Evolution of resistance and progression to disease during clonal expansion of cancer

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Abstract

Inspired by previous work of Iwasa, Nowak, and Michor (2006), and Haeno, Iwasa, and Michor (2007), we consider an exponentially growing population of cancerous cells that will evolve resistance to treatment after one mutation or display a disease phenotype after two or more mutations. We prove results about the distribution of the first time when k mutations have accumulated in some cell, and about the growth of the number of type k cells. We show that our results can be used to derive the previous results about the tumor grown to a fixed size.

1 Introduction

The mathematical investigation of cancer began in the 1950s, when Nordling (1953), Armitage and Doll (1954, 1957), and Fisher (1959) set out to explain the age-dependent incidence curves of human cancers. For a nice survey see Frank (2007). Armitage and Doll (1954) noticed that log-log plots of cancer incidence data are linear for a large number of cancer types; for example, colorectal cancer incidence has a slope of 5.18 in men and 4.97 in women. The authors used this observation to argue that cancer is a multi-stage process and results from the accumulation of multiple genetic alterations in a single cell. The math underlying this hypothesis was very simple. Suppose X_i are independent and have an exponential distribution with rates u_i (i.e., the density function is $u_i e^{-u_i t}$ and the mean is $1/u_i$). Noting that the sum $X_1 + \cdots + X_k$ has a density function that is asymptotically

$$u_1 \cdots u_k \frac{t^{k-1}}{(k-1)!} \quad \text{as } t \to 0, \tag{1}$$

the authors inferred that the slope of the age-incidence curve was the number of stages minus 1, making colon cancer a six-stage process.

Later on, Knudson (1971) performed a statistical analysis of retinoblastoma, a childhood eye cancer. His study showed that familial cases of retinoblastoma have an earlier age of onset than the sporadic cases that emerge in families without a history of the disease. Based on age incidence curves in the two groups, he hypothesized that two mutagenic events or "hits" are necessary to cause cancer in the sporadic case, but in individuals with the inherited form of the disease, a single hit is sufficient since one mutation is already present at birth. This study led to the concept of a tumor suppressor gene, i.e., a gene which contributes to tumorigenesis if inactivated in both alleles. See Knudson (2001) for a survey.

Knudson's research led to an explosion of papers on the multi-stage theory of carcinogenesis too numerous to list here. Most studies, like the ones cited in the last two paragraphs, merely fit curves to data on age specific incidence without considering a population genetic model for the cell population. Iwasa et al. (2004,2005) were the first to study waiting times in this way. They used a Moran model for a population of a fixed size N in which type i cells are those with $i \geq 0$ mutations, and type i mutates to type $i+1$ at rate u_{i+1}. Let τ_k be the first time at which there is a type k-cell. They considered a variety of scenarios based on the relative fitnesses of mutants. In the neutral case, i.e., if the mutation does not alter the fitness or growth rate of the cell, they showed:

Theorem 1. *In a population of N cells, τ_2 is approximately exponentially distributed with rate $Nu_1u_2^{1/2}$, provided $1/\sqrt{u_2} \ll N \ll 1/u_1$.*

They called this result "stochastic tunneling" because the 2's arise before the 1's reach fixation. Durrett, Schmidt, and Schweinsberg (2009), see also Schweinsberg (2008), generalized this result to cover τ_k.

In many cases, such as leukemia and polyps in colon cancer, the cell population does not have constant size. For these reasons, Iwasa, Nowak, and Michor (2006) considered the time to develop one mutation in an exponentially growing population and Haeno, Iwasa, and Michor (2007) extended the analysis to waiting for two mutations. Their model is a multi-type branching process in which type i cells are those with $i \geq 0$ mutations. Type-i cells give birth at rate a_i and die at rate b_i, where $\lambda_i = a_i - b_i > 0$. The previous papers consider a number of different possibilities but here will restrict our attention to the case in which $i \to \lambda_i$ is increasing.

We suppose that during their lifetimes, type-i cells mutate at rate u_{i+1} becoming type $i+1$'s. This is slightly different than the previous approach of having mutations with probability u_{i+1} at birth, which translates into a mutation rate of a_iu_{i+1}, and this must be kept in mind when comparing results. In applications, the mutation rates are small compared to birth and death rates, so the reduction of the birth rate of type-i's to $a_i(1 - u_{i+1})$ is an insignificant difference.

1.1 Growth of type-0's

The number of type-0 cells, $Z_0(t)$, is a branching process, so if $Z_0(0) = 1$, $EZ_0(t) = e^{\lambda_0 t}$ and $e^{-\lambda_0 t} Z_0(t)$ is a nonnegative martingale. Well known results imply that $e^{-\lambda_0 t} Z_0(t) \to W_0$ as $t \to \infty$. A closed-form formula for the generating function $Ex^{Z_0(t)}$ is known, see (15). To find the Laplace transform of W_0, we let $x = \exp(-\theta e^{-\lambda_0 t})$ in the closed form solution and look at the limit as $t \to \infty$ to conclude

$$Ee^{-\theta W_0} = \frac{b_0}{a_0} + \left(1 - \frac{b_0}{a_0}\right) \frac{1 - b_0/a_0}{1 - b_0/a_0 + \theta}$$

From this we see that if δ_0 is a pointmass at 0, and $\lambda_0 = a_0 - b_0$

$$W_0 =_d \frac{b_0}{a_0}\delta_0 + \frac{\lambda_0}{a_0} \text{exponential}(\lambda_0/a_0) \tag{2}$$

where the exponential(r) distribution has density re^{-rt} and mean $1/r$.

If we let $\Omega_0^0 = \{Z_0(t) = 0 \text{ for some } t \geq 0\}$ then (14) below implies $P(\Omega_0) = b_0/a_0$, i.e., $W_0 = 0$ if and only if the process dies out. Letting $\Omega_\infty^0 = \{Z_0(t) > 0 \text{ for all } t \geq 0\}$ we have

$$(e^{-\lambda_0 t} Z_0(t) | \Omega_\infty^0) \to V_0 = \text{ exponential}(\lambda_0/a_0) \tag{3}$$

and hence the Laplace transform

$$Ee^{-\theta V_0} = \frac{\lambda_0}{\lambda_0 + a_0\theta} = (1 + c_{\theta,0}\theta)^{-1}. \tag{4}$$

where $c_{\theta,0} = a_0/\lambda_0$. Here and in what follows, c's are constants that only depend on the birth and death rates, and not on the mutational rates.

