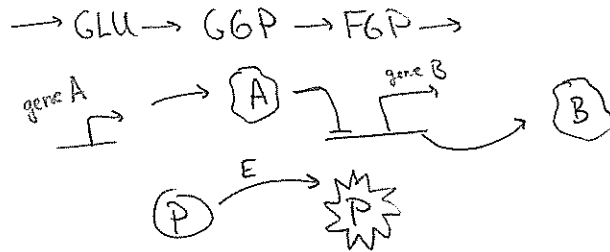


# AMATH 382 - Computational Modeling of Cellular Systems

2016 01 06

## Chapter 1 - Modelling in Molecular Biology

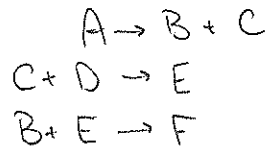
Cellular phenomena are often described by interaction diagrams



- interactions (arrows) represent processes leading to changes: formation, elimination, or interconversion of molecules
- These static diagrams describe dynamic phenomena

## Chapter 2 - Chemical Reaction Networks

Consider the reactions



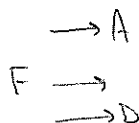
These can be represented in a graph



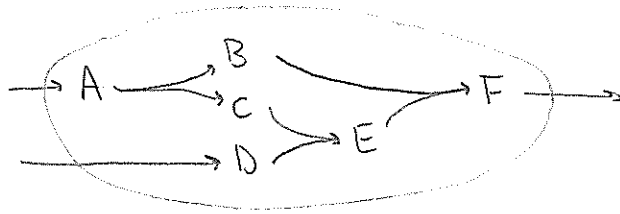
The species are the nodes. The reactions are the edges  
This network is closed (no transfer of mass (or energy, or information)) with the "outside world".

Closed reaction networks run to thermal equilibrium - all (net) reaction rates are zero.

Biochemical reaction networks are typically open.  
eg if we add



"the rate constant is not necessarily constant"

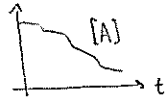


This network can support a dynamic equilibrium in which there is a steady state flux through the network.

## Reaction Kinetics

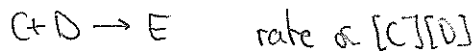
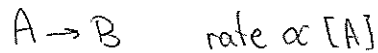
Two key assumptions

- i) spatial homogeneity: well-stirred reaction vessel, allows us to define the concentration of each species  $[A]$ .
- ii) Large numbers of molecules (the continuum hypothesis)



-allows continuously varying concentrations

The Law of Mass Action: the rate of a reaction is proportional to the product of the reactant concentrations



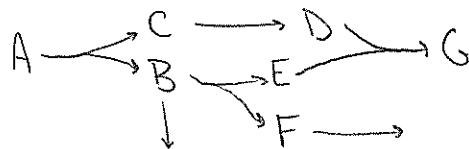
→ Constant of proportionality/rate constant



"constant"  $K$  depends on environment

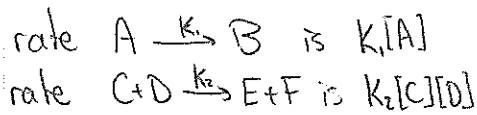
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## Chemical Reaction Networks



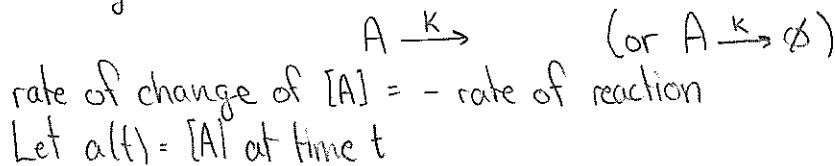
assignment of rates to reactions: chemical kinetics

Law of Mass Action for spatially homogeneous systems with large molecular populations: rate of reaction proportional to product of reactant concentrations



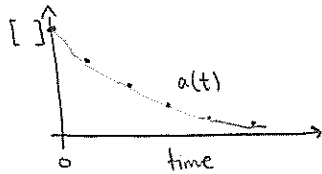
Examples

I) Decay



$\frac{d}{dt} a(t) = -ka(t)$  }  $\rightarrow$  a differential equation:  
 solution is a function  $a(t)$   
 "the time rate of change of"      rate of reaction

