Practical: Introduction to stochastic simulation

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Introduction

This practical introduces the principles of stochastic simulation: that is, simulations which capture the randomness inherent in real disease and demographic processes. Most of the models encountered so far involved the construction of rate equations (Ordinary Differential Equations or ODE's) to describe the numbers of events (say new infections) per unit time. We shall see that when numbers are small, this method can provide nonsensical results, as subjects typically come in integer numbers!

Both 'normal' differential equation models (known as deterministic) and stochastic models emerge from a consideration of the random events of the epidemic. An event is an occurrence such as a susceptible becoming infected, an individual dying or being born. In a deterministic approach, we consider the mean number of a particular event occurring in unit time. This is a rate and we construct ODE rate equations from them. In a stochastic simulation, we draw a random number with the same mean to represent the number of events that occurred. A key difference between deterministic and stochastic models is that a deterministic model will always produce the same output, whereas a stochastic model will produce different output for every simulation.

Example 1: Single stochastic growth model

We begin with EXAMPLE1. This is a simple simulation of a birth process. Each individual has a birth rate (births/unit time), r. In a short time, dt, we would expect $r\,dt$ new births for each individual. Thus, in a population of size N there will be $rNdt$ births. Hence the ODE equation for change in population size is

$$\frac{dN}{dt} = rN$$

where r is the growth rate per individual per unit time. The solution of this equation is exponential growth i.e., $N(t) = N(0)\exp(rt)$, where $N(0)$ is the initial population at time $t = 0$. The time for the population to double is $ln(2)/r$ and if we begin with one individual (N(0) = 1) and r = 0.5 then there will be two individuals after time $ln(2)/0.5$, four after $2\times(ln(2)/0.5)$ and so on... (The unit of time is the week for all examples in this practical).

For a stochastic simulation, the probability that an individual gives birth in a short time, dt, is given by $r\,dt$. The same probability applies to each of the N individuals. Hence the number of new births will be binomially distributed:

$$\text{births in } dt = Bin(rdt, N)$$

Check the Berkeley Madonna code in EXAMPLE 1 to see how this is implemented. Note that as the ODE equation deals with mean values, N doesn't have to be a whole number. For the stochastic simulation, N is always a whole number of individuals.

- Open the Berkeley Madonna model EXAMPLE1.

- Click <*RUN*> and you will see the model solution. The exact solution lies on the same line as N_ODE, which is a numerical solution of the model and the stochastic solution is shown in green. Click <*RUN*> multiple times. What do you notice? The stochastic model doesn't agree with the exact and numerical solution, and varies each time the model is run.

- On Page 2 the same graph is plotted on a semi-log scale. What do you notice about the solutions? The stochastic solutions are highly variable for early low population levels, but linear and close to parallel for later times/larger populations.

- Epidemics frequently undergo a period of exponential growth, although it may take some time to get

started. Can you generate any stochastic runs to illustrate this? Yes. Also easier to do if you reduce r.

- When *N* gets big (say >10) what do you notice about the stochastic run? Will it meet up with the exact solution if it runs for long enough? Once N gets sufficiently large the solutions should look parallel, but not equal (the lines are not expected to meet up). This is because for large N the mean is a good description of the behaviour (the standard error is proportional to 1/sqrt(N)). N.B. parallel on log scale means increasing difference on normal scale.

- Try some different values of r using the slider, do these conclusions change? The main conclusions don't change, but for small *r* the stochastic growth can be slow to take off. For larger *r* the stochastic realisation matches the deterministic solution more closely.

Some summary statistics: Madonna allows the user to perform multiple simulations using Batch Runs. Select <*Parameters*><*Batch Runs*> then <*OK*>. Set the number of runs to 10 and choose the "Keep Runs Separate" option. Press <*OK*>. Now repeat this but enter "100" in the # of Runs box. This is to show them how to do Batch Runs, producing multiple solutions.

Finally repeat once more but select the "Compute Mean" option. Madonna will now perform 100 simulations and calculate the mean at each time point. This is plotted instead of the individual simulations. How does the mean compare with the exact solution? 100 simulations should give almost the same answer as the exact solution.

