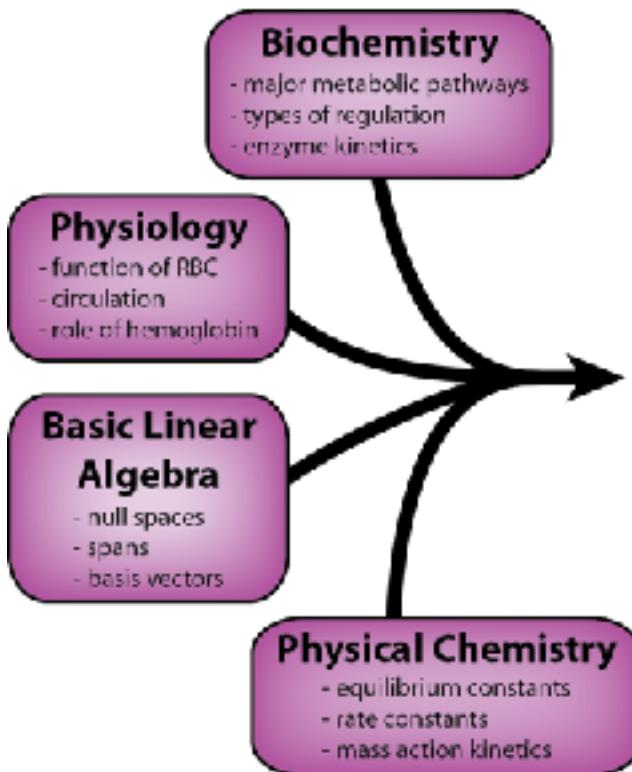
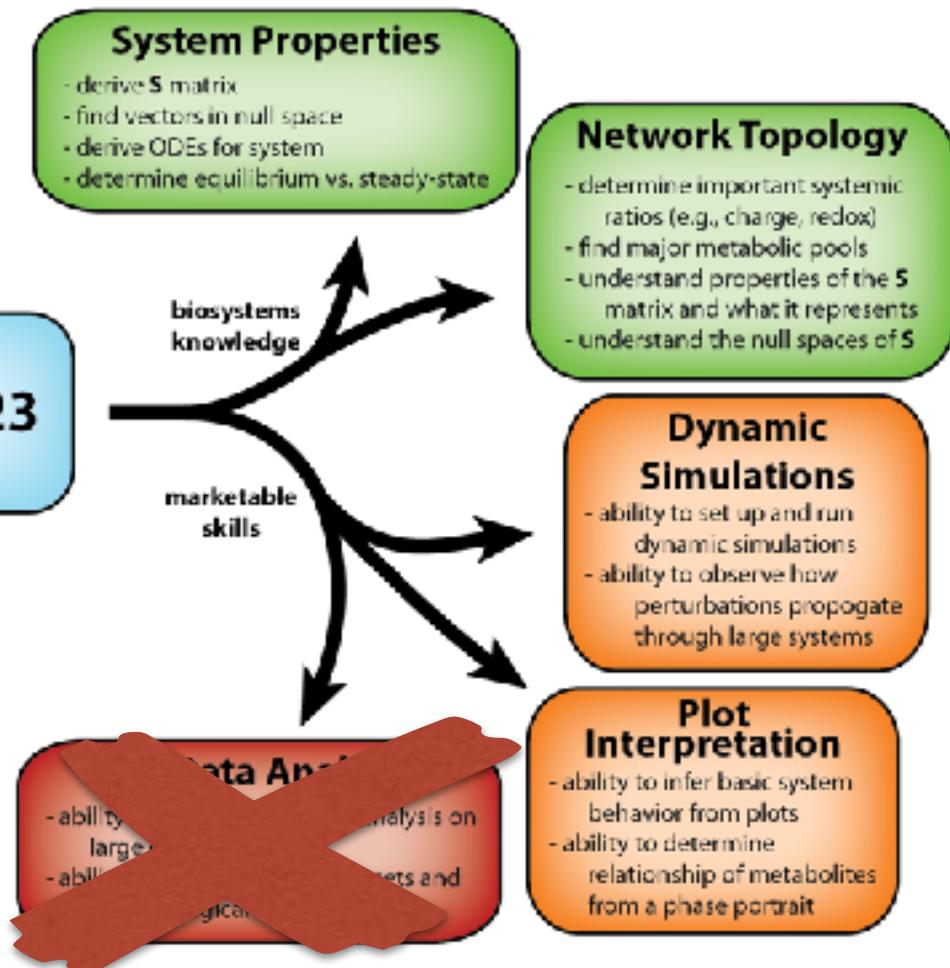


