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The waiting time for a second mutation: An alternative to the Moran model

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HIGHLIGHTS

- We model the waiting time for two successive mutations.
- Our model is an alternative to the Moran model with mutations.
- We get an exact formula for the waiting time distribution.

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ABSTRACT

The appearance of cancer in a tissue is thought to be the result of two or more successive mutations. We propose a stochastic model that allows for an exact computation of the distribution of the waiting time for a second mutation. This models the time of appearance of the first cancerous cell in a tissue. Our model is an alternative to the Moran model with mutations.

1. The model

The idea of successive mutations to trigger the appearance of a cancerous cell goes back to at least Ref. [1]. The first mathematical model proposed for this phenomenon goes back to [2]. There has been a great deal of discussion on the number of successive mutations necessary to get a cancerous cell. It seems that this number depends on the organ, see Refs. [3,4]. However, some authors have argued that two mutations models are flexible enough to model most cancers, see Refs. [5,6]. This is the point of view we adopt.

We now describe our model. We are interested in the time it takes for a given organ to have a first cancerous cell. We assume that all cells are in one of three stages: healthy, precancerous (i.e. type 1) and cancerous (i.e. type 2). We start the process with all cells healthy. As the cells divide precancerous cells may appear due to a type 1 mutation on a healthy cell. A type 2 mutation on a precancerous cell makes the cell cancerous.

The number of type 1 mutations is modeled by a Poisson process with rate $\mu_1 \nu$. We think of μ_1 as a mutation rate and ν as a division rate. Our model does not take into account the number of organ cells. Mutations are thought to appear at cell division. Hence, the relevant parameter is the rate at which cells divide (i.e. ν) rather than the total number of cells.

A type 2 mutation appears on a type 1 cell. The appearance of type 2 mutations can be modeled by a number of different processes and we will give several examples. We now state our two hypotheses for the second mutation process.

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Let $N_1(t)$ be the number of type 1 mutations that have occurred up to time t. Let $T_1 < T_2 < \cdots$ be the arrival times of this Poisson process. The ith type 1 mutation appears at some time $T_i = t_i$. We let a (random) waiting time S_i start at time t_i. A type 2 mutation appears at time S_i. The minimum of these waiting times (i.e. the first time a type 2 mutation appears in the tissue) is denoted by τ_2.

Given that $N_1(t) = k$ and that $T_1 = t_1, T_2 = t_2, \ldots, T_k = t_k$ we assume for $i = 1, \ldots, k$ that

$$P(S_i > t | T_i = t_i) = h(t, t_i) \quad \text{for } t > t_i. \tag{1.1}$$

Note that we are assuming that h does not depend on i. Our second hypothesis concerns the conditional independence of the random variables S_i. More precisely,

$$P(S_1 > t, \ldots, S_k > t | N_1(t) = k, T_1 = t_1, \ldots, T_k = t_k) = h(t, t_1) \times \cdots \times h(t, t_k). \tag{1.2}$$

Let U be uniformly distributed in $(0, t)$ and

$$m_2(t) = E(h(t, U)).$$

Here is our main result.

Theorem 1. *Let τ_2 be the time for the first type 2 mutation to appear. Then,*

$$P(\tau_2 > t) = \exp[\mu_1 \nu t\big(-1 + m_2(t)\big)].$$

We have picked the Poisson rate $f(\mu_1, \nu) = \mu_1 \nu$ because this seems natural but the formula holds for any f as the reader can easily check.

Since $h(t, s)$ is in $[0, 1]$ for all $0 \le s \le t$ we have

$$-1 \le -1 + m_2(t) \le 0.$$

That is, the second mutation appears in the formula of Theorem 1 through a bounded function. That is in sharp contrast with the role of the first mutation in the formula. This is consistent with [7] view of carcinogenesis. His hypothesis is that first mutations must hit a stem cell to be relevant. However, he also believes that stem cells (unlike other cells) have low mutation rates (a defective stem cell tends to die rather than try to repair itself). Hence, we are protected (for the most part) from cancer because $\mu_1 \nu$ is low, see also Ref. [8].

We now give three examples for which we can compute $m_2(t)$ explicitly. All our examples have the property that $h(t, s) = h(t - s, 0)$ for $t > s > 0$. Hence, $m_2(t) = E(h(t - U, 0))$.

Example 1.1. Assume that a type 1 cell mutates into a type 2 cell after an exponential time with rate μ_2. That is,

$$h(t, t_i) = P(S_i > t | T_i = t_i) = \exp(-\mu_2(t - t_i)) \quad \text{for } t > t_i.$$

In this example type 1 cells do not give birth or die. They stay put waiting for a type 2 mutation. If we think of a type 1 cell as a mutated stem cell this is consistent with the biological picture, see Ref. [9]. We have

$$m_2(t) = E(h(t - U, 0)) = \frac{1}{t} \int_0^t \exp(-\mu_2(t - s))\mathrm{d}s = \frac{1}{\mu_2 t}(1 - \exp(-\mu_2 t)).$$

Example 1.2. Assume that a type 1 cell dies after an exponential time with rate δ. Assume also that during its lifetime it may mutate (independently of everything else) to a type 2 cell with rate μ_2. In this example type 1 cells do not give birth. Then, $1 - h(t, 0)$ (i.e. the probability that a type 2 mutation occurs by time t on a type 1 cell that appeared at time 0) can be computed by

$$1 - h(t, 0) = \int_A \delta \exp(-\delta s)\mu_2 \exp(-\mu_2 u)\mathrm{d}s\mathrm{d}u$$

where

$$A = \{(s, u) : 0 \le u < s, 0 \le u < t\}.$$

Hence,

$$1 - h(t, 0) = \frac{\mu_2}{\delta + \mu_2}(1 - \exp(-(\delta + \mu_2)t)).$$

Therefore,

$$m_2(t) = E(h(t - U, 0)) = \frac{\delta}{\delta + \mu_2} + \frac{1}{t}\frac{\mu_2}{(\delta + \mu_2)^2}(1 - \exp(-(\delta + \mu_2)t)).$$

Example 1.3. Assume that each type 1 cell gives birth to a new cell at rate λ. There are no deaths. This is the well-known Yule process, see Ref. [10] for instance. Starting with a single type 1 cell the probability to have exactly $n \ge 0$ births by time t is

$$\exp(-\lambda t)(1 - \exp(-\lambda t))^n.$$