Mathematical Biosciences 270 (2015) 143–155

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Editorial

From within host dynamics to the epidemiology of infectious disease: Scientific overview and challenges

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ARTICLE INFO

Article history:
Available online 16 October 2015

Keywords:
Epidemiology
Host–parasite interactions
Infectious diseases
Malaria
Modeling
Systems biology

ABSTRACT

Since their earliest days, humans have been struggling with infectious diseases. Caused by viruses, bacteria, protozoa, or even higher organisms like worms, these diseases depend critically on numerous intricate interactions between parasites and hosts, and while we have learned much about these interactions, many details are still obscure. It is evident that the combined host–parasite dynamics constitutes a complex system that involves components and processes at multiple scales of time, space, and biological organization. At one end of this hierarchy we know of individual molecules that play crucial roles for the survival of a parasite or for the response and survival of its host. At the other end, one realizes that the spread of infectious diseases by far exceeds specific locales and, due to today's easy travel of hosts carrying a multitude of organisms, can quickly reach global proportions.

The community of mathematical modelers has been addressing specific aspects of infectious diseases for a long time. Most of these efforts have focused on one or two select scales of a multi-level disease and used quite different computational approaches. This restriction to a molecular, physiological, or epidemiological level was prudent, as it has produced solid pillars of a foundation from which it might eventually be possible to launch comprehensive, multi-scale modeling efforts that make full use of the recent advances in biology and, in particular, the various high-throughput methodologies accompanying the emerging –omics revolution. This special issue contains contributions from biologists and modelers, most of whom presented and discussed their work at the workshop *From within Host Dynamics to the Epidemiology of Infectious Disease*, which was held at the Mathematical Biosciences Institute at Ohio State University in April 2014. These contributions highlight some of the forays into a deeper understanding of the dynamics between parasites and their hosts, and the consequences of this dynamics for the spread and treatment of infectious diseases.

1. Introduction

The need to cope with infectious diseases has always been a basic feature of the human condition, and in spite of the enormous advancements in modern medicine and hygiene, such diseases continue to be a scourge without equal. According to best estimates, malaria claimed about 600,000 deaths in 2013, among 200 million or more infected individuals in about 100 countries [1,2]. Approximately 35 million individuals currently live with HIV/AIDS [3], about 9 million with tuberculosis [4], and 3–5 million with severe cases of influenza [5]. Almost 20 million Americans acquire sexually transmitted diseases each year, and infectious diseases are the leading cause of death among adults under the age of 60 [6]. In addition to the enormous pain and suffering caused by these diseases, the time spent for patient care and the economic costs due to lost work are enormous. In the United States alone, the costs of infectious diseases are about $120 billion per year, and antibiotic resistance in pathogenic bacteria incurs estimated costs of about $5 billion each year [7]. A pandemic flu outbreak in the U.S. is projected to have an economic impact of hundreds of billion dollars, even without accounting for disruptions to society and commerce [8].

These are staggering numbers that beg the question of how science may help alleviate the causes, symptoms, and consequences of infectious diseases. Of course, this question is neither new to biology and medicine, nor is it to mathematical modeling. However, it deserves to be given new attention, as the –omics revolution and the emerging field of systems biology are beginning to complement the

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http://dx.doi.org/10.1016/j.mbs.2015.10.002
0025-5564/

traditional repertoire of biomedical methods and technologies with genuinely new tools and techniques that carry the potential of great progress. As with all innovations, these new tools have been applied at first to low-hanging fruit, but both fields, experimental –omics and computational systems biology, have matured to a point where one might legitimately ask whether their capabilities might be ready for a new, concerted attack on infectious diseases. This special issue, like the workshop where many of the materials described here were discussed [9], attempts to highlight some of the promising advances that are presently emerging toward this goal with respect to mathematical and computational methods. A particular case, which is in many ways representative and is addressed in several of the articles, as well as in this introduction, is malaria. Nevertheless, the same or similar scientific problems arise in many of the other infectious diseases, *mutatis mutandis*.

As recently as a few decades ago, mathematical modelers were frequently told that biology and medicine were too complicated for modeling. After all, diseases are complex, involving thousands of molecules and complicated interactions between pathogens, hosts, and, indeed, societies and their environments, whereas models at the time usually consisted of a handful of variables. Also, it was claimed that there was no way that a computer could ever mimic, let alone surpass, the mind of an experienced physician. At the time, the critique was justified to some degree, although it ignored, for instance, the great progress in our understanding of the spread of epidemics and of the drivers that allow a disease either to flourish or to perish. These models, often abstracted to the bare bones of disease processes and devoid of all possibly distracting details, established the fundamental structure of infectious diseases, their progression, timing, and ultimate outcome (for recent reviews, see, *e.g.*, [10,11]). Times have changed dramatically since the earlier epidemiological models, as computers now beat Grand Masters in chess, and biomedical information is increasing so rapidly that no physician can keep up even with a specialty subfield of medicine. As a case in point, a PubMed search for "immunology" reveals that about 100,000 papers related to the subject were published in 2013 and 2014, a number that corresponds to one new paper about every 10 min, day in, day out, without ceasing.

