Branching Processes in Biology - Case Studies and Simulations

Snježana Lubura Strunjak, Vanja Wagner

November 3, 2020

These materials represent a collection of interesting topics on applications of branching processes in biology. In order to better understand the examples presented in these materials, students are encouraged to replicate the simulations and modify various interactive plots using the accompanying RStudio workbook `branching.Rnw`. To download and set RStudio and please follow this link `https://rstudio.com/products/rstudio/download/`. The linked website also provides a large repository of user manuals, code examples and tutorials for beginners. You can change the code in the workbook freely and export a new PDF file with your personalized outputs. If you are not that accustomed to the R environment, you can easily customize plots and simulations in the workbook by searching for changeable parameters and functions (just search for `%INTERACTIVE`).

1 The Galton-Watson Process

The Galton-Watson process is the oldest, simplest and best known branching process.
Description of the process:

A single ancestor particle lives for exactly one unit of time, and at the moment of death it produces a random number of progeny according to a prescribed probability distribution. Each of the first-generation progeny behaves, independently of each other, as the initial particle did. It lives for a unit of time and produces a random number of progeny. Each of the second-generation progeny behaves in the identical way, and so forth.

Let us suppose that the number of progeny produced by each particle is a non-negative integer random variable with distribution function $\{p_k;\, k = 0, 1, 2, \ldots\}$, and denote by $f(s)$ the progeny probability generating function.

1.1 Backward equation

Any particle existing in the process, except for the ancestor of the process, can be assigned to a subprocess traceable to a particular first-generation offspring of the ancestor.

The number Z_{n+1} of particles in the generation $n+1$ of the process (or at time $n+1$) is equal to the sum of the particles counts in the generation n of all the Z_1 subprocesses initiated by the first-generation offspring of the ancestor particle. Let $Z_{1,n+1}^{(j)}$ denote the number of individuals at time $n+1$ in the process started by a single ancestor born at time 1 (here the additional superscript (j) denotes the jth iid copy). Then,

$$Z_{n+1} = \begin{cases} Z_{1,n+1}^{(1)} + \cdots + Z_{1,n+1}^{(Z_1)}, & Z_1 > 0 \\ 0, & Z_1 = 0 \end{cases}$$

or

$$Z_{n+1} = \sum_{i=1}^{Z_1} Z_{1,n+1}^{(j)}. \tag{1}$$

Random variables $Z_{1,n+1}^{(j)}$ are independent identically distributed copies and their common distribution is identical to that of Z_n, hence equation (1) can be written as

$$Z_{n+1} = \sum_{j=1}^{Z_1} Z_n^{(j)}.$$

Let $f_n(s)$ denote the probability generating function of Z_n. Since $Z_0 = 1$ implies $f_0(s) = s$, we have

$$f_n(s) = f^{(n)}(s) = \underbrace{f\{\cdots[f}_{n \text{ times}}(s)]\cdots\}.$$

1.2 Forward equation

Another approach for modeling this kind of process is based on the fact that any particle in the $(n+1)$st generation of the process can be traced to its parent in the nth generation of the process.

Let Z_{n+1} be the number of particles in the generation $n+1$ of the process (or at time $n+1$). Let $\{X_{in}\}_{i\geq 1, n\geq 0}$ be a doubly infinite array of iid rv's such that $\mathbb{E}[X_{10}] = m < \infty$. We think about X_{in} as the number of progeny of the ith particle existing in generation n. Then,

$$\begin{aligned} Z_0 =& 1 \\ Z_{n+1} =& \begin{cases} X_{1n} + \cdots + X_{Z_n,n}, & \text{if } Z_n > 0, \\ 0, & \text{if } Z_n = 0, \end{cases} \quad n \geq 1 \end{aligned}$$

or

$$Z_{n+1} = \sum_{i=1}^{Z_n} X_{in}\,; \tag{2}$$

that is, the number of individuals (particles, cells), in the $(n+1)$st generation of the process is equal to the number of progeny of all individuals in the generation n. In this approach the new recursion for probability generating function holds:

$$f_{n+1}(s) = f_n[f_1(s)] = f_n[f(s)].$$

For the simulation example in this article we will use the forward equation approach to simulate Galton-Watson process. In our model we assume that $p_0 + p_1 < 1$ and that $p_j \neq 1$ for any j.

1.3 Moments

The moments of the process, when they exist, can be expressed in the terms of the derivatives of $f(s)$ at $s = 1$. We have

$$\mathbb{E}(Z_1) = f'(1-) \equiv m.$$

Using the chain rule of differentiation we get

$$\begin{aligned} \mathbb{E}(Z_n) =& f_n'(1-) = f_{n-1}'(1-) f'(1-) = \cdots = m^n. \\ Var(Z_n) =& \begin{cases} \frac{\sigma^2 m^{n-1}(m^n-1)}{m-1}, & m \neq 1, \\ n\sigma^2, & m = 1, \end{cases} \end{aligned}$$

where $\sigma^2 = Var(Z_1)$ is the variance of the progeny count.

1.4 Extinction

Let us define by $\mathbb{P}(\lim_{n\to\infty} Z_n = 0)$ the probability that the process ever becomes extinct, i.e. *the extinction probability of the process* $\{Z_n\}$.

