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Evolutionary Dynamics

Assignment #03

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1.1 Chromosomal instability

1.1.1 a

Calculate three ratios $C = \frac{CIN}{no-CIN}$ and show that C is independent of time 1. Neutral CIN : if we assume that genes with CIN are neutral (have no fitness advantages or disadvantages) we can conclude that mutation rate from state $A(+-) \to A(--)$ is Nu_2 and from $A(+-CIN) \to A(--CIN)$ is Nu_3. So we can create a linear ODE system. From lecture we know that its solutions for X_2 (i.e. A(–)) and Y_2 (i.e. A(– CIN)) are the following:

$$X_2(t) \approx Nu_1u_2 \times \frac{t^2}{2}$$

$$Y_2(t) \approx u_1u_ct^2$$

So, our rate is

$$\frac{Y_2}{X_2} = \frac{u_1u_ct^2}{\frac{Nu_1u_2t^2}{2}} = \frac{2u_c}{Nu_2}$$

We can see that there is no time variable here, so the process is independent of time. Now remembering that $U_c = 2 \times n_1 \times (u + p_0) + 2 \times n_2 \times u$ and $U_2 = u + p_0$ and substituting it into equation above we have

$$C_1 = \frac{2u_c}{Nu_c} = \frac{4n_1(u + p_0) + 4n_2u}{N(u + p_0)} = \frac{4n_1(2u) + 4n_2u}{N(2u)} = \frac{4n_1 + 2n_2}{N}$$

2. Costly CIN in small compartments: if we assume that genes with CIN have fitness less then 1 ($r < 1$) (probably because of defense system like apoptosis etc) we shall modify the ODE system above , because U_c (mutation of normal allele into CIN allele) now is not just U_c but depends on fitness R_c and population size N, so can be calculated by Moran Process. So, no $U_c = N \times p \times U_c$ now. Now, the solution of that new ODE system is:

$$X_2 \approx \frac{Nu_1u_2t^2}{2}; Y_2 \approx Npu_1u_ct^2$$

So, our final ratio is

$$C_2 = \frac{Y_2}{X_2} = \frac{2pu_c}{u_2} = \frac{4n_1p(u+p_0)+4n_2up}{u+p_0} = \frac{4n_1p(2u)+4n_2up}{2u} = 4n_1p+2n_2p$$

where p is determined by Moran Process as follows:

$$p = \frac{1-\frac{1}{r}}{1-\frac{1}{r^N}}$$

We can see C2 is also independent of time.

3. Costly CIN in large compartments: for large compartments we will never achive Y0 and Y1 states (A(++)CIN and A(+-CIN)) because NpU_c is vanishingly small, but new tunnel transition from X_1 to Y_2 CIN will play its role. That new rate R can be calculated as follows:

$$R = \frac{Nu_cru_3}{1-r}$$

So, new ODE system has the following solutions:

$$X_2 \approx \frac{Nu_1u_2t^2}{2}; Y_2 \approx \frac{Ru_1t^2}{2}$$

So our rate is

$$C_3 = \frac{Y_2}{X_2} = \frac{R}{Nu_2} = \frac{u_cru_3}{(1-r)u_2} = \frac{(2n_1(2u)+2n_2u)ru_3}{(1-r)2u} = \frac{(2n_1+n_2)ru_3}{1-r}$$

1.1.2 b

Computing the real values of c:

1. Neutral CIN

$$C = \frac{4n_1+2n_2}{N} = \frac{4\times5+2\times3}{10} = \boxed{2.6}$$

2. Costly CIN in small compartments

$$p = \frac{1-\frac{1}{r}}{1-\frac{1}{r^N}} = \frac{1-\frac{1}{0.9}}{1-\frac{1}{0.9^{10}}} = 0.05948$$

$$C_2 = 4n_1p+2n_2p = 2p(2n_1+n_2) = 2\times0.05948(2\times5+3) = \boxed{1.5465}$$

