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EVOLUTION AND DRUG RESISTANCE: A COMPUTATIONAL STUDY

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I will describe the results of stochastic simulations of an idealized population of microorganisms subject to four types of mutations (deleterious, beneficial, resistance-activating and mutator-activating, in quantities M_d, M_b, M_r and M_m, respectively, at each birth) and to the eventual introduction of a drug that kills every nonresistant strain. The first two kinds of mutation are usually studied in population dynamics research and directly affect fitness of individuals. The mutator-activating mutations activate idealized mutator alleles that increase the genomic mutation rate U (on which depend all mutation rates) of their owners.

If $\mathcal{P}(\lambda)$ and $\mathcal{E}(\lambda)$ respectively denote the Poisson and exponential probability distributions of mean λ and an organism of fitness f originates an offspring of size N distributed according to $N \sim \mathcal{P}(f)$ in each replication round, where mutations occur with rates $M_k \sim \mathcal{P}(U_k)$, $U_k = p_k U$, $k = d, b, r, m$, and p_k are proportionality factors, then the effect of mutations on the fitness of an individual is described by

$$f = f_{\text{mother}} \cdot \left[\prod_{\alpha=1}^{M_d}(1 - s_d^{\alpha})\right] \cdot \left[\prod_{\beta=1}^{M_b}(1 + s_b^{\beta})\right] \cdot \left[\prod_{\gamma=1}^{M_r}(1 - s_r^{\gamma})\right], \tag{1}$$

where $s_k^{\text{greek}} \sim \mathcal{E}(\lambda_k)$, and their effect on the genomic mutation rate is

$$U = U_{\text{mother}} \cdot \left[\prod_{\delta=1}^{M_m}(1 + \mu^{\delta})\right] \tag{2}$$

where $\mu^{\delta} \sim \mathcal{E}(\lambda_{\mu})$.

There is also a carrying capacity to keep bounded the population size, since, depending on its fitness, each strain leaves a Poisson-distributed number of descendants to the next generation, what could lead to explosive growth.

This model was originally described in [1] and displays nontrivial dynamics. That authors described preliminary results that, under specific conditions, revealed mutator enrichment (i.e., an increase of relative frequency of mutator alleles) at the moment of drug introduction and suggested this could be related to efficient pathogen suppression, but promised further study to confirm this hypothesis and to systematically search for optimal control strategies. To the best of my knowledge, they never did such research and that is the aim of this work.

Some of my results seem to be at odds with that article. I kept detailed records of dynamical characteristics of the populations not described in the original work that help understanding the phenomenon of mutator enrichment and searching for optimal pathogen suppression strategies. Besides that, by exploiting the flexibility of the computational model, I also studied the effects of horizontal transmission (in contrast with the vertical one, defined by heredity) and of some alternative dynamics. Hopefully the computational model here described may also be extended to allow the study of multidrug resistance [2].

References

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