Theorem 1 *The extinction probability of the* $\{Z_n\}$ *process is the smallest non-negative root* q *of the equation* $s = f(s)$*, where* $f(s)$ *denotes the probability generating function of* X_{10}*. It is equal to* 1 *if* $m \leq 1$*, and it is less than* 1 *if* $m > 1$*.*

1.5 Application: Cell Cycle Model Simulation

We consider the standard Galton-Watson process where $p_k = 0$ for $k \geq 3$. We assume $p_2 + p_1 + p_0 = 1$. We want to calculate using simulations the number of cells in the population after n periods.
For the simulation we need to define values for p_1, p_2 and n. Let
p_2=

```
[1] 0.85
```

p_0=

```
[1] 0.15
```

Since we know that $p_1 = 1 - p_0 - p_2$, we now calculate
p_1 =

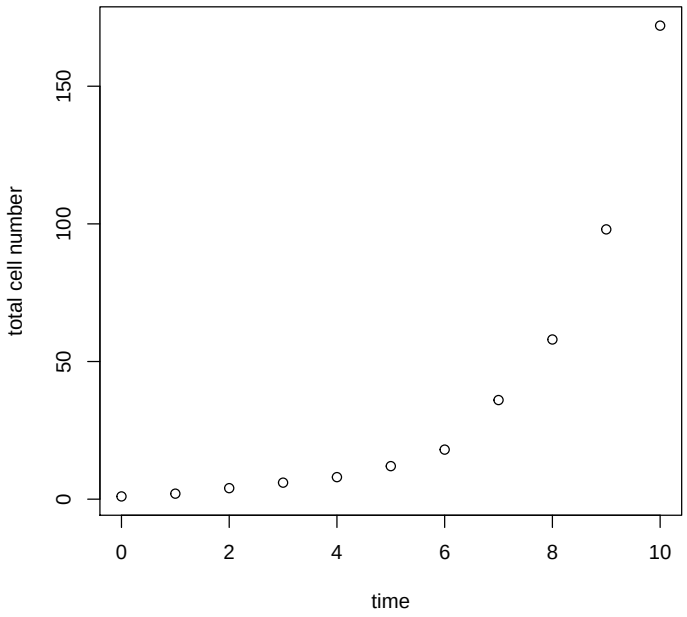
```
[1] 0
```

n =

```
[1] 10
```

Now we will simulate the number of cells during n periods. For the simulation we will use formulas (2) with $Z_0 = 1$. The simulated values are shown in the following figure.

Figure 1: The graph of total cell number during n periods



Let us calculate m for this example. Since

$$m = p_0 + p_1 + 2p_2,$$

we have that
$m =$

```
[1] 1.7
```

Since $m > 1$ we can conclude from Theorem 1 that the probability that process eventually become extinct is less than 1.

1.6 Mean value of Z_n - Simulation exercise

In this exercise we will simulate $N = 100$ values of $Z_1, \ldots, Z_n$.

We will denote by $z_{11}, \ldots, z_{1N}$ the values we will get for Z_1 in this N simulations, by $z_{21}, \ldots, z_{2N}$ the values we will get for Z_2 in this N simulations,..., and by $z_{n1}, \ldots, z_{nN}$ the values we will get for Z_n in this N simulations.

Then we will calculate values:

$$\begin{aligned} m_1 &= \frac{z_{11} + \cdots z_{1N}}{N} \\ m_2 &= \frac{z_{21} + \cdots z_{2N}}{N} \\ &\vdots \\ m_n &= \frac{z_{n1} + \cdots z_{nN}}{N} \end{aligned}$$

The values $m_1, ..., m_n$ are estimated values of $\mathbb{E}[Z_1], \ldots, \mathbb{E}[Z_n]$ from the simulations. We would like to compare this values with the true values $\mathbb{E}[Z_1], \ldots, \mathbb{E}[Z_n]$. Since $\mathbb{E}[Z_1] = m, \mathbb{E}[Z_2] = m^2, \ldots, \mathbb{E}[Z_n] = m^n$, we will plot values $m_1, \ldots, m_n$ together with values $m, m^2, \ldots, m^n$ to compare them.

For the simulation we will use

$$n = 10, p_2 = 0.85, p_0 = 0.15, N = 100.$$

We can calculate m (as before) and we get
$m =$

```
[1] 1.7
```

Hence, the values for $m, m^2, \ldots, m^n$ are:

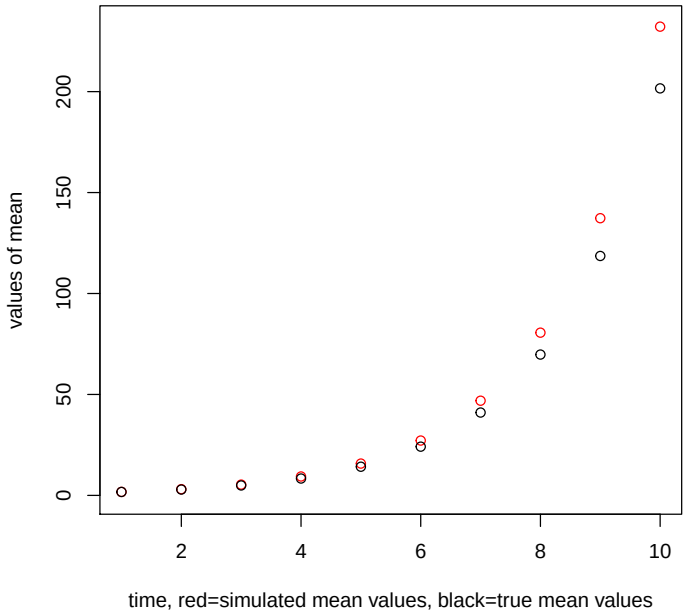
```
 [1]   1.70000   2.89000   4.91300   8.35210  14.19857  24.13757  41.03387
 [8]  69.75757 118.58788 201.59939
```

After we simulate $N = 100$ times the values for $Z_1, \ldots, Z_n$, we calculate $m_1, \ldots, m_n$ and get:

```
 [1]   1.72   3.08   5.34   9.36  15.76  27.16  46.90  80.60 137.30 232.18
```

To compare simulated (estimated) values for $\mathbb{E}[Z_1], \ldots, \mathbb{E}[Z_n]$, i.e. $m_1, \ldots, m_n$, with the true ones, we plot all of them on the same graph (see the following figure).

Figure 2: The comparison of simulated and true values of $\mathbb{E}[Z_1], \ldots, \mathbb{E}[Z_n]$



1.7 Homework

1. Now go through this exercise from the beginning and change values of p_0 and p_2. Let n be equal to 100. For each combination of probabilities calculate m and plot the graph of total number of cells. Can you make some conclusions about the total number of cells? (Hint: Look at the value of m and use Theorem 1.)

2. Also, you can change the initial number of cells (in this example it is equal to 1) and see what happens with the total number of cells.

[1] D.E.Axelrod and M.Kimmel, Branching Processes in Biology. Springer, 2002.

2 Multitype Processes - The Galton-Watson Process Model

In this case study we present models involving branching processes with many types of particle. The progeny of a cell may exhibit a new trait that differs from their parent and may pass on the new trait to their own progeny. Such a change is usually considered to be due to a single irreversible mutation event. However, a possibility exists that the observed change may be due to an event that has a finite probability of being reversible or may be the result of more than one mutational event.

There are many models of cell growth and mutation. Given parameter values, these models predict the distribution of the number of nonmutant and mutant cells at time t in population started at time 0 by a single nonmutant cell.

The observable variables of interest:

$N(t)$ = the expected total number of nonmutant and mutant cells at time t,
$r(t)$ = the expected number of mutant cells at time t,
$P_0(t)$ = the probability of mutant cells being absent from the population at time t.

2.1 The Galton-Watson process model

In this model, cells mutate immediately following division. The hypothesis of the model are:

- Two types of cells exist in the population: type-0 nonmutant cells and type-1 mutant cells.
- All cells in the population have interdivision times equal to $\ln 2$.
- Each cell, at the moment of division, gives birth to two daughter cells. The type of each of the daughters may or may not be the same as that of the mother cell.
- Following division, a type-0 daughter cell undergoes irreversible transformation into a type-1 cell with probability α. The constant α is now called the transition or mutation probability.

It can be shown (see [1] for details) that

$$\begin{aligned} N(t) =& 2^t, \\ r(t) =& 2^t - [2(1-\alpha)]^t, \\ P_0(t) =& (1-\alpha)^{2^{t+1}-2}, \quad t = 0, 1, 2, \ldots \end{aligned}$$

Given experimental values of $N(t)$, $r(t)$ and $P_0(t)$, it is possible to estimate the mutation probability α in model.

2.2 The Positive Regular Case of the Multitype Galton-Watson Process

This is the variant of the multitype Galton-Watson process. We follow evolution of a population composed of particles of k types. An ancestral particle of type i lives for a unit time interval, and in the moment of death, it produces a random number of progeny particles of generally all k type.

The numbers of its progeny of all types constitute a random vector with non-negative integer entries. A progeny of type j starts, independently of all other progeny, a subprocess with itself as the ancestor, by producing at the moment of death, a random vector of progeny of all types. The distribution of this subprocess depends only on the type of the ancestral particle.

The counts of particles of all types existing at time n in the process started by an ancestor of a fixed type constitute a random vector denoted by $\mathbf{Z}_n = (Z_n^1, \ldots, Z_n^k)$. The distribution of this vector depends on the type of the ancestral particle of the process.

2.3 Application: A Model of Two Cell Populations

Description of the model:

Let us consider two cell populations evolving according to the following rules:

1. Both populations have fixed interdivision times equal to 1.
2. In both populations, the divisions are entirely effective (i.e. each parent cell produces exactly two progeny initially of the same type).
3. After division each type-1 progeny (independent of the other) switches to type-2 with probability p_{12} and remains type-1 with probability $p_{11} = 1 - p_{12}$.
4. Analogously, each type-2 progeny (independently of the other) switches to type-1 with probability p_{21} and remains type-2 with probability $p_{22} = 1 - p_{21}$.

Under these assumptions, the proliferation of the cells is described by a 2-type Galton-Watson process.

Simulation of the model:

For the simulation study we need to determine:

- initial number of cells of each type, i.e. Z_0^1 and Z_0^2,
- the probabilities p_{12} and p_{21},
- the time n.

Let
n=

```
[1] 10
```

$Z_0^1 =$

```
[1] 1
```

$Z_0^2 =$

```
[1] 1
```

$p_{12} =$

```
[1] 0.1
```

$p_{21} =$

```
[1] 0.12
```

Since we know that $p_{11} = 1 - p_{12}$ and $p_{22} = 1 - p_{21}$, we can calculate values
$p_{11} = 1 - p_{12} =$

```
[1] 0.9
```

$p_{22} = 1 - p_{21} =$

```
[1] 0.88
```

Now we will simulate the number of type-1 and type-2 cells after n periods. The simulated values are shown in the following figures.

