Exact Methods for Computing Biological System Dynamics

Drew Endy (http://mit.edu/endy/)

Goals Covered Last Time

G. What is the difference between a reaction rate and a reaction propensity?

H. How can we make this stuff compute faster?

Goals for Today

I. How is reaction time updated w/o resampling?

J. Back to the biology! What is this stuff good for? [Genetic Memory]

68. Summary of Next Reaction method's algorithm.

> 1a. Set initial numbers of molecules for all species, set time at zero, generate reaction dependancy graph.
>
> 1b. Compute a_i for all reactions
>
> 1c. Compute reaction event times for all reactions via $= (1/a)*\ln(1/r)$
>
> 1d. Store a and   values.
>
> 2. Find the reaction which will occur next. Carry out reaction and update time.
>
> 3a. Update a for any reaction whose substrate numbers have changed.
>
> 3b. Update times for any reaction whose a was updated (see **69** below).
>
> 3c. Compute new a and t for reaction that executed (a la' 1c).
>
> 4. Go to step 2.

69. How do we update ts? First, recompute a for any reaction whose substrate numbers have changed. Then...

$$t_{new} = (a_{old} / a_{new})(t_{old}-t) + t$$

[review graphically in class]

70. So, what we can we use this stuff to consider (i.e., analyze and design)? Let's consider a simple memory element called a "latch." In electronics, a latch is a device that can exist of one of two states, and thus can store one bit of information. If we can store information then we can record events. We could then use this information to program the behavior of cells to do stuff in response to past experiences (e.g., a cell-cycle counter that programs cells to change their behavior as a function of cell age).

71. What's a simple genetic latch? We can use two cross regulating repressors, A and B, to engineer a genetic latch. A turns off B and vice versa. When A is high, B is low, and so on. [We discussed this on the first day of this section]. The behavior of this system can be described via a state diagram. We could also simulate it's behavior over time.

[sketch out state diagram]

[sketch out time course]

72. What determines a good latch? How fast it can change states? How reliably it maintains state? Let' s consider the reliability question. Look at the state diagram. What's going to determine the chance that the latch spontaneously switches from one memory state to the other? [Such events are called "spontaneous switching events"].

73. Analytical / computational. I've not yet seen an analytical framework that can be used to exactly determine the spontaneous switching rates for a two-protein bistable latch. There must be one for a reduced representation of the system. But, in the mean-time, we can use a discrete reaction event simulator to estimate the spontaneous switching rate.

74. How else could we store state inside cells? In the above latch we are storing state via the levels of proteins. Is this the best way to go? How else could we store state? One idea is to write to DNA. For example, there are enzymes that let you switch the orientation of DNA. These enzymes are called invertases.