Chapter 2: Models of cancer evolution

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1 Introduction

To develop an understanding of cancer evolution and its implications, e.g. for therapy, we examine some simple models of mutation and population growth. This is based on branching processes, Markov processes (either discrete or continuous time) that describe probabilistic growth processes. A key assumption is that cells are independent, i.e. birth and death rates are independent of population size, composition and neighbouring cells. Although a strong assumption, it is likely to be true until resource competition occurs which will only occur once tumours are of sufficient size.

The branching process material is predominantly taken from [1] where the reader can find additional results.

2 Branching process models of cancer evolution

We consider first a simple (continuous time) branching process model. Let $Z(t)$ be the number of cells at time t. Cells give birth at rate a, and die at rate b.

$$\text{Birth} : Z \to Z+1, \text{ rate } aZ, \text{ Death} : Z \to Z-1, \text{ rate } bZ. \tag{1}$$

The growth rate is thus $\lambda = a - b$. Thinking of $Z(t)$ as the tumour size, interest in this model comes from the extinction probability ρ, the size at time t and the time to reach size M (e.g. detection threshold, such as visible by X-rays).

We note that cells are independent, which gives rise to exponential growth; $\frac{d}{dt}E[Z(t)] = \lambda E[Z(t)]$, giving $E[Z(t)] = e^{\lambda t}$ with one cell initially. This model is thus only appropriate for early stages of tumour growth whilst resources are not limiting. To calculate the extinction probability $\rho = P(Z(t) = 0 \; for \; some \; t \geq 0)$, consider the first event, where the cell either dies (probability $b/(a+b)$) or gives birth in which case there are 2 independent branching processes (each of which would then have to die out, probability ρ^2),

$$\rho = \frac{b}{a+b} + \frac{a}{a+b}\rho^2 \tag{2}$$

Rearranging gives the quadaratic $(\rho - 1)(a\rho - b) = 0$, ie $\rho = 1$ or $\rho = b/a$. The extinction probability is thus $\rho = min(1, b/a)$, and each cell produced after division has this probability of its lineage dying out.

The distribution of this branching process is in fact solvable, see eg [1]; in brief the generating function $F(x,t) = E[x^{Z(t)}]$ satisfies

$$\frac{\partial F}{\partial t} = -(a+b)F + aF^2 + b = (1-F)(b - aF)$$

to give

$$F(x,t) = \frac{b(x-1) - e^{-\lambda t}(ax - b)}{a(x-1) - e^{-\lambda t}(ax-b)} \tag{3}$$

which corresponds to the generalised geometric distribution ($a > b$),

$$p_0 = \alpha, p_n = (1-\alpha)(1-\beta)\beta^{n-1}, \; for \; n \geq 1 \tag{4}$$

where $\alpha = b(e^{\lambda t}-1)/(ae^{\lambda t}-b)$, $\beta = a(e^{\lambda t}-1)/(ae^{\lambda t}-b)$. This can be proved by computing the generating function of the generalised geometric distribution. This reproduces the extinction probability b/a by taking $t \to \infty$.

We will make use of the following result, [1]
Theorem 1. Suppose $a > b$, then as $t \to \infty$, $e^{-\lambda t}Z(t) \to W$,

$$W = \frac{b}{a}\delta_0 + \frac{\lambda}{a}Exp\left(\frac{\lambda}{a}\right)$$

where δ_0 is the point mass at 0. Thus,

$$P(W=0) = \frac{b}{a},\ P(W > x|W > 0) = exp\left(-\frac{x\lambda}{a}\right)$$

This implies that $e^{-\lambda t}Z(t)$ is exponentially distributed when conditioned on not dying out.

Time to reach the detection threshold M

Tumours have to be a certain size before they are detectable by screening methods such as X-ray. It is estimated that the detection threshold for chronic myeloid leukemia is $M = 10^5$ cells.

The time to reach M is an exit time problem. An alternative approach is to use the limiting distribution $e^{-\lambda t}Z(t) \to V$, with $V \sim Exp(\lambda/a)$. Define $T_M = min(t|Z(t) = M)$. Then, within this approximation we have,

$$P(T_M \leq t) = P(V \geq e^{-\lambda t}M) = \exp\left(-\frac{\lambda M e^{-\lambda t}}{a}\right) \tag{5}$$

which is a double exponential or Gumbel distribution. This distribution has mass for $T_M < 0$, a consequence of the approximation; however in practice the probability $P(T_M < 0) = \exp -\lambda M/a$ is negligible. The probability density is $f_{T_M} = -\frac{d}{dt}P(T_M \leq t)$; thus, the average time to reach size M is given by,

$$E[T_M] = \frac{\lambda^2 M}{a}\int_{-\infty}^{\infty} te^{-\lambda t}\exp\left(-\frac{\lambda M e^{-\lambda t}}{a}\right)dt \tag{6}$$

