Hematopoiesis Simulator User Manual

February 6, 2018

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Chapter 1

Introduction

Hematopoiesis, or blood cell production, is the formation, development and specialization of blood cells. Hematopoiesis originates from hematopoietic stem cells (HSC). HSC reside in the bone marrow and can replicate (self-renew), can apoptose (die) and can differentiate into multi-potent progenitor cells. Multipotent progenitor cells then further replicate (expand) and specialize, giving rise to morphologically recognizable lineage-specific marrow precursor cells which ultimately develop into mature blood cells. The behavior and decision-making, including fate decision-making of HSC, is not certain since it is not directly observable and cannot be accurately recreated *in vitro*. Similarly, although it is clear that hematopoiesis is maintained by multipotent progenitor direct progeny of HSC (short-term repopulating cells, STRC), the dynamics of their contributions is also uncertain.

This simulator is a visualization and experimentation tool for a two-compartment stochastic process used to model hematopoiesis *in vivo* introduced by Abkowitz et al. (1996 [1]). The simulator allows the user to visualize blood cell production as it occurs in virtual animals. It can therefore be used to help researchers understand stochastic processes, and offers an easy method to test possible experiments, likely outcomes, and conceivable physiologies. For example, one may stimulate the efficacy of gene therapy; test what advantage a subclone might require to persist or to dominate in a specific fashion; simulate CHIP (clonal hematopoiesis of indeterminate potential), how paroxysmal nocturnal hemoglobinuria (PNH) develops in the setting of marrow failure or how myeloproliferative disorders evolve and progress; and assess model validation. The tool has the potential to be useful for both basic and preclinical research.

Chapter 2

A Stochastic Model for Hematopoiesis

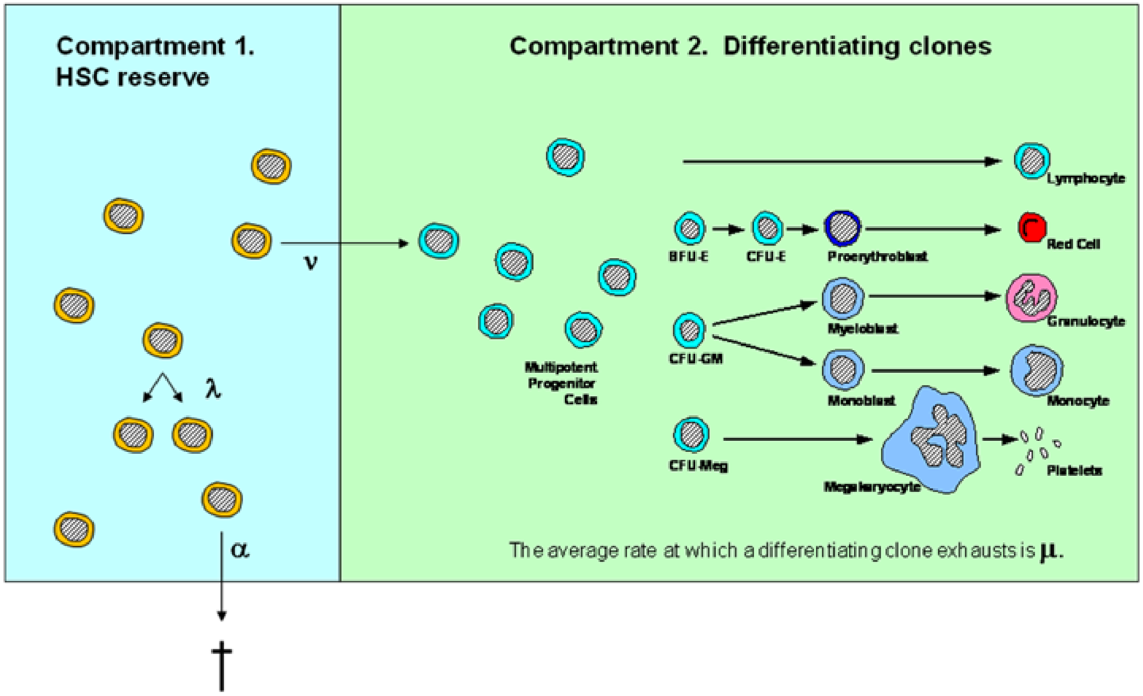


Figure 2.1: A two-compartment stochastic model for hematopoiesis.

A mathematical model describes a natural phenomenon or practical problem quantitatively. The two predominant categories of models are deterministic and stochastic. Stochastic models are more versatile than deterministic models since they integrate uncertainties and allow for the assessment of variability. They are particularly useful when there is incomplete knowledge of a system or of the component behaviors. For example, HSC replicate (self-renew), differentiate, and die depending on their genetic and epigenetic programming and the input of adjacent microenvironmental cells and cytokines. The details of how each fate decision occurs is unknown. However, fate decisions have average rates, and therefore probable likelihoods, and are amenable to modeling using a stochastic approach. Stochastic modeling is empirically useful for complex networks such as hematopoiesis.