Prereqs and Skill Development

“Inputs”

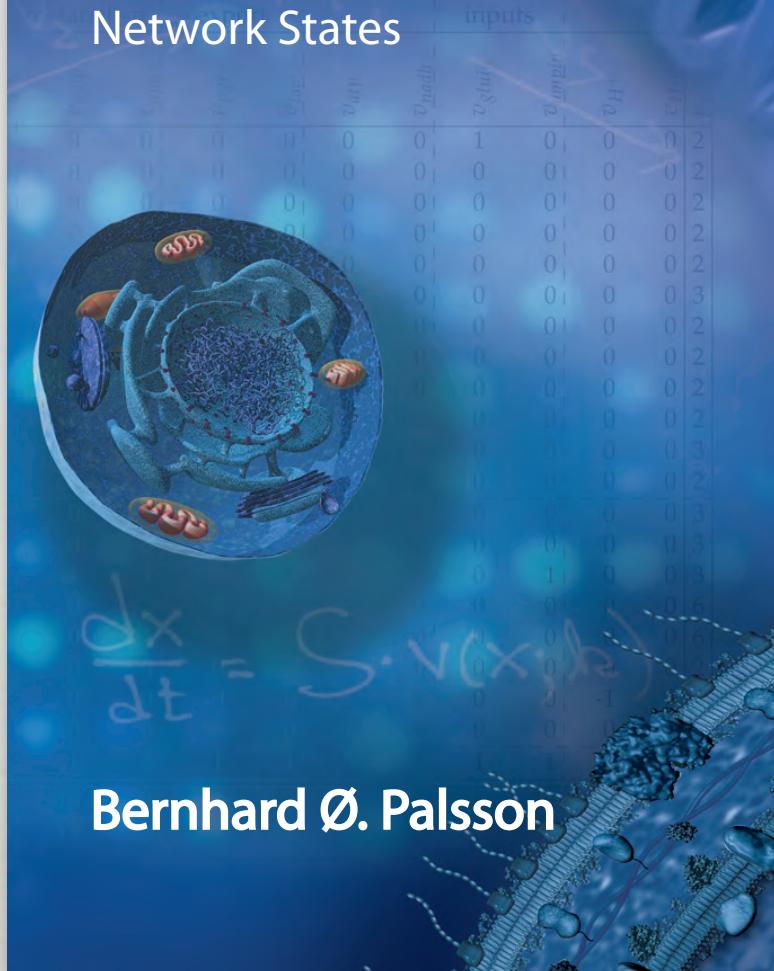


“Outputs”



Systems Biology

Simulation of Dynamic Network States



Lecture #2

Basics of Kinetic Analysis

Outline

1. Fundamental concepts
2. The dynamic mass balances
3. Some kinetics
4. Multi-scale dynamic models
5. Important assumptions

