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ROTATING ANTIBIOTICS DOES NOT MINIMIZE SELECTION FOR RESISTANCE

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In their recent paper in this journal Beardmore and Peña-Miller [1] use optimal control theory to determine strategies that maximally delay the emergence of resistance to antibiotic therapy. Specifically they determine optimal treatment regimens for two different models from the literature [2, 3] and conclude that appropriate schemes of rotating antibiotic usage select optimally against antibiotic resistance. Using the same models and parameters we show that this conclusion is not warranted, and that instead strategies based on optimal mixing, i.e. optimally dividing the drugs between appropriately sized patient groups, are always at least as good as optimal cycling, but in most cases considerably better.

In their paper Beardmore and Peña-Miller refer to two optimization problems to minimize resistance in a patient population treated with two antibiotics A and B. *Problem 1* consists of finding the treatment strategy that minimizes the integral over the total number of infected individuals based on a population dynamical model originally formulated in ref [2] and given by eq. 1 in ref [1]. *Problem 2* consists of finding the treatment strategy that minimizes the average prevalence of resistance in a patient population based on a different population dynamical model originally formulated in ref [3] and given by eq. 2 in ref [1].

Instead of using a control theoretic approach, we repeat part of Beardmore and Peña-Miller's analysis by means of straightforward computer simulations. We focus here only on strategies that can realistically be implemented in clinical settings and disregard the more complex non-periodic bang-bang solutions that can only be derived using a control-theoretic approach and rely on the availability of a model that perfectly describes the patient population dynamics. Moreover, we show here only results regarding *Problem 2*, although we have performed the equivalent simulations also for *Problem 1*.

To determine the optimal mixing strategy for *Problem 2* we scanned through all values of partitioning drug use in the patient population (i.e. $0.1 \leq \tau_1 \leq 0.4$ with step size 0.005 and $\tau_2 = 0.5 - \tau_1$) and then determined the optimal mixing strategy as that partitioning which minimizes the average prevalence of resistance over the time window over which the simulations are run. To find the optimal periodic cycling regime we determined for each period $T = t_A + t_B$ the optimal

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time partitioning of drug usage for by scanning through $0 \leq t_A \leq T$ with steps of $0.01 \times T$ for $T = 1, 2, 5, 10, 25, 50$ days. Because the optimal rotation strategy may not be periodic, we also implemented an adaptive treatment strategy as suggested by Beardmore and Peña-Miller (i.e. Rules 1 and 2 in ref. [1]). This treatment strategy relies on measurements of the prevalence of resistance in the population at predefined intervals t_{eval}. Treatment is switched to the other drug whenever resistance against the current drug exceeds that of the other drug. This strategy was proposed by Beardmore and Peña-Miller as a practically feasible treatment strategy that is a good approximation to the impracticable optimal non-periodic rotation regimes found by optimal control theory.