As illustrated in Figure 2.1, each HSC has several options. HSC can replicate, apoptose, or differentiate into multi-potent progenitor cells that are capable of giving rise to committed progenitors, precursors, and more mature blood cells (i.e., can enter Compartment 2 and head a differentiating clone). Rates are termed λ (for the average replication (self-renewal) rate of a hematopoietic stem cell), α (for the average apoptosis (death) rate of a hematopoietic stem cell), and ν (for the average rate at which a hematopoietic stem cell differentiates (enters Compartment 2, that is becomes a short-term repopulating cell (STRC) able to give rise to differentiating clones that directly supports hematopoiesis). Differentiating clones contribute to blood cell production for a mean time of $1/\mu$.

Multiple studies have suggested that there is an upper limit K for the total number of HSCs (Abkowitz et al., 2002 [4]), and therefore, for the purpose of modeling, we let N denote the number of HSCs (i.e., number of HSC in Compartment 1) at any point in time, and K, the maximal capacity of the hematopoietic stem cell reserve (maximum number of HSC in Compartment 1). For the purposes of simulation, users can choose rates for all these parameters, and can either model a bounded hematopoietic reserve (of size K) or an unbounded reserve (where K is not considered a variable).

There are two assumptions for this model. One is that fate decisions are *Markovian.* That is, a cell's fate decision does not depend on its history, but rather on its immediate inputs. The other is that all contributing clones contribute equally. Since we can only observe probabilistic function of the committed clones. Thus this stochastic model is a hidden two-compartment model — the reserve compartment where the HSCs reside is unobservable and the committed cells compartment, also called contributing compartment, is assessed indirectly.

The simulator allows for two types of HSC—a and b type. Their rate parameters λ, α, ν, and μ may differ . The sum of a-type and b-type HSCs has the upper limit K discussed previously.

A stochastic process is a collection of random variables $(X_\alpha; \alpha \in T)$ where T is some index set. The random variables take values in a state space S and governed by a probability measure P (Guttorp, 1995 [7]). A Markov process $\{X_t\}$ is a stochastic process with the property that the future states are independent of the past states, given the present state. Let $\{R(t), C(t)\} = \{R_a(t), R_b(t), C_a(t), C_b(t)\}$ denote the Markov population process, where $R(t)$ and $C(t)$ are the sizes of the reserve and contributing compartment at time t, respectively. Note that both $R(t)$ and $C(t)$ are two–dimensional — containing type–a and type–b cells. That is, $R(t) = R_a(t) + R_b(t)$ and $C(t) = C_a(t) + C_b(t)$ at time t.

In a time interval $(t, t+h)$ for small h, the transition probabilities are as follows:

$$\begin{aligned}
\text{Birth: } & Pr(\, R(t+h) = r+1 \mid R(t) = r\,) = \lambda r h + o(h) \\
\text{Death: } & Pr(\, R(t+h) = r-1 \mid R(t) = r\,) = \alpha r h + o(h) \\
\text{Emigration: } & Pr(\, R(t+h) = r-1,\, C(t+h) = c+1 \mid R(t) = r,\, C(t) = c\,) = \nu r h + o(h) \\
\text{Exhausting: } & Pr(\, C(t+h) = c-1 \mid C(t) = c\,) = \mu c h + o(h)
\end{aligned}$$

It follows that the distribution of the time to the next event is an exponential with rate

$$R(t)(\lambda + \alpha + \nu) + C(t)\mu$$

and the probabilities of the events are:

$$\begin{aligned}
\text{Birth: } & \frac{R(t)\lambda}{R(t)(\lambda+\alpha+\nu)+C(t)\mu} \\
\text{Death: } & \frac{R(t)\alpha}{R(t)(\lambda+\alpha+\nu)+C(t)\mu} \\
\text{Emigration: } & \frac{R(t)\nu}{R(t)(\lambda+\alpha+\nu)+C(t)\mu} \\
\text{Exhausting of a progenitor cell: } & \frac{C(t)\mu}{R(t)(\lambda+\alpha+\nu)+C(t)\mu}
\end{aligned}$$

Let $Y(t)$ denote the number of type–a cells in a sample obtained from the contributing compartment at time t. Denote the total number of cells in the sample by $n(t)$. Given $C_a(t)$ and $C_b(t)$, $Y(t)$ has a hypergeometric distribution, that is

$$Pr(\, Y(t) = k\,) = \frac{\binom{C_a(t)}{k}\binom{C_b(t)}{n(t)-k}}{\binom{C(t)}{n(t)}},$$

where $k = 0, 1, \ldots, n(t)$. It is reasonable to use binomial approximation to the hypergeometric distribution because of the large number of cells in the contributing compartment. Define the selection probability