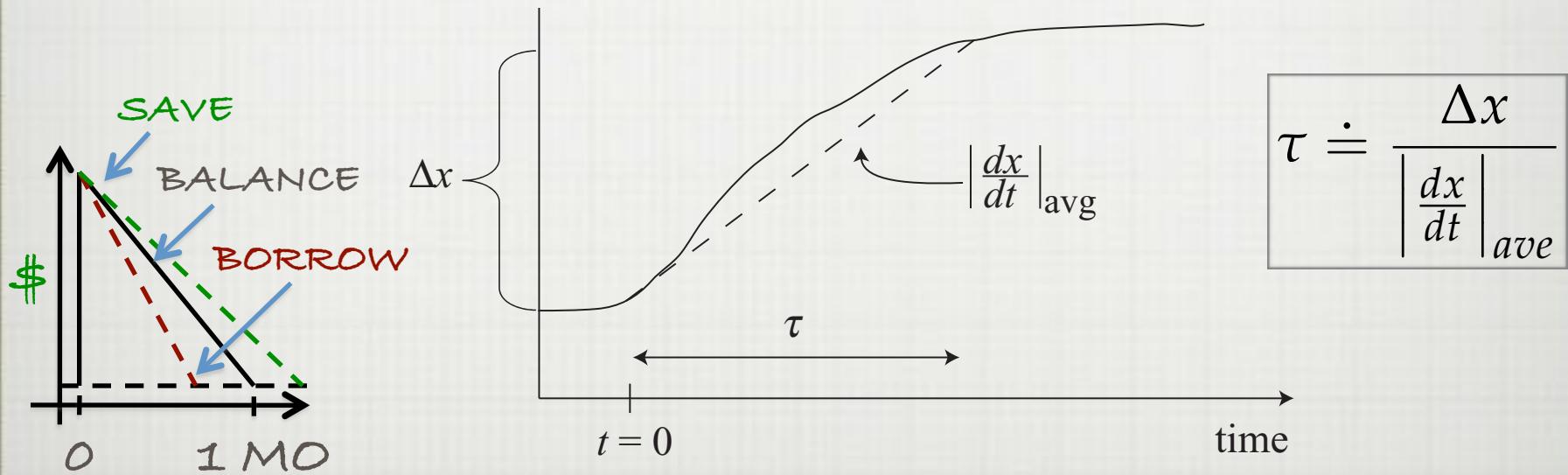
FUNDAMENTAL CONCEPTS

Fundamental Concepts

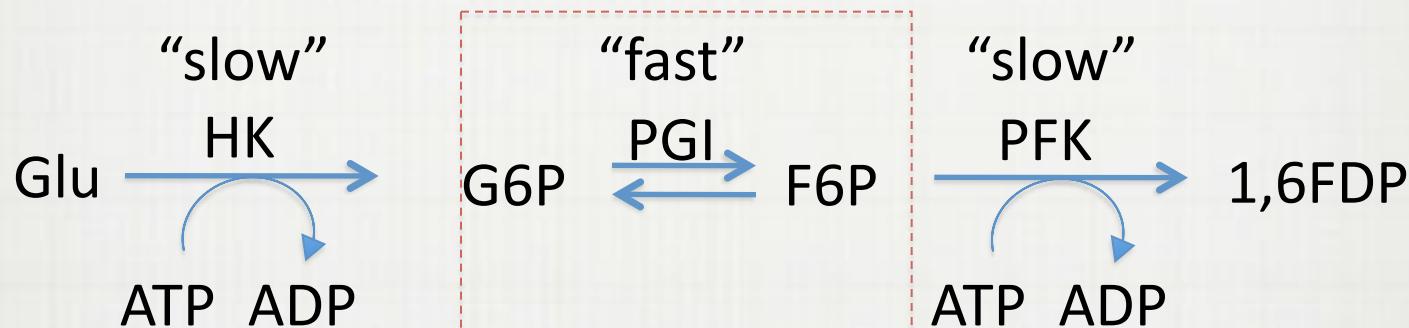
- Time constants:
 - measures of characteristic time periods
- Aggregate variables:
 - ‘pooling’ variables as time constants relax
- Transitions:
 - the trajectories from one state to the next
- Graphical representation:
 - visualizing data

Time Constants

- A measure of the time it takes to observe a significant change in a variable or process of interest

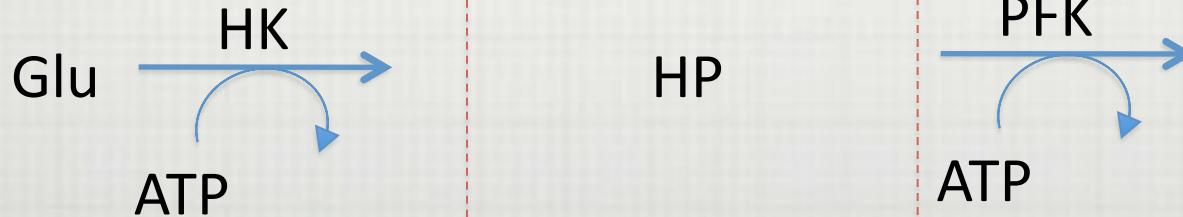


Aggregate Variables: primer on “pooling”

