Matched Asymptotic Analysis of the Luria–Delbrück Distribution in a Reversible Fluctuation Assay

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Abstract

We study a fluctuation test where cell colonies grow from a single cell to a specified population size before undergoing treatment. During growth, cells may acquire resistance to treatment and pass it to their offspring with a small probability. Unlike the classical Luria–Delbrück test, which assumes irreversible resistance, our model allows resistant cells to revert to a drug-sensitive state. This modification, motivated by recent research on drug resistance in cancer and microbial cells, does not alter the central part of the Luria–Delbrück distribution, where the Landau probability density function approximation remains applicable. However, the right tail of the distribution deviates from the power law of the Landau distribution, with the correction factor given by the Landau cumulative distribution function. Using singular perturbation theory and asymptotic matching, we derive uniformly valid approximations and describe tail corrections for populations with different initial cell states. Our approach generalizes the framework of [2] by incorporating reversible transitions.

Model formulation

We model population growth with a two-type branching process where each cell has an independent, exponentially distributed cell cycle, with the same mean for both cell types. Cells divide at the end of the cycle; the state of the daughter cell is chosen probabilistically depending on the mother cell:

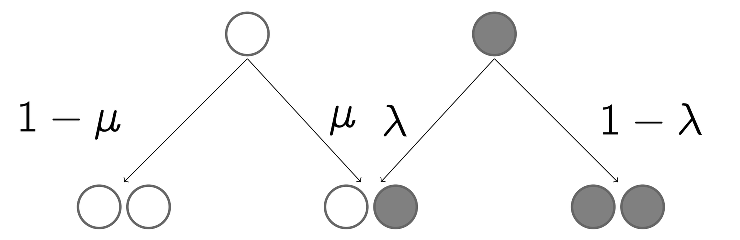


Figure 1. Four possible division outcomes of sensitive (white ball) and resistant (black ball) cells with corresponding probabilities.

Probability $P_N(m)$ of observing m resistant cells as the total population reaches N satisfies the master equation:

$$P_{N+1}(m) = \frac{1}{N}\Big\{ P_N(m-1)\big[\mu(N-(m-1)) + (1-\lambda)(m-1)\big] + P_N(m)\big[(1-\mu)(N-m)+\lambda m\big]\Big\}.$$

In this poster, we assume a single sensitive cell as the initial condition ($N_0 = 1$, $m_0 = 0$). Other cases discussed in [1].

Methods

We examine the asymptotic behavior of $P_N(m)$ as $\mu, \lambda \to 0$. The table below summarizes approximations of $P_N(m)$ across different regimes and their validity:

	$m = O(1)$	$m = O(N) = N - m$	$N - m = O(1)$
$N = O(1)$	regular (1)		
$N = O\left(\frac{1}{\mu}\right)$	left (4)	regular coarse-grained (2)	right (5)

Regular solution:

When the population size is of order $N = O(1)$ and $\mu, \lambda \to 0$, a regular power series expansion in the perturbation parameter μ is derived. The leading-order term yields

$$P_N(m) \sim \frac{\mu N}{m(m+1)}, \tag{1}$$

matching the result derived for the unidirectional case [2].

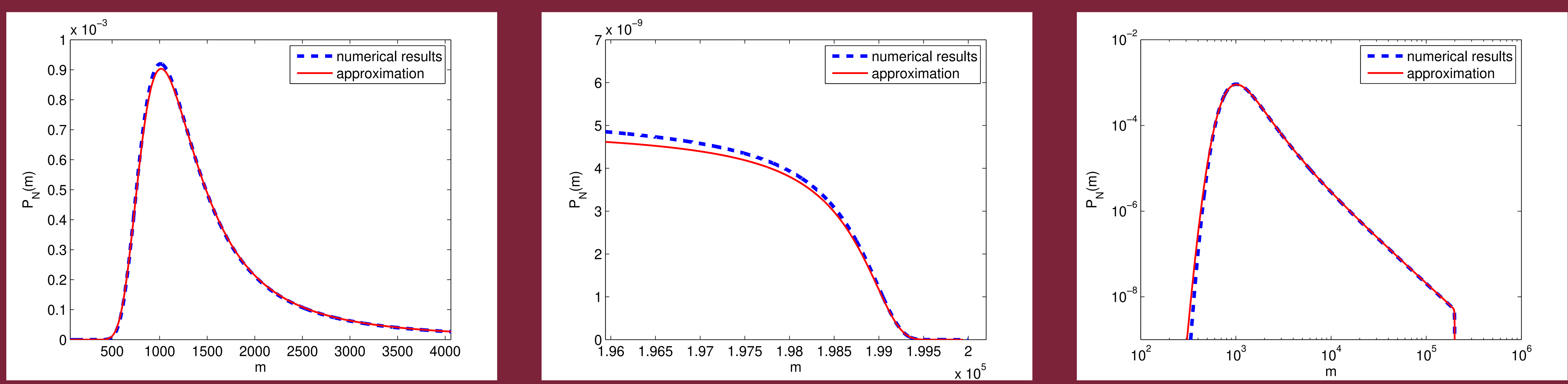
Regular coarse-grained solution:

The regular coarse-grained solution given as

$$P_N(m) \sim \frac{\mu N}{m^2} \tag{2}$$

holds between the boundary layers and can be combined with them into a uniform composite approximation.

Reversible resistance introduces **a boundary-layer at the right tail** of the distribution that is described by the **Landau cumulative distribution function**.



(a) Left-boundary Landau PDF approximation used: $P_N(m) \sim \frac{1}{\mu N} f_{Landau}\left(\frac{m}{\mu N} - \ln \mu N\right)$, *as derived for the unidirectional model in [2].*

(b) Right-boundary Landau CDF approximation used: $P_N(m) \sim \frac{\mu}{N} F_{Landau}\left(\frac{N-m}{\lambda N} - \ln \lambda N\right)$.

(c) Composite Landau PDF/CDF approximation used: $P_N(m) \sim \frac{1}{\mu N} f_{Landau}\left(\frac{m}{\mu N} - \ln \mu N\right) F_{Landau}\left(\frac{N-m}{\lambda N} - \ln \lambda N\right)$.

Figure 2. Probability $P_N(m)$ of having m resistant cells in a population of $N = 2 \times 10^5$ cells as calculated numerically (blue dashed lines) and its asymptotic approximations (red solid lines). The population starts from a single sensitive cell ($N_0 = 1$, $m_0 = 0$). Perturbation parameters: $\mu = \lambda = 10^{-3}$.

Left boundary-layer solution:

Here we focus on the distinguished large-population, low-mutation regime with $\mu N = O(1)$. A left boundary-layer arises for $m = O(1)$. We derive the boundary-layer solution using the generating function $G_N(x) = \sum_{m=0}^{N} P_N(m)x^m$, which converts the master equation into the difference–differential form

$$N(G_{N+1}(x) - G_N(x)) = (x-1)(\mu N + (1-\mu-\lambda)x\partial_x)G_N(x). \tag{3}$$

An intermediate-asymptotics Ansatz $G_N(x) \sim N^{-\beta}H(x,y)$ leads to a PDE whose solution yields a parametric family. Matching to regular regimes determines constants and the scaling exponent β, yielding

$$P_N(m) \sim f_{L-C}(m; \mu N), \tag{4}$$

where f_{L-C} is the Lea-Coulson probability mass function (PMF).

Right boundary-layer solution:

By symmetry ($m_0 \leftrightarrow N_0 - m_0$, $\lambda \leftrightarrow \mu$), the result (4) extends to the right boundary-layer, with $N - m = O(1)$ and $\lambda N = O(1)$, yielding

$$P_N(m) \sim \frac{\mu}{N} F_{L-C}(N-m-1; \lambda N), \tag{5}$$

where F_{L-C} is the Lea-Coulson cummulative distribution function (CDF).

Log-composite solution:

The log-composite solution is constructed as

$$P_N(m) \sim \frac{\text{left} \times \text{regular coarse-grained} \times \text{right}}{\text{left overlap} \times \text{right overlap}}, \tag{6}$$

where the 'left overlap' and 'right overlap' terms are obtained via the asymptotic matching principle, yielding

$$P_N(m) \sim f_{L-C}(m; \mu N) F_{L-C}(N-m-1; \lambda N). \tag{7}$$

Landau distribution:

As the shape parameter μN increases, the Lea–Coulson PMF is well approximated by the Landau probability density function f_{Landau} [2] and its CDF by the Landau cumulative distribution F_{Landau}. These approximations are illustrated in Figure 2: panel (a) shows the left-boundary PDF approximation [2], panel (b) the right-boundary CDF approximation, and panel (c) the full composite approximation combining both.

REFERENCES

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