1.2 Type-1 Results

Let τ_1 be the time of occurrence of the first type-1. Since type-1's are produced at rate $u_1 Z_0(t)$,

$$P(\tau_1 > t | Z_0(s), s \leq t, \Omega_\infty^0) = \exp\left(-u_1 \int_0^t Z_0(s) ds\right) \tag{5}$$

τ_1 will occur when $\int_0^t Z_0(s)\, ds$ is of order $1/u_1$. A typical choice for $u_1 = 10^{-5}$, so $1/u_1$ is a large number, and we can use the approximation $(Z_0(s)|\Omega_\infty^0) \approx e^{\lambda_0 s} V_0$. Evaluating the integral, taking the expected value, and using (4), we conclude that

$$\begin{aligned} P(\tau_1 > t | \Omega_\infty^0) &\approx E \exp\left(-u_1 V_0 (e^{\lambda_0 t} - 1)/\lambda_0\right) \\ &= \frac{\lambda_0}{\lambda_0 + a_0 u_1 (e^{\lambda_0 t} - 1)/\lambda_0} = \left(1 + c_{\tau,1} u_1 (e^{\lambda_0 t} - 1)\right)^{-1} \end{aligned} \tag{6}$$

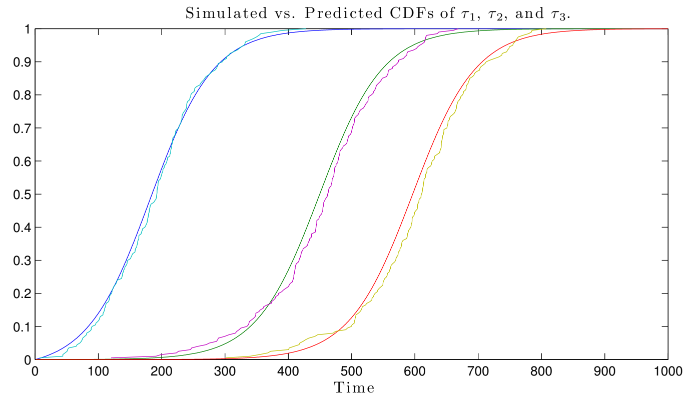

Figure 1: Results of 200 runs of the system with $a_0 = 1.02$, $a_1 = 1.04$, $a_2 = 1.06$ $b_i = 1.0$, $u_i = 10^{-5}$. Smooth curves the limit results for τ_i when $i = 1, 2, 3$.

where $c_{\tau,1} = a_0/\lambda_0^2$. The median $t^1_{1/2}$ of the distribution has $\lambda_0^2 = a_0 u_1 (e^{\lambda_0 t^1_{1/2}} - 1)$ so

$$t^1_{1/2} = \frac{1}{\lambda_0} \log \left(1 + \frac{\lambda_0^2}{a_0 u_1} \right) \tag{7}$$

Figure 1 shows that (6) agrees well with the values of τ_1 observed in simulations. Parameters are given in the figure caption.

Our next step is to consider the growth of $Z_1(t)$. In Section 3 we show that

$$M_t = e^{-\lambda_1 t} Z_1(t) - \int_0^t u_1 e^{-\lambda_1 s} Z_0(s)\, ds \text{ is a martingale}$$

and use this to conclude

Theorem 2. *$e^{-\lambda_1 t} Z_1(t) \to W_1$ a.s. with*

$$EW_1 = u_1/(\lambda_1 - \lambda_0).$$

On Ω^0_∞ we will eventually get a type-1 mutant with an infinite line of descent so $\{W_1 > 0\} \supset \{\Omega^0_\infty\}$.

Let $T_M = \min\{t : Z_0(t) = M\}$. The results of simulations given in Figure 3 of Iwasa, Nowak, and Michor (2006) show that when $\log P(W_1 > x | T_M < \infty)$ is plotted versus $\log x$, a straight line results. Since their M is large, this suggests that $(W_1 | \Omega^0_\infty)$ has a power law tail. As we will now show, this is only approximately correct. To begin, we consider $Z^*_i(t)$, the number of type-i's at time t in a system with $Z^*_0(t) = e^{\lambda_0 t} V_0$ for all $t \in (-\infty, \infty)$. Let

$$c_{h,1} = \frac{1}{\lambda_0} \left(\frac{a_1}{\lambda_1} \right)^{\lambda_0/\lambda_1 - 1} \Gamma(1 - \lambda_0/\lambda_1) \Gamma(\lambda_0/\lambda_1 + 1)$$

Theorem 3. $e^{-\lambda_1 t} Z_1^*(t) \to V_1$ *a.s. with*

$$Ee^{-\theta V_1} = 1/(1 + c_{\theta,1} u_1 \theta^{\lambda_0/\lambda_1})$$

where $c_{\theta,1} = c_{\theta,0} c_{h,1}$*, and hence*

$$P(V_1 > x) \sim c_{V,1} u_1 x^{-\lambda_0/\lambda_1}$$

where $c_{V,1} = c_{\theta,1}/\Gamma(1 - (\lambda_0/\lambda_1))$.

Iwasa, Nowak, and Michor (2006)'s $\alpha = \lambda_0/\lambda_1$, so our result is consistent with the conclusions given in their (15a) and (15b). The big values of V_1 come from mutations at negative times, so W_1 does not have a power law tail. To upper bound the difference between the distributions of W_1 and V_1 note that the expected number of type-1's produced at times $t \leq 0$ is $u_1 a_0/\lambda_0^2$. In the concrete example considered in Figure 1, $a_0 = 1.02$, $b_0 = 1$, and $u = 10^{-5}$ which is 0.0255 so this does not change the limiting distribution by much and the simulated distributions will look like power laws.

A useful consequence of the proof of Theorem 3 is

Corollary. *If we condition on the value of* V_0 *then* $V_1 = \lim_{t\to\infty}$ *is the sum of points of a Poisson process on* $(0, \infty)$ *with intensity* $Cu_1 V_0 x^{-\lambda_0/\lambda_1}$.

Here the Poisson points are the sizes of the contributions of different mutations to the limit V_1.

