Exact Methods for Computing Biological System Dynamics

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Goals Covered Last Time

C. What is the underlying physics models used by exact methods?

D. How can we use this model to compute when a reaction will take place?

Goals for Today

E. Review how the physics model leads to computational method

F. What is the complete computational method?

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

46. **Review. From physics model to computational method**

47. Givens:

    i. A self-mixing volume, V.

    ii. V contains a system of N chemical species, S_1 -> S_N

    iii. Each species, S_i, is present at some number of molecules, X_i

    iv. Species, S_i, participate in M chemical reactions, R_1 -> R_M

    v. Each time a reaction event occurs substrate molecules are converted into product molecules in accordance with the stoichiometry of that particular reaction.

48. What can we compute (from previous lecture)?

    i. a_i is the probability that reaction i will occur in the next time interval.
    $$a_i = c_u \times h_u.$$

    ii. c_u is the average probability that a <u>particular</u> combination of R_u reactant molecules will react. Computed via hard-sphere, will mixed, Arrhenius model.

    iii. h_u is the number of unique reactant (i.e., substrate) combinations.for reaction R_u at time, t. Computed via combinations.

49. We've some probability that a particular reaction will take place in the next bit of time, a_i. This leads to an <u>exponential *distribution*</u> of times at which this reaction event will take place. I.e., the reaction is likely to take place at some point in time, if it does great, if it doesn't then the probability that it will take place in the future is the chance that it's not yet taken place multiplied by the chance that it will happen in the future, and so on.

50. From this exponential, if we want to compute one instance of a time that a particular reaction will next take place, we can use the following equation...

$$= (1/a)*\ln(1/r)$$

where   is a randomly sampled time that a reaction next takes place

a is the reaction propensity (chance of reaction)

r is a random number drawn from a unit uniform distribution

51. Say what? OK. I'm sure a mathematician somewhere is screaming but here's how I think about it. Solve the above equation for r. You get...

$$r = \exp[-a^* \ ]$$

Then, graphically, what this leads to is... first sample along the Y-axis of an exponential probability density function using a uniform distribution scaled to the maximum PDF value at   = 0 (note that this is a). Then, lookup the value of   for any value of r. See figure below:

1. sample a scaled unit uniform distribution, **r**

2. "look up" the time a reaction next occurs, **t**

t
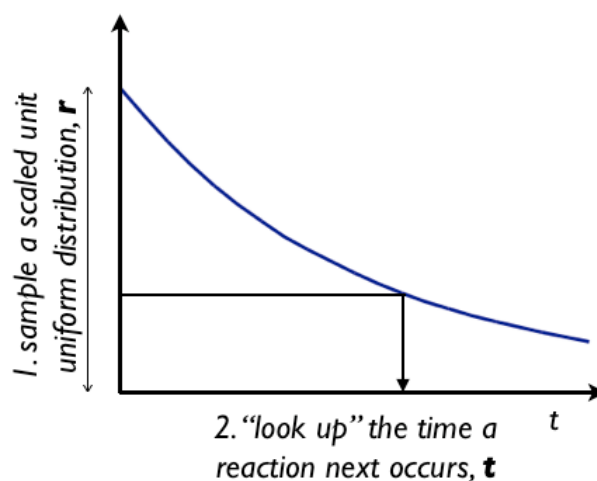
52. **What is the complete computational method?** So far we can compute a time for a single instance of one reaction event? How about computing the behavior of a system of coupled chemical reaction events? To do this we need some way to compute which reaction will take place first (next), execute that reaction, and re-compute which reaction will take place next, continuing until we're satisfied. Or,

i. Initialize the system (time = zero, X_i.numbers of molecules).

ii.Compute which reaction takes place (from M total reactions) and when.

iii. Execute the first reaction event, updating X_i.numbers.

iv. Repeat as desired, starting at step ii.

53. OK. So how do we do this for a set of M reactions. The first approach is called Gillespie's "Direct Method." Here's how it works:

   i. Compute a_i for all reactions and the sum of a_i

   ii. Compute when a reaction will occur next. $= (1/\sum a)*\ln(1/r)$

   iii. Compute which reaction occurs (the probability of the i-th reaction occurring is $a_i / \sum a$). You can use a sample a uniform distribution to do this.

   iv. Carry out the appropriate reaction, update time to   , and goto step i.

Note that the Direct Method requires computing two random numbers per reaction event (one to sample when the next reaction event occurs, a second to determine reaction reaction fires).

54. Another approach is called Gillespie's "First Reaction Method." Here's how it works:

   i. Compute a_i for all reactions.

   ii. Compute next reaction event times for all reactions via $= (1/a)*\ln(1/r)$

   iii. Find the reaction that occurs first (hence the name of the method)

   iv. Carry out the first reaction, update time to   , and goto step i.

Note that the First Reaction Method requires computing M random numbers per reaction event (one for each reaction in the system) and also requires sorting the reaction times to figure out which reaction event occurs first.

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

Most folks think about and use continuous, approximate methods. Thus, most descriptions (models) of biological systems use continuous rate constants to describe reaction kinetics. Can we convert from continuous reaction rate constants to reaction propensities? Yes. The key is to look at the units of the constants.

Consider the following system: A <-> B+C

A -> B+C, with rate k_{off} = 1/time

B+C -> A, with rate k_{on} = 0.6E9/molar/time

k_{off} is a first-order reaction, whose rate is equivalent to the chance that an individual reaction event will take place, *c*.

k_{on} is a second-order reaction. Here, the units don't match. We need to convert from 1/molar/second to 1/#/time. Molar has units of moles per volume. So, the units of k_{on} are 1/(moles/volume)/time. We can convert this to 1/#/time by multiplying the denominator by the (numbers of molecules / mole) and the volume of the system.

56. Here's an example. Consider:

B+C -> A, with rate k_{on} = 0.6E9/molar/time in a reaction the size of a bacteria (1E-15 L)

$c = k_{on}$ / V/A$_{\#}$ = 0.6E9 / [6E23#/mole x 1E-15L] = 1/#/time.

57. For higher order reactions c = k / V$^{(N-1)}$/A$_{\#}$, where N is the reaction order.