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Mathematics of Rare Events in Evolution

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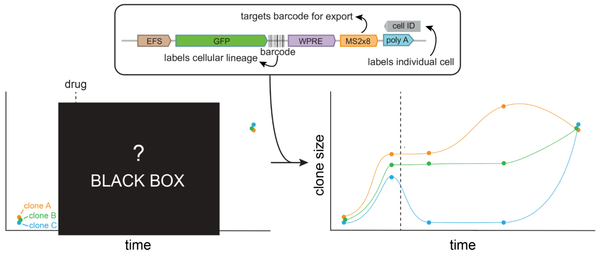
Biological systems can adapt through both genetic mutations and non-genetic mechanisms, presenting a complex challenge for understanding evolutionary processes. While Luria and Delbrück's groundbreaking experiment in the 1940s revealed that adaptation occurs through pre-existing mutations, the statistical framework has not been fully developed into quantitative tools that can reveal both genetic and non-genetic mechanisms of adaptation. We are developing novel mathematical and experimental approaches to address this fundamental challenge.

We are developing new experimental and mathematical frameworks for solving inverse problems involving heavy-tailed distributions, a key feature of evolutionary processes. **Our framework extends beyond classical statistical approaches that assume finite means and variances, enabling us to analyze rare events that occur in the tails of distributions—a critical aspect of evolutionary adaptation that has been difficult to quantify.** On the mathematical end, we exploited an important mathematical property of Luria-Delbruck distributions - Levy stability - to greatly advance a solution to the inverse problem with rare events. Recall that a distribution P(m) is Levy stable if the sum M = m1 + m2, where m1 and m2 are both sampled from P(m) has the same distribution as P(m) (up to changes in parameters). For evolutionary processes, we find that the Laplace transform of P(m), P(s), is given by: $ln\, \tilde{P}(s) \approx - \mu N(1 - 1/\sigma\, E_{1+1}/\sigma(s))$, where E is the special function known as the generalized exponential integral and μ,N are mutation rate and population size respectively. We showed that properties of E(s) imply Levy stability. This mathematical fact enables a powerful workflow for experiments because in reality, barcode abundances are rarely uniform and consequently, actual population size per barcode can vary over an order of magnitude. However, because of Levy stability, we can combine barcodes to normalize population sizes prior to selection. Consequently, we only need to solve the inverse problem for the canonical Luria Delbruck process with equal population sizes per barcode.

To complement our mathematical developments, we are adapting an innovative experimental system that captures the temporal dynamics of adaptation (**Figure**). By engineering living cells to export nanoparticles containing lineage DNA barcodes, we can now track cell lineages dynamically as they respond to environmental challenges. This breakthrough allows us to move beyond traditional endpoint measurements and observe the complete trajectory of adaptation. Our work so far has revealed a fundamental difference in how rare events impact adaptation depending on the fitness effects of mutations. When mutations have modest fitness effects ($\sigma < 1$), the distribution of outcomes becomes independent of population size, suggesting predictable adaptation. However, with strong fitness effects ($\sigma > 1$), rare events dominate the dynamics, making outcomes more history-dependent. This insight provides new mathematical tools for quantifying uncertainty in evolutionary predictions and understanding how different types of adaptative mechanisms contribute to survival under stress.



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