In the Knudson two-hit model, two copies of a tumor suppressor gene must be mutated (and rendered inoperative) to initiate some forms of cancer. (e.g., two copies of the Rb gene must be lost to initiate retinoblastoma.) Let $X(t)$ denote the number of mutated copies of a tumor suppressor gene at time $t$, where $0 \leq X(t) \leq 2$.

Suppose that if there have been no mutations, then each tumor suppressor gene mutates independently at an exponential rate $\lambda$. If one copy is mutated, then the remaining copy mutates at an exponential rate $\mu$. Generally, $\mu > \lambda$, but you may assume $\mu = \lambda$ today.

In the following work, assume that this process can be modeled as a continuous time Markov chain, and that damaged genes cannot be repaired.

1. (2 points) Carefully write the transitional probabilities $P_{0,j}(t)$ for $0 \leq j \leq 2$.

**Solution:** For each copy of the TSG, the probability that it does not mutate by time $t$ is $e^{-\lambda t}$. Therefore,

$$P_{0,0}(t) = e^{-\lambda t} e^{-\lambda t}.$$  

For $P_{0,1}(t)$, we need the probability that either copy 1 mutates and copy 2 does not, OR copy 2 mutates and copy 1 does not:

$$P_{0,1}(t) = (1 - e^{-\lambda t}) e^{-\lambda t} + e^{-\lambda t} (1 - e^{-\lambda t}) = 2e^{-\lambda t} (1 - e^{-\lambda t}).$$  

Lastly, $P_{0,2}$ is the probability that both mutate.

$$P_{0,2}(t) = (1 - e^{-\lambda t}) (1 - e^{-\lambda t}).$$

2. (2 points) Write the transitional probabilities $P_{1,j}(t)$ for $0 \leq j \leq 2$.

**Solution:** This is actually even easier. If there is one mutated copy, it cannot be repaired, so

$$P_{1,0}(t) = 0.$$  

Next, without loss of generality, we can relabel the gene copies such that copy 1 is mutated and copy 2 is not. Therefore, $P_{1,1}(t)$ is the probability that the second copy is not mutated:

$$P_{1,1}(t) = e^{-\lambda t}.$$  

Similarly

$$P_{1,2}(t) = (1 - e^{-\lambda t}).$$

3. (2 points) Write the transitional probabilities $P_{2,j}(t)$ for $0 \leq j \leq 2$.

**Solution:** This is even easier still. Because mutated genes are not repaired in this example, there is no transition away from the state $X(t) = 2$. Thus,

$$P_{2,0}(t) = 0, \quad P_{2,1}(t) = 0, \quad \text{and} \quad P_{2,2}(t) = 1.$$
4. (2 points) Verify that the transitional probabilities $P_{0,j}(t)$ are self-consistent.

**Solution:** For any given state, the transition probabilities must sum to 1. For simplicity of notation, define $\alpha = e^{-\lambda t}$. Then

$$P_{0,0}(t) + P_{0,1}(t) + P_{0,2}(t) = \alpha^2 + 2\alpha(1 - \alpha) + (1 - \alpha)(1 - \alpha)$$

$$= \alpha^2 + (1 - \alpha)(1 + \alpha)$$

$$= \alpha^2 + 1 - \alpha^2 = 1.$$

5. (2 points) As $t \to \infty$, which of the $P_{0,j}$ is most probable? What can you conclude about the relationship between cancer and age?

**Solution:** Note that

$$\lim_{t \to \infty} P_{0,0}(t) = 0, \quad \lim_{t \to \infty} P_{0,1}(t) = 0, \quad \text{and} \quad \lim_{t \to \infty} P_{0,2}(t) = 1.$$

Thus, in the very long term, both copies of the TSG will be lost. While the process of carcinogenesis is complex, it does suggest that at the very least, the probability of having a cell lose two TSGs increases with age, and thus the risk of getting cancer also increases with age. Indeed, this is borne out by mountains of epidemiological data.