013) (see also Challenge 7, Frost et al., 2015), and accounting for the fact that the genotype to phenotype to fitness map is likely to be context-dependent, and the within-host fitness landscape may change (see also Challenge 3, Gog et al. (2015); and Challenge 6, Frost et al. (2015), on the challenges of developing genotype to phenotype maps). In particular, the fitness of a genotype will often depend on the frequency of all other genotypes, as a result of immune system activity. Machine-learning and modelling approaches can be used to bridge the in vitro and in vivo levels (Kouyos et al., 2011), but given the nature of the underlying in vitro data such approaches currently neglect crucial within-host fitness determinants such as the immune system. This poses the challenge of finding novel ways to parameterize the activity of the host's immune system from data (e.g., Metcalf et al., 2011) and incorporate it into the models for pathogen fitness, and the associated (and shifting) fitness landscapes.

Beyond the individual host, other instances of population structure (e.g., age groups or host species) may influence pathogen evolution. If these host classes additionally compete or otherwise interact, this will affect the pathogen's evolution, and any evolutionary outcomes are likely to depend on the details of this interaction. The next generation matrix approach is useful for these types of systems (Diekmann et al., 2010), as are approaches that renormalize the system to describe group-level reproduction (Ball et al., 1997), but few general mathematical principles are known, and furthermore, parameterizing such models given available data remains challenging (Funk et al., 2013) (see also Buhnerkempe et al., 2015).

Bringing together all these various threads to estimate an all-encompassing fitness value for any particular pathogen genotype is a major challenge, and would be even if all the data were available. Even though conceptual and mathematical frameworks for dealing with such multi-scale processes have been developed (Park et al., 2013; Lion et al., 2011), such calculations can be extremely cumbersome, and their interpretation complex, particularly when evolution operates at different scales, as is the case for pathogens.

2. Developing models to capture the impact of co-infection on the evolutionary process

For many pathogens, infection by multiple strains or other pathogens may have little or no epidemiological impact – the key distinction is simply whether a host is infected, or not (as for measles, for instance). However, there are pathogens for which coinfection alters pathogen dynamics, and this can have two major impacts on evolutionary processes. First, coinfection can lead to genetic exchange between co-infecting pathogens (especially for viruses and bacteria) that may be essential to immune escape, or host jumps. Such exchanges may occur both among pathogens of the same species (e.g. homologous recombination) or among pathogens of different species (transformation, transduction, conjugation) (see Challenge 5, Frost et al. (2015) for more details). Second, coinfection may be associated with within-host competition (e.g., mouse malaria parasites may compete for red blood