ETH zürich D BSSE Computational Biology Group

Evolutionary Dynamics

Exercises 10

Prof. Dr. Niko Beerenwinkel
Dr. Katharina Jahn
Dr. Rob Noble
28th November 2019

Problem 1: Moments of the Galton-Watson process **(4 points)**

In a Galton-Watson branching process the number of particles at iteration n is given by Z_n. Given the mean and the variance of the number of particles at the first iteration $m = \mathrm{E}[Z] = \mathrm{E}[Z_1]$ and $\sigma^2 = \mathrm{Var}[Z]$, use the pgf of Z_n to prove that

(a) $\mathrm{E}[Z_n] = m^n$;

(b) $\mathrm{Var}[Z_n] = \begin{cases} \frac{\sigma^2 m^{n-1}(m^n-1)}{m-1} & \text{if } m \neq 1 \\ n\sigma^2 & \text{if } m = 1. \end{cases}$

Problem 2: The Luria-Delbrück experiment **(6 points)**

Luria and Delbrück [1943] demonstrated that bacteria acquire resistance to a virus through a mechanism of accumulated mutation rather than adaptation. Cells grow at a rate β, such that $N(t) = N(0)e^{\beta t}$, and they give stochastically rise to a mutant (resistant) offspring with rate α. Hence the number of cells that directly arise through mutation are a non-homogeneous Poisson process with time dependent rate $\lambda(t) = \alpha N(t)$. Thus, the distribution of the number of mutations that occur in $[0,t]$ is Poissonian with parameter $\Lambda(t) = \int_0^t \lambda(\tau)\mathrm{d}\tau$. In absence of the virus, mutant cells grow at the same rate as normal bacteria.

(a) Compute the probability $P_0(t)$ that no mutations have occurred at time t. Show that the mutation rate α can be estimated as $\alpha = \frac{\beta \ln \rho}{1-e^{\beta t}}$, where ρ is the ratio of experiments in which resistance was not found (estimator for $P_0(t)$). Assume $N(0) = 1$.

Hint: use

$$\begin{aligned} P_0(t) &= P(0 \text{ mutants in } [0,\Delta t])P(0 \text{ mutants in } [\Delta t, 2\Delta t]) \cdots P(0 \text{ mutants in } [t-\Delta t, t]) \\ &\approx (1-\alpha N(0)\Delta t) \cdots (1-\alpha N(t-\Delta t)\Delta t) \\ &\approx e^{-\alpha N(0)\Delta t} \cdots e^{-\alpha N(t-\Delta t)\Delta t} \end{aligned}$$

and let $\Delta t \to 0$. Explain the assumptions made in this calculation.

(b) Derive α from the expression for P_0 derived in the lecture for the Galton-Watson process and explain the differences.

(c) Compute the expected number of mutant cells at time t, $m(t)$, and their variance $\sigma^2(t)$.
Hint: The expected number of new mutant cells that arise in the interval $\tau + \mathrm{d}\tau$ is:

$$\nu(\tau + \mathrm{d}\tau) = \lambda(\tau)\mathrm{d}\tau.$$

Compute to which size these newly generated subclones have grown to at time t and express $m(t)$ as their superposition.
Consider a similar strategy for the variance. Use that the new mutant cells arising in $\tau + \mathrm{d}\tau$ are Poissonian variables and remember that $\mathrm{Var}[aX] = a^2 \mathrm{Var}[X]$.

(d) Luria and Delbrück used the mean and variance to distinguish the proposed mechanism of mutations stochastically accumulating prior to viral infection from an active adaptation scenario. Suppose that in the adaptation case, bacteria have no resistance, but stochastically acquire resistance upon infection with high rate δ. In this short period of time, the population size can be considered constant. What would be the resulting relation between the expected number of resistant cells and their variance? Compare this with your results from the accumulation scenario, part (c).

References

Salvador E Luria and Max Delbrück. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics*, 28(6):491, 1943.