Dynamics of Drug Resistance: Optimal Control of an Infectious Disease

Keywords: optimal control; antimicrobial resistance; health care management; infectious disease models; dynamic health policy.

Extended Abstract

Antimicrobial resistance—bacteria, viruses, fungi, and parasites that are no longer susceptible to some or all available treatments—is an urgent public health concern (Hayden 2006; Centers for Disease Control and Prevention 2013; Laxminarayan et al. 2013; Spellberg et al. 2013; Laxminarayan 2014; World Health Organization 2014). Infections that were once easily cured are becoming more difficult to treat, requiring more intensive care and more expensive therapies (Williams and Heymann 1998; Arias and Murray 2009). Reports of infections with pathogens that are resistant to all but a few remaining drugs are increasing in frequency (Centers for Disease Control and Prevention 2013; World Health Organization 2014). Though inappropriate use of treatment is often cited as driving antimicrobial resistance, even the appropriate use of treatment contributes to resistance (Spellberg et al. 2013). Therefore, treatment policies must consider not only the benefit of treating current patients, but also the impact of increased resistance on the treatment benefits for future patients. Current studies primarily focus on evaluating and comparing various treatment policies using detailed disease-specific models and numerical methods (see Lipsitch et al. 2007; Brockmann et al. 2008; Eichner et al. 2009; Xiao et al. 2016) which limits the generalizability of their conclusions. Analytical results are notably lacking, in part because incorporating resistance increases the dimensionality of the problem’s state space, contributing to analytical intractability.

In this paper, we seek to establish general, analytical insights into whether or not, or specifically under what conditions, the last available drug for a given infectious disease should be reserved for future use. We study an established family of susceptible–infected–susceptible (SIS) infectious disease models expanded to include drug resistance (see Spicknall et al. 2013). The dynamics of SIS models generally represent diseases such as tuberculosis, *Helicobacter pylori*, and sexually transmitted diseases such as gonorrhea, chlamydia, and syphilis. We examine the problem of minimizing the cost of an infectious disease when only one drug remains. The problem is formulated as an optimal control problem with two continuous state variables: disease prevalence and drug “quality” (the fraction of infections that are drug-susceptible). Treatment with the drug expedites recovery (if the infecting strain is not
resistant to the drug), but recovered individuals are subject to reinfection. Use of the drug reduces the prevalence of the drug-susceptible strain and allows the drug-resistant strain to become the dominant type. These dynamics incorporate the spread of drug resistance through natural selection and capture the long-term trade-off between drug consumption and conservation. We analytically identify the optimal treatment policy and properties of the optimal value function providing generalizable insights for this class of models.

Addressing the key policy question, we prove that when the disease transmission rate is constant, the optimal prescription policy is of bang-bang type with a single switching time. In plain language, this means that it is optimal to use the drug for everyone, regardless of disease prevalence, until the level of resistance is so high that it is no longer economical to treat anyone. However, it is not uncommon for the disease transmission rate to be a (decreasing) function of prevalence as higher prevalence and awareness of the disease may lead to social distancing, increased adoption of preventive health or hygiene behaviors, or higher-intensity cleaning procedures at health care facilities (Nigmatulina and Larson 2009; Aleman et al. 2009; Gilchrist et al. 2015; Ambrosch and Rockmann 2016; Manfredi and D’Onofrio 2013). If the disease transmission rate is not constant, we find that it is optimal to reserve the drug for relatively larger outbreaks and in some cases to use the drug to treat some, but not all, infected individuals (the optimal control may include a singular arc). These findings have policy implications for antimicrobial stewardship and the reservation of last-line drugs as a national and international health priority (World Health Organization 2017b). In addition, these findings inform policy modelers that if the population response to the disease affects the disease transmission rate, it is critically important to incorporate a non-constant disease transmission rate into their models as it can structurally change the optimal policy.

In addition to analytically identifying the optimal treatment policy, we provide a semi-closed form expression for the social planner’s optimal value function characterizing sets of conditions under which SIS infectious disease models (or their variants) are not amenable to numerical analysis. Specifically, we show that the optimal value function is not $C^1$ (continuously differentiable) and, depending on the discount rate, may not be Lipschitz continuous, indicating that numerical approaches to this family of dynamic infectious disease models may not be computationally stable. This is an important warning for analysts seeking to use detailed disease-specific simulation models to evaluate treatment policies and guide real-world policy. Computational error caused by the numerical instability of the model in certain regions propagates to the whole state space and can cause a particular type of policy to be identified as optimal when it is not. Thus, Lipschitz continuity of control problems based on SIS dynamics with drug-resistance cannot be assumed and should be verified first.
From a technical perspective, this paper makes significant contributions to the optimal control literature. Control problems with more than one continuous state variable are rarely analytically solvable. The arguments presented in our proofs can be generalized to other deterministic or stochastic control problems (in particular those with piecewise deterministic dynamics, see Davis 1984 for further detail). Specifically, we prove the optimality of our policy by verifying that its value function satisfies the Hamilton-Jacobi-Bellman (HJB) equation. This task must be carried out in both the action and inaction regions implied by the candidate value function. Although the verification step is often straightforward in the inaction region, verifying that the HJB equation holds in the action region is often challenging. Verification in the action region requires ruling out the possible existence of an inaction region within the candidate action region. In our case, this translates to eliminating the possibility of a second switching time or that the optimal policy includes a singular arc. The proof argument of our main result streamlines this task by proving that the HJB equation holds inside the action region if it holds on the boundary of the action region. Verifying the HJB equation on this boundary is often much easier than conducting a verification for all points in the interior of the action region. Our proof argument is by contradiction and its elements can be readily adapted to other control problems.

Finally, we apply our framework to extensively drug resistant gonorrhea to gain disease-specific policy insights. Gonorrhea is a non-fatal sexually transmitted disease affecting nearly 1 million Americans each year (Centers for Disease Control and Prevention 2017a). Though gonococcal infections are rarely fatal, patients who do not receive treatment or in whom treatment is delayed may experience costly and life-altering complications including pelvic inflammatory disease (PID), infertility, ectopic pregnancy, epididymitis, arthritis, and cellulitis (Centers for Disease Control and Prevention 2017a). Gonorrhea infections can be treated with antibiotics; however, gonorrhea has progressively developed resistance to the antibiotics used to treat it (reviewed in Unemo and Shafer 2014). Due to high levels of resistance across multiple classes of antibiotics, current treatment guidelines recommend a combination of two antibiotics from different classes: ceftriaxone (an injected third-generation cephalosporin) with azithromycin (a macrolide) (Centers for Disease Control and Prevention 2012). However, strains of gonorrhea exhibiting high-level clinical resistance to all third-generation cephalosporins combined with resistance to nearly all other available antibiotics have been reported in several countries and the reality of untreatable gonorrhea is on the near-term horizon (Bolan et al. 2012; Unemo and Nicholas 2012; Unemo and Shafer 2014; Papp et al. 2017; Lefabvre et al. 2018). We apply our framework to identify the threshold level of resistance at which it is no longer economical to treat anyone with a gonorrhea infection and the expected time to reach this threshold for the US general population.