In fact, for linear differential equation models, the exact solution is the mean of the stochastic simulations. How close the mean gets to the exact solution is determined only by the number of stochastic simulations. This conclusion breaks down when there is the possibility of extinction, as examined in example 3 and also for non-linear models.

Example 2: Stochastic growth model

Here, we extend the code developed in Example 1 to perform multiple runs simultaneously using arrays in Berkeley Madonna. This also allows us look at estimates of the mean over many runs and how that depends on the number of runs.

- Open the Madonna model EXAMPLE2.

- Look at the equations for the stochastic simulations. Notice that there is now a subscript [i] to denote an individual simulation and this ranges from 1 to *nsim* (written as e.g. *N*[1..*nsim*]).

- Click <*RUN*> and you will see the model solutions as before. Increase the number of simulations slider, *nsim*, to perform 10, 100 and 1000 simulations. On Page 3 you will see the mean of these simulations. How do they compare with the exact solution? The mean should agree pretty well as it does Batch runs all in one go!

- Variation in the mean over *n* simulations decreases proportional to $\sqrt{n}$, so more simulations get closer to the true value. A single simulation of 1000 replicates gets very close to the exact solution, but individual runs may be far away (Look at Page 3). 1000 runs should fill the graph with every possible value of N on a Log scale below the fastest growing solution.

Example 3: Stochastic growth and death model

We next extend Example 2 by introducing deaths at a per-capita rate *s* per week. The ODE for *N* is made up of the difference between the mean growth rate and the mean death rate:

$$\frac{dN}{dt} = rN - sN$$

The difference (*r*-*s*) is the *net* growth rate and the solution is either exponential growth or decline i.e.,

$N(t) = N(0)\exp((r-s)t)$. If births exceed deaths ($r > s$) the population grows. If deaths exceed births ($s > r$) the population shrinks.

In the stochastic simulation, we have to be more careful as we are dealing with individuals. Each individual has a probability of reproducing and of dying in some short interval, *dt*. However, it can't die and then give birth! These two dependent events that can happen are known as *competing hazards*. To calculate the number of births and deaths in a short time, we first calculate the number of births *or* deaths,

$$\text{Births or deaths in } dt,\ \text{n} = Bin((r+s)dt, N)$$

and then decide which were births and which deaths

$$\text{Deaths in } dt = Bin(s/(r+s), n)$$

Check the Berkeley Madonna code to see how this is done.

Another consequence of dealing with individuals is the possibility of extinction. If the population contains a single individual and they die, no more can be generated and the population will be zero from then on. In this system, individuals are created by individuals. Extinction can also occur in an infectious disease model, since infected individuals are only generated by other infected individuals. In an ODE model, populations are not whole numbers and extinction cannot occur. This is an important shortcoming of deterministic models.

- Open EXAMPLE3.
- In this model $r = 0.5$ and $s = 0.3$, what do you predict for the population? We expect approximately exponential growth with some cases of stochastic extinction.
- Set nsim to 10. Roughly how often does the population die out? Note that you should have N0 = 1 here. Extinction occurs about 6/10 times - count the number of lines still present at the end of the simulation on Page 2. You can also increase nsim to 1000 and look at fade_fraction on page 2.

For models which exhibit extinction behaviour, extinction is possible whenever the relevant population is small. Hence, it's often possible to define a critical community size, above which extinction is very unlikely (*but not impossible*).

- Set nsim back to 100. Look at Page 2; is there a safe threshold initial population (N0) above which growth looks assured? (Set STOPTIME at about 15) Increasing nsim will improve your accuracy here. Anything over 5-10 looks reasonably assured of not dying out. You could also do a parameter plot of N0 vs fade_fraction.

How might we estimate the probability of fade-out? Look at the Model equations. The array fade[1..*nsim*] takes the value 1 if $N > 0$ and 0 otherwise. The average value of fade[1..*nsim*] is therefore the probability of not fading out.

- Set N0 back to 1 and re-run the model. Look at Page 2. What is the fade-out fraction after 28 weeks? 60%. In this model (but not in all) the probability of early extinction for a run is 1/R0 and R0 is r/s.
- Try reversing the values of r and s to give a negative net growth rate (s >r). What is the new fade-out fraction? E.g. set s = 0.5 and r = 0.3. This generates net loss and assures 100% of fade-outs.