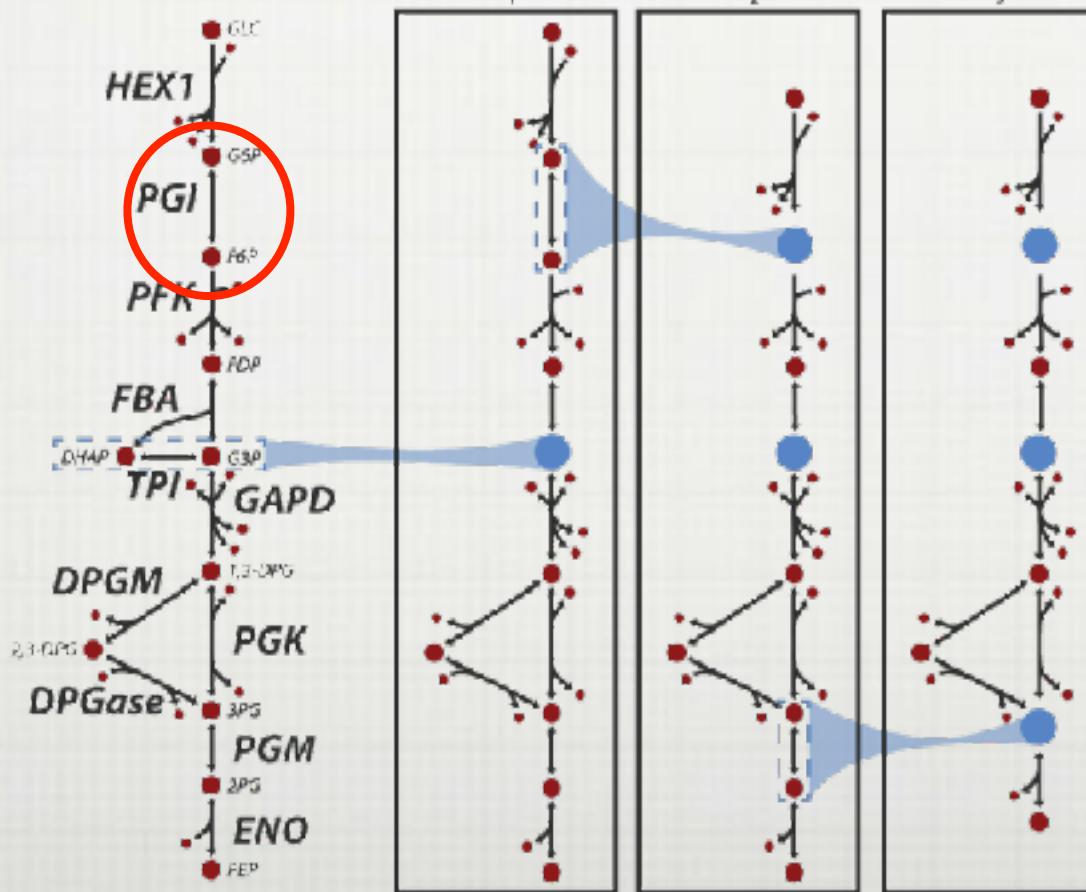


Time scale separation (TSS)
Temporal decomposition

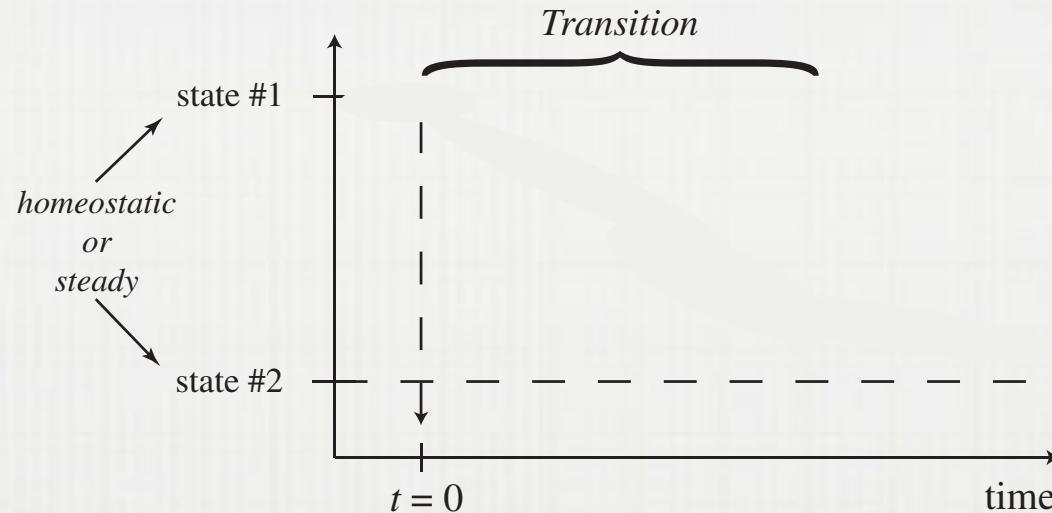
Aggregate pool
 $HP = G6P + F6P$



Graphical representation