1.3 Type-2 Results

We can derive an approximation for the waiting time for the first type 2, τ_2, by using the same reasoning in (5) and (6) for τ_1.

$$P(\tau_2 > t | Z_1(s), s \leq t, \Omega_\infty^0) \approx \exp\left(-u_2 V_1 e^{\lambda_1 t}/\lambda_1\right) \tag{8}$$

Taking expected values and using Theorem 3, we obtain

$$P(\tau_2 > t | \Omega_\infty^0) \approx \left(1 + c_{\tau,2} \mu_2 e^{\lambda_0 t}\right)^{-1}$$

where $\mu_2 = u_1 u_2^{\lambda_0/\lambda_1}$, $c_{\tau,2} = c_{\theta,1} \lambda_1^{-\lambda_0/\lambda_1}$, and we have omitted the -1 after $e^{\lambda_0 t}$ because it is not important in this result. Solving we get an approximation for the median value of τ_2:

$$t_{1/2}^2 \approx \frac{1}{\lambda_1} \log\left(\frac{1}{u_2}\right) + \frac{1}{\lambda_0} \log\left(\frac{1}{u_1 c_{\tau,2}}\right) \tag{9}$$

and it follows easily that

$$P(\tau_2 > t_{1/2}^2 + x/\lambda_0) \to \frac{1}{1 + e^x} \tag{10}$$

Figure 1 compares (10) with simulations of τ_2.

1.4 Type-k Results

To study the growth of the number of type k's for $k \geq 2$, we note that

$$e^{-\lambda_k t} Z_k(t) - \int_0^t u_k e^{-\lambda_k s} Z_{k-1}(s) ds \quad \text{is a martingale}$$

and use this conclude that

Theorem 4. *For $k \geq 2$, $e^{-\lambda_k t} Z_k(t) \to W_k$ a.s. with*

$$EW_k = \prod_{j=1}^{k} \frac{u_j}{\lambda_k - \lambda_{j-1}}$$

Using the approach in the proof of Theorem 3 we can show that if we let

$$c_{h,k} = \frac{1}{\lambda_{k-1}} \left(\frac{a_k}{\lambda_k}\right)^{\lambda_{k-1}/\lambda_k - 1} \Gamma(1 - \lambda_{k-1}/\lambda_k)\Gamma(\lambda_{k-1}/\lambda_k + 1)$$

and $\mu_k = \prod_{j=1}^{k} u_j^{\lambda_0/\lambda_{j-1}}$ then we have

Theorem 5. *$e^{-\lambda_k t} Z_k^*(t) \to V_k$ a.s. with*

$$Ee^{-\theta V_k} = \left(1 + c_{\theta,k}\mu_k \theta^{\lambda_0/\lambda_k}\right)^{-1}$$

and hence $P(V_k > x) \sim c_{V,k}\mu_k x^{-\lambda_0/\lambda_k}$, where $c_{V,k} = c_{\theta,k}\Gamma(1 - \lambda_0/\lambda_k)$.

As before, this gives us estimates for the waiting time distribution

$$\begin{aligned} P(\tau_{k+1} > t|\Omega_\infty^0) &\approx E\exp(-V_k u_{k+1} e^{\lambda_k t}/\lambda_k) \\ &= \left(1 + c_{\tau,k+1}\mu_{k+1} e^{\lambda_0 t}\right)^{-1} \end{aligned}$$

where $c_{\tau,k+1} = c_{\theta,k} c_{h,k}^{\lambda_0/\lambda_k}$. Again, we can solve to find the median

$$t_{1/2}^{k+1} = \sum_{j=1}^{k+1} \frac{1}{\lambda_{j-1}} \log\left(\frac{1}{u_j}\right) + \frac{1}{\lambda_0} \log\left(\frac{1}{c_{\tau,k+1}}\right) \tag{11}$$

and it follows easily that

$$P(\tau_{k+1} > t_{1/2}^{k+1} + x/\lambda_0) \to \frac{1}{1 + e^x} \tag{12}$$

Note that the shape of the limit distribution is the same as for τ_2 but is translated in time. Figure 1 compares (12) whne $k = 3$ with simulations of τ_3.

1.5 Fixed size results

In Iwasa, Nowak, and Michor (2006) and Haeno, Iwasa, and Michor (2007), the authors consider the system at T_M, the first time at which there are M type-0 cells. With a little more work, we are able to reproduce and extend their results.

1.5.1 $P(\tau_1 < T_M)$

Using the calculation in (5),

$$
\begin{aligned}
P(\tau_1 > T_M | Z_0(s), s \le T_M, \Omega^0_\infty) &= \exp\left(-u_1 \int_0^{T_M} Z_0(s)\, ds\right) \\
&\approx \exp\left(-Mu_1 \int_0^\infty e^{-\lambda_0 s}\, ds\right) = \exp\left(-Mu_1/\lambda_0\right) \qquad (13)
\end{aligned}
$$

If we let $\tilde{Z}_1(t) = (Z_1(t)|Z_0(0) = 0, Z_1(0) = 1)$, i.e., the branching process started with no type 0's and one type 1, then similar reasoning shows

$$
\begin{aligned}
&P(Z_1(T_M) > 0 | Z_0(s), s \le T_M, \Omega_\infty) \\
&\qquad = 1 - \exp\left(-u_1 \int_0^{T_M} Z_0(s) P(\tilde{Z}_1(T_M - s) > 0)\, ds\right)
\end{aligned}
$$

Using $Z_0(s) \approx Me^{-\lambda_0(T_M - s)}$, changing variables $r = T_M - s$, and using (17) below to evaluate $P(\tilde{Z}_1(T_M - s) > 0)$ the above

$$
\approx 1 - \exp\left(-u_1 M \int_0^{(1/\lambda_0)\log M} e^{-\lambda_0 r} \frac{\lambda_1}{a_1 - b_1 e^{-\lambda_1 r}}\, dr\right)
$$

where we have stopped the integral when $Z_0(t_M - r) \approx Me^{-\lambda_0 r} = 1$. Changing variables $y = e^{-\lambda_0 r}$, $dy = -\lambda_0 e^{-\lambda_0 r}\, dr$ the integral becomes

$$
\frac{1}{\lambda_0} \int_0^1 \frac{\lambda_1}{a_1 - b_1 y^\alpha}\, dy
$$

where $\alpha = \lambda_1/\lambda_0$, which agrees with (7) of Iwasa, Nowak, and Michor (2006) once one changes variables $a_0 = r$, $b_0 = d$, $u_1 = ru$. Their derivation of this result is not completely rigorous because they suppose that the number of resistant cells, R_x, produced when $Z_0(t) = x$ are independent, whereas the occupation times $|\{t \le T_M : Z_t(0) = x\}|$ are correlated, but evidently this does not produce a significant error.

