Controlling the evolution of resistance

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ABSTRACT

Evolution has long been understood as the driving force for many problems of medical interest. The evolution of drug resistance in HIV and bacterial infections is recognized as one of the most significant emerging problems in medicine. In cancer therapy, the evolution of resistance to chemotherapeutic agents is often the differentiating factor between effective therapy and disease progression or death. Interventions to manage the evolution of resistance have, up to this point, been based on steady-state analysis of mutation and selection models. In this paper, we review the mathematical methods applied to studying evolution of resistance in disease. We present a broad review of several classical applications of mathematical modeling of evolution, and review in depth two recent problems which demonstrate the potential for interventions which exploit the dynamic behavior of resistance evolution models. The first problem addresses the problem of sequential treatment failures in HIV; we present a review of our recent publications addressing this problem. The second problem addresses a novel approach to gene therapy for pancreatic cancer treatment, where selection is used to encourage optimal spread of susceptibility genes through a target tumor, which is then eradicated during a second treatment phase. We review the recent *in vitro* laboratory work on this topic, present a new mathematical model to describe the treatment process, and show why model-based approaches will be necessary to successfully implement this novel and promising approach.

1. Introduction

The evolution of resistance has long been understood as the root cause of many problems in medicine. High mutation rates, short generation times and large populations make microorganism or viral infections situations in which dramatic evolutionary behavior can be observed in real time [1]. Likewise, in cancer therapy, high levels of genetic instability and high rates of cell turnover insure that resistance will quickly develop to any chemotherapeutic agent [37].

The extent of this problem has lead to significant work in modeling evolutionary dynamics, in order to design treatments that mitigate this risk. Accurate estimates of mutation and turnover rates, together with characterization of resistance mutations, are used to choose the formulation, dosing, and duration of treatment for HIV infection, bacterial infection, and cancer chemotherapy. An excellent primer on the mathematics of various types of evolution-

ary models can be found in [51]; this book also contains an excellent bibliography on classical applications of evolutionary models.

Evolutionary modeling has also been used to create conditions in which evolution is encouraged. Viral therapies have emerged which target tumor cells [35]. The potency of these treatments is often enhanced by creating an artificial environment in which increased potency results in increased fitness, after which the virus is allowed to evolve freely, resulting in a more potent therapy [33].

These applications of evolutionary modeling are critical to successful treatment of disease. However, these traditional applications of modeling can all be classified as "steady-state" applications; they manipulate conditions such that the likelihood of a desired treatment outcome is maximized, but the treatment options considered are static only. In recent years, a number of new applications of evolutionary modeling, in which dynamic treatment options are considered, have begun to emerge. These treatment options excite the transient dynamics of the mutation–selection equations, resulting in complicated dynamics. The complicated and sometimes counterintuitive treatment schedules which arise from this are excellent applications for modern control methods.

In the broader field of biomedicine, Dr. McAvoy and colleagues published an excellent snapshot review of various ways in which process control concepts are being applied in medicine [6]. In the spirit of that paper, we seek to do the same for emerging appli-

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