Evolutionary Dynamics

Exercise 5

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Problem 1: Pathways of carcinogenesis

Consider three independent mutations $\{1,2,3\}$. Each mutation occurs after an exponentially distributed waiting time $T_i \sim \exp(\lambda_i)$, $i = 1,2,3$.

  (a) What is the probability for the path $P = 3 \to 1 \to 2$? **(1 point)**

  (b) Assume cancer arises if any two of the three genes are mutated. How many possible genotypes are there? How many pathways? Compute the expected waiting time until any two out of three genes are mutated. **(1 point)**

  (c) Now consider d independent mutations. How many paths exist leading to the genotype $\{1, \ldots, d\}$ with all mutations present? If cancer already arises after any k mutations, how many different paths are there? **(1 point)**

Problem 2: Neutral Wright-Fisher process

Consider the neutral Wright-Fisher process for a system of N cells of two different types $\{A, B\}$. Let $X(t)$ denote the number of A-cells at time t. The process has the transition matrix

$$P_{i,j} = \mathrm{Prob}[X(t) = j \mid X(t-1) = i] = \binom{N}{j} \left(\frac{i}{N}\right)^j \left(\frac{N-i}{N}\right)^{N-j},$$

that is, $X(t) \mid X(t-1) = i$ is binomially distributed with parameter $p = i/N$.

  (a) Compute the conditional expectation $\mathrm{E}[X(t) \mid X(0) = i]$. **(1 point)**

  (b) Compute the conditional variance $\mathrm{Var}[X(t) \mid X(0) = i]$. **(1 point)**

  Hint: Show that

$$\mathrm{Var}[X(t) \mid X(0) = i] = V_1 + (1 - 1/N)\,\mathrm{Var}[X(t-1) \mid X(0) = i]$$

  where $V_1 = \mathrm{Var}[X(1) \mid X(0) = i]$. You can then use the expression above to derive the final result (no explicit calculation needed for this last step).

  (c) Derive an approximation for $\mathrm{Var}[X(t) \mid X(0) = i]$ for large population size N. Compare the variance of the Wright Fisher process to the variance of the Moran process, explain the difference(s). **(1 point)**

(d) Show that in the Wright-Fisher process, the heterozygosity H_t at time t satisfies **(1 point)**

$$E[H_t \mid X_0 = i] = H_0(i)\left(1 - \frac{1}{N}\right)^t$$

and hence decreases exponentially at rate $1/N$. Compare this behaviour with the Moran model.

Note: Heterozygosity in this context is defined as the probability that two individuals chosen at random from the population are of different types.

Problem 3: Wave approximation

Consider the wave approximation of the Wright-Fisher model for cancer progression. Here, the growth of a clone with j mutations is given by

$$\dot{x}_j = sx_j(j - \langle j \rangle).$$

For small times, the average fitness $s\langle j \rangle = s\sum_j jx_j$ can be considered constant. Use this throughout your calculations.

(a) Find the analytic solution for the initial condition $x_j(0) = 1/N$. **(1 point)**

(b) The rate at which an additional mutation in a clone with j mutations occurs is given by $udx_j(t)$. Find the time τ when the cumulative probability exceeds $1/N$. **(1 point)**

(c) Compute the waiting time until the next mutation for a mutation rate $u = 10^{-7}$/cell generation, $d = 80$ genes and a fitness advantage of $s = 1.15\%$ per mutation. Use that $j - \langle j \rangle \approx \sqrt{\ln N}$ with $N = 10^7$ cells and assume a cell generation time of 1 day. **(1 point)**