This can be evaluated using variable $z = \lambda M e^{-\lambda t}/a$, then integrate by parts to give,

$$E[T_M] = -\frac{1}{\lambda}\int_0^{\infty} log_e\left(\frac{az}{\lambda M}\right)e^z dz = \frac{1}{\lambda}log_e\left(\frac{M\lambda}{a}\right) + \frac{1}{\lambda}\gamma \tag{7}$$

where $\gamma = -\int_0^{\infty} e^{-z}log_e z dz = 0.57721...$ is Euler's constant.

2.1 Multi-type branching processes

The branching process above is easily extendable to include other cell types. Let $Z_i(t)$ be the number of cells at time t of type i. Cells of type i give birth (to individuals of type i) at rate a_i, die at rate b_i (growth rate $\lambda_i = a_i - b_i$) and give birth to individuals of type $i+1$ at rate u_{i+1}. We consider a tumour starting with a single cell of type 0. We define the probability space $\Omega^0_\infty = \{Z_0(t) > 0 \text{ for all } t \geq 0\}$, i.e. the tumour does not die out.

Time of first occurence of type 1 cells

Let τ_1 be the time of first occurence of type 1. Type 1s are produced at rate $u_1 Z_0(t)$, so conditional on type 0 not dying out we have,

$$P(\tau_1 > t|Z_0(s), s \leq t, \Omega^0_\infty) = \exp -u_1\int_0^t Z_0(s)ds \tag{8}$$

which follows from the the rate of loss of probability,

$$\frac{d}{dt}P(\tau_1 > t|Z_0(s), s \leq t, \Omega^0_\infty) = -u_i Z_0(t) P(\tau_1 > t|Z_0(s), s \leq t, \Omega^0_\infty)$$

Using the limiting approximation $Z_0(s)|_{\Omega^0_\infty} \approx e^{\lambda_0 t} V_0$, $V_o \sim Exp(\lambda_0/a_0)$, the integral in (8) can be performed to give,

$$P(\tau_1 > t|Z_0(s), s \leq t, \Omega^0_\infty) = \exp -\frac{u_1(e^{\lambda_0 t} - 1)V_0}{\lambda_0}.$$

By taking expectations over Z_0 we obtain (ignoring 1 relative to $e^{\lambda_0 t}$, which is expected to be large as u_1 is small),

$$P(\tau_1 > t|\Omega^0_\infty) = E\left[\exp -\frac{u_1 e^{\lambda_0 t} V_0}{\lambda_0}\right] = \left(1 + \frac{a_0 u_1 e^{\lambda_0 t}}{\lambda_0^2}\right)^{-1} \tag{9}$$

where we have used the Laplace transform,

$$E[e^{-\theta V_0}] = \int_0^\infty e^{-\theta x} \frac{\lambda_0}{a_0} e^{-\lambda_0 x/a_0} dx = \left(1 + \frac{a_0\theta}{\lambda_0}\right)^{-1}$$

The median will thus read, $(P(\tau_1 > t|\Omega^0_\infty) = 1/2)$,

$$t^1_{1/2} \approx \frac{1}{\lambda_0} log\left(\frac{\lambda_0^2}{a_0 u_1}\right)$$

Since the new cell (of type 1) may not give rise to a surviving population, we can also define σ_1 the time of first occurence of type 1 that gives rise to a family that does not die out. The rate of birth of successful type 1 mutations is $u_1\lambda_1/a_1$. The above formula can thus be simply adjusted by $u_1 \to u_1\lambda_1/a_1$.

Has a tumour mutated before detection?

A key message of successful cancer treatment is early detection and treatment. This is based on the observation that later detection is often associated with failed treatment, specifically cancer typically recurs on a timescale of the order of months with a resistant tumour. Using the models above we can calculate the probability that at the onset of treatment (or detection) that a mutation conferring resistance had already occurred; upon treatment the resistant clone has a growth advantage and grows out.

