Laboratory Notebook

Beginning 05-29-2016

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Contents

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Objective: Refine Gillespie algorithm proof-of-concept, and continue background research.

1 Gillespie algorithm proof-of-concept

After reviewing my first version of my code[1], JJ had feedback on some changes to make, which I'll go through and fix one by one.

$\Rightarrow$ τ should be generated with a different random number than the number used for determining the reaction.

- Changed τ to use a new, freshly generated number.

$\Rightarrow$ An unnecessary division in the code when calculating the propensity array can be removed for efficiency.

- Removed the unnecessary division and timed execution with and without using the `time` command. Too much variation in execution times to determine any significant change.

$\Rightarrow$ How would I modify the array of propensity functions if, for example, reaction 2 were changed from $X \rightarrow 2X$ to $2X \rightarrow 3X$? Reactions like this can be found in sexual reproduction and chemical reactions.

- I need to look into this more. My first guess would be maybe I need to square the propensity or probability of that reaction, since two reagents are involved.

Before I spend more time trying to answer the last point, I'm going to review some more background materials. I'll start by reading the Wikipedia page on antimicrobial resistance, and go from there.

[1] Git commit `4105445`

June 2, 2016

Objective: Continue background research on antimicrobial resistance and plasmids.

0.1 Background

Antimicrobial Resistance

- Broader topic than just bacteria and antibiotics
- 3 primary ways resistance arises in bacteria
  - Natural resistances
  - Genetic mutation
  - Acquiring resistance from another species **What we're studying with plasmids**
- All classes of microbes develop resistances
- Present in all parts of the world

Mutation

- Low probability of mutating resistances
- Some mutations can produce enzymes that render antibiotics inert
- Some mutations can eliminate the targets of certain antibiotics

Acquired Resistances

- *Conjugation* is passing genetic material from one bacteria to another via **plasmids** and **transposons**. This requires physical contact
- *Transformation* is when a bacteria absorbs genetic material from a free plasmid in its environment
- Viruses can also take genetic material from a bacterium and inject it into other bacteria
- **Horizontal** transfer is sharing genetic material with other bacteria
- **Vertical** transfer is sharing genetic material through reproduction with daughter cells
- **Transposons** are small amounts of DNA that can move between genetic elements like chromosomes and plasmids.

Plasmids

- Cannot reproduce on their own, without a host bacterium
- Widely distributed
- Bacteria can hold many plasmids per cell
- Plasmid genomes have *core* genes for transmission and replication and *accessory* genes that encode traits.

The Plasmid Paradox

"Plasmids impose a fitness cost on their bacterial hosts that generates selection against plasmid carriage under conditions in which plasmid genes do not provide any benefit to the host ... The great irony of the plasmid paradox is that exposure to conditions that select for plasmid-carried genes can also ultimately lead to plasmid loss."

- Recurrent horizontal transfer
- Genes encoded

Skype with Prof. Dong

- For the $2X \rightarrow 3X$ reaction mentioned in yesterday's entry, the propensity array element for the new reaction must be multiplied by two. Since it involves two reagents now, it's twice as probable. *(Why doesn't this make it half as probable?)*
- The theoretical line should follow the solution to the ODE, which in the simplest case is just the exponential.

  This should be plotted on a semi-log plot (meaning logarithmic y-axis) since it's an exponential function. The slope of this line will be the exponent.
- It would be helpful to average the five independent Gillespie algorithm runs that are executed, and compare the average line to the theoretical line.

  However, the Gillespie algorithm has an element of randomness in the time steps it takes. Therefore, between separate runs, times of datapoints will not line up. Without having points with the same time, we can't meaningfully average them. We're not sure what the answer is to this yet, but we're putting it on hold for now.

  We also discussed the central limit theorem, and how if you increase the population size in the simulation, the simulation runs become far closer to the theoretical model. As the population grows, the standard deviation of the mean is reduced, and the Gaussian that describes the distribution of the runs gets narrower.

  In biology, the opposite is often the case, where very small populations lead to wide Gaussians, and much noisier data. For example, in our research, if a parent cell has 5 plasmids and produces two daughters, it's likely that the plasmids will

be distributed 3 to one, 2 to the other. However, that's just likely, not guaranteed. If this doesn't happen, and if for example one daughter receives all 5 and the other none, this small initial difference can hugely affect the system as it grows.

- We would like to start discussing a journal article every week to become more familiar with the literature surrounding this topic. To that end, I've been provided with a first article to read[1].
- We talked a little about the background research I had done, and a little more in depth about a few of the topics I'd read on. We talked about how cells can lose plasmids without dying, releasing them back into their environment.
- Finally, we discussed next steps for simulation.

Next Steps

Currently[1], the simulation only models the following two reactions

$$X \xrightarrow{\mu_1} \emptyset \tag{0.1}$$

$$X \xrightarrow{\mu_2} 2X \tag{0.2}$$

which correspond to death and reproduction respectively. However, in order to move forward, we'd like to expand the reactions considered.

Theory

We can simulate a bacterium transforming by taking in a plasmid from its environment with a new set of reactions

$$X \xrightarrow{\mu_1} 2X \tag{0.3}$$

$$X \xrightarrow{\alpha} Y \tag{0.4}$$

$$Y \xrightarrow{\mu_2} 2Y \tag{0.5}$$

where X is a bacterium that has not absorbed any plasmids and Y is a plasmid carrier. Eqn. 0.4 represents transformation, the process by which a bacterium takes a free plasmid from its environment.

From this, we can quickly see that as per the plasmid paradox mentioned before, $\mu_1 > \mu_2$. In addition, we can determine the cost to fitness of owning a plasmid to be

$$\frac{\mu_1}{\mu_2} \tag{0.6}$$

.

However, the ratio of X to Y will depend significantly on α, the probability of transformation. We can rewrite the above reactions as differential equations

[1] Git commit `5932c50`

$$\frac{dX}{dt} = \mu_1 X - \alpha X \tag{0.7}$$

$$\frac{dY}{dt} = \mu_2 Y + \alpha X \tag{0.8}$$

that describe the growth of each population. These have analytical results, but may be manipulated into a form that has an exact solution. I'll need to find this exact solution so I can verify my simulations are producing the proper output.

Once I have the simulation working, I'd like to look at behaviors like how large α can get before Y dominates X.

In addition, α doesn't have to be constant, and in fact should depend on plasmid concentration. I will make it into a function that depends on the plasmid concentration, P.

I'd also like to map the transition of where X and Y dominate. I can do this by plotting $\frac{mu_1}{mu_2}$ vs α, and then highlighting regions where each dominate. This will allow us to explore how X and Y change with α.

For now, we will use these 3 reactions and only vary α in order to try and find the $\frac{mu_1}{mu_2}$ vs α relation.

In the future, we'd like to perform this simulation on a lattice to take spatial configuration of the bacteria into account, but for now we will assume a well-mixed environment.

Bibliography

[1] Mukund Thattai, Alexander van Oudenaarden *Intrinsic noise in gene regulatory networks* PNAS vol. 98 no. 15 2001. http://www.pnas.orgycgiydoiy10.1073ypnas.151588598/