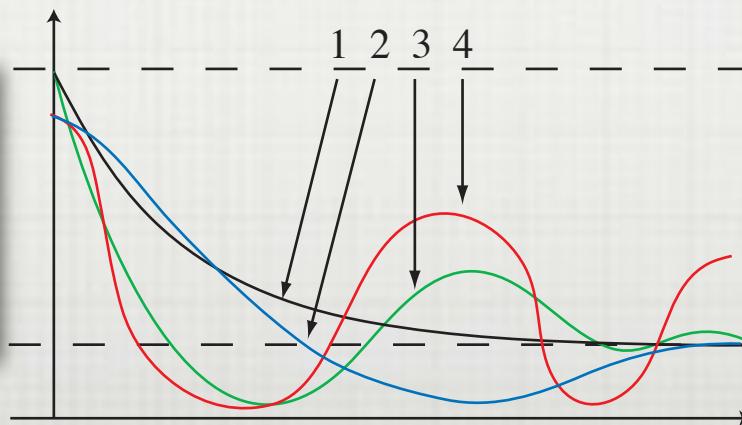


Transitions



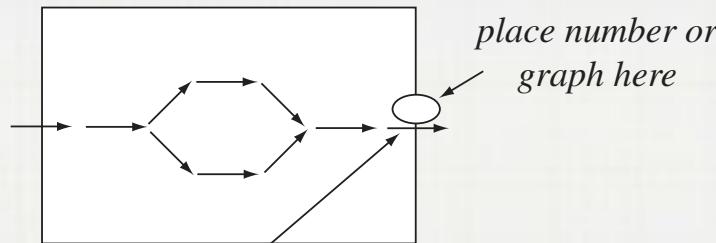
Transient response:

1. “smooth” landing
2. overshoot
3. damped oscillation
4. sustained oscillation
5. chaos (not shown)

