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Characterizing monotherapy and combination therapy of influenza

Two classes of antivirals are used to treat influenza infections: adamantanes, which prevent the virus from releasing its genetic material into the cell nucleus; and neuraminidase inhibitors (NAIs), which prevent newly formed virions from detaching from infected cells. Unfortunately, viral strains can become resistant to an antiviral through a single amino acid mutation, and there has been a recent rapid rise in the number of circulating viral strains that are resistant to at least one class of antivirals. In an effort to combat the emergence of resistant strains, researchers have begun to investigate combination therapy using two or sometimes three different antivirals. To determine the optimal treatment options, it is important to properly characterize the efficacy of both monotherapy and combination therapy.

Monotherapy is characterized by determining the effect of a drug as a function of the dose. This function is characterized by two parameters: the IC_{50}, the drug concentration needed to achieve half the maximum effect; and ε_{max}, the maximum possible effect of the drug. IC_{50} is often measured experimentally and is used to characterize the susceptibility of a viral strain to a particular antiviral. ε_{max}, however, is not typically measured. We use mathematical models of influenza infections to determine both the IC_{50} and ε_{max} of oseltamivir, the most commonly used NAI, from experimental infections. We then use the models to investigate the role of both IC_{50} and ε_{max} in characterizing the efficacy of NAI treatment and show that ε_{max} is just as important as IC_{50} in characterizing the efficacy of the drug.

We then combine the results of our analysis of oseltamivir with analysis results of a similar experiment using amantadine to evaluate combination therapy. Combination therapy is characterized by determining whether certain dose combinations of two drugs are synergistic, when the combined effect of the drugs is greater than the sum of the individual effects, or antagonistic, when the combined effect of the drugs is less than the sum of the individual effects. Our models predict that oseltamivir and amantadine will combine synergistically for some dose combinations, but that the location of the synergistic region depends on the measurement time. Additionally, we find that the synergistic region does not necessarily occur for doses that suppress the infection, calling into question the relevance of synergy.

Our results suggest that current methods of characterizing the efficacy of drug treatment of influenza are inadequate. In the case of monotherapy, ε_{max} should routinely be measured in addition to IC_{50} in order to completely characterize a viral strain's susceptibility to a drug. In the case of combination therapy, we find that synergy is an inadequate measure to characterize the efficacy of the treatment because it is dependent on measurement time and because it does not measure the actual efficacy of the treatment.