Research in recent years has brought forth plentiful new information that was obtained with methods of the traditional branches of biology and medicine, entirely novel experimental options afforded by the field of –omics, and incomparably greater computer and modeling power than just a few years ago. As a consequence, new types of questions and strategies pertaining to infectious diseases have come within the reach of computational modeling. Some of these strategies attempt to improve our generic understanding of diseases, while others address specific approaches toward specific diseases, as well as crisply targeted means of intervention at the molecular, physiological, societal, and global disease levels.

As specific case studies must involve the key particularities of the investigated disease, as well as crucial details regarding their pathogens and hosts, some of the new models have a drastically different appearance than the abstracted base models that preceded them in infectious disease research. New disease models may consist of hundreds of variables and parameters, which mandates a shift of their analytical focus from rigorous algebra and calculus to large-scale simulations of possibly important scenarios, exploratory Monte-Carlo simulations and, as some traditional biologists derogatorily used to say, "fishing expeditions" that have the goal of "seeing what's out there" and generating novel hypotheses based on it.

Thus, the field of computational disease research is in the midst of an exciting transition that permits, and indeed requires, both, pure mathematical modeling that targets the fundamental structures governing disease processes, as well as larger-scale computational approaches that pinpoint weaknesses in a pathogen's mode of attack, which might be exploited for manipulation, treatment, and possibly eradication of the disease. Adding to the excitement of the new opportunities is not only the fact that drastically new and much refined biological experiments are becoming possible, which were unthinkable just a decade ago, but also that biologists are increasingly eager to work with modelers toward a common goal. This eagerness is a tremendous asset to the field of computational systems biology, and its importance for the modeler arguably exceeds that of some of the new biological technologies, because the close interaction with subject area biologists is invaluable for the computational scientist when designing effective models. However, with the willingness to collaborate comes the challenge of truly effective communication between separate fields with different terminologies and expectations. This challenge will be revisited toward the end of this article.

As a paradigm for the challenges facing infectious disease modelers, the next section summarizes key aspects of malaria. Although much simplified, this summary will indicate how truly complex, multi-scaled, and multifaceted infectious diseases are.

2. Malaria as the paradigm infectious disease

Malaria is a persistent and recurring infectious disease that is prevalent in close to 100 countries in Africa, Southeast Asia, and the Americas. The disease directly threatens about half of the world's population. All estimates regarding malaria naturally come with a large margin of error, and the 2014 World Malaria Report gives a range of 124–283 million infected individuals in 2013, most of whom were young children, and about 600,000 deaths. People of all ages lacking any or sufficient immunity are at high risk, and pregnant women comprise an especially vulnerable group that suffers severe consequences (reviewed in [2,12]).

The disease is caused by five species of the apicomplexan parasitic protists in the genus *Plasmodium: P. falciparum, P. vivax, P. malariae, P. ovale*, and *P. knowlesi.* The two dominant parasite species affecting humans are *P. falciparum*, which is present worldwide, although most prevalent in Sub-Saharan Africa, and *P. vivax*, which is encountered primarily in Asia and South America, although it is a severe problem in at least 50 countries [13,14]. In addition, *Plasmodium knowlesi* has gained increasing attention over the last 10 years as a zoonotic parasite that naturally infects macaques in the forests of South East Asia but is making its way into human habitats, with thousands of cases of clinical illness on record and at least 16 deaths reported to date [15–17]. Modelling the transmission of each of these species, and accounting for frequently occurring ecological and epidemiological changes, is a major task that has been aided in recent years by novel strategies and tools using geographic information systems (GIS) and sophisticated spatial decision support systems (SDSS) [18].

The challenges in understanding the disease begin with the parasite's life cycle, which involves two hosts, namely female mosquitoes of the genus *Anopheles* and humans or non-human primates (NHPs) [19,20], and a multitude of evolutionarily honed host–parasite interactions. Not all, but several other mammals, birds and reptiles can also be infected with *Plasmodium* parasites, but these species of *Plasmodium* are not infectious to humans [21–23].

Various intervention strategies, including the elimination of mosquito breeding sites, insecticide spraying, promotion of the use of protective insecticide-treated bed-nets, and improved treatments, have led to substantial reductions in the number of clinical malaria cases over the past 5–10 years [1,2,12,24]. However, effective coverage with such interventions is still limited on a global scale, has many logistical challenges, and is not necessarily sustainable. Pharmaceutical treatments are confronted with the parasite's ability to become resistant to their modes of action; in essence, by evolving to survive in the presence of these drugs. As a result, drug resistance remains a looming global concern that prohibits the ensured effective treatment of parasitized individuals. Indeed, this issue must be continually addressed in the context of today's global malaria elimination