3. Costly CIN in large compartments

$$C_3 = \frac{((2n_1+n_2)ru_3)}{(1-r)} = \frac{((2\times5+3)0.9\times0.01)}{(1-0.9)} = \boxed{1.17}$$

2.1 Linear process of colonic crypt transformation

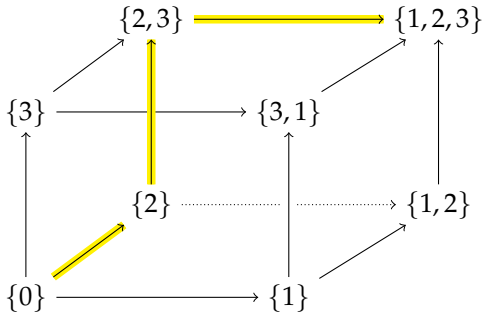
3.1 Multistage theory

4.1 Pathways of carcinogenesis

4.1.1 a

The probability of the path $P = 2 \to 3 \to 1$ for three independent mutations occurring after exponentially distributed waiting time $T_i \sim exp(\lambda_i), i = 1, 2, 3$ is:

$$P = J_1 \to \cdots \to J_k = J_2 \to J_3 \to J_1$$



$$\text{Prob(P)} = \prod_{i=1}^{3} \frac{\lambda_{Ji}}{\sum\limits_{J \in \text{Exit}_i} \lambda_J} = \frac{\lambda_2}{\sum\limits_{J \in \text{Exit}_i = 1,2,3} \lambda_J} \times \frac{\lambda_3}{\sum\limits_{J \in \text{Exit}_i = 1,3} \lambda_J} \times \frac{\lambda_1}{\sum\limits_{J \in \text{Exit}_i = 1} \lambda_J} = \boxed{\frac{\lambda_2 \lambda_3}{(\lambda_1 + \lambda_2 + \lambda_3) \times (\lambda_3 + \lambda_1)}}$$

4.1.2 b

All possible genotypes starting from the wt (no mutation occurred) are 8: $\{0\}; \{1, 2, 3\}; \{12, 23, 31\}; \{123\}$. Considering 2 out of 3 mutations one will obtain 6 possible pathways. Then, the expected waiting time is (where k is the number of mutations expected and p the number of pathways):

$$E[T_k] = \sum_{p=1}^{6} \sum_{n=1}^{k=2} \frac{1}{\sum\limits_{J \in \text{Exit}_i} \lambda_J} \times \text{Prob}(P) = \sum_{p=1}^{6} \sum_{n=1}^{k=2} \frac{1}{\sum\limits_{J \in \text{Exit}_i} \lambda_J} \times \prod_{i=1}^{3} \frac{\lambda_{Ji}}{\sum\limits_{J \in \text{Exit}_i} \lambda_J}$$

$$\begin{aligned} E[T_{p_{1-6}}] =& (\frac{1}{\lambda_1 + \lambda_2 + \lambda_3} + \frac{1}{\lambda_2 + \lambda_3}) \times (\frac{\lambda_1}{\lambda_1 + \lambda_2 + \lambda_3}) + \\ &+ (\frac{1}{\lambda_1 + \lambda_2 + \lambda_3} + \frac{1}{\lambda_1 + \lambda_3}) \times (\frac{\lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}) + \\ &+ (\frac{1}{\lambda_1 + \lambda_2 + \lambda_3} + \frac{1}{\lambda_1 + \lambda_2}) \times (\frac{\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3}) \end{aligned}$$

4.1.3 c

Considering d independent mutation, there are exactly $d \times (d-1) \times (d-2) \times \cdots \times 1 = d!$ pathways to the genotype where all the mutations are present at the same time. If cancer arises after k mutation, there are $d \times (d-1) \times (d-2) \times \cdots \times (d-k+1) = \frac{d!}{(d-k)!}$ paths.

5.1 Neutral Wright-Fisher process

6.1 Wave approximation