Modelling Biochemical Reaction Networks

# Lecture 14: Stochastic theory of reaction kinetics

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### Recommended reading

- ▶ Fall, Marland, Wagner and Tyson, section 11.1.6
- ▶ Gillespie, J. Phys. Chem. 81, 2340 (1977).

## Stochastic theory of well-mixed reactions

- Consider a bimolecular elementary reaction  $A + B \rightarrow C$ .
- Imagine a random selection of one particular molecule of A, and one particular molecule of B.
- ► For this particular pair, there is some probability per unit time that they will react, called the stochastic rate constant c. Units: s<sup>-1</sup>
- Because the system is well mixed and we picked our A and B randomly, this probability per unit time is the same for any other (A,B) pair.
- There are  $N_A N_B$  different (A,B) pairs.
- The probability that one pair reacts in a short time Δt (short enough that the probability of two reactions is negligible) is

### $cN_AN_B\Delta t$

#### Stochastic theory of well-mixed reactions Reaction propensity

- ► The quantity a = cN<sub>A</sub>N<sub>B</sub> is called the reaction propensity. It tells us how likely a reaction is to occur per unit time. Larger propensities ⇐⇒ faster reactions
- ► a can always be written as a factor of a stochastic rate constant and a statistical factor (h) for the number of different combinations of reactant molecules available to react: a = ch.

Stochastic theory of well-mixed reactions Statistical factors

Zero-order reaction  $\rightarrow A: h = 1$ (Inflow or synthesis at constant rate) First-order reaction  $A \rightarrow B: h = N_A$ Second-order reaction  $A + B \rightarrow C: h = N_A N_B$ Second-order reaction  $2A \rightarrow B: h = \frac{N_A (N_A - 1)}{2}$  Stochastic theory of well-mixed reactions Stochastic rate constants

- Rate of reaction = number of reactive events per unit time, usually expressed as an equivalent concentration change per unit time
- Propensity = probability of a reactive event per unit time
- In the limit of a large number of molecules, and give or take some theoretical issues we'll skip over, events/time = probability/time
  [A probability of 0.5 s<sup>-1</sup> means that we expect roughly one

reactive event every 2 s, which corresponds to a rate of 0.5 events/s.]

The stochastic (c) and mass-action (k) rate constants are therefore related by some unit conversions, and statistical factors. Stochastic theory of well-mixed reactions Stochastic rate constants

Recall: Rate would typically have units of mol  $L^{-1}s^{-1}$ .

Zero-order reaction  $\rightarrow A$ : a = c (in events/s)

Get mol  $L^{-1}s^{-1}$  by converting events to moles of events (dividing by *L*) and dividing by the volume, so c = LVk.

Note: The mass-action rate constants are independent of V, which means that the stochastic rate constants may depend on V.

First-order reaction  $A \rightarrow B$ :  $a = cN_A$ 

Divide both sides by *L* and *V* to convert to a rate, and note that  $N_A/(LV) = [A]$ , thus rate = c[A], so c = k.

#### Stochastic theory of well-mixed reactions Stochastic rate constants

Second-order reaction  $A + B \rightarrow C$ :  $a = cN_AN_B$ 

Divide both sides by *L* and *V* to convert to a rate, then convert  $N_A$  and  $N_B$  to concentrations, and get rate = cLV[A][B], so c = k/(LV).

Second-order reaction 2A  $\rightarrow$  B:  $a = c \frac{N_A(N_A-1)}{2}$ 

Deterministic rates are appropriate when  $N_A$  is large, so  $N_A - 1 \approx N_A$ . Mass-action rate =  $k[A]^2$ Conclude, after a bit of work, that c = 2k/(LV).

### Statistics of chemical reactions

Suppose that we have r chemical reactions, each with its own propensity a<sub>i</sub>, i = 1, 2, ..., r.

• Define 
$$a_0 = \sum_{i=1}^r a_i$$
.

- The probability that any given reaction will occur per unit time is a<sub>i</sub>.
  - ⇒ If  $a_i$  is bigger than  $a_j$  by a factor of (say) 2, then reaction *i* is twice as likely to occur as reaction *j* in a time interval  $\Delta t$ .
  - $\Rightarrow$  Reaction *i* is twice as likely to be the next reaction to occur.
  - ⇒ In general,  $a_i/a_0$  is the probability that reaction *i* is the next one of the *r* reactions to occur.
- The time before the next reaction occurs is a random variable with distribution  $p(\tau) = a_0 e^{-a_0 \tau}$ .

### Stochastic simulations

- Computers typically have a random number generator that generates pseudo-random numbers distributed uniformly between 0 and 1.
- $\blacktriangleright$  We can generate an exponentially distributed  $\tau$  (time to next reaction) by

$$\tau = \frac{1}{a_0} \ln \left( \frac{1}{r_1} \right)$$

where  $r_1$  is a uniformly distributed random number on (0,1].

### Stochastic simulations

"Line up" the reaction probabilities a<sub>i</sub>/a<sub>0</sub> and then use a second uniformly distributed random number, r<sub>2</sub>, to choose which reaction happens next.



 Update numbers of molecules based on what reaction happened, increase time by \(\tau\), then recompute the propensities and start again.

## Gillespie stochastic simulations in **xppaut**

- Capability not documented in all currently distributed versions of manual
- Set up: set parameters, initial numbers of molecules
- ODE file must contain the following: @ METH=discrete (unless you use the .dif filename extension)
- Also consider setting large values for BOUND, TOTAL (number of simulation steps) and NJMP (interval between points reported in the data file)
- Give equations for propensities
- Use special z=gill(0,a1,a2,...)
  - After each step, z(0) contains τ, and z(i) contains 1 if reaction *i* occurred, and 0 otherwise.
  - Update time variable (can't be called t) and numbers of molecules