

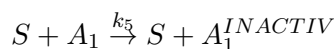
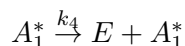
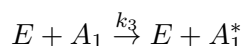
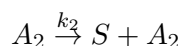
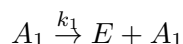
Info: You can work in groups, but all solutions must be written up independently. Many of the written problems –which are not assigned directly from the class textbook– are taken from a variety of other textbooks/papers. If any question requires a computational component, provide your written answer on one sheet, then the printout of your Mathematica notebook only for that problem on separate sheets following your write-up for that problem. Then repeat for each problem. i.e. do **not** staple a Mathematica notebook printout for all problems at the end of your problem set. **Only codes that are commented *at every step* and *whose logic can be easily followed* will be graded.**

DUE: Tuesday February 11th, 3PM. To be handed in within the first five minutes of class.

Please use the fundamental theorem of simulation to sample from exponential distributions and categorical distributions in the following problems.

Problem 1: Stochastic binary decisions.

Cells fate decisions are often based on small initial fluctuations that are amplified and reinforced (through feedback) over time. These events are called stochastic binary decisions (Artyomov et al., PNAS, 104, 18958, 2007). We will now simulate such a process. Consider the following set of chemical reactions:



where A_1 is an agonist and A_2 is its antagonist. E is an enzyme that converts A_1 into its protected form A_1^* and A_1^* , in turn, stimulates the production of E (positive feedback). We are interested in the steady state amount of A_1^* . If S is present it can permanently de-activate A_1 .

(a) Start with 10 agonists and 10 antagonists with $k_1 = k_2 = k_d = k_4 = 1$, $k_3 = 100$, $k_5 = 100$.

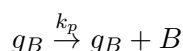
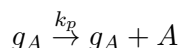
Simulate the process to completion using Gillespie's algorithm and histogram the final amount of A_1^* . Explain, in words, the result you obtain.

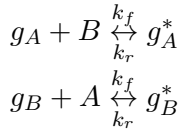
(b) Repeat the simulation and histogramming of part (a) starting with 1000 agonists and 1000 antagonists. Explain, in words, how your histogram differs from that of part (a).

(c) If you had solved the corresponding rate equations explain in words what you would expect the steady state population of A_1^* to look like.

Problem 2: The genetic toggle switch and stochastic bistability.

The toggle switch (Gardner et al. Nat. 403, 339-342) is a common feedback loop motif in systems biology and it exhibits a fascinating behavior called 'stochastic bistability'. We will now simulate this behavior. Consider the following chemical reactions involving two proteins, A and B :





where k_d are degradation rates and k_p are production rates for both proteins. g_A is the gene responsible for the production of A which can be converted into an inactive form g_A^* by binding to B . Vice versa for g_B . Assume you only have one gene available in the cell so that $g_A + g_A^* = 1$ and $g_B + g_B^* = 1$. Also, assume throughout that $g_A^* + g_B^* = 1$, $k_d < k_p$ and $k_r < k_f n_B, k_f n_A$.

(a) Simulate the chemical reactions starting with $n_A = 0$ and $n_B = 0$ for many time steps. Adjust your rates until you see stochastic switching events between periods when A exceeds B in number and B exceeds A in number. You should see stochastic hopping between two solutions (which we call "fixed points").

(b) Would you expect to see this stochastic switching occur if you had started with a large amount of n_A and n_B initially? In technical language, qualitatively explain (in words) how the fixed point structure changes for the corresponding rate equations.

(c) The condition that $g_A^* + g_B^* = 1$ is called the exclusive switch. Relax this condition and re-simulate the toggle switch. What new fixed point appears?