Solutions 2: Luria-Delbrück experiment

BIO-369

Prof. Anne-Florence Bitbol
EPFL

1 Simulation of the "jackpot" distribution

a) We assume that all the cells in a culture divide at the same time, and that every time a cell divides, there is a probability μ that one (not two) of the daughter cells will mutate to a form that is resistant to phage. Consider a division round such that there are N_{WT} wild-type cells in the parent generation. We want to calculate the number m of new mutants that appear after these cells divide. For each parent cell, we have a probability μ that one of the daughter cells is mutant, and this is independent for each parent cell. Thus, m follows a binomial law:

$$P(m) = \binom{N_{WT}}{m} \mu^m (1-\mu)^{N_{WT}-m} . \tag{1}$$

In the case of rare events, specifically if $\mu \ll 1$ while $N_{WT} \gg 1$ such that $\lambda = \mu \times N_{WT}$ is finite, the binomial distribution Eq. 1 simplifies to the Poisson distribution

$$P(m) = \frac{\lambda^m e^{-\lambda}}{m!} . \tag{2}$$

Because mutations are rare events, the Poisson distribution can be used instead of the binomial distribution to describe the number of new mutants m right after each doubling. Moreover, $\lambda = \mu \times N_{WT}$.

b) We find a variance very close to the mean. In fact, for the Poisson distribution, the mean and variance are both equal to λ.

c) After g division rounds, there should be $n_0 2^g$ cells total. With $n_0 = 200$ and $g = 21$, this yields 419 430 400 cells. They include wild-type and mutant cells. Executing the Python code 3 times shows that the number of mutant cells is highly variable, but the total number of cells should always be the same.

d) See Jupyter notebook.

e) We find a variance much larger than the mean, showing that the distribution of the number of mutants after growth is not a Poisson distribution (for the Poisson distribution, the mean and variance are both equal to λ). Repeating the whole process 3 times yields quite different results (but with a variance always much larger than the mean), showing the large variability of the process, and the difficulty to accurately estimate the mean and variance of the distribution of $N_{mut,f}$ from such experiments.

f) We expect that the "jackpots" arise when a culture includes bacteria that acquire the resistance mutation early in the growth process. This can be seen in the plot: the cultures that contain many mutants are those that get the mutation earliest. However, most cultures do not develop the resistance mutation early, because then, there are still few individuals and mutations are rare.

2 Analysis of experimental data

a) See Jupyter notebook.

b) See Jupyter notebook.

c) To calculate the mean and variance of the number of resistant mutants across all replicate cultures in the experiment, we need to take into account the fact that we do not have raw data but counts of how many replicates yield each number of mutants. We find a variance much larger than the mean, showing that the experimental distribution is not a Poisson distribution, and consistent with the idea of mutational jackpots.