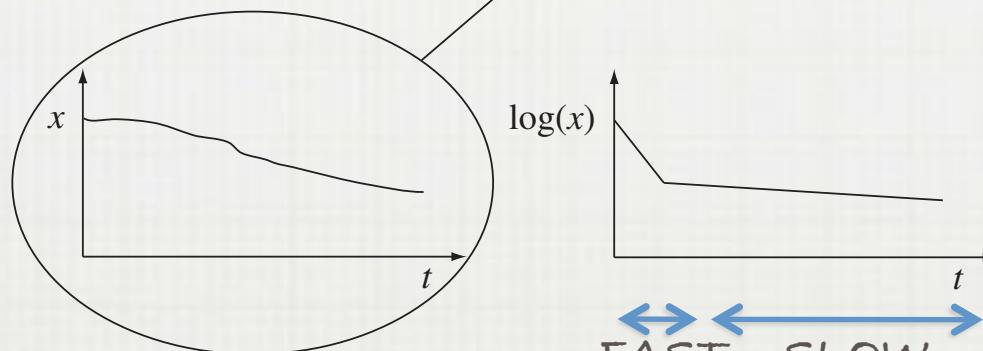


Representing the Solution

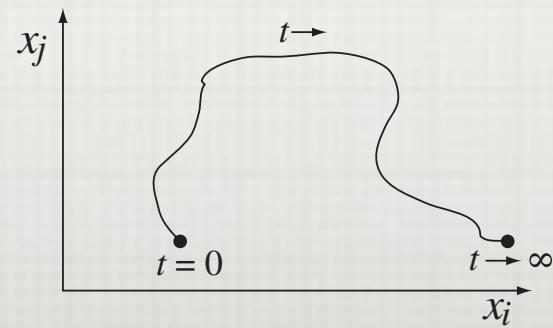
(a) Map



(b) Time profiles



(c) Dynamic phase portraits

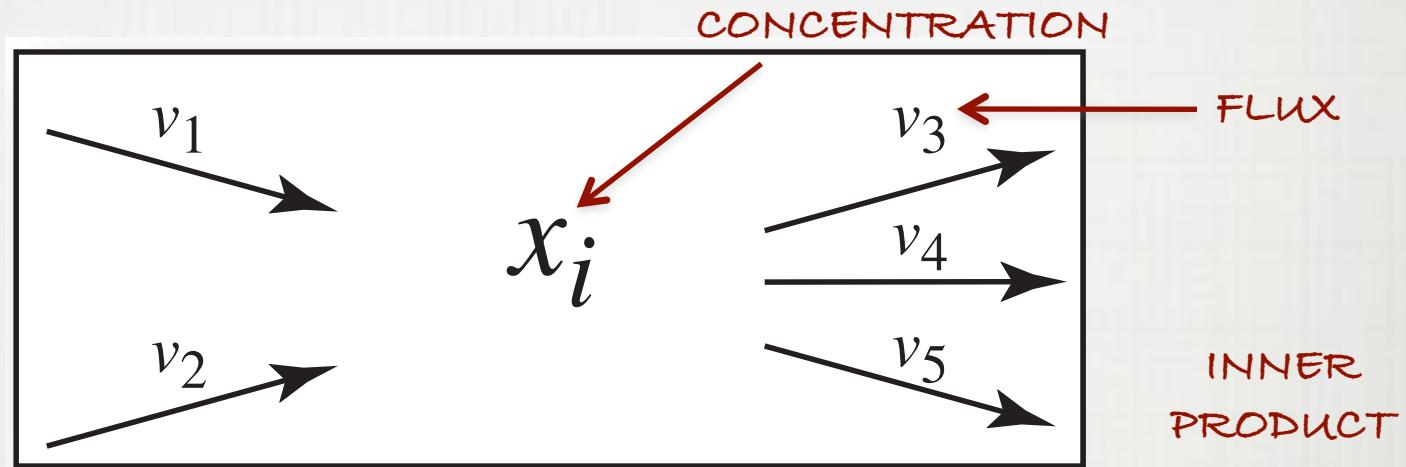


EXAMPLE:



THE DYNAMIC MASS BALANCES

Mass balance equations:



$$\begin{aligned}\frac{dx_i}{dt} &= v_1 + v_2 - v_3 - v_4 - v_5 \\&\quad \xleftarrow{\text{formation}} \qquad \qquad \qquad \xleftarrow{\text{degradation}} \\&= \langle (1, 1, -1, -1, -1), (v_1, v_2, v_3, v_4, v_5)^T \rangle \\&= \langle \mathbf{s}_i^x \cdot \mathbf{v} \rangle\end{aligned}$$

Units on Key Quantities

Dynamic Mass Balance

$$\frac{dx}{dt} = Sv(x; k)$$

Dimensionless
mol/mol

Mass (or moles)
per volume
per time

Mass (or
moles) per
volume

1/time, or
1/time • conc.

Example: 1 mol ATP/
1 mol glucose

mM/sec
μM/sec

mM
μM

sec⁻¹
sec⁻¹ μM⁻¹

Need to know ODEs and Linear Algebra for this class

PChem flashback

SOME KINETICS

Kinetics/rate laws

$$\frac{dx}{dt} = S v(x; k)$$

Two elementary types of reactions:

