ETH zürich D BSSE Computational Biology Group

Evolutionary Dynamics

Exercises 4

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Problem 1: TSG inactivation for small populations
Consider the approximate model of TSG inactivation for small populations $N \ll 1/\sqrt{u_2}$,

$$\begin{aligned}\dot{X}_0 &= -u_1 X_0 \\ \dot{X}_1 &= u_1 X_0 - N u_2 X_1 \\ \dot{X}_2 &= N u_2 X_1 .\end{aligned}$$

(a) Explain why a type 1 cell typically reaches fixation before a type 2 cell arises. (**tutorial discussion**)

(b) Solve the equations numerically with $u_1 = 10^{-7}$, $u_2 = 10^{-10}$, $N = 10$ and plot the result for times up to $t = 10^8$. How do you interpret the plots? (**tutorial discussion**)

(c) Solve this set of ODEs analytically for the initial conditions $X_0(0) = 1$, $X_1(0) = X_2(0) = 0$, to obtain the probability of finding both TSG alleles inactive at time t. **(Additional Exercise)**

Hint: For the analytical approach, solve the system iteratively for X_0, then for X_1 and X_2. A linear ODE $x'(t) + bx(t) = f(t)$ can be integrated by multiplying both sides with the integrating factor e^{bt}, because $[e^{bt}x]' = e^{bt}x' + be^{bt}x$. Thus, $x(t) - x(t_0)e^{-b(t-t_0)} = e^{-bt}\int_{t_0}^{t} e^{b\tau} f(\tau)\mathrm{d}\tau$. To compute X_2 use the conservation of probability.

Problem 2: TSG inactivation for medium and large populations
Consider two models for TSG inactivation: One for a medium-sized population with population size $1/\sqrt{u_2} \ll N \ll 1/u_1$ and one for a large-sized population with population size $N \gg 1/u_1$. Here u_1 and u_2 denote the mutation rates for inactivating the first and second allele.

(a) $P(t)$ is the probability that at least one cell with two hits has arisen before time t. Calculate the time $t_{0.5}$ such that $P(t_{0.5}) = 0.5$ for the cases $N = 10^5$ and $N = 10^{11}$ using a suitable model for each population size. The mutation rates are $u_1 = 10^{-8}$ and $u_2 = 10^{-4}$. **(1 point)**

(b) In this context of TSG inactivation briefly explain the concept of rate limiting events for overall cancer progression and why the number of these events depends on the population size. **(1 point)**

Problem 3: Chromosomal instability
For TSG inactivation with chromosomal instability (CIN) we have distinguished three cases: *neutral CIN*, *costly CIN in small compartments*, and *costly CIN in large compartments*. Cancer can thus either arise from two subsequent "normal" mutations, or by a normal mutation followed by CIN. Without CIN, the rate of the second mutation can be expressed as $u_2 = u + p_0 \approx 2u$, where $u \approx 10^{-7}$ is the normal point mutation rate per cell division and p_0 the rate of LOH. With CIN, the rate of the second mutation is approximately $u_3 = 0.01$. Assuming there are n_1 class I and n_2 class II CIN genes, the rate u_c of producing a CIN mutant can be expressed as $u_c = 2n_1(u + p_0) + 2n_2 u \approx 2(2n_1 + n_2)u$.

(a) Calculate the ratio C of cancers that are initiated with CIN to those initiated without CIN for the three CIN scenarios and show that C is independent of time. **(2 points)**

(b) Explicitly compute C for $n_1 = 6$, $n_2 = 4$ and $N = 10$ cells, in the case of neutral CIN and costly CIN in small compartments, and $N = 200$ for large compartments. Assume a relative fitness disadvantage of $r = 0.9$ in the costly cases. Compare the ratios in a few sentences.

(2 points)

Problem 4: Linear process of colonic crypt transformation

The colon consists of approximately $M = 10^7$ crypts, each consisting of $N = 10^3$ cells. The mutation rate per gene is of order of $u = 10^{-8}$ per cell division. We assume a generation time of 1 day. Consider an oncogenic mutation causing a selective advantage $s = 10\%$ in the following three scenarios:

(a) Homogeneous tissue: Use the Moran model to calculate the expected number of neoplastic crypts (i.e. crypts in which all cells are mutated) at age 50. **(1 point)**

(b) Single stem cell: By a similar calculation, compute the number of transformed crypts at age 50, if the cells in each crypt originate from a single stem cell. Stem cells replicate more slowly with a generation time of approx. 10 days. **(1 point)**

(c) Multiple stem cells: Use the Moran model to compute the number of neoplastic crypts after 50 years, assuming that each crypt is maintained by a pool of $N_S = 4$ stem cells. Assume the same fitness advantage $s = 10\%$. **(1 point)**

(d) Discuss which tissue architecture prevents best the initiation of cancer. **(1 point)**