1.5.2 $Z_1(T_M)$

Working backward from T_M, assuming deterministic growth of type-0 cells at rate $e^{\lambda_0 s}$, and using a calculation from the proof of Theorem 3, we can show

$$
E \exp\left(-\frac{\theta Z_1(T_M)}{(Mu_1)^{\lambda_1/\lambda_0}}\right) \approx \exp\left(-u_1 \int_{-\infty}^0 Me^{\lambda_0 s}(1 - \tilde{\phi}_{-s}(\theta(Mu_1)^{-\lambda_1/\lambda_0}))\, ds\right)
$$

This leads to

Theorem 6. *As $M \to \infty$, $Z_1(T_M)/(Mu_1)^{\lambda_1/\lambda_0}$ converges to U_1 in distribution where*

$$E(\exp(-\theta U_1)) = \exp(-c_{1,\theta} u_1 \theta^{\lambda_0/\lambda_1})$$

and $c_{1,\theta}$ is the constant in Theorem 2.

As in Theorem 3 it follows that $P(U_1 > x) \sim c_{V,1} u_1 x^{-\lambda_0/\lambda_1}$. From Theorem 6 we see that if $(Mu_1)^{\lambda_1/\lambda_0} \ll M$, i.e., $M \ll u_1^{-\lambda_1/(\lambda_0-\lambda_1}$ then Haeno, Iwasa, and Michor (2007) are justified in looking at the time when the number of type 0's reaches M rather than when the total population reaches M, see their page 2211. In the concrete example considered in Figure 1, this is $M \ll 10^{2.5}$.

1.5.3 $P(\tau_2 < T_M)$

Using the reasoning for $P(\tau_1 < T_M)$, one can show

$$P(Z_2(T_M) > 0) \approx 1 - \exp\left(-\frac{u_1}{\lambda_0}\int_1^M 1 - P\left(\tilde{Z}_2\left(\frac{1}{\lambda_0}\log\left(\frac{M}{x}\right)\right) > 0\right)\, dx\right)$$

After a change in notation, this is (3) in Haeno, Iwasa, and Michor (2007). To make the connection see their (A3). However, this formula is not very useful, since $P(\tilde{Z}_2(t) > 0)$ is not easy to compute. See their appendix A. One can get a better formula by using Theorem 6 and (8) to conclude

$$P(\tau_2 < T_M) \approx E\exp(-u_2 U_1 (Mu_1)^{\lambda_1/\lambda_0}/\lambda_1) = E\exp(-\theta U_1)$$

with $\theta = u_2(Mu_1)^{\lambda_1/\lambda_0}/\lambda_1$. Using the last result with Theorem 6, one can determine the relative proportions of types 0 and 1 at time τ_2. We leave the details to the reader.

1.6 Summary

Here, we have derived results for τ_k, the waiting time for the first type k, in a branching process model for an exponentially growing population of cancerous cells. To obtain simple formulas we considered a modification in which $Z_0^*(t) = e^{\lambda_0 t} V_0$ for all $t \in (-\infty, \infty)$. In this case

$$P(\tau_k > t) \approx \left(1 + c_{\tau,k}\mu_k e^{\lambda_0 t}\right)^{-1}$$

where $\mu_k = \prod_{j=1}^k u_j^{\lambda_0/\lambda_{j-1}}$ and $c_{\tau,k}$ is an explicit constant that only depends on the birth and death rates.

$$c_{\tau,k} = \frac{a_0}{\lambda_0}\lambda_{k-1}^{-\lambda_0/\lambda_{k-1}} \prod_{i=1}^{k-1}\left[\frac{1}{\lambda_{i-1}}\left(\frac{a_i}{\lambda_i}\right)^{\lambda_0/\lambda_i - 1}\Gamma(1-\lambda_0/\lambda_i)\Gamma(1+\lambda_0/\lambda_i)\right]^{\lambda_0/\lambda_{i-1}}$$

Note that the exponential is $e^{\lambda_0 t}$ for all values of k. Simulations show that despite the fact that various approximations were made in the derivations, the theoretical results agreed well with simulation.

To obtain results for the waiting times via induction, we had to also consider $Z_k^*(t)$, the number of type-k individuals at time t. $e^{-\lambda_k t} Z_k^*(t) \to V_k$ where

$$Ee^{-\theta V_k} = \left(1 + c_{\theta,k}\mu_k \theta^{\lambda_0/\lambda_k}\right)^{-1}$$

Invoking a Tauberian theorem we then concluded that V_k has a power law tail

$$P(V_k > x) \sim c_{V,k}\mu_k x^{-\lambda_0/\lambda_k}$$

confirming simulations of Iwasa, Nowak, and Michor (2006). These results consider the process at a fixed time t, but lead easily to results for the system at time T_M at which there are M type-0 cells, and can be used to obtain results at time S_M when the total tumor size is M.

The remainder of the paper is devoted to proofs. Section 2 establishes the branching process results we need. Theorems 1 and 2 are proved in Section 3, Theorem 3 in Section 4, Theorem 4 in Section 5, and Theorem 5 in Section 6.

2 Branching process results

We begin by computing the extinction probability, ρ. By considering what happened on the first jump

$$\rho = \frac{b_0}{a_0 + b_0} \cdot 1 + \frac{a_0}{a_0 + b_0} \cdot \rho^2$$

Rearranging gives $a_0\rho^2 - (a_0 + b_0)\rho + b_0 = 0$. Since 1 is a root, the quadratic factors as $(\rho - 1)(a_0\rho - b_0) = 0$, and

$$\rho = \begin{cases} b_0/a_0 & \text{if } a_0 > b_0 \\ 1 & \text{if } a_0 \le b_0 \end{cases} \tag{14}$$

The generating function $F(x,t) = Ex^{Z_0(t)}$ can been computed by solving a differential equation. On page 109 of Athreya and Ney (1972), or in formula (5) of Iwasa, Nowak, and Michor (2006) we find the solution:

$$F(x,t) = \frac{b_0(x-1) - e^{-\lambda_0 t}(a_0 x - b_0)}{a_0(x-1) - e^{-\lambda_0 t}(a_0 x - b_0)} \tag{15}$$

Subtracting this from 1 gives

$$1 - F(x,t) = \frac{\lambda_0(x-1)}{a_0(x-1) - e^{-\lambda_0 t}(a_0 x - b_0)} \tag{16}$$

Setting $x = 0$, we have

$$P(Z_0(t) > 0) = 1 - F(0,t) = \frac{\lambda_0}{a_0 - b_0 e^{-\lambda_0 t}} \tag{17}$$

$e^{-\lambda_0 t} Z_0(t)$ is a nonnegative martingale and converges to a limit W_0, with $EW_0 = 1$ and

$$\{W_0 > 0\} = \{Z_0(t) > 0 \text{ for all } t\} \equiv \Omega^0_\infty$$

To compute the Laplace transform $Ee^{-\theta W_0}$ when $a_0 > b_0$, we set $x = \exp(-\theta e^{-\lambda_0 t})$ in (15) to get

$$\frac{b_0(\exp(-\theta e^{-\lambda_0 t}) - 1) - e^{-\lambda_0 t}(a_0 \exp(-\theta e^{-\lambda_0 t}) - b_0)}{a_0(\exp(-\theta e^{-\lambda_0 t}) - 1) - e^{-\lambda_0 t}(a_0 \exp(-\theta e^{-\lambda_0 t}) - b_0)}$$