In this model, the fade-out fraction tends to s/r if $r > s$ and 100% if $s > r$.

- What happens when births equal deaths? Can you balance the population? For these parameter values, there is no 'preferred' population size and the population wanders around randomly (until an extinction occurs). All populations will eventually hit zero and fade out. Note that in this case, 1/R0 = 1.

Example 4: Stochastic SIS model

The models discussed so far have exhibited unbounded growth, extinction or a population that simply 'wanders about' randomly. An important and relevant example of a system with a stable population is disease transmission and recovery in a finite population, known as the SIS model (susceptible-infected-susceptible). In this model, we have to consider infection events, which happen with a probability $\beta I\, dt / N$ per susceptible individual, and recovery events, with a probability $\nu\, dt$ per infected individual. The ODE representation of model is

$$\frac{dS}{dt} = -\beta SI / N + \nu I,$$
$$\frac{dI}{dt} = \beta SI / N - \nu I$$

The analytical solution to this ODE can be shown to be:

$$I(t) = I^* \frac{1}{1 + (I^* / I_0 - 1)\exp(-(\beta - \nu)t)},$$

where I_0 is initial population of infected individuals and $I^*=N(1-\nu/\beta)$. After sufficient time, the infection and recovery processes balance each other. This occurs when the infectious population reaches its equilibrium value I^*. We can write this as

$$I^* = N(1 - 1/R_0)$$

since R_0 is defined as β/ν. At this point, the disease can be said to be endemic in the population.

The stochastic simulation of this system is constructed in the usual way (see the BM code). Its behaviour, however, differs significantly from the deterministic for some parameter values. We'll investigate these in the rest of this section.

- Open the model EXAMPLE4. Note that this example has two possible initial conditions, representing an epidemic or an endemic scenario, which can be switched between by commenting out one line or the other.

- First, we look at the endemic situation where there is a continuous population of infected individuals (check in the code that the correct initial condition is in place). Try varying the contact rate (β), recovery rate (ν) and total population (N) parameters. How do they affect the equilibrium population of infected individuals? Check these equilibrium values against the analytic expression given above. Note that the endemic stable infected population is given by I*=N(1-1/R0), where N=I+S. For small values of β/ν the mean over simulations will tend to decline due to stochastic fade-out of some runs, but even for large values of β/ν the mean over simulations will not match the analytical solution exactly due to non-linear effects.

- Accuracy of the deterministic solution. With default parameter values, vary N from around 400 down to about 50. How does deterministic solution (I_det) compare to the mean value of I from the stochastic simulation? The stochastic simulation, averaged over all runs, should be noticeably below the deterministic solution. This difference should reduce as N increases. At smaller values of N stochastic fadeout becomes a substantial issue.

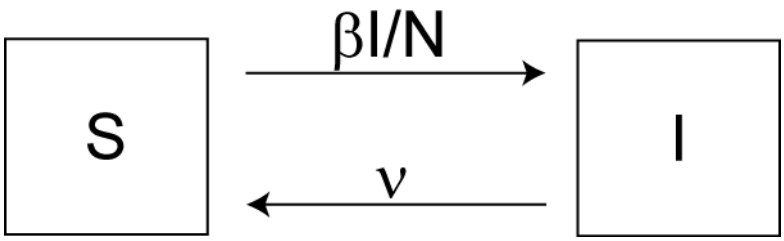
You should notice that simulated *I* value varies around the deterministic solution for large *N*, but that the deterministic solution increasingly overestimates the stochastic average for smaller values. (As so often, the difference is proportional to 1/sqrt(N)). This error is due to the non-linear infection term, βSI/N. The number of susceptibles (S) and infected (I) are negatively correlated, since when an individual leaves one class, he enters the other. This correlation term is absent from the ODE model which then overestimates the force of infection, giving a higher population of infecteds.