Expectation: solution  $a(t)$  should match experimental observations



Unsatisfying solution procedure: guess  
 First take  $k = -1$  (not physical), model:

$\frac{d}{dt} a(t) = a(t)$

solution:  $a(t) = e^t, a(t) = De^t$

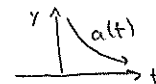
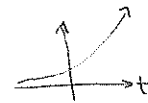
next take  $k = 1$

$\frac{d}{dt} a(t) = -a(t)$

solution:  $a(t) = De^{-t}$

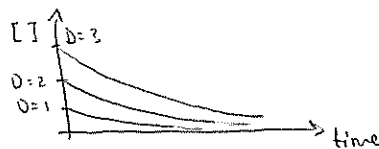
generally

$\frac{d}{dt} a(t) = -ka(t) \Rightarrow a(t) = De^{-kt}$



Note that at time  $t=0$ , we have  $a(0) = De^{(-0)} = D$ . So  $D$  is the concentration at time 0, called the initial condition.

Solution behaviour.



exponential decay

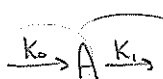
long-term (or asymptotic) behaviour:  $a(t)$  tends to zero.

rate of decay dictated by  $K$

$$\text{half-life: } T_{1/2} = \frac{\ln 2}{K}$$

$$\text{time constant: } \frac{1}{K}$$

## II) Production & Decay



zeroth order reaction, rate:  $[S]^0 K_0 = K_0$

$$\text{notation: } a(t) = [A](t)$$

$$\frac{d}{dt} a(t) = \text{rate of production} - \text{rate of consumption}$$

$$\frac{d}{dt} a(t) = K_0 - K_1 a(t)$$

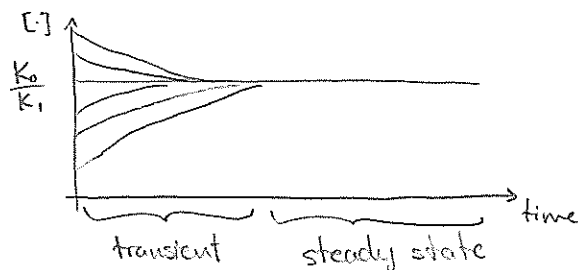
Expectations: long-term (asymptotic) behaviour:

In (dynamic) steady-state  $[A]$  will no longer be changing ( $\frac{d}{dt} a(t) = 0$ ).

Let  $a^{ss} =$  steady state  $[A]$ . So

$$K_1 - K_1 a^{ss} = 0 \Rightarrow a^{ss} = K_0 / K_1$$

Expected behaviour:

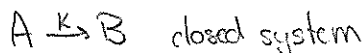


Solution (exercise 2.14):

$$a(t) = D e^{-kt} + \frac{K_0}{K_1}$$

time constant:  $\frac{1}{K_1}$

## III) Irreversible conversion



let  $a(t) = [A]$  at time  $t$

$b(t) = [B]$  at time  $t$

$$\frac{d}{dt} a(t) = -K a(t), \quad \frac{d}{dt} b(t) = K a(t)$$

As before,

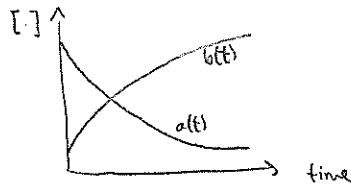
$$a(t) = D e^{-kt}$$

Then to find  $b(t)$ , use closure. Conservation:

$$[A](t) + [B](t) = T, \text{ constant}$$

So

$$b(t) = T - a(t)$$



Note typically Moiety conservation, not mass conservation

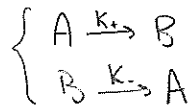
eg.  $A + B \rightarrow C$  conservation:  $[A](t) + [C](t) = T_1$ ,  $[B](t) + [C](t) = T_2$ .