Figure 3: The graph of total type-1 cell number during n periods

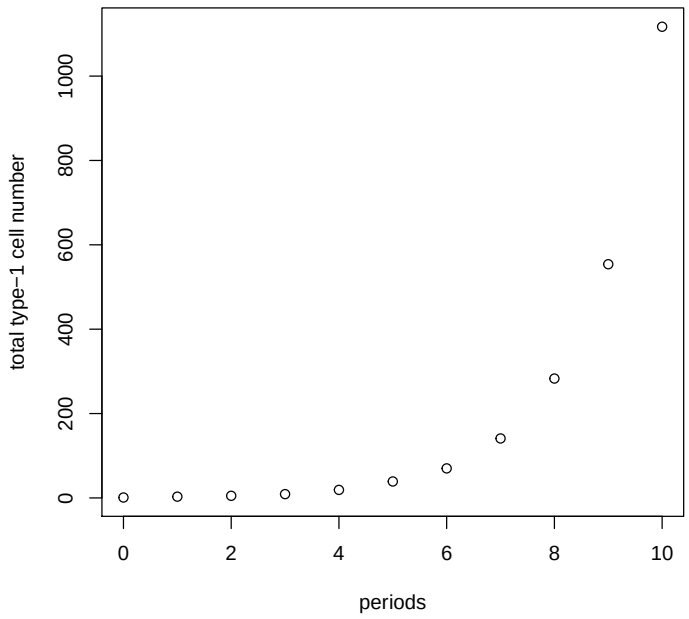
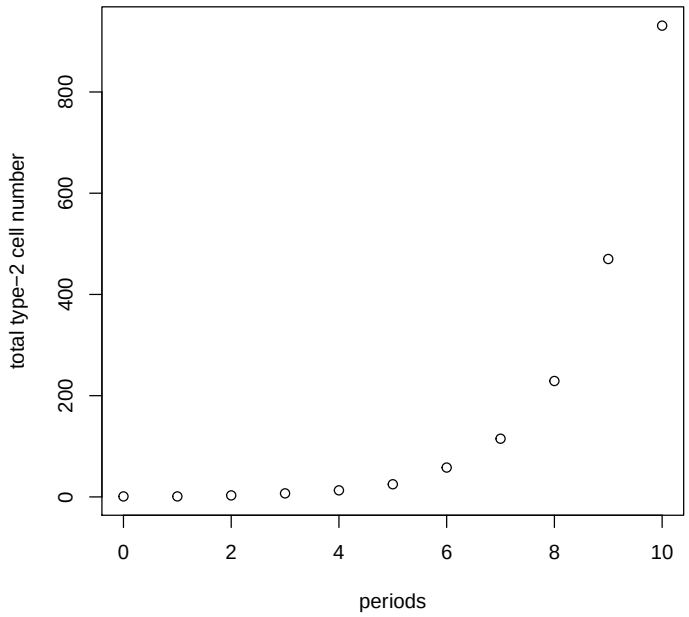


Figure 4: The graph of total type-2 cell number during n periods



Let us calculate the ratio $\frac{p_{21}}{p_{12}}$. With given values of p_{12} and p_{21}, this ratio is equal to

$\frac{p_{21}}{p_{12}} =$

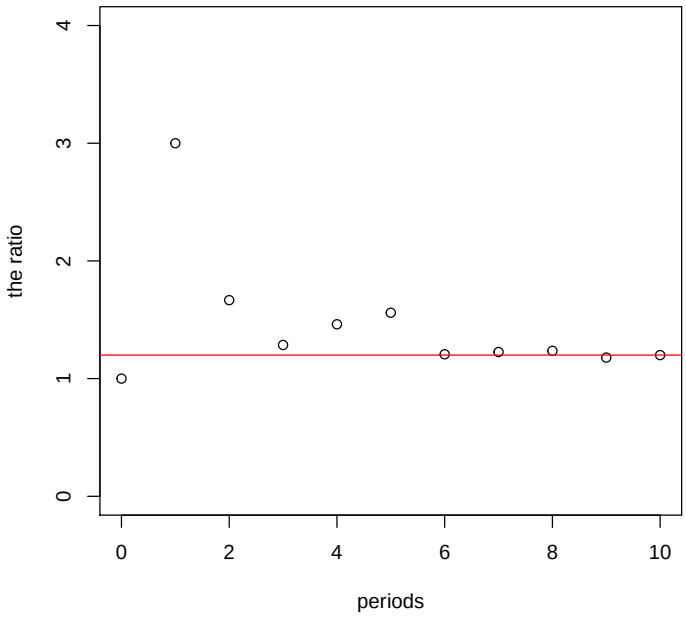
```
[1] 1.2
```

Since the process in this section is positively regular, it is well known (see [1] for details) that the proportion of the type-1 and type-2 cells is asymptotically determined by the ratio $\frac{p_{21}}{p_{12}}$.

Let us denote by $prop_t$ the ratio $\frac{Z_t^1}{Z_t^2}$, $t = 0, 1, 2, \ldots, n$. For the simulated values of Z_t^1 and Z_t^2, the graph of ratios $prop_t$, $t = 0, 1, \ldots, n$ is given in the following figure.

Note: the ratio is closer to the value $\frac{p_{21}}{p_{12}}$ when n is large.

Figure 5: The graph of ratio of total type-1 cell number and total type-2 cell number during n periods



2.4 Homework

1. Now go through this exercise from the beginning and change values of p_{12} and p_{21}. What conclusion can you make from the graph of the ratios?

2. Let n be equal to 15. For at least 3 combinations of probabilities p_{12} and p_{21} plot the graph of total number of type-1 cells and type-2 cells.

3. When $n = 15$ what is your conclusion about the ratios of total type-1 cell number and total type-2 cell number during n periods?

4. Only change the initial number of type-1 cells Z_0^1 and type-2 cells Z_0^2 and make a conclusion about the total number of type-1 and type-2 cells after n periods.

[1] D.E.Axelrod and M.Kimmel, Branching Processes in Biology. Springer, 2002.

3 Clonal Resistance Theory of Cancer Cells

The aim of cancer chemotherapy is to achieve remission (disappearance of clinically detectable cancers) and then to prevent relapse (the regrowth of cancer). In many cases, the failure of chemotherapy is associated with the growth of cells resistant to the applied treatment. There are two conceivable modes of drug resistance:

- resistant cells might exist in tumors before treatment;
- resistant cells might be induced by the treatment.

