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Escape times for branching processes with random mutational fitness effects

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Abstract

We consider a large declining population of cells under an external selection pressure, modeled as a subcritical branching process. This population has genetic variation introduced at a low rate which leads to the production of exponentially expanding mutant populations, enabling population escape from extinction. Here we consider two possible settings for the effects of the mutation: Case (I) a deterministic mutational fitness advance and Case (II) a random mutational fitness advance. We first establish a functional central limit theorem for the renormalized and sped up version of the mutant cell process. We establish that in Case (I) the limiting process is a trivial constant stochastic process, while in Case (II) the limit process is a continuous Gaussian process for which we identify the covariance kernel. Lastly we apply the functional central limit theorem and some other auxiliary results to establish a central limit theorem (in the large initial population limit) of the first time at which the mutant cell population dominates the population. We find that the limiting distribution is Gaussian in both Cases (I) and (II), but a logarithmic correction is needed in the scaling for Case (II). This problem is motivated by the question of optimal timing for switching therapies to effectively control drug resistance in biomedical applications.

Keywords: Branching processes; Weak convergence; Escape from extinction; Population dynamics

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1. Introduction

Genetic variation often drives the process of population escape from extinction. For example, populations of bacteria or cancer cells declining under drug treatment can produce resistant variants capable of thriving under treatment, resulting in population rebound. Although new therapies are constantly being developed to target these drug-resistant mutants, one major question in the biomedical community today is: when should these second-line drugs be administered? Motivated by this question, here we consider a subcritical population of drug-sensitive cells in which a low rate of random genetic variation drives the production of a (possibly heterogeneous) population of resistant mutants. We are interested in studying the temporal dynamics of escape from extinction via this mechanism, and in particular here we obtain refined estimates of the stochastic time at which the resistant population first becomes dominant in the population. Characterization of this 'crossover' time, its variability, and how it depends on fundamental parameters of the drug profile and cell type, is useful in determining the optimal time to switch therapies and target different disease subpopulations. More generally, this work contributes to a growing literature aimed at developing theoretical tools for the design of dynamic treatment strategies that optimally utilize multiple drugs to control heterogeneous, evolving disease cell populations [9,10,4].

Random mutational fitness landscapes. We will consider a general setting where genetic variation can result in deterministic or random changes to the fitness of resistant cells. Under this setting genetic variation may produce a spectrum of effects on cellular fitness, resulting in a potentially highly heterogeneous population of resistant escape mutants. This type of intrinsic stochasticity in drug resistant populations has recently been a subject of intense biological interest and experimental investigations. For example, in a recent study experimentalists observed variability in inter-mitotic times in lung cancer cells with the T790M point mutation, which confers resistance to anti-cancer drugs erlotinib and gefitinib [12]. Another investigation revealed that within a clonal population of mycobacteria, there is significant heterogeneity among cells due to asymmetric cell division which renders them differentially resistant to several clinically important classes of antibiotics [1]. In light of these experimental developments, in this work we study the stochastic time of interest under cases where genetic variation produces both deterministic and random fitness effects in resistant cells, drawn from a mutational fitness landscape.

We build upon several previous related works. In the current investigation, we are interested in studying changes in the composition of the population which take place on a logarithmic time scale. Thus we utilize a time scaling considered in the works of Jagers, Sagitov, and Klebaner [8,7], where the authors characterized process dynamics on the time scale of extinction of a subcritical branching process. In a previous work we established law of large numbers approximations of two escape times under this time scaling in the case of deterministic fitness effects [6]. In a joint work with Durrett, Mayberry and Michor [5], we also considered the impact of random mutational fitness effects on total population growth rate in expanding populations where multiple mutations are possible within the same cell. There it was shown that the addition of random fitness effects resulted in a polynomial time delay in the growth of the total population. Here we observe a consistent phenomenon, in that the addition of noise results in a decrease in the growth rate by a logarithmic term in the current time scale.

The main results in this paper are as follows. Theorem 1 establishes a law of large numbers approximation for the crossover time in the setting of random and deterministic fitness effects. Next, we prove a functional central limit theorem for the resistant cell population in Theorem 2.