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Changing The Landscape - Can We Use Drugs To Steer Evolution Away From Resistant Phenotypes?

Multidrug treatments are becoming more important as resistance to antibiotics and cancer treatment increases. We explore the possibility of multidrug treatments in which drugs are administered sequentially. The aim is to use a first drug to drive the evolution of a pathogen to a certain point in the fitness landscape from which there is no mutational path to a genotype of peak fitness in the landscape of the second drug. In other words, we aim to exploit resistance to one drug to enhance the effectiveness of a second.

A number of earlier studies have shown that certain trajectories within a fitness landscape may be inaccessible. For example, a peak fitness may be inaccessible from a given genotype if that genotype is a local optimum. In randomly generated landscapes of N alleles with 2 states the expected number of local optima is 2^N / (N+1) and the average length of an evolutionary walk is log(N+1). This suggests evolution in these landscapes need not each a global optimum of fitness.

However it has been shown that an adaptation in a given environment which decreases fitness in a second may later be reversed in the second. This suggests that the fitness landscapes of drugs used in combination must correlate in a very specific way else the evolution in response to the first maybe be undone when the second rug is applied. Whilst previous research has focussed mainly on evolution in bacterial pathogens we believe the concepts are highly generalizable and applicable to cancer cells too. As such we consider fitness landscapes in an abstract setting.

We consider paths of mutation with respect to a pair of landscapes, calling a mutation path from one genotype to another reversible if it can be traversed by single-gene fitness-increasing mutations in one landscape and traversed in the reverse direction in the second landscape.

We experiment with fitness landscapes generated by the NK model and analyse the topology of such landscapes in pairs to count paths which are reversible. This gives a notion of correlation between landscapes: two landscapes are considered correlated if they have a low number of reversible paths between them. We show that a high correlation is essential to finding drugs suitable for sequential use. Further we consider the effect of the ruggedness of landscapes on correlation and find a high degree of ruggedness alone is not sufficient to generate highly correlated landscapes.