As $t \to \infty$, $e^{-\lambda_0 t} \to 0$, so $\exp(-\theta e^{-\lambda_0 t}) \to 1$, $\exp(-\theta e^{-\lambda_0 t}) - 1 \sim -\theta e^{-\lambda_0 t}$, and the above simplifies to

$$\approx \frac{-b_0 \theta e^{-\lambda_0 t} - e^{-\lambda_0 t}\lambda_0}{-a_0 \theta e^{-\lambda_0 t} - e^{-\lambda_0 t}\lambda_0} = \frac{b_0\theta + \lambda_0}{a_0\theta + \lambda_0}$$

Dividing top and bottom of this by a_0 and recalling $\lambda_0 = a_0 - b_0$ we have

$$= \frac{(b_0/a_0)\theta + 1 - (b_0/a_0)}{\theta + 1 - (b_0/a_0)} = \frac{b_0}{a_0} + \left(1 - \frac{b_0}{a_0}\right)\frac{1 - (b_0/a_0)}{\theta + 1 - (b_0/a_0)}$$

To invert the Laplace transform, we note that if δ_0 is the point mass at 0 then $p\delta_0 + (1-p)$exponential(ν) has Laplace transform

$$p + (1-p)\frac{\nu}{\nu + \theta} = \frac{p\theta + \nu}{\theta + \nu}$$

so $p = b_0/a_0$, in agreement (14), and $\nu = 1 - (b_0/a_0)$.

3 Growth of the number of type 1's

Our first result is no harder to prove for a general k than it is for $k = 1$, so to avoid repeating the proof later we do it in general now. By considering the times $s \le t$ at which mutations occur and the growth rate of the resulting branching processes of type-k cells,

$$EZ_k(t) = \int_0^t EZ_{k-1}(s) u_k e^{\lambda_k(t-s)}\, ds \tag{18}$$

Lemma 1. *$M_t = e^{-\lambda_k t} Z_k(t) - \int_0^t u_k e^{-\lambda_k s} Z_{k-1}(s)\, ds$ is a martingale.*

Proof. Let $\mathcal{F}_t$ be the σ-field generated by $Z_j(s)$ for $0 \le j \le k$ and $s \le t$. Taking differences

$$M_{t+h} - M_t = e^{-\lambda_k(t+h)} Z_k(t+h) - e^{-\lambda_k(t)} Z_k(t) - \int_t^{t+h} u_k e^{-\lambda_k s} Z_{k-1}(s)\, ds$$

Using the expected value formula (18) we see that

$$E(Z_k(t+h)|\mathcal{F}_t) = e^{\lambda_k h} Z_k(t) + E\left(\int_t^{t+h} u_k Z_{k-1}(s) e^{\lambda_k(t+h-s)}\, ds \middle| \mathcal{F}_t \right)$$

Multiplying by $e^{-\lambda_k(t+h)}$ gives

$$E\left(e^{-\lambda_k(t+h)} Z_k(t+h) - e^{-\lambda_k t} Z_k(t) - \int_t^{t+h} u_k Z_{k-1}(s) e^{-\lambda_k s}\, ds \middle| \mathcal{F}_t \right) = 0$$

The desired result, $E(M_{t+h} - M_t|\mathcal{F}_t) = 0$, follows. $\square$

Proof of Theorem 2. If $\lambda_1 > \lambda_0$ then $I_1 = \int_0^\infty u_1 e^{-\lambda_1 s} Z_0(s)\, ds$ converges and has

$$EI_1 = u_1 \int_0^\infty e^{-(\lambda_1 - \lambda_0)s}\, ds = u_1/(\lambda_1 - \lambda_0)$$

$X_t = -M_t$ is a martingale with $\sup E(X_t^+) \le EI < \infty$, so by the martingale convergence theorem (see e.g., (2.10) in Chapter 4 of Durrett (2005)), X_t converges to a limit X. Since $I_1(t) = \int_0^t u_k e^{-\lambda_k s} Z_0(s)\, ds \to I_1$ as $t \to \infty$, it follows that $e^{-\lambda_1 t} Z_1(t) \to W_1$. The martingale starts at 0 so $Ee^{-\lambda_1 t} Z_1(t) = EI_1(t) \to EI_1$ and it follows from Fatou's lemma that $EW_1 \le EI_1$.

To conclude that $EW_1 = EI_1$, we will show $\sup_t E(e^{-\lambda_1 t} Z_1(t))^2 < \infty$. We will hold off on the proof until we can use induction to address all W_k at once in Section 4, see Lemma 5.

Proof of Theorem 3. To obtain information about the distribution of V_1, recall that $Z_1^*(t)$ is the number of type-1's at time t in the system with $Z_0^*(t) = e^{\lambda_0 t} V_0$ for $t \in (-\infty, \infty)$, let $\tilde{Z}_1(t)$ be the number of 1's at time t in the branching process with $Z_0(0) = 0$, $Z_1(0) = 1$, and let $\tilde{\phi}_{1,t}(\theta) = Ee^{-\theta \tilde{Z}_1(t)}$.

Lemma 2. $E\left(e^{-\theta Z_1^*(t)}|V_0\right) = \exp\left(-u_1 \int_{-\infty}^t V_0 e^{\lambda_0 s}(1 - \tilde{\phi}_{1,t-s}(\theta))\, ds\right)$

Proof. We begin with the corresponding formula in discrete time:

$$\begin{aligned}
E\left(e^{-\theta Z_1^*(n)} \middle| Z_0(m), m \le n\right) &= \prod_{m=-\infty}^{n-1} \sum_{k_m=0}^{\infty} e^{-u_1 Z_0(m)} \frac{(u_1 Z_0(m))^{k_m}}{k_m!} \tilde{\phi}_{1,n-m-1}(\theta)^{k_m} \\
&= \prod_{m=-\infty}^{n-1} \exp\left(-u_1 Z_0(m)(1 - \tilde{\phi}_{1,n-m-1}(\theta))\right) \\
&= \exp\left(-u_1 \sum_{m=-\infty}^{n-1} Z_0(m)(1 - \tilde{\phi}_{1,n-m-1}(\theta))\right)
\end{aligned}$$