- Fade-out can occur when the endemic infected population is small. Go to page 2 in the simulation. Set β=0.5, ν=0.3, and gradually reduce N from the default value of 100. From what value do fade-outs start happening? Can you explain what's happening to the difference between mean stochastic behaviour and the deterministic? Do a parameter plot of meanFadeout[final value] against N from 150 to 10. What do you notice? Estimate a critical community size. What's going on is that some of the 'stable' endemic populations of infecteds are fading out. Hence the average over all populations goes down. The parameter plot should show no fade-outs for large N, with fadeouts starting around N=80 and total fade-out by N=10. Critical community size is therefore around N=80.

- Finally, we look at a growing epidemic starting from a single individual. In the code, comment out the initial condition for endemic behaviour and comment in the epidemic one (That is, remove the line of code by adding a semi-colon at the start of the line so that we have Inf0 = 1). Set N high (300+) and nsim to 1000. What proportion of fade-outs are you getting? You should get the same fade-out rate as in example 3. Can you explain why? This SIS system is analogous to the birth/death example previous to it (at least during the growth phase). β is the 'birth rate' of infecteds (but only in a fully susceptible population) and the recovery rate, μ, is their death rate. The parameter values should be the same, so the behaviour should be too.

Example 5: Stochastic simulation of an SIR model

The final part of the practical is to investigate the behaviour of a Susceptible-Infected-Recovered (SIR) model. The code to do this in Berkeley Madonna can be easily adapted from the SIS code in previous section. Let's remind ourselves of the SIS structure:

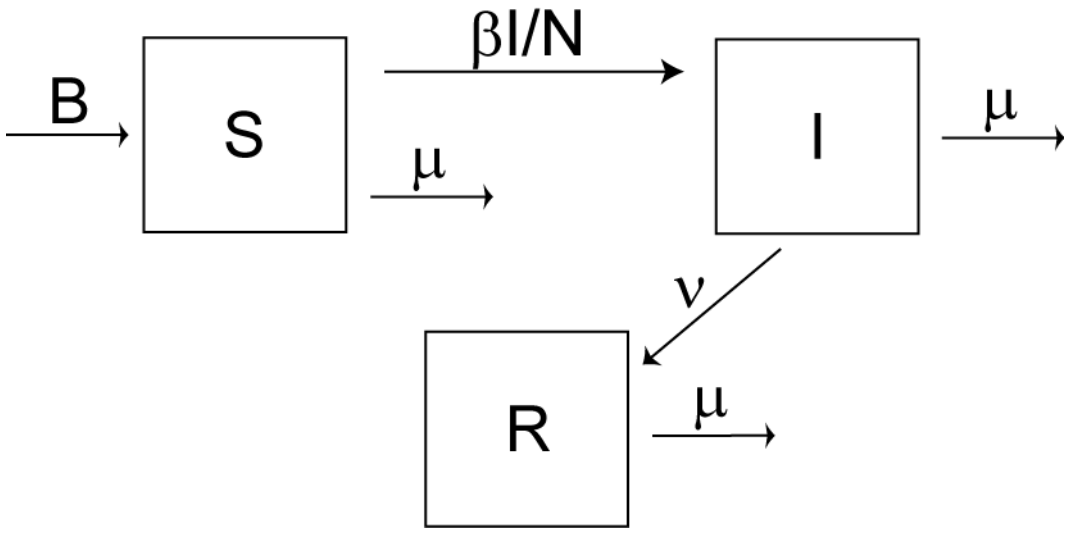


The SIS model in the diagram above has two compartments, S and I, although since the total population, N, is constant, S=N-I and only one is needed. There are only two possible events:

Event	Rate per head
Infection (S→I)	βI/N
Recovery (I→S)	ν

As described in the stochasticity lecture, at each time step, the number of each kind of event is evaluated and the populations updated. Check the code for example 4 to see how this model is constructed in Berkeley Madonna.

The structure of the SIR model is shown below. It has one extra compartment, *R*, representing recovered and immune individuals and 4 extra events: death of susceptible, infected and recovered individuals at rate μ, and birth of new susceptibles at rate *B*. To simplify, in any time period, we can make the number of births equal to the sum of the number of deaths. This keeps the total population constant.



