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Evolutionary Dynamics

Assignment #03

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Wednesday 31st October, 2012

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

1. Homogenous tissue (well-mixed compartment).
First, we will find a prob of a single mutant with fitness $r = 1.05$ to take over the compartment of size $N = 1000$ (Moran Process)

$$p = \frac{1 - \frac{1}{r}}{1 - \frac{1}{r^N}} = \frac{1 - \frac{1}{1.05}}{1 - \frac{1}{1.05^{1000}}} = 0.0476$$

Then, we find the prob of a compartment has been taken by mutated cell after 50 years (25550 days) is

$$p = 1 - e^{-Nupt} = 1 - e^{-1000 \times 10^{-8} \times 0.0476 \times 18250} = 0.0086528$$

Now, we have $M = 10^7$ crypts so we could expect $M \times 0.0086528 =$ **86528 neoplastic crypts**

2. Single Stem cell (linear process).

Since the stem cell is the only one which is mater in linear crypt, we could calculate the probability of compartment being taken by mutation of a stem cell in 50 years as follows $t = 50 \times \frac{365}{10} = 1825$:

$$p = 1 - e^{-ut} = 1 - e^{-10^{-8} \times 1825} = 1.825 \times 10^{-5}$$

so, we expect $10^7 \times p =$ **182.5 neoplastic crypts**

3. Multiple stem cells (5 cells)

This is actually the same case as well-mixed compartment but with effective population size of 5, because any of stem cell can mutate and originate a cancer, so

$$p = \frac{1 - \frac{1}{r}}{1 - \frac{1}{r^N}} = \frac{1 - \frac{1}{1.05}}{1 - \frac{1}{1.05^5}} = 0.22$$

$$p = 1 - e^{-Nupt} = 1 - e^{-5 \times 10^{-8} \times 0.22 \times 18250} = 2.0075 \times 10^{-5}$$

so, we expect $10^7 \times p =$ **200.74 neoplastic crypts**

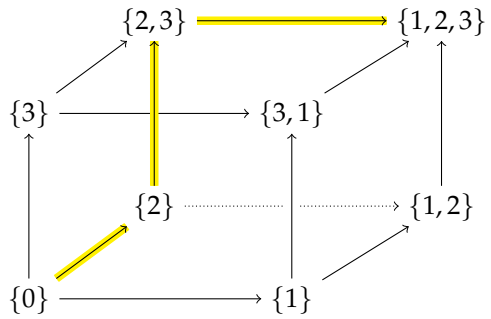
3.1 Multistage theory

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