Breaking up the time-axis into intervals of length h and letting $h \to 0$ and using $Z_0^*(s) = \bar{W}_0 e^{\lambda_0 s}$ gives the result in continuous time. $\square$

Replacing θ by $\theta e^{-\lambda_1 t}$ and letting $t \to \infty$

$$E\left(e^{-\theta V_1} | V_0\right) = \lim_{t\to\infty} \exp\left(-u_1 V_0 \int_{-\infty}^{t} e^{\lambda_0 s}(1 - \tilde{\phi}_{1,t-s}(\theta e^{-\lambda_1 t}))\, ds\right) \tag{19}$$

To calculate the limit, we note that by (3)

$$\tilde{Z}_1(t-s)e^{-\lambda_1(t-s)} \Rightarrow \frac{b_1}{a_1}\delta_0 + \frac{\lambda_1}{a_1}\ \text{exponential}(\lambda_1/a_1) \tag{20}$$

so multiplying by $e^{\lambda_1 s}$ and taking the Laplace transform, we have

$$1 - \tilde{\phi}_{t-s}(\theta e^{-\lambda_1 t}) \to \frac{\lambda_1}{a_1}\int_0^\infty (1 - e^{-\theta x})(\lambda_1/a_1)e^{\lambda_1 s}e^{-xe^{\lambda_1 s}\lambda_1/a_1} dx \tag{21}$$

Using this in (19) and interchanging the order of integration

$$E\left(e^{-\theta V_1}|V_0\right) = \exp\left(-u_1 V_0 h(\theta)\right)$$

where

$$h(\theta) = (\lambda_1^2/a_1^2)\int_0^\infty (1 - e^{-\theta x})\left[\int_{-\infty}^\infty e^{\lambda_0 s}e^{\lambda_1 s}e^{-xe^{\lambda_1 s}\lambda_1/a_1} ds\right] dx. \tag{22}$$

Changing variables $u = xe^{\lambda_1 s}\lambda_1/a_1$, $e^{\lambda_1 s}ds = a_1\, du/(\lambda_1^2 x)$ in the inside integral and then $y = \theta x$, $dy = \theta dx$ in the outside integral

$$\begin{aligned} h(\theta) &= \frac{\lambda_1^2}{a_1^2}\int_0^\infty (1 - e^{-\theta x})\left[\int_0^\infty \frac{a_1}{x\lambda_1^2}\left(\frac{a_1 u}{\lambda_1 x}\right)^{\lambda_0/\lambda_1} e^{-u}\, du\right] dx \\ &= \frac{1}{a_1}\left(\frac{a_1\theta}{\lambda_1}\right)^{\lambda_0/\lambda_1}\int_0^\infty (1-e^{-y})y^{-\lambda_0/\lambda_1 - 1}\, dy \int_0^\infty u^{\lambda_0/\lambda_1}e^{-u}\, du \end{aligned} \tag{23}$$

To make this easier to evaluate we integrate by parts in the first integral to convert it into

$$\frac{\lambda_1}{\lambda_0}\int_0^\infty e^{-y}y^{-\lambda_0/\lambda_1}\, dy$$

and both integrals are values of the Γ function: $\Gamma(z) = \int_0^\infty t^{z-1}e^{-t}\, dt$.

At this point we have shown

$$h(\theta) = c_{h,1}\theta^{\lambda_0/\lambda_1} \tag{24}$$

where the constant

$$c_{h,1} = \frac{1}{\lambda_0}\left(\frac{a_1}{\lambda_1}\right)^{\lambda_0/\lambda_1 - 1}\Gamma(1 - \lambda_0/\lambda_1)\Gamma(\lambda_0/\lambda_1 + 1) \tag{25}$$

Taking the expected value of $\exp(-u_1 V_0 h(\theta))$ now, and using (4) we have

$$E\left(e^{-\theta V_1}\right) = \frac{1}{1 + c_{\theta,1} u_1 \theta^{\lambda_0/\lambda_1}} \tag{26}$$

where $c_{\theta,1} = c_{h,1} a_0/\lambda_0$.

To show that V_1 has a power law tail, we note that as $\theta \to 0$,

$$1 - E\left(e^{-\theta V_1}\right) \sim c_{\theta,1} u_1 \theta^{\lambda_0/\lambda_1} \tag{27}$$

and then use a Tauberian theorem from Feller Volume II (pages 442–446). Let

$$\omega(\lambda) = \int_0^\infty e^{-\lambda x} dU(x)$$

Lemma 3. *If L is slowly varying and U has an ultimately monotone derivative u, then $\omega(\lambda) \sim \lambda^{-\rho} L(1/\lambda)$ if and only if $u(x) \sim x^{\rho-1} L(x)/\Gamma(\rho)$.*

To use this result we note that if $\phi(\theta)$ is the Laplace transform of the probability distribution F, then integrating by parts gives

$$\int_0^\infty e^{-\theta x} dF(x) = (e^{-\theta x})(F(x) - 1)\Big|_0^\infty - \theta \int_0^\infty e^{-\theta x}(1 - F(x))\, dx$$

so we have

$$1 - \phi(\theta) = \theta \int_0^\infty e^{-\theta x}(1 - F(x))\, dx$$

Using (27), it follows that

$$\frac{1 - E(e^{-\theta V_1})}{\theta} \sim c_{\theta,1} u_1 \theta^{\lambda_0/\lambda_1 - 1}$$

and we conclude

$$P(V_1 > x) \sim c_{V,1} u_1 x^{-\lambda_0/\lambda_1}$$

where $c_{V,1} = c_{\theta,1}/\Gamma(1 - (\lambda_0/\lambda_1))$.

Proof of the Corollary. If S is the sum of Poisson mean λ number of independent random variables with distribution μ then

$$\begin{aligned}
Ee^{-\theta S} &= \sum_{k=0}^\infty e^{-\lambda} \frac{\lambda^k}{k!} \left(\int e^{-\theta x} \mu(dx) \right)^k \\
&= \exp\left(-\lambda + \lambda \int e^{-\theta x} \mu(dx) \right) \\
&= \exp\left(- \int (1 - e^{-\theta}) \lambda \mu(dx) \right)
\end{aligned}$$

Let $A = Cu_1V_0$, $\lambda_\epsilon = \int_\epsilon^\infty Ax^{-\lambda_0/\lambda_1}\,dx$ and μ_ϵ have density $\lambda_\epsilon^{-1}Ax^{-\lambda_0/\lambda_1}$ on (ϵ,∞). If S_ϵ is the sum of Poisson mean λ_ϵ number of independent random variables with distribution μ_ϵ then

$$Ee^{-\theta S_\epsilon} = \exp\left(-\int_\epsilon^\infty (1-e^{-\theta})Ax^{-\lambda_0/\lambda_1}\,dx\right)$$

Letting $\epsilon \to 0$ and comparing with (23) gives the desired result. □

4 Proof of Theorem 4

We begin by computing $EZ_k(t)$ using $EZ_k(t) = \int_0^t EZ_{k-1}(s)u_ke^{\lambda_k(t-s)}ds$.

$$EZ_k(t) = u_1u_2\cdots u_k\sum_{j=0}^k \frac{e^{\lambda_jt}}{\Gamma_{j,k}} \qquad \text{for } k \geq 1 \tag{28}$$

where $\Gamma_{j,k} = \prod_{i\leq k, i\neq j}(\lambda_j - \lambda_i)$.

