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Perspective

Time Dependent Drug Concentrations and Development of Multiple Medication Resistance during Combination Therapy

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DISCRIPTION

Research into various treatment plans intended to stop or delay the establishment of resistance have been prompted by the growth in drug resistance. Because of its effectiveness in cancer treatments, as well as bacterial, fungal, and viral infections, combination treatments have received particular attention. HIV, malaria, and tuberculosis have all been successfully treated using combination medications. Combination medicines capacity to fight antibiotic resistance is predicated on the notion that the simultaneous development of resistance to multiple antibiotics is incredibly exceptional. This happens at a pace corresponding to the product of the mutation rates for drug resistance to each drug for separate resistance mutations.

The capacity to anticipate the development of single or double resistance from quantitative or numerical modeling can assist in the creation of ways to lessen resistance. Since mutations are random occurrences, one of the key objectives is to calculate or estimate the probability that resistant cells are present in the population at a specific point after the medication treatment has begun. Estimated the probability of extinction of a branching process with multiple types of mutations, for populations consisting entirely of sensitive cells at the start of the treatment. This method enables them to assess the probability of a successful therapy, or a therapy that kills both sensitive and mutant cancer strains at very long intervals after the treatment began.

When numerous mutations occur in succession, exponential growth may not be appropriate even though it can be a decent approximation for studying the genesis of single mutations. This is due to the possibility of subsequent mutations occurring during advanced growth phases. At that stage interactions between cells may have become relevant, in particular when the population approaches its carrying capacity. In order to model such such instances, one need to go beyond simple unconstrained reproduction to model how the strains acquire resistance, we consider a multi-strain continuous-time birth–death process with mutations. The birth and death rates can vary over time, making the dynamics a so-called 'non homogeneous' process

Three scenarios will be investigated at the first is exponential for growth, which is used to represent, for instance, bacterial populations that have infinite resources and can grow endlessly. In the second scenario, there is no competition between individuals of various strains, but there is logistic growth for each strain. This covers circumstances in where resources are scarce yet each strain makes use of a different resource (as can happen if a strain develops a resistance mutation that enables it to inhabit a new ecological or spatial niche. The analysis in the previous section was limited to scenarios with constant model parameters throughout time. Most frequently, medication schedules that change over time are used to provide medications, leading to time-dependent growth and death rates. The majority of medication therapies use periodic dosing regimens, which results in periodic time-dependences of drug concentrations.

Researchers take into account two different types of time-dependence for the drug concentrations when modeling the pharmacokinetics of various repeat drug administration methods. In the first case, medication concentrations are constant throughout time and have a sinusoidal profile. This simulates the pharmacokinetics, for instance, of repeated antibiotic delivery by an extravascular route (e.g. oral administration). The drug concentration profiles in the second scenario are made up of a periodic series of pulses that, for example, represent intermittent intravenous dosage. When the concentration of the pertinent medications is high enough, the growth rates of the drug-affected strains become negative. This effectively lowers the number of cells in the affected strains.

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