Population survival, environmental fluctuations, and phenotypic switching

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Phenotypic variation among clonal cells can increase population survival in changing environments. We explore survival as a function of phenotypic switching rates, as well as growth and death rates in a randomly changing environment. We define domains in the space defined by phenotypic switching rates where survival is guaranteed, uncertain or excluded. We observe non-trivial outcomes, such as fast-growing cells out-competing the more resistant phenotypes, making the population more susceptible to environmental changes.

***Keywords* — Phenotypic switching, environmental fluctuation, cell survival strategies, drug resistance.**

I. Introduction

INDIVIDUAL cells within clonal populations can show phenotypic variation due to internal stochastic processes [1-3]. Variation between individual cells can be beneficial as well as detrimental to the survival of a population exposed to stress [4].

Variation in the level of proteins relevant for growth or survival among individual cells in a population likely plays a role in drug resistance and disease. This is because cellular diversity assures the existence of a subpopulation that is most fit or survives best under selective growth conditions or evolutionary pressure.

Optimal phenotypic switching strategies for population fitness have been studied theoretically as well as experimentally [5-7]. These studies have measured population growth to determine fitness, and generally concluded that slow phenotype switching cells outperform fast phenotype switching cells when the environment is changing slowly and vice versa when the environment is changing quickly.

Here we focus on whole population survival rather than population growth with an emphasis on survival during drug treatment.

II. Methods and Results

We use a stochastic model where cells switch randomly between Low (L) to High (H) expression states of a gene required for survival in stress (such as drug treatment), while the environment switches between Normal (N) to Stressful (S) states. Cells reproduce by incorporating Metabolite molecules (M) and die at rates dependent on their gene expression and environmental states. Metabolite is added at a constant rate, and is removed by spontaneous degradation as well as by cell growth.

We developed an analytical approach to estimate cell survival using the traces and determinants of the growth matrices for cells. In the calculations, M was assumed to be at its maximum concentration when the number of cells was low, so that cell growth was also at its maximum. This assures that if the calculations predict no survival then all cells will die in the simulations as well.

The states of cell survival were classified as stable survival (where survival is guaranteed regardless of the environment), unstable survival (where cell survival depends on a delicate local balance between environmental switching and phenotypic switching), and stable death (where death is guaranteed regardless of switching).

Precisely predicting population survival becomes more difficult at parameter regimes where cell survival is unstable. While it can be inferred whether a population can survive for a given combination of environmental switching rates, the inverse problem is more difficult. The exact environmental switching rates necessary for survival depend on combinations of the growth rate of L cells in the N state, and the resistance of H cells to death while in the S state.

III. Conclusion

In conclusion, we have developed a model for studying the survival of stochastic phenotypic switchers in fluctuating environments as a function of switching rates, as well as growth and death rates. We have partitioned the parameter space according to population survival, and observed interesting outcomes. For example, one would expect growth rates to always promote population survival. However, we found regions where lower cell growth increased cell survivability.

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