Proof. Let X_j be independent exponential(γ_j), and let p_k is the density function of $X_0 + \cdots + X_k$, which satisfies the recursion

$$p_k(t) = \int_0^t p_{k-1}(s)\gamma_ke^{-\gamma_k(t-s)}\,ds$$

Armitage (1952) has shown, see his paragraph 4, that

$$p_k(t) = (-1)^{k+1}\gamma_0\cdots\gamma_k\sum_{j=0}^k \frac{e^{\lambda_jt}}{\Delta_{j,k}}$$

where $\Delta_{j,k} = \prod_{i\leq k, i\neq j}(\gamma_i - \gamma_i)$. If we take $\gamma = -\lambda_i$ then comparing the two recursions and their initial condition $EZ_0(t) = e^{\lambda_0t}$ and $p_0(t) = \gamma_0e^{-\gamma_0t}$ shows

$$p_k(t) = (-1)^{k+1}EZ_k(t)\frac{\lambda_0\cdots\lambda_k}{u_1\cdots u_k}$$

The derivation of the formula for $p_k(t)$ only uses calculus which relies on the γ_i are distinct, so the desired result follows. □

Let $I_k(t) = \int_0^t u_ie^{-\lambda_is}Z_{k-1}(s)ds$ and $I_k = I_k(\infty)$.

Lemma 4. *For $k \geq 1$, $EI_k < \infty$.*

Proof Using $EZ_0(t) = e^{\lambda_0 t}$ and (28)

$$EI_k = E\int_0^\infty u_k e^{-(\lambda_k-\lambda_{k-1})s}\left(e^{-\lambda_{k-1}s}Z_{k-1}(s)\right)ds < \infty \qquad \Box$$

To prove Theorem 4 now, observe that $X_t = I_k(t) - e^{-\lambda_k t}Z_k(t) \le I_k$ is a martingale and dominated by an integrable random variable, so (2.10) of Chapter 4 of Durrett (2005) implies $X_t \to X$ a.s. Since $I_k(t) \to I_k$ a.s., it follows that $e^{-\lambda_k t}Z_k(t) \to W_k$. (28) implies that

$$Ee^{-\lambda_k t}Z_k(t) \to \frac{u_1 u_2 \cdots u_k}{\Gamma_{k,k}}$$

To prove that $EW_k = EI_k$ we will show

Lemma 5. *For $k \ge 0$, $\sup_t E(e^{-\lambda_k t}Z_k(t))^2 < \infty$.*

Proof. The base case is easy. We look at the derivative $\frac{d}{dt}E(e^{-\lambda_0 t}Z_0(t))^2$

$$\begin{aligned}
&= -2\lambda_0 E(e^{-\lambda_0 t}Z_0(t))^2 + e^{-2\lambda_0 t}\left(E[a_0 Z_0(t)(2Z_0(t)+1)] - E[b_0 Z_0(t)(2Z_0(t)-1)]\right)\\
&= e^{-2\lambda_0 t}(a_0+b_0)EZ_0(t) = e^{-\lambda_0 t}(a_0+b_0)
\end{aligned}$$

And it follows that $\sup_t E(e^{-\lambda_0 t}Z_0(t))^2 < \infty$. Next, we suppose $\sup_t E(e^{-\lambda_{k-1}t}Z_{k-1}(t))^2 \le c_{k-1} < \infty$ and consider the derivative $\frac{d}{dt}E(e^{-\lambda_k t}Z_k(t))^2$

$$\begin{aligned}
&= -2\lambda_k E(e^{-\lambda_k t}Z_k(t))^2 + e^{-2\lambda_k t}E[a_k Z_k(t)(2Z_k(t)+1)]\\
&\quad - e^{-2\lambda_k t}E[b_k Z_k(t)(2Z_k(t)-1)] + e^{-2\lambda_k t}E[u_k Z_{k-1}(t)(2Z_k(t)+1)]\\
&= (a_k+b_k)e^{-2\lambda_k t}EZ_k(t) + u_k e^{-2\lambda_k t}E[Z_{k-1}(t)(2Z_k(t)+1)]
\end{aligned}$$

To bound $2u_k e^{-2\lambda_k t}E[Z_{k-1}(t)Z_k(t)]$, we use the Cauchy-Schwarz inequality and $y^{1/2} \le 1+y$ for $y \ge 0$ to get

$$\begin{aligned}
&\le 2u_k e^{-(\lambda_k-\lambda_{k-1})t}E[e^{-2\lambda_{k-1}t}Z_{k-1}^2(t)]^{1/2}E[e^{-2\lambda_k t}Z_k^2(t)]^{1/2}\\
&\le 2u_k e^{-(\lambda_k-\lambda_{k-1})t}c_{k-1}^{1/2}\left(1 + E[e^{-2\lambda_k t}Z_k^2(t)]\right)
\end{aligned}$$

Comparison theorems for differential equations imply that $E(e^{-\lambda_k t}Z_k(t))^2 \le m(t)$ where $m(t)$ is the solution of the differential equation

$$\frac{d}{dt}m(t) = a(t)m(t) + b(t), \quad m(0) = 0 \tag{29}$$

with $a(t) = 2u_k c_{k-1}^{1/2}e^{-(\lambda_k-\lambda_{k-1})t}$, and

$$b(t) = (a_k+b_k)e^{-2\lambda_k t}EZ_k(t) + 2u_k e^{-2\lambda_k t}EZ_{k-1}(t) + 2u_k c_{k-1}^{1/2}e^{-(\lambda_k-\lambda_{k-1})t}$$