Conservation is reflected in the model:

$$\frac{d}{dt}(a(t) + b(t)) = -ka(t) + ka(t) = 0$$

$$\Rightarrow a(t) + b(t) = T \text{ constant}$$

IV) Reversible conversion



$$\frac{d}{dt} a(t) = k_- b(t) - k_+ a(t), \quad \frac{d}{dt} b(t) = k_+ a(t) - k_- b(t)$$

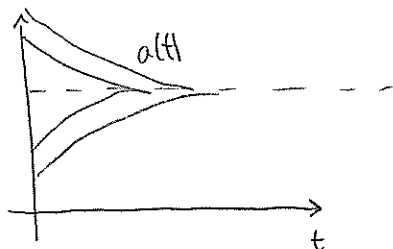
Again conservation:  $a(t) + b(t) = T$  constant

steady state:  $k_+ a^{ss} = k_- b^{ss}$

$$\frac{b^{ss}}{a^{ss}} = \frac{k_+}{k_-} = \text{equilibrium constant } K_{eq} \text{ for the reaction}$$

Solution (exercise):

$$a(t) = D e^{-(k_+ + k_-)t} + \frac{k_- T}{k_+ + k_-}$$



time constant  $\frac{1}{k_+ + k_-}$

## Numerical Simulation of Differential Equation Models

- We will not be able to derive analytic solution formulas for most models of interest

- Instead, we resort to numerical simulation of system behaviour.

Idea: Construct particular solutions by stepping forward from a given initial condition

Euler's Method (Euler, 1707-1783):

For the equation

$$\frac{d}{dt} a(t) = f(a(t))$$

approximate

$$\frac{d}{dt} a(t) \approx \frac{a(t+h) - a(t)}{h}$$

h small

$$\frac{a(t+h) - a(t)}{h} = f(a(t))$$

rearrange to an update formula

$$a(t+h) = a(t) + hf(a(t))$$

Procedure: start with  $a(0)$  given

$a(0)$  given

$$(t=0) \quad a(h) = a(0) + hf(a(0))$$

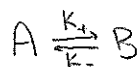
$$(t=1) \quad a(2h) = a(h) + hf(a(h))$$

$$(t=2) \quad a(3h) = a(2h) + hf(a(2h))$$

Result: a set of points  $(0, a(0)), (h, a(h)), (2h, a(2h)), \dots$  which approximate the model solution  $a(t)$   
(See picture in text.)

## Model Reduction

eg.



$$\frac{d}{dt} a(t) = -k_+ a(t) + k_- b(t),$$

$$\frac{d}{dt} b(t) = k_+ a(t) - k_- b(t)$$

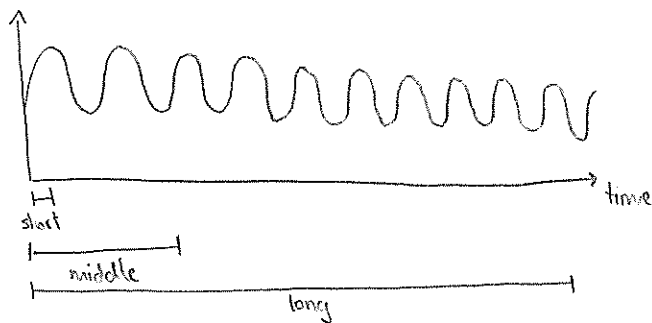
conservation:  $a(t) + b(t) = T$

reduced model:

$$\frac{d}{dt} a(t) = -k_+ a(t) + k_- (T - a(t)), \quad b(t) = T - a(t)$$

## Time-scale Separation

Biological processes occur over a wide arrange of timescales, all of which can't be meaningfully described by a single model.

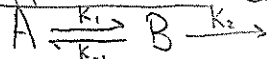


Procedure: choose a timescale of interest

- (much) shorter processes are presumed "frozen", slow variables appear as constant parameters
- (much) faster processes are presumed "instant", fast variables are continually in equilibrium with respect to model dynamics

Two approaches (for faster processes):

The Rapid equilibrium approximation: Consider the network



Model:

$$\frac{d}{dt} a(t) = -k_1 a(t) + k_{-1} b(t)$$

$$\frac{d}{dt} b(t) = k_1 a(t) - k_{-1} b(t) - k_2 b(t)$$

Two processes: interconversion ( $A \rightleftharpoons B$ ), time constant  $\frac{1}{k_1 + k_{-1}}$   
decay ( $B \rightarrow$ ), time constant  $\frac{1}{k_2}$

Suppose the interconversion is fast (compared to decay)  
 $k_1 + k_{-1} \gg k_2$ , ie  $\frac{1}{k_1 + k_{-1}} \ll \frac{1}{k_2}$

→ conversion rapidly reaches equilibrium, and equilibrium will be maintained  
(See picture in text.)