Drug resistance was extensively studied in bacteria and the resulting ideas have been applied to understand drug resistance in cancer cells. One possible hypothesis is the following:

- in the absence of the treatment drug the mutations from sensitivity to resistance are rare, irreversible events that occur spontaneously;
- the mutation in resistance to a drug arises independently of resistance to another drug.

Although simplistic, this model is useful in understanding the initiation and growth of drug-resistant cancer cells.

We explore the branching process approach to a theory of resistance, which has become influential in the cancer research community. It was originally developed by Coldman and Goldie (for further results and references see Section 4.2 in [1]). We will re-derive some of the original results, using Markov time-continuous branching processes. The assumptions of the theory are as follows:

- The cancer cell population is initiated by a single cell which is sensitive to the cytotoxic (chemotherapeutic) agent. The population proliferates without losses.
- Interdivision time of cells is a random variable with a given distribution.
- At each division, with given probability, a single progeny cell mutates and becomes resistant to the cytotoxic agent.
- Mutations are irreversible.

We wish to compute the probability that when the tumor is discovered, it does not contain any resistant cells. Only in such a situation, is the use of a cytotoxic agent effective. If even a small subpopulation of resistant cells exists, the cancer cell population will eventually reemerge despite the therapy.

3.1 The Branching Process Model for Single-Mutation Case

Let us rewrite the above hypotheses of clonal resistance into the language of branching processes. The model is as follows:

1. In the process, there exist two types of particles, labeled 0 (sensitive) and 1 (resistant).
2. The process is initiated by a single type 0 particle.
3. The life spans of particles are independent random variables, distributed exponentially with parameter $\lambda > 0$.
4. Each particle, at death, divides into exactly two progeny particles:
   - A 0-particle produces either two 0-particles, with probability $1 - \alpha$, or one 0 and one 1-particle, with probability $\alpha > 0$.
   - A 1-particle produces two 1-particles.

Thus, we have a two-type time-continuous Markov branching process. We use the following notation:

- $F_0(s_0, s_1; t)$ is the joint *probability-generating function* (pgf) of the numbers of cells of both types, present at time t, in the process initiated at time 0 by a type 0 cell. If we denote by S_t^0 and S_t^1 the number of cells labeled 0 and 1 at time t for this process, then
$$F_0(s_0, s_1; t) = \mathbb{E}\left[s_0^{S_t^0} s_1^{S_t^1}\right];$$
- $F_1(s_1; t)$ is the probability generating function of $\widetilde{S}_t^1$, the numbers of cells of type 1 present at time t in the process initiated at time 0 by a type 1 cell, i.e.
$$F_1(s_1; t) = \mathbb{E}\left[s_1^{\widetilde{S}_t^1}\right];$$
- $f_i(s_0, s_1)$ is the joint probability generating function of numbers of offspring (N_0^i, N_1^i) of types 0 and 1 of one particle of type i,
$$f_i(s_1, s_2) = \mathbb{E}\left[s_0^{N_0^i} s_1^{N_1^i}\right],\ i = 0, 1;$$
- $M_i(t)$ is the expected number of cells labelled i at time t, $i = 0, 1$,
$$M_0(t) = \mathbb{E}[S_t^0],$$
$$M_1(t) = \mathbb{E}[S_t^1 + \widetilde{S}_t^1].$$

First note that, by model assumption 4, we have

$$f_0(s_0, s_1) = (1 - \alpha)s_0^2 + \alpha s_0 s_1,$$
$$f_1(s_0, s_1) = s_1^2. \tag{3}$$

Furthermore, functions F_0 and F_1 satisfy the following system of differential equations

$$\frac{dF_i}{dt} = -\lambda(F_i - f_i(F_0, F_1)),\ i = 0, 1, \tag{4}$$

with initial conditions $F_i(s_0, s_1; 0) = s_i$. By (3) the system of differential equations (4) becomes

$$\begin{aligned}\frac{dF_0}{dt} &= -\lambda F_0 + \lambda(1-\alpha)F_0^2 + \lambda\alpha F_0 F_1\\ \frac{dF_1}{dt} &= -\lambda F_1 + \lambda F_1^2.\end{aligned} \tag{5}$$

Note that the right-hand side of the second differential equation is a quadratic function of the unknown function F_1. These type of differential equations are of the so-called Riccatti type. One can easily check that the solution to this equation is of the form[1]

$$F_1(s_1; t) = \frac{s_1}{s_1 + (1-s_1)e^{\lambda t}}. \tag{6}$$

Now the right-hand side of the first equation in (5) is again a quadratic function of the unknown function F_0 (note that the function F_1 is a known function). Therefore it is also of Riccatti type, with the solution of the form

$$F_0(s_0, s_1; t) = \frac{s_0 e^{-\lambda t}[e^{-\lambda t}s_1 + (1-s_1)]^{-\alpha}}{1 + s_0([e^{-\lambda t}s_1 + (1-s_1)]^{1-\alpha} - 1)s_1^{-1}}. \tag{7}$$

Next, we recall the relation of the moments of a random variable and the corresponding probability generating functional. For $t \geq 0$,

$$\begin{aligned}M_0(t) &= \frac{\partial F_0}{\partial s_0}(1, 1; t) = e^{\lambda(1-\alpha)t},\\ M_1(t) &= \frac{\partial F_0}{\partial s_1}(1, 1; t) + \frac{dF_1}{ds_1}(1; t) = e^{\lambda t} - e^{\lambda(1-\alpha)t}.\end{aligned}$$

Since $\alpha \in (0, 1)$, the exponent λt is greater than the exponent $\lambda(1-\alpha)t$, so $e^{\lambda t}/e^{\lambda(1-\alpha)t} \to \infty$ as $t \to \infty$. This implies that $M_1(t)$ becomes arbitrarily larger than $M_0(t)$, for t large enough. Therefore, we conclude that, in absence of intervention, the resistant cells eventually outgrow the sensitive ones.

Furthermore, functions F_0 and F_1 also determine the probability $P(t)$ of no-resistant cells at time t,

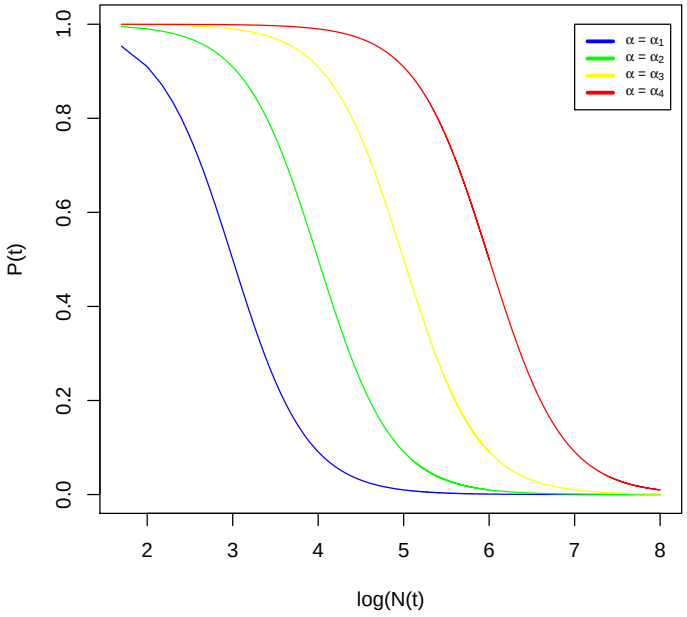
$$P(t) = F_0(1, 0; t) + F_1(0; t) = \frac{1}{(1-\alpha) + \alpha e^{\lambda t}} = \frac{1}{(1-\alpha) + \alpha[M_0(t) + M_1(t)]}. \tag{8}$$

From this equation we can conclude the following (see [2] and the references thereafter):

[1] As an exercise, check for yourself.

- The probability that there are no resistant cells at time t is inversely related to the total expected number of cells $N(t) = e^{\lambda t}$.
- For different (small) mutation rates α, the plots of $P(t)$ are approximately shifted, with respect to each other, along the $\log(N(t))$ axis, see the following interactive figure.

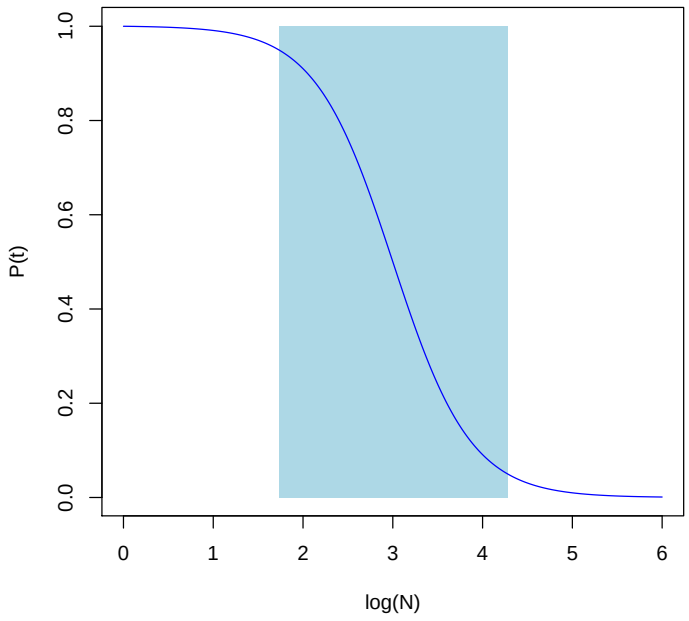
Figure 6: Probability $P(t)$ of no resistant cells in population at time t depending on the tumor size $N(t) = e^{\lambda t}$ (on log scale) for different values of the mutation rate α.



You can access this plot in the accompanying branching.Rnw file in RStudio and examine plots for different values of α. The initial values are set to $\alpha_i = 10^{-(i+2)}$. $i = 1, \ldots, 4$.

- The time interval in which the resistant clone is likely to emerge, i.e., in which $P(t)$ falls from near 1 to near 0, for example, from 0.95 to 0.05, constitutes a relatively short window, see the following figure. Therefore, the therapy should be prompt and radical to decrease cell number and probability $(1 - P(t))$ of emerging resistance.

Figure 7: The time interval (in log population size $\log N_t$) in which the resistant clone is likely to emerge, i.e. where $P(t) \in [p, 1-p]$ for some small p.



You can access this plot in the accompanying branching.Rnw file in RStudio and examine plots for different values of p and α. The initial values are set to $\alpha = 10^{-3}$ and $p = 0.05$).

3.2 Possible alternatives and generalizations

One possible alternative to the assumption 4 in the model presented above is to assume that a sensitive progeny cell may mutate independently with probability $\alpha \in (0, 1)$. This means that

$$\begin{aligned}
\mathbb{P}(N_0^0 = 0, N_1^0 = 2) &= \alpha^2 \\
\mathbb{P}(N_0^0 = 1, N_1^0 = 1) &= 2\alpha(1-\alpha) \\
\mathbb{P}(N_0^0 = 2, N_1^0 = 0) &= (1-\alpha)^2.
\end{aligned}$$

This implies that the joint pgf of (N_0^0, N_1^0) is now of the form

$$f_0(s_0, s_1) = ((1-\alpha)s_0 + \alpha s_1)^2.$$

Under this assumption the system of differential equations (4) does not admit a closed-form solution for F_0. Note that the differential equation for F_1 is the

same as before, so we have a closed-form solution (6) for F_1. Nevertheless, by examining the asymptotic behavior of F_0 we can obtain the following Riccatti-type differential equation for the probability of no resistance cells at time t:

$$\frac{dP(t)}{dt} = -\lambda P(t) + \lambda(1-\alpha)^2 P(t)^2,\ P(0) = 1.$$

One can easily check that the solution to this equation is of the form

$$P(t) = \frac{1}{(1-(1-\alpha)^2)e^{\lambda t} + (1-\alpha)^2},\ t \geq 0.$$

Note that, for small α this probability is approximately equal to the probability (8) from the previous model with parameter 2α (since $\alpha^2 << \alpha$).

A possible generalization to the model is to allow for several different mutations of a single cell. This allows the study of the so-called cross-resistance, that is resistance to more than one drug treatment. Since combinations of two or more drugs are frequently used in therapy, these types of generalizations are very important. To examine a two-mutation case the following alternative to assumption 4 is proposed:

- a sensitive cell divides into two sensitive cells, or one sensitive and the other resistant to treatment 1, or one sensitive and the other resistant to treatment 2 , with probabilities $1-\alpha_1-\alpha_2$, α_1, α_2, respectively;
- a cell resistant to treatment i divides into two cells resistant to treatment i, or one resistant to treatments i and the other resistant to both treatments, with probabilities $1-\widetilde{\alpha}_i$, $\widetilde{\alpha}_i$, respectively, $i = 1, 2$;
- a cell resistant to both treatments divides into two cells resistant to both treatments.

This generalized assumption now leads to a 4 by 4 of differential equations analogous to (4), which does not have a closed-form solution. Nevertheless, when $\alpha_1 = \alpha_2 = \widetilde{\alpha}_1 = \widetilde{\alpha}_2$ on can obtain a closed form for the probability $P(t)$ of no resistance cells at time t by analyzing the asymptotic behavior of this system. For further details see [3].

[1] D.E.Axelrod and M.Kimmel, Branching Processes in Biology. Springer, 2002.
[2] A.J.Coldman, Modeling resistance to cancer chemoterapeutic agents. in Cancer Modeling, Marcel Dekker, 1987.
[3] J.H.Goldie, A.J.Coldman and G.A.Gudauskas, Rationale for the use of alternating-resistant chemotherapy. *Cancer Treatment Reports* **66** (1982), 439–449.

4 Accidental Superspreaders in Branching Processes Models

In this study we will examine a common misconception about superspreading events arising in models based on simple branching processes. Superspreading is a situation where relatively few individuals cause a large number of secondary infections, while a majority of infected individuals cause few (or no) infections at all. It is an important phenomenon in human and animal epidemiology; understanding its causes and consequences is a priority for epidemiological research. Progress has been made by modelling superspreading as a demographic phenomenon, allowing variation in infectivity between individuals.

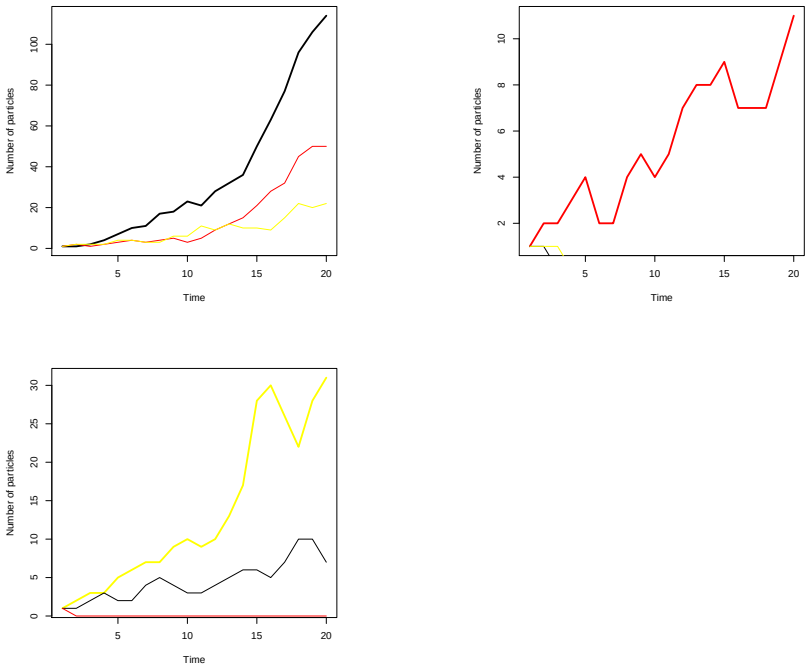
The assumption of nonhomogeneity among individuals (through the infection rate or other model parameters) is crucial for modeling superspreading events via branching processes. When investigating homogeneous branching process models, one can notice events in which a large number of infected individuals are infected through a small number of initial spreaders. That is, we can notice that a large number of particles in the simple branching process at some time are descendants of one (or few) ancestor particles. These types of events are *accidental superspreading events*, since they do not arise as a consequence of some specific property or behavior of the superspreading particle.