The table of events for the SIR system is therefore

Event	Rate per head
Infection (S→I)	βI/N
Recovery (I→R)	ν
Susc. death (S→)	**μ**
Inf. death (I→)	**μ**
Rec. death (R→)	**μ**
Births (→S)	**Sum of deaths**

with new events in bold. Note that there are two competing hazards for S (death and infection) and for I (death and recovery). For this system, $R_0 = \beta/(\mu+\nu)$ and the new equilibria are

$$S^* = \frac{1}{R_0},$$

$$I^* = \frac{N\mu}{\beta}(R_0 - 1)$$

Open the Berkeley Madonna model EXAMPLE 5. This is an adaptation of the EXAMPLE 4, with lines which have been added or changed marked with a comment starting ;; SIR: Note how the new variable, I, is introduced and initialised and the new events are handled. Ask a demonstrator to explain any changes you don't understand.

Dynamics:

The behaviour of the SIR model is in some ways similar and in some ways different from the simpler SIS model.

- Ensure that you are looking at the epidemic situation (i.e. set initial *I* to 1 and *S* to *N*-1). Run the model and look at the curves for the mean number of infected people over time. How does this differ from the prediction under the SIS model? Why does it differ? The number of infected individuals takes off exponentially, peaks and then declines to very low numbers (i.e. an epidemic sweeps through the population). The number of infecteds eventually crashes in this model because individuals become immune, and so the pool of susceptibles diminishes.

- Look at the curves for the number of infected people in each of the *nsim* independent simulations. Does the epidemic always follow the same trajectory? What could cause them to take off at different times? The trajectory is slightly different each time. Small stochastic changes in the number of infected individuals early on can delay the onset of the epidemic, leading to different peaking times.

- Why does the number of susceptibles slowly increase over time after the main epidemic? Unlike previous examples this is an open system, meaning there is natural birth and death in the model.

Individuals are always born susceptible in this model, and so the pool of susceptibles slowly replenishes.

Fadeout:
We can look at probability of fade-out for the SIR system in the same way as for the SIS.

- Produce a graph of the variable 'meanFadeout'. What do the two phases of fadeout in this graph represent? The first phase represents fadeout due to the (random) death of the relatively few infected individuals, bringing the epidemic to a halt before it can take off. The second phase represents loss of infection because the epidemic has exhausted itself, and now the population is immune.

- The probability of fadeout (in the first of the two phases) from a single infected individual is the same for SIR as SIS, and is equal to $1/R_0$. Given the different structures of SIS and SIR, why should this behaviour be the same? In the early stages of the epidemic the two models are identical, and so the fadeout fraction is the same. A caveat to this point is that we allow for birth and death in the SIR model but not the SIS model, so although the $1/R_0$ result holds, R_0 is actually slightly different between the models.

- Try varying the fraction of the population that's initially immune (by setting Susc0 = 0.5*N in the code). What happens to the proportion that fades out? Why? A much larger number of simulations experience stochastic fadeout.

Critical Community Size:
We can look at critical community size for the SIR system in the same way as for the SIS. Set initial I to INT(I*) and S to INT(N/ R_0). This should be the endemic solution (the INT is needed because these quantities should be whole numbers).

- As with the SIS model, investigate the fade-out fraction as the total population is varied. Set runtime to 1000 weeks and R_0 to 3 by changing β. When you've identified roughly the size of the critical population, run a parameter plot of meanFadeout against N to illustrate it. Scan total population size from around 1000 up to about 3 million in a geometric series (this may be quite slow due to the large populations). How does your answer compare to that from the SIS model? Comment on the difference (Hint: look at the expression for I* above and think about the parameter values). A population size of around 2 million is sufficient to ensure the infection does not fade out. This is much larger than the SIS model, the reason being that susceptibles are only replenished by natural birth.

- How does this result compare to the result derived in the Stochasticity lecture? This is roughly in line with the results from the lecture.

Stochastically-driven resonance
The open SIR system also exhibits some interesting and complex behaviours.

- Set R_0 to 3 and N to 1 million. Look at a single realisation (nsim=1). What do you notice about the shape of the disease prevalence time series over 2000 weeks? Can you explain this periodic behaviour? The epidemic recurs periodically. This is due to the gradual replenishment of the susceptible population by natural birth (this is not to be confused with seasonality – there are no seasonally driven effects in this model).