The probability of interest is $P(Z_1(T_M) > 0|\Omega^0_\infty)$; the probability the resistant clone (type 1) already exists at detection. The possibly more obvious probability of generating a type 1 by mutation before T_M,

$$P(\tau_1 > T_M|Z_0(s), s \leq T_M, \Omega^0_\infty) = \exp -u_1 \int_0^{T_M} Z_0(t)dt \tag{10}$$

does not allow for the fact that the type 1 cells may have died out at the detection time T_M. To compute this probability, we note that mutations to type 1 occur at rate $u_1 M e^{-\lambda_0 s}$ at time $T_M - s$ as $Z_0(t) \approx V_0 e^{\lambda_0 t}$. From (3) we have the generating function for Z_1, from which we can calculate,

$$P(Z_1(t) > 0|Z_1(0) = 1) = 1 - F(0, t) = \frac{\lambda_1}{a_1 - b_1 e^{-\lambda_1 t}}$$

Thus, a type 1 cell generated at $T_M - s$ has a probability $\frac{\lambda_1}{a_1 - b_1 e^{-\lambda_1 s}}$ of surviving until T_M. The number of mutations to type 1 that occur prior to T_M is thus Poisson, whilst survival to T_M thins this Poisson process (again a Poisson process). The number of mutations prior to T_M that survive to T_M is thus Poisson with mean, [1]

$$\mu(M) = M u_1 \int_0^\infty e^{-\lambda_0 s} \frac{\lambda_1}{a_1 - b_1 e^{-\lambda_1 s}} ds = \frac{M u_1}{\lambda_0} \int_0^1 \frac{\lambda_1}{a_1 - b_1 t^{\frac{\lambda_1}{\lambda_0}}} dt$$

[1] Proof?

changing variables to $t = e^{-\lambda_0 s}$. It follows that

$$P(Z_1(T_M) > 0|\Omega_\infty^0) = 1 - e^{-\mu(M)} \tag{11}$$

In the special case where mutation does not change the growth rate (but type 1 is resistant to therapy, whilst type 0 isn't and dies out under therapy), we have $\lambda_1 = \lambda_0$, and thus

$$P(Z_1(T_M) > 0|\Omega_\infty^0) = 1 - \exp\left(-\frac{u_1 M}{b_0} log_e\left(\frac{a_0}{a_0 - b_0}\right)\right)$$

We can also compute $P(\tau_1 > T_M|\Omega_\infty^0)$ under the same approximations,

$$P(\tau_1 > T_M|\Omega_\infty^0) \approx \exp -u_1 M \int_0^\infty e^{-\lambda_0 s} ds = \exp -\frac{u_1 M}{\lambda_0}, \tag{12}$$

Since $a_0 > b_0$, we have $P(\tau_1 > T_M|\Omega_\infty^0) \geq P(Z_1(T_M) > 0|\Omega_\infty^0)$ as expected.

Similarly the probability of generating a type 1 that gives rise to a family that does not die out can be computed, $P(\sigma_1 > T_M|\Omega_\infty^0)$.

Example: Chronic myeloid leukemia is treated through drugs such as imatinib, dasatinib and nilotinib. The probability of a preexisting resistance to any of these was examined [2]. They set the detection threshold $M = 10^5$ cells, and from *in vitro* studies estimated growth parameters $a_0 = 0.008, b_0 = 0.003$ per year. The mutations (single nucleotide substitutions in the protein BCR-ABL) that provide resistance are known giving $u_1 = 8 \times 10^{-10}$ yr^{-1}. For instance the mutant T351I (Threonine instead of Isoleucine at position 315 in the gene sequence) has parameters $a_1 = 0.0088, b_1 = 0.003$ giving, (evaluating (11) numerically, and using (12)),

$$P(Z_1(T_M) > 0|\Omega_\infty^0) = 0.0126$$

$$P(\tau_1 \leq T_M|\Omega_\infty^0) = 1 - e^{-0.016} = 0.0159$$

$$P(\sigma_1 \leq T_M|\Omega_\infty^0) = 1 - e^{-0.0105} = 0.0105$$

As expected $P(\tau_1 \leq T_M|\Omega_\infty^0) > P(Z_1(T_M) > 0|\Omega_\infty^0)$ as the former does not allow for die out before time T_M, whilst $P(Z_1(T_M) > 0|\Omega_\infty^0) > P(\sigma_1 \leq T_M|\Omega_\infty^0)$ as the latter conditions on the clone Z_1 surviving for all time, former only to time T_M.

The probability of resistance $P(Z_1(T_M) > 0|\Omega_\infty^0)$ is thus 0.0126. Performing the calculations over all the 11 possible resistance mutations, the probability that at detection there are no resistant types is 0.87, while the probability that there is one resistant type is 0.12, and two 0.01, [2]. Since different mutations confer resistance to a different selection of drugs, the efficacy of combination therapy (multiple drugs) can also be examined.