Model reduction (to focus on slow time scale): presume the interconversion is in equilibrium at all times.

Equilibrium condition:

$$\frac{[B]}{[A]} = \frac{k_1}{k_{-1}} \quad \leftarrow \text{This does not actually hold at any time instant for the true model}$$

We'll generate an approximate model. Let  $\tilde{a}(t)$  and  $\tilde{b}(t)$  be the concentrations in the approximate model. Then

$$\frac{\tilde{b}(t)}{\tilde{a}(t)} = \frac{k_1}{k_{-1}}$$

for all  $t$ . The reduced network  
(equilibrated pool of A, B) →

Introduce  $\tilde{c}(t) = \text{total concentration in this pool} = \tilde{a}(t) + \tilde{b}(t)$ . We want to find rate  $k_2 \tilde{b}(t)$  in terms of  $\tilde{c}(t)$ . Observe

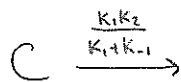
$$\tilde{c}(t) = \tilde{a}(t) + \tilde{b}(t) = \frac{k_{-1}}{k_1} \tilde{b}(t) + \tilde{b}(t) = \left(\frac{k_{-1}}{k_1} + 1\right) \tilde{b}(t) = \frac{k_{-1} + k_1}{k_1} \tilde{b}(t)$$

$$\Rightarrow \tilde{b}(t) = \frac{k_1}{k_1 + k_{-1}} \tilde{c}(t)$$

rate of decay

$$k_2 \tilde{b}(t) = k_2 \left( \frac{k_1}{k_1 + k_{-1}} \tilde{c}(t) \right) = \frac{k_1 k_2}{k_1 + k_{-1}} \tilde{c}(t)$$

model:



$$\frac{d}{dt} \tilde{c}(t) = - \frac{k_1 k_2}{k_1 + k_{-1}} \tilde{c}(t)$$

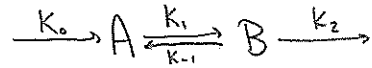
$$\tilde{a}(t) = \frac{k_{-1}}{k_1 + k_{-1}} \tilde{c}(t)$$

$$\tilde{b}(t) = \frac{k_1}{k_1 + k_{-1}} \tilde{c}(t)$$



## Approach II: Quasi-steady state assumption

Consider



with  $k_1 + k_{-1} \gg k_2$ . Focus on the dynamics of a species. Note A is involved only in "fast" processes. We presume that species A reaches its steady state quickly with respect to the rest of the system dynamics.

Full model:

$$\frac{d}{dt} a(t) = k_0 - k_1 a(t) + k_{-1} b(t) \quad \leftarrow \text{fast}$$

$$\frac{d}{dt} b(t) = k_1 a(t) - k_{-1} b(t) - k_2 b(t) \quad \leftarrow \text{slow ("frozen" on a fast timescale)}$$

For b frozen, a reaches a steady state  $a^{ss}$  given by

$$0 = k_0 - k_1 a^{ss} + k_{-1} b.$$

This defines a quasi-steady-state for a:

$$a^{qss} = \frac{k_0 + k_{-1} b}{k_1}.$$

Now, as b varies on the slow timescale, a "keeps up" by staying always in this quasi-steady-state

$$a^{qss}(t) = \frac{k_0 + k_{-1} b(t)}{k_1}.$$

Procedure: Replace the differential equation for a with  $a = a^{qss}$

$$a(t) = a^{qss}(t) = \frac{k_0 + k_{-1} b(t)}{k_1}$$

$$\frac{d}{dt} b(t) = k_1 a^{qss}(t) - k_{-1} b(t) - k_2 b(t)$$

$$= k_1 \left( \frac{k_0 + k_{-1} b(t)}{k_1} \right) - k_{-1} b(t) - k_2 b(t)$$

$$= k_0 + \cancel{k_{-1} b(t)} - \cancel{k_{-1} b(t)} - k_2 b(t)$$

$$= k_0 - k_2 b(t)$$

(See picture in text.)