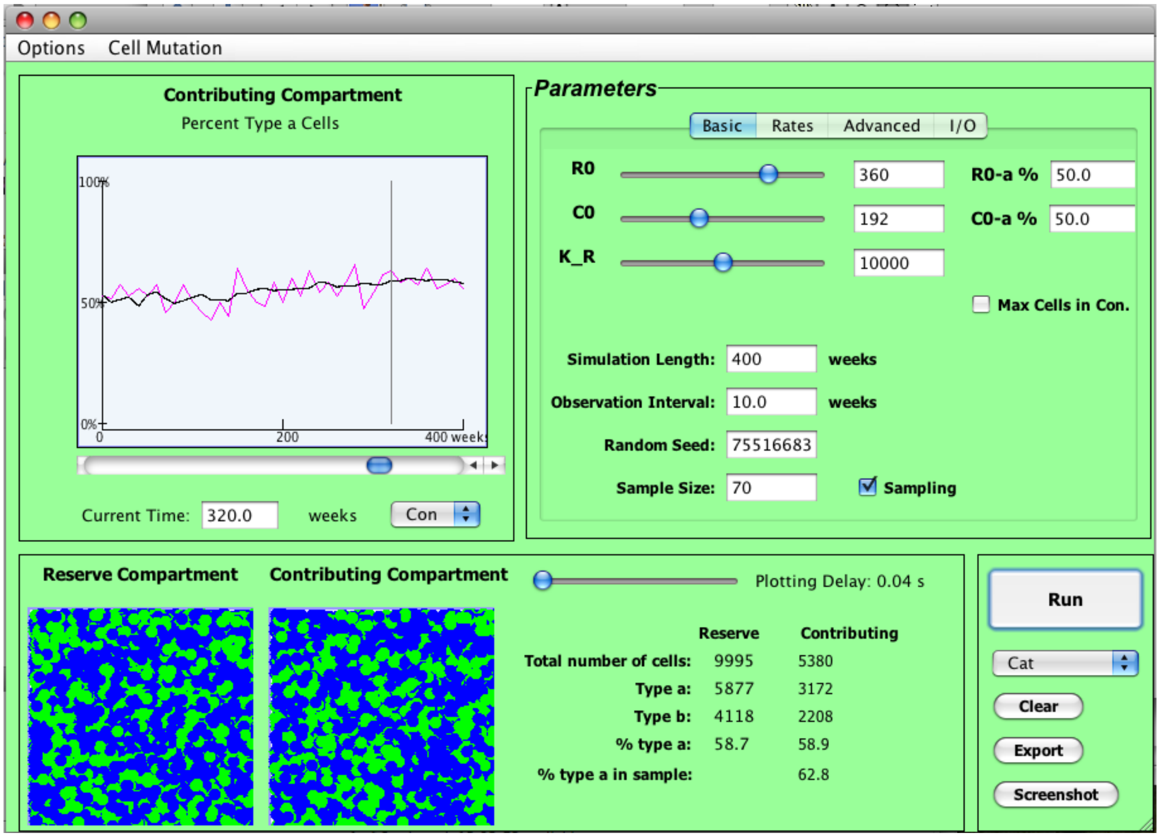
$$P_c(t) := \frac{C_a(t)}{C(t)} = \frac{C_a(t)}{C_a(t) + C_b(t)}.$$

Thus $Y(t) \sim \text{Binomial}(n(t),\, P_c(t))$.

This model has been used to describe hematopoiesis in cats (Abkowitz et al., 1996 [1]), mice (Abkowitz et al., 2000 [3]), primates (Shepherd et al., 2007 [10]) and humans (Shepherd et al. 2004 [9]; Catlin et al., 2011 [5]). More detailed models as in (Fong et al., 2009 [12]) and (Xu et al., 2016 [13]) are essentially refinements extending the same basic structure posited by this two-compartment model, and intuition gained here largely carries over. The estimated parameters are consistent with other in vivo or model-based parameter determinations (Abkowitz and Guttorp, 2009 [6]).

Chapter 3

Hematopoiesis Simulator



R0 360

C0 192

K_R 10000

R0-a % 50.0

C0-a % 50.0

□ Max Cells in Con.

Simulation Length: 400 weeks

Observation Interval: 10.0 weeks

Random Seed: 75516683

Sample Size: 70 ☑ Sampling

Current Time: 320.0 weeks

Plotting Delay: 0.04 s

	Reserve	Contributing
Total number of cells:	9995	5380
Type a:	5877	3172
Type b:	4118	2208
% type a:	58.7	58.9
% type a in sample:		62.8

Figure 3.1: Current version of the Hematopoiesis Simulator

3.1 Overview

This Java-based simulator that visualizes the stochastic model over time (Figure 3.1) is available for non-commercial use at `http://depts.washington.edu/ventures/UW_Technology/Express_Licenses/hemsim.php`.

To date, our program allows researchers to vary the four rate parameters λ, α, ν, and μ independently for the two types of HSCs, the initial total number of cells and percentage of type–a cells in each compartment, and the capacities of the reserve compartment and the committed cells compartment, respectively. For instance, it can be used to simulate the evolution of myeloproliferative disorders and the emergence of normal HSCs and progeny cells in the setting of marrow failure. The simulation length (in weeks) and the way samples are collected can be altered as well. In addition, the simulator offers the option to adjust replication fates when $N \leq K$. That is, when the total number of cells in the reserve compartment is greater than or equal to K and the next event to happen is replication, the simulator will generate a random number between 0 and 1 instead of ignoring the event. If this number is greater than a specified percentage, the new cell will survive and commit to progenitor cell lineages, i.e., the total number of cells in the contributing compartment will increase by 1; otherwise, the replication will be neglected. The percentage criteria can be modified. Moreover, the simulator provides the functionality to repeat the simulation in latest run, display the control values (parameters, initial values, etc), save the current set of control values, and load previously saved set.

The simulator produces graphical outputs and summary statistics for both compartments. The time series of the percentage of type-a cells in each compartment is plotted. One can view the cellular composition graph and statistics of the two compartments in the process of simulation and revisit a certain time by using a slider. The simulator also offers control over the delay time between each sampling. The simulation results can be exported into a file under a given name. One can save a screenshot image as well.

The simulator is written in Java using version 6. The portability of Java code removes the platform restriction on the simulator. The simulator is composed of two main parts: the simulation engine and the presentation layer. The simulation engine is responsible for carrying out the stochastic simulation. It is built into its own jar file and can be invoked by other programming languages, such as `R` (R Development Core Team, 2009 [8]), a language and environment for statistical computing and graphics, via `rJava` interface (Urbanek, 2009 [11]). The presentation layer accepts user input, sends a request to the simulation engine and renders the output graphically.

3.2 Setting up

Before using Hematopoiesis Simulator, please make sure that the current version of Java is Version 6. Java downloads for all operating systems can be found at `http://www.java.com/en/download/manual.jsp`.

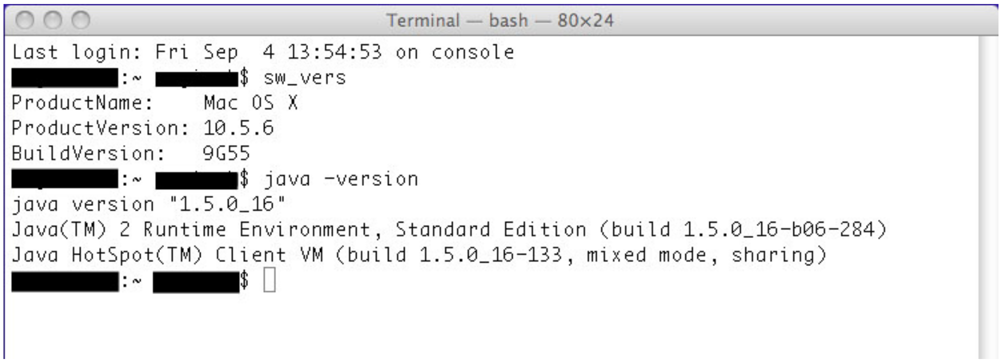
Windows To check the current Java version, go to `http://www.java.com/en/download/help/testvm.xml`.

Mac To check Java version, type `java -version` in a terminal; to check the Mac OS X version, type `sw_vers` as shown in Figure 3.2. Use *Software Update* on the Apple menu (Figure 3.3) to check that you have the most up-to-date version of Java. The default Java version can be altered via *Java Preferences* (search "Java Preferences" via *Spotlight*, open *Java Preferences*, and then follow the instructions).

To run the Simulator, double click the jar file in Windows or Mac or type

```
java -jar path-to-the-jar-file
```

in a UNIX system.



```
Last login: Fri Sep  4 13:54:53 on console
[redacted]:~ [redacted]$ sw_vers
ProductName:    Mac OS X
ProductVersion: 10.5.6
BuildVersion:   9G55
[redacted]:~ [redacted]$ java -version
java version "1.5.0_16"
Java(TM) 2 Runtime Environment, Standard Edition (build 1.5.0_16-b06-284)
Java HotSpot(TM) Client VM (build 1.5.0_16-133, mixed mode, sharing)
[redacted]:~ [redacted]$ 
```

Figure 3.2: Checking Java version and Mac OS X version via Terminal.

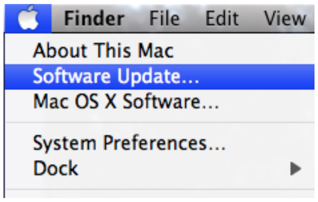
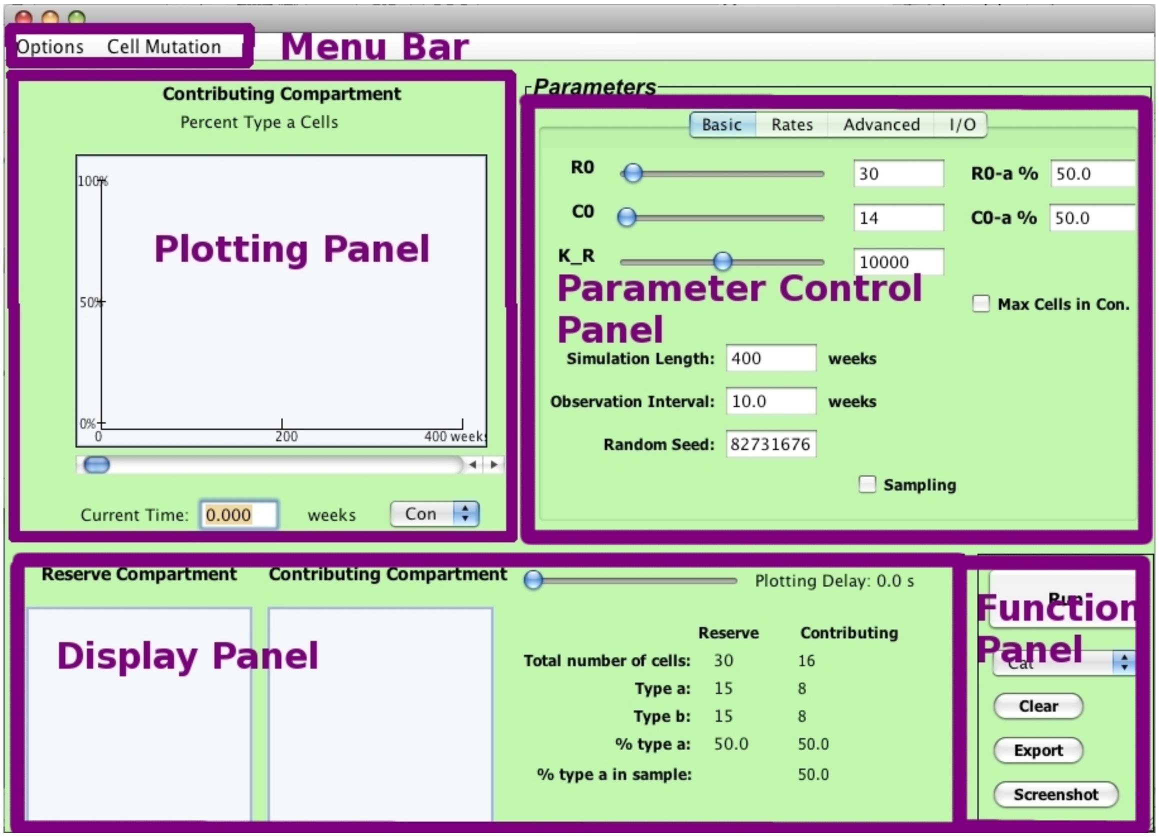