These calculations can be used to establish treatment windows for cancer therapy to maximise efficacy, limiting the probability of resistant clones [3], whilst ODE models allow optimal temporal treatment schedules to be determined [4].

Size of (resistant) type 2 at detection.

Section 12 in Durrett.

Growth of Z_1

See [1] for interesting results on finiteness.

2.2 Accumulation of neutral (passenger) mutations.

So far we have focused on key mutations – the driver mutations that give a selective advantage and mutations that confer drug resistance. But mutation is a random process that will occur throughout the genome; thus neutral, or passenger mutations will also arise. One of the key problems in identifying the evolutionary pathway of a cancer is that the driver mutations (those that confer a fitness

advantage) are hidden amongst a larger set of neutral passenger mutations. We can approximate the distribution of these passenger mutations as follows.

The interest here is determining the distribution of the sizes of the different clones - under the infinite alleles model each mutation gives rise to a new clone. Define $F_t(x)$ as the expected number of neutral mutations present in more than x individuals at time t. Then define the population site frequency spectrum as the limit for large times, which can be computed for the Yule model,

$$F(x) = \lim_{t\to\infty} F_t(x) = \frac{\nu}{\lambda x}$$

where ν is the (neutral) mutation rate, λ the population growth rate. Thus the distribution of number of neutral mutations with frequency x has a power law behaviour as $1/x^2$.

The Yule model is the branching process in absence of death (b=0 in (1)). We separate mutation from division, i.e. a mutation event results in an individual changing type. Let $Y(t)$ be the number of individuals at time t, and define $T_j = min_t\{Y_t = j\}$; thus $T_1 = 0$. The j individuals at time T_j start independent Yule process $Y^1, Y^2 ... Y^j$ with,

$$lim_{s\to\infty} e^{-\lambda s} Y^i(s) = \zeta_i$$

where the ζ_i are independent exponential variates with mean 1 (see Theorem 1) and time $s = t - T_j$.

Mutations occur at rate $j\nu$ in the j individuals, whilst the rate of growth is $j\lambda$; thus the number of mutations N_j that occur whilst there are j individuals is geometrically distributed (success probability $\lambda/(\lambda+\nu)$ that event is a division),

$$P(N_j = k) = \left(\frac{\nu}{\lambda+\nu}\right)^k \frac{\lambda}{\lambda+\nu}$$

with mean $E[N_j] = \nu/\lambda$.

A mutation that occurs in individual i whilst there are j individuals will have frequency $r_i = \zeta_i / \sum_{k=1}^{j} \zeta_k$ as $t \to \infty$. The probability that this frequency is above x is,

$$P(r_i > x) = (1-x)^j$$

as $r_i \sim Beta(1, j-1)$ [2]. Summing over the history of the process, as a neutral mutation with frequency $> x$ can occur whilst there are any number of individuals, the expected number of neutral mutations with frequency $> x$ in the population (at $t \to \infty$)) is

$$\frac{\nu}{\lambda} \sum_{j=1}^{\infty} (1-x)^j = \frac{\nu}{\lambda x}$$

3 Models with fixed size N

The branching process models above all had exponential growth, i.e. the total population size was unbounded. In many circumstances it is more appropriate to consider the population size as fixed $= N$. Then birth and death are linked; a birth event requires someone else to die.

Moran Process. A Markov chain where X is the number of individuals in a population with allele A (remainder have allele a). Population size is N and both A, a have the same fitness (neutral evolution). At each step an individual is chosen for death, and another for birth. Then the transition matrix (P_{ij} probability of transition $i \to j$) is,

$$P_{i,i-1} = \frac{N-i}{N}\frac{i}{N},\ P_{i,i+1} = \frac{N-i}{N}\frac{i}{N},\ P_{ii} = 1 - P_{i,i-1} - P_{i+1,i}$$

The mean $E[X_{i+1}|X_i] = X_i$ as expected from neutrality. This MC has two absorbing states, $X = 0$ where allele A dies out, and $X = N$, allele A becomes fixed. The fixation probability of A when

[2] Proof. P21 [1]

there are i individuals of type A is i/N. This follows since each individual has probability $1/N$ of being the ancestor at fixation. What is the mean time to absorption?.

Selection is easy to incorporate into this model, modelling different birth rates by an individual's fitness. Generally, let there be N_i individuals of type i ($\sum_i N_i = N$) with fitness f_i, then the events with non-zero probabilities are,

$$P(N_i \to N_i + 1, N_j \to N_j - 1) = \frac{N_i f_i}{\sum_k N_k f_k} \frac{N_j}{N}$$

References

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