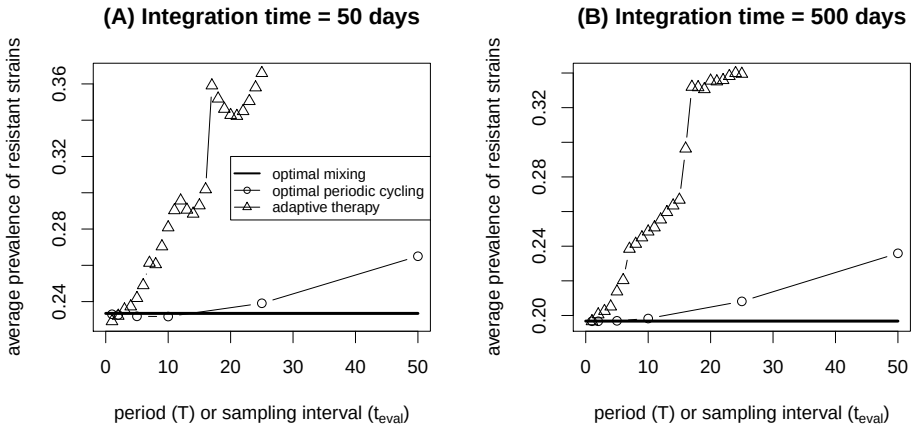

FIGURE 1. Optimal mixing (thick solid line) generally performs at least as well as but often much better than optimal periodic cycling (circles) or adaptive treatment (triangles). The simulations shown here are based on *Problem 2* (for comparison see figs. 2 and 6 in ref. [1]). The optimal treatment strategy is that which minimizes the average prevalence of resistance over the entire time over which the simulations are run, here referred to as the integration time. In panel A the integration time is 50 days as in ref. [1]. In panel B the integration time is 500 days. Comparison of optimal periodic cycling with optimal mixing shows that the mixing strategy generally outperforms the cycling strategy. Optimal periodic cycling only marginally outperforms optimal mixing for short cycling periods T and the short integration time of 50 days (panel A). This marginal benefit is likely attributable to transient dynamics resulting from the initial conditions as the benefit disappears if the problem is integrated over longer times (panel B). Similarly, adaptive therapy (see main text) only marginally outperforms mixing if the sampling interval t_{eval} is small and the integration time is short (compare panels A and B). For sampling intervals that could be used realistically in clinical settings, adaptive therapy performs considerably worse than optimal periodic cycling or mixing.

The results of our numerical optimization of *Problem 2* are shown in figure 1 and correspond to the results shown in the figures 2 and 6 of ref. [1]. We use the same set of (asymmetric) parameters and initial conditions as in ref. [1] (specified as $p^{(2)}$ and $s_0^{(2)}$ in ref. [1]). Fig. 1A corresponds to figure 2c in ref. [1] (but is there mistakenly referred to as problem 1). In panel A we integrated only over 50 time days, where as in panel B we integrated over 500 days to reduce the effects of transients that result from the particular choice of initial conditions. In all plots the black line shows the value of the time averaged optimization criterion for optimal mixing. The circles and triangles give the corresponding value for optimal periodic mixing and adaptive therapy, respectively.

We see that optimal mixing generally outperforms optimal periodic cycling. Only for small period lengths T and only for the short integration time of 50 days optimal periodic cycling marginally outperforms optimal mixing (see panel A, and fig 2c in ref. [1]). However, comparison with panel B shows that this marginal benefit of optimal periodic cycling disappears for the longer integration time of 500 days and is therefore likely attributable to transient dynamics resulting from the particular choice of initial conditions. Notably, in ref. [1] the initial condition for *Problem 2* was chosen such that the resistant variant with higher fitness cost was more abundant than that with lower fitness cost at the start of the simulation. Given the chosen fitness costs, it would have been more natural to assume that the variant with higher fitness cost would be less abundant at the start of the simulation and thus the chosen initial conditions presumably amplify the effects of any transient dynamics. Adaptive treatment strategies also marginally outperforms optimal mixing if resistance is measured at high frequency (i.e. $t_{eval} < 3$ days), but as for optimal periodic cycling this is only observed if the integration time is short (compare fig1A and 1B and see fig. 6 in ref. [1]).

We have also performed analogous simulations for *Problem 1* (data not shown). Here, we found that optimal mixing always outperforms optimal periodic cycling, even for the shorter integration time of 50 days. Transient effects may be weaker for this problem, because the initial conditions for *Problem 1* are chosen such that both resistant variants are absent at the start of the simulation.

Beardmore and Peña-Miller argue that for both *Problem 1* and *2* the optimal treatment strategy is one of non-periodic cycling, which can be determined by optimal control theory. Apart from the fact that optimal control theory cannot be implemented for any real problem of resistance management, because it relies on complete knowledge of the correct model underlying population dynamics and all its parameters, it is important to note that these optimal strategies are only marginally (i.e. $< 1\%$) better than optimal mixing (see figure 3 in ref. [1]). Moreover, it is conceivable that also this marginal improvement disappears, when integrating over longer time periods.

We do not contend the mathematical correctness of Beardmore and Peña-Miller's analysis, but we are concerned that the reader is led to draw the conclusion that optimal cycling regimes generally outperform optimal mixing regimes. Resistance in management in hospitals is a serious problem as antibiotic resistance is costing many patient lives. Therefore it is important to make clear that within the context of the models investigated here there is no evidence supporting the conclusion that any realistically implementable cycling strategy outperforms optimal mixing. The superiority of optimal cycling regimes in ref. [1] is limited to *Problem 2* and may have resulted from initial transient behavior that does not play a role when integrating

over longer and more realistic time spans. We emphasize, however, that our as well as Beardmore and Peña-Miller's results have been obtained only in the framework of the two simple models originally published in refs. [2, 3]. In particular, these models neglect any stochastic effects that likely arise in small patient populations as are characteristic for hospital wards. More complex and realistic models of the patient population dynamics may well lead to different conclusions. In our view, the final word on cycling versus mixing may well not have been spoken yet.

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