Solving (29) gives

$$m(t) = \int_0^t b(s)\exp\left(\int_s^t a(r)\,dr\right)$$

Since $a(t)$ and $b(t)$ are both integrable, $m(t)$ is bounded. $\Box$

5 Proof of Theorem 5

Let $\mathcal{F}_t^{k-1}$ be the σ-field generated by $Z_j^*(s)$ for $j \le k-1$ and $s \le t$. Let $\tilde{Z}_k(t)$ be the number of type k's at time t in the branching process with $Z_k(0) = 1$ and $Z_j(0) = 0$ for $j \le k-1$, and let $\tilde{\phi}_{k,t}(\theta) = Ee^{-\theta \tilde{Z}_1(t)}$. The reasoning of Lemma 2 implies

$$E(e^{-\theta Z_k^*(t)} | \mathcal{F}_t^{k-1}) = \exp\left(-u_k \int_{-\infty}^t Z_{k-1}^*(s)(1 - \tilde{\phi}_{k,t-s}(\theta))\, ds \right)$$

Replacing $Z_{k-1}^*(s)$ by $e^{\lambda_{k-1}s} V_{k-1}$, θ by $\theta e^{-\lambda_k t}$, and letting $t \to \infty$

$$E\left(e^{-\theta V_k} | \mathcal{F}_\infty^{k-1}\right) = \lim_{t\to\infty} \exp\left(-u_k V_{k-1} \int_{-\infty}^t e^{\lambda_{k-1}s}(1 - \tilde{\phi}_{k,t-s}(\theta e^{-\lambda_k t}))\, ds \right) \tag{30}$$

At this point the calculation is the same as the one in Section 3 with 1 and 0 replaced by k and $k-1$ respectively, and we conclude that

$$E\left(e^{-\theta V_k} | \mathcal{F}_\infty^{k-1}\right) = \exp\left(-u_k V_{k-1} h_k(\theta)\right) \tag{31}$$

where $h_k(\theta) = c_{h,k} \theta^{\lambda_{k-1}/\lambda_k}$ and

$$c_{h,k} = \frac{1}{\lambda_{k-1}} \left(\frac{a_k}{\lambda_k}\right)^{\lambda_{k-1}/\lambda_k - 1} \Gamma(1 - \lambda_{k-1}/\lambda_k)\Gamma(\lambda_{k-1}/\lambda_k + 1)$$

Let $c_{\theta,k} = c_{\theta,k-1} c_{h,k}^{\lambda_0/\lambda_k}$. When $k = 2$ taking expected value and using Theorem 3 gives

$$Ee^{-\theta V_2} = \left(1 + c_{\theta,2} u_1 u_2^{\lambda_0/\lambda_1} \theta^{\lambda_0/\lambda_2}\right)^{-1}$$

Using this in (31)

$$Ee^{-\theta V_3} = \left(1 + c_{\theta,3} u_1 u_2^{\lambda_0/\lambda_1} u_3^{\lambda_0/\lambda_2} \theta^{\lambda_0/\lambda_3}\right)^{-1}$$

The pattern should be clear so we leave to the reader to check the induction step. The result for $P(V_k > x)$ follows from Lemma 3, and the proof of Theorem 5 is complete.

6 Proof of Theorem 6

We are interested in finding

$$\lim_{M\to\infty} \exp\left[-u_1 \int_{-\infty}^0 M e^{\lambda_0 s}(1 - \tilde{\phi}_{-s}(\theta(Mu_1)^{-\lambda_1/\lambda_0}))\, ds \right]$$

First, we make the change of variables $s = t - \frac{1}{\lambda_0}\log(Mu_1)$.

$$= \lim_{M\to\infty} \exp\left[-\int_{-\infty}^{\frac{1}{\lambda_0}\log(Mu_1)} e^{\lambda_0 t}(1 - \tilde{\phi}_{\frac{1}{\lambda_0}\log(Mu_1)-t}(\theta(Mu_1)^{-\lambda_1/\lambda_0}))\, dt \right]$$

Taking the limit as $M \to \infty$ is essentially the same calculation as (21).

$$= \exp\left[-\int_{-\infty}^{\infty} e^{\lambda_0 t}\frac{\lambda_1}{a_1}\int_0^{\infty}(1-e^{-\theta x})(\lambda_1/a_1)e^{\lambda_1 t}e^{-xe^{\lambda_1 t}\lambda_1/a_1}\,dx\,dt\right]$$

We conclude by recognizing this double integral as $h(\theta)$ defined in (22) and computed in (24).

References

Armitage, P. (1953) A note on the time-homogeneous birth process. *J. Royal Statist. Soc.* 15, 90–91

Armitage, P., and Doll, R. (1954) The age distribution of cancer and a multi-stage theory of carcinogenesis. *Brit. J. Cancer.* 8, 1–12

Armitage, P., and Doll, R. (1957) A two-stage theory of carcinogenesis. *Brit. J. Cancer.* 11, 161–169

Durrett, R. (2005) *Probability: Theory and Examples.* Third Edition, Duxbury Press

Durrett, R., Schmidt, D., and Schweinsberg, J. (2009). A waiting time problem arising from the study of multi-stage carcinogenesis. *Ann. Appl. Prob.* 19, 676–718.

Fisher, J.C. (1959) Multiple mutation theory of carcinogenesis. *Nature.* 181, 651–652.

Frank, S.A. (2007) *Dynamics of Cancer: Incidence, Inheritance and Evolution.* Princeton Series in Evolutionary Biology

Haeno, H., Iwasa, Y., and Michor, F. (2007) The evolution of two mutations during clonal expansion. *Genetics.* 177, 2209–2221

Iwasa, Y., Michor, F. and Nowak, M.A. (2004) Stochastic tunnels in evolutionary dynamics. Genetics. 166, 1571–1579

Iwasa, Y., Michor, F., Komarova, N.L. and Nowak, M.A. (2005) Population genetics of tumor suppressor genes.*J. Theor. Biol.* 233, 15–23

Iwasa, Y., Nowak, M.A., and Michor, F. (2006) Evolution of resistance during clonal expansion. *Genetics.* 172, 2557–2566

Knudson, A.G. (1971) Mutation and cancer: statistical study of retinoblastoma. *Proc. Natl. Acad. Sci. USA* 68, 820–823

Knudson, A.G. (2001) Two genetic hits (more or less) to cancer. *Nature Reviews Cancer.* 1, 157–162

Michor, F., Hughes, T.P., Iwasa, Y., Branford, S., Shah, N.P., et al. (2005) Dynamics of chronic myeloid leukemia. *Nature.* 435, 1267–1270

Nordling, C.O. (1953) A new theory on cancer inducing mechanisms. *British J. Cancer.* 7, 68–72

Schweinsberg, J. (2008) The waiting time for m mutations. *Electron. J. Probab.* 13, 1442–1478.