Figure 3.3: *Software Update* on the Apple menu.

3.3 Interface



Current Time: 0.000 weeks Con

R0 30 R0-a % 50.0

C0 14 C0-a % 50.0

K_R 10000

□ Max Cells in Con.

Simulation Length: 400 weeks

Observation Interval: 10.0 weeks

Random Seed: 82731676

□ Sampling

Plotting Delay: 0.0 s

	Reserve	Contributing
Total number of cells:	30	16
Type a:	15	8
Type b:	15	8
% type a:	50.0	50.0
% type a in sample:		50.0

Figure 3.4: Simulator interface in Mac OS X.

As shown in Figure 3.4, the interface consists of the menu bar, plotting panel, display panel, parameter control panel, and the function panel. The parameter control panel is a tabbed panel which allows users to change initial condistions and parameters for simulations. The function panel contains the essential functional buttons (Figure 3.5).

The default values of some parameters vary according to the creature selected from the list in the function panel (Figure 3.5). The list consists of cat, mouse, human, and baboon. The default selection is cat as shown in Figure 3.4. To remove all existing graphs and restore default values for current selected creature, click the *Clear* button. Again, parameters can be selected arbitrarily and are not restricted to these four preloaded creatures.

To run a simulation, click the *Run* button. Then the button will display "Stop" until the simulation completes. To stop the simulation, click the *Stop* button. The *Screenshot* button is used to save a screenshot image with given file name to the working directory.

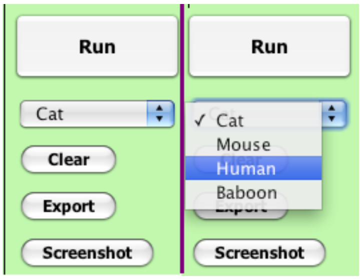
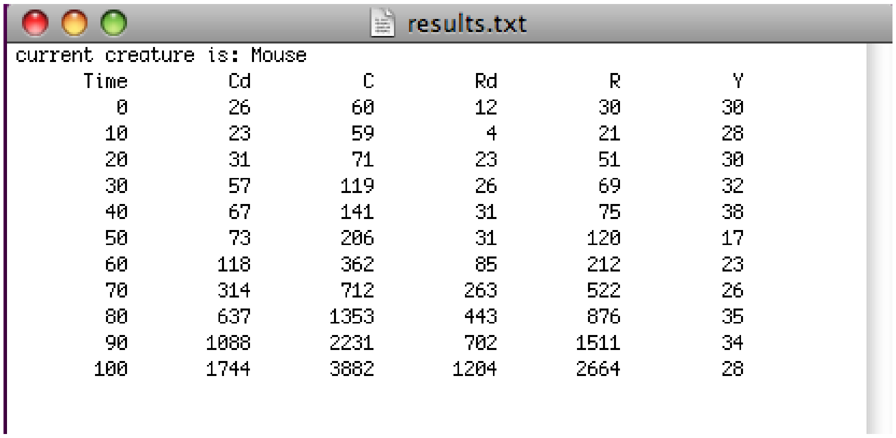


Figure 3.5: Function panel and the creature list.



```
current creature is: Mouse
      Time          Cd          C          Rd          R          Y
         0          26         60          12         30         30
        10          23         59           4         21         28
        20          31         71          23         51         30
        30          57        119          26         69         32
        40          67        141          31         75         38
        50          73        206          31        120         17
        60         118        362          85        212         23
        70         314        712         263        522         26
        80         637       1353         443        876         35
        90        1088       2231         702       1511         34
       100        1744       3882        1204       2664         28
```

Figure 3.6: Example of simulation results saved as plain text file.

3.4 Saving Results

To save the simulation results, click the *Export* button. Then the simulator will ask for the file name and save the results in the format of plain text with suffix *.txt* in the same directory as the jar file. Figure 3.6 shows an example of the simulation results.

Another option is to save the results as R file by using the *Export results as R file* menu button in *Options* submenu as shown in Figure 3.7. Execute the code and you will see the simulation data saved as data.frame object in R.

3.5 Multiple Runs

To perform multiple runs at once, find the *Multiple runs* button under the *Options* submenu, and select the type of file to export as shown in Figure 3.7. The simulator will then ask for the desired number of runs and the file name. Besides plain text and R files described in Section 3.4, you also have the options to save

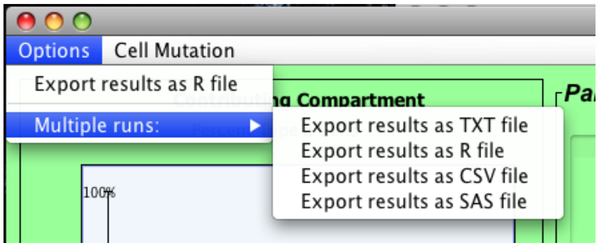
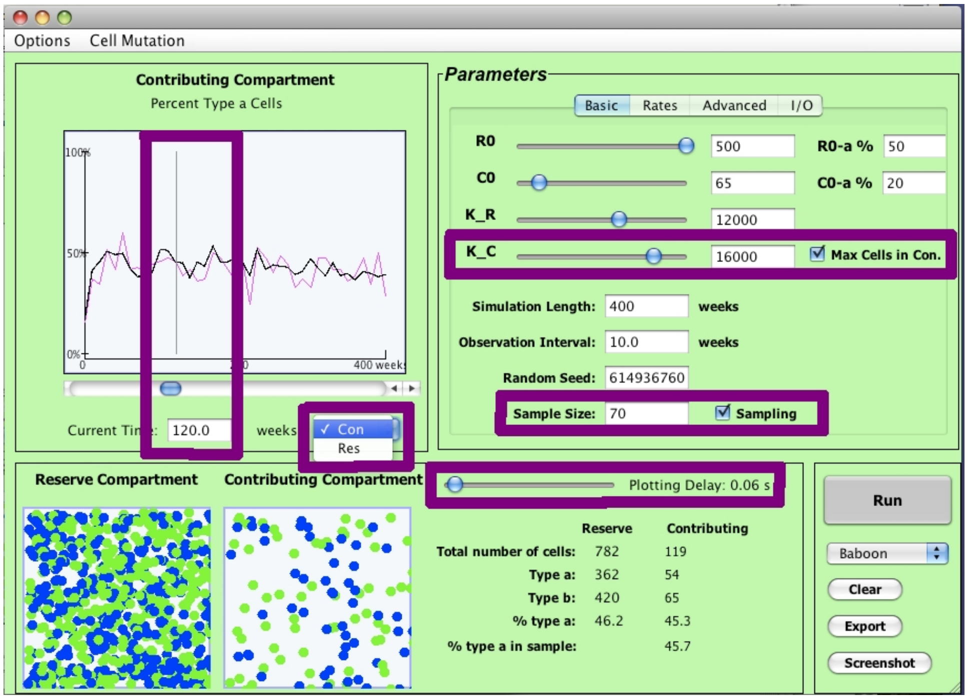


Figure 3.7: *Options* submenu in the menu bar.



Current Time: 120.0 weeks

R0 500 R0-a % 50

C0 65 C0-a % 20

K_R 12000

K_C 16000 ☑ Max Cells in Con.

Simulation Length: 400 weeks

Observation Interval: 10.0 weeks

Random Seed: 614936760

Sample Size: 70 ☑ Sampling

Plotting Delay: 0.06 s

	Reserve	Contributing
Total number of cells:	782	119
Type a:	362	54
Type b:	420	65
% type a:	46.2	45.3
% type a in sample:		45.7

Figure 3.8: Plotting panel, display panel, time series slider, plotting delay slider, maximum number of cells in the contributing compartment, and the sampling checkbox.

results as either comma-separated values (CSV) file with suffix *.csv* or SAS code with suffix *.sas*.

All the runs will use the same set of parameters except the random seed. To change the parameters, see Section 3.9.

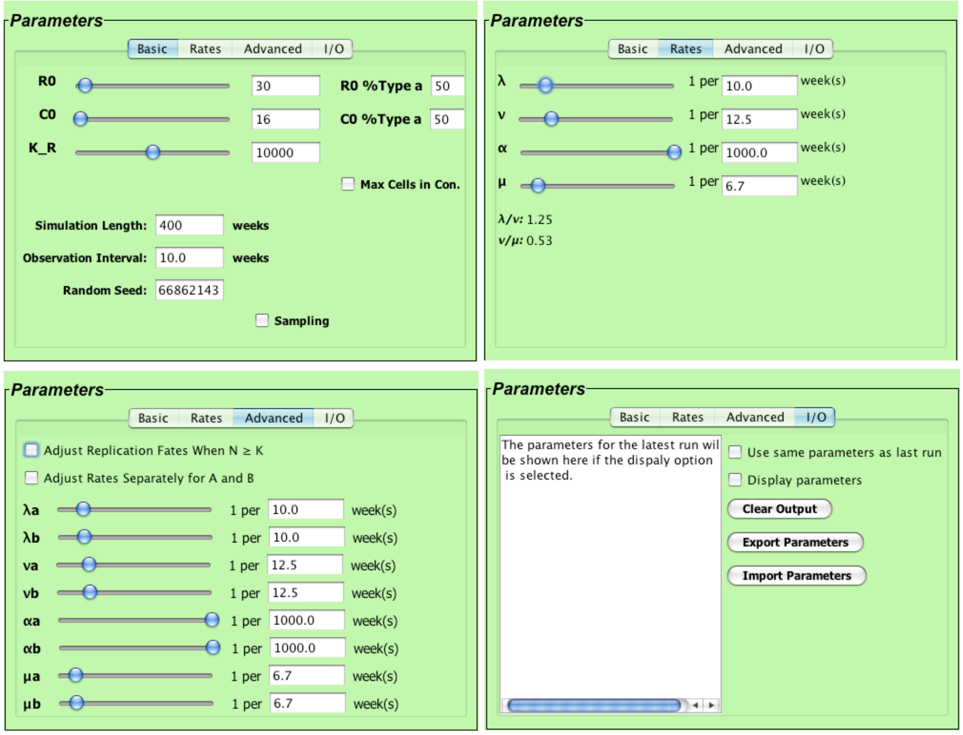
3.6 Advanced/Customized Experiments

While these capabilities already provide users the flexibility to conduct a vast range of virtual experiments, in some cases one may want to run a large number of simulations according to more custom rules. For instance, the multiple runs option provides the capability to conduct a large batch of simulations under some number of parameter settings. However, one may wish to automate a large number of simulations, with each trial varying a particular parameter value slightly, over a fine grid of parameter values. This would require a brief piece of user supplied code, for instance a for loop, that the multiple runs option does not enable.

Such instances can be handled via bypassing the graphical interface and directly accessing the simulation routines in the java code. One may write a brief Java function as a wrapper around the simulator core, or use shell scripts and access the core from the command line. The Java source files and instructions are provided online in a Github repository, available at `https://github.com/jasonxu90` .

3.7 Graphical Display

The time series of the percentage of type-a cells in each compartment is displayed in the plotting panel (Figure 3.8). One can choose the plot of either the Reserve Compartment or the Contributing Compartment from the list in the plotting panel as shown in Figure 3.8. The display panel presents the cellular composition graph and statistics of the two compartments. One can revisit a certain time and view the statistics by using the time series slider in the plotting panel. One can also justify the plotting delay time using a slider in the display panel. The unit of the plotting delay slider is 0.01 second and the default is no delay.



R0 30 R0 %Type a 50
C0 16 C0 %Type a 50
K_R 10000
□ Max Cells in Con.
Simulation Length: 400 weeks
Observation Interval: 10.0 weeks
Random Seed: 66862143
□ Sampling

λ 1 per 10.0 week(s)
v 1 per 12.5 week(s)
α 1 per 1000.0 week(s)
μ 1 per 6.7 week(s)
λ/v: 1.25
v/μ: 0.53

□ Adjust Replication Fates When N ≥ K
□ Adjust Rates Separately for A and B
λa 1 per 10.0 week(s)
λb 1 per 10.0 week(s)
va 1 per 12.5 week(s)
vb 1 per 12.5 week(s)
αa 1 per 1000.0 week(s)
αb 1 per 1000.0 week(s)
μa 1 per 6.7 week(s)
μb 1 per 6.7 week(s)

The parameters for the latest run wil be shown here if the dispaly option is selected.
□ Use same parameters as last run
□ Display parameters

Figure 3.9: Subpanels of the parameter control panel.

3.8 Sampling

When the checkbox *Sampling* is selected, Simulator will display a textfield for the sample size (Figure 3.8). The default size is 70. At the same time, the plot of percent of type-a cells in the sample will be displayed in pink in the plotting panel.

3.9 Parameters and Initial Values

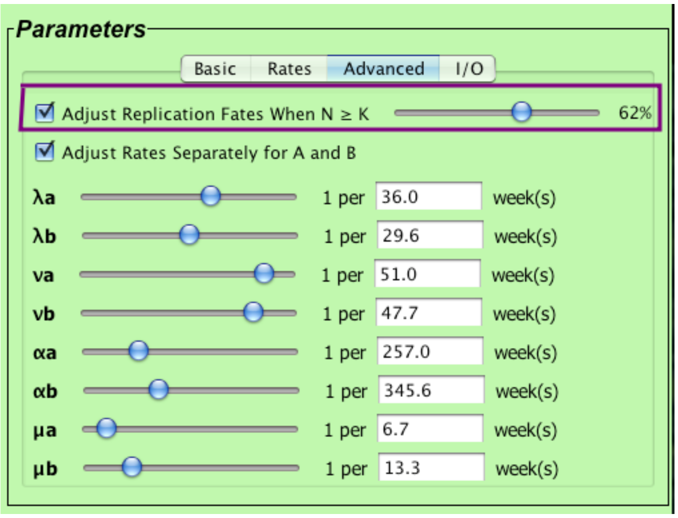
The parameter control panel has four subpanels, which can be switched by clicking on the tabs on the top of the panel (Figure 3.9). It offers control over the initial conditions and various parameters in our stochastic model.

