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Tempo and mode of inhibitor-mutagen therapies: a multidisciplinary approach

The continuous emergence of drug-resistant viruses is a major obstacle for the successful treatment of viral infections, and is steadily spurring the design of new therapeutic strategies [1]. Correspondingly, there is a pressing need to understand the dynamical effect of antiviral therapies on complex, diverse and fast mutating viral populations. Indeed, the evolutionary dynamics of viral populations is at the basis of some recently suggested therapeutic strategies, such as lethal mutagenesis and lethal defection, that use mutagenic agents to induce viral extinction [2,3]. Despite both procedures have proved to be effective *in vitro*, the use of high doses of mutagen *in vivo* could involve severe side effects. On the other hand, low doses allow the virus to get adapted through the rapid appearance of resistance mutants. Hence, research on combination therapies arises as a step towards reducing doses while keeping low the probability that the virus becomes resistant to the drug cocktail.

Here we discuss combination therapies involving two dissimilar drugs: the mutagen ribavirin, and an inhibitor of the viral replication, guanidine. These drugs were used *in vitro* to analyse the performance of their sequential versus simultaneous administration in the control of infections by foot-and-mouth disease virus [4]. Contrary to the well known case when two inhibitors are used, it was found that sequential administration of the inhibitor followed by the mutagen is more effective than simultaneous treatment. In order to explore the reasons for this behavior we designed a simple computational model representing the dynamical response of the viral population to the two drugs. It shows that the two-edged role of the mutagen, reducing the viable offspring of the virus but also favouring the appearance of resistant mutants, causes an interaction between inhibitor and mutagen that determines the efficience of this therapy. In agreement with the theoretical predictions, laboratory experiments confirm in particular cases that the suitability of simultaneous or sequential administration depends on the administered dose. The model predicts the dynamic response of the viral population for any dose combination and, in particular, determines the amount of inhibitor and mutagen required to minimise the probability of appearance of resistant mutants. Knowledge of the

relevant model parameters is obtainable by means of few, simple experiments, such that our predictions could be extended to other viral systems.

References

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