To try to understand accidental superspreading, we are going to examine a very simple branching process, consisting of three initial particles - **black**, **red** and yellow. In the first model, the particles die out after a fixed (deterministic) time. Each particle upon death produces, independently of other particles, a random number of offspring following the distribution

$$\begin{pmatrix} 0 & 1 & 2 \\ \frac{1}{4} & \frac{1}{3} & \frac{5}{12} \end{pmatrix}.$$

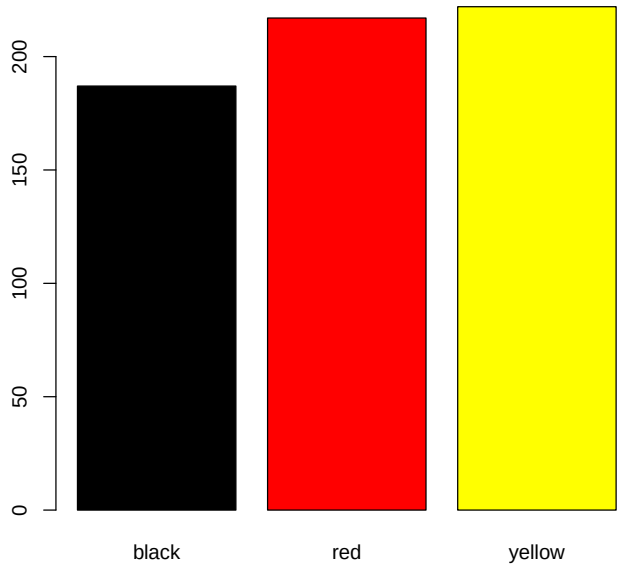
In this example, we are simulating $N = 1000$ spreading scenarios involving these three particles, in the time span of $n = 20$ identical moments. We can observe events where a particle of each color is responsible for the majority of particles at time $t = 20$.

Figure 8: A plot of three accidental superspreader events. You can access this plot in the accompanying branching.Rnw file in RStudio and examine plots for different simple distributions of number of descendants.



But the superspreading event is not contributed to any specific color, since the percentage of superspreading events in these N simulations by color is comparable. This can be seen in the following bar plot.

Figure 9: Bar plot of number of superspreading events by colour in $N = 1000$ simulations. The events without a specific superspreader are omitted.

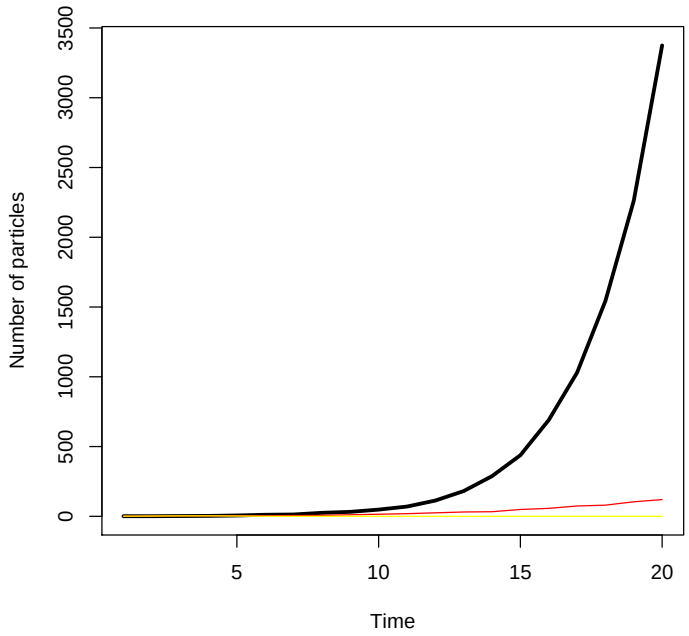


In order to correctly incorporate characteristics of a superspreader, we need to allow a certain nonhomogeneity to the model. Our next simple model will do precisely that, by changing the distribution of the number of offspring of black particles to

$$\begin{pmatrix} 0 & 1 & 2 & 3 \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{pmatrix}.$$

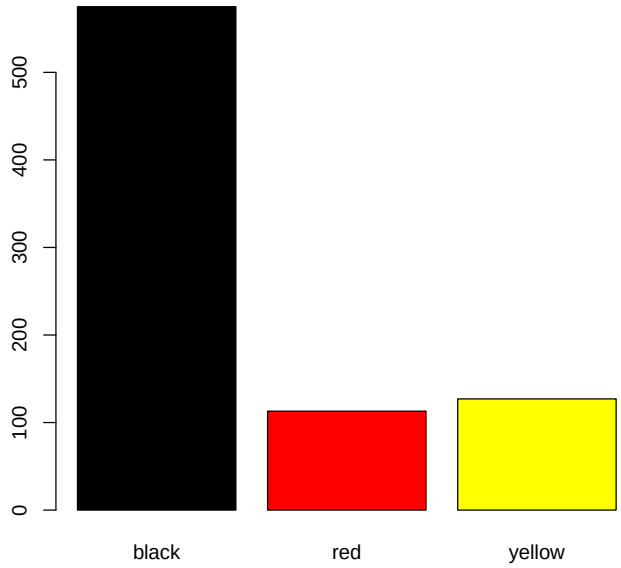
Note that this distribution has a wider range and larger expected value than the distribution from the previous model. This means that we are allowing for a bigger infectivity rate of the black particles, compared to the red and yellow particles. To see this, we repeat a simulation of $N = 1000$ spreading scenarios, now allowing for this nonhomogeneity.

Figure 10: A plot of a superspreader event. You can access this plot in the accompanying branching.Rnw file in RStudio and examine plots for different simple distributions of number of descendants.



Although this model still allows for accidental superspreading events (events when the majority of the particles at time $t = 20$ are yellow or red), the percentage of superspreading events in these N simulations contributed to the black particle is significantly higher.

Figure 11: Bar plot of number of superspreading events by color in $N = 1000$ simulations. The events without a specific superspreader are omitted.



As an alternative to this model allowing for true superspreaders, we consider the following mixing distribution: a black particle

- is a superspreader with probability $\frac{1}{3}$
- is an ordinary particle with probability $\frac{2}{3}$.

As expected, in this mixed model the percentage of superspreading events contributed to the black particle is somewhat lower than in the previous pure-superspreader setting. Nevertheless, superspreading is still dominantly contributed to the black particle.

Figure 12: Bar plot of number of superspreading events by color in $N = 1000$ simulations. The events without a specific superspreader are omitted.