The initial numbers of cells in the Reserve Compartment (Compartment 1 in Figure 2.1) and the Contributing Compartment (Compartment 2 in Figure 2.1) are denoted by $R0$ and $C0$, respectively. The upper limit for the total number of cells in the Reserve Compartment is denoted by K_R. When the checkbox *Max Cells in Con.* is selected, Simulator will display a slider and corresponding textfield for the maximum number of cells in the Contributing Compartment, denoted by K_C, as shown in Figure 3.8. These parameters can be modified via either the sliders or the textfields. The default values of $R0$ and $C0$ vary according to the creature selected, whereas default K_R and K_C are both 10,000. When $R0$ is changed, $C0$ will be changed automatically to maintain certain ratio. But the modification of $C0$ alone does not affect $R0$.

The initial percentages of type-a cells in the Reserve Compartment and the Contributing Compartment are displayed in the textfields labeled “R0-a %” and “C0-a %”, respectively. Their default values are both 50%.

The default simulation length is 400 weeks, except for mouse, which is 100 weeks. The default observation interval is 10 weeks. The random seed enables a simulation to be repeated. The seed is randomly generated before each simulation. The Simulator offers the option to use the same parameters as last run, which will be discussed in Section 3.11.

Recall that each HSC can replicate, apoptose, or differentiate into progenitor cells with average rates



☑ Adjust Replication Fates When N ≥ K 62%

☑ Adjust Rates Separately for A and B

λa 1 per 36.0 week(s)

λb 1 per 29.6 week(s)

νa 1 per 51.0 week(s)

νb 1 per 47.7 week(s)

αa 1 per 257.0 week(s)

αb 1 per 345.6 week(s)

μa 1 per 6.7 week(s)

μb 1 per 13.3 week(s)

Figure 3.10: Advanced subpanel of the parameter control panel.

λ, α, and ν, respectively (see Chapter 2). When a HSC differentiates, it gives rise to a differentiating clone with an average exhausting rate μ. In the subpanel labeled "Rates", the rates λ, α, ν, and μ can be modified via either the sliders or textfields (Figure 3.9). Their default values depend on the creature selected. The ratios λ/ν and ν/μ are displayed below the sliders.

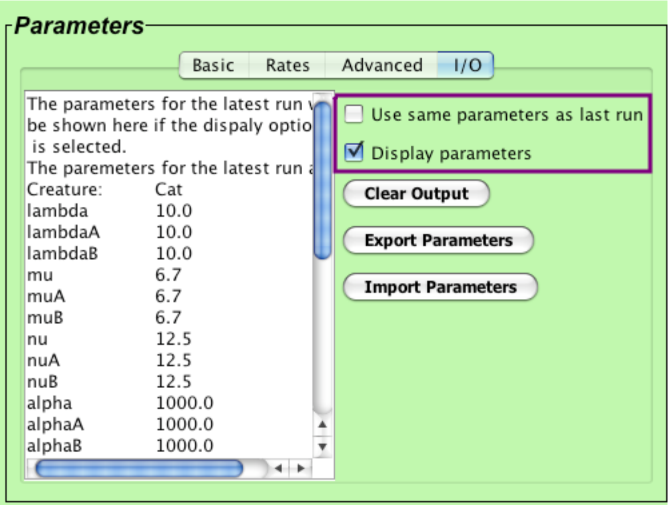
3.10 Advanced Parameter Control

Figure 3.10 illustrates the subpanel labeled "Advanced." Simulator allows users to specify different rates for the two types of cells after the *Adjust Rates Separately for A and B* checkbox is selected. Otherwise, the pairs of parameters will be changed simultaneously.

When the checkbox *Adjust Replication Fates When* $N \geq K$ is selected, Simulator will display a slider for a percentage. That is, when the total number of cells in the reserve compartment is greater than or equal to K and the next event to happen is replication, the simulator will generate a random number between 0 and 1 instead of ignoring the event. If this number is greater than a specified percentage, the new cell will survive and commit to progenitor cell lineages, i.e., the total number of cells in the contributing compartment will increase by 1; otherwise, the replication will be neglected. The percentage criteria can be modied via a slider.

3.11 Importing and Exporting Parameters

The "I/O" subpanel of the parameter control panel offers the options to export current parameters and import saved parameters (Figure 3.11). Both output and input are in the format of plain text file. The file names will be given by users and the files are saved in the same directory as the jar file. After at least one simulation has been run, users can choose to use the same parameters as last run by selecting the corresponding checkbox. In addition, the parameters for the latest run will be shown in the text area if the *Display parameters* checkbox is selected. The *Clear Output* button will clear the outputs in the text area.



```
The parameters for the latest run v
be shown here if the dispaly optio
 is selected.
The paremeters for the latest run a
Creature:       Cat
lambda          10.0
lambdaA         10.0
lambdaB         10.0
mu              6.7
muA             6.7
muB             6.7
nu              12.5
nuA             12.5
nuB             12.5
alpha           1000.0
alphaA          1000.0
alphaB          1000.0
```

□ Use same parameters as last run

☑ Display parameters

Figure 3.11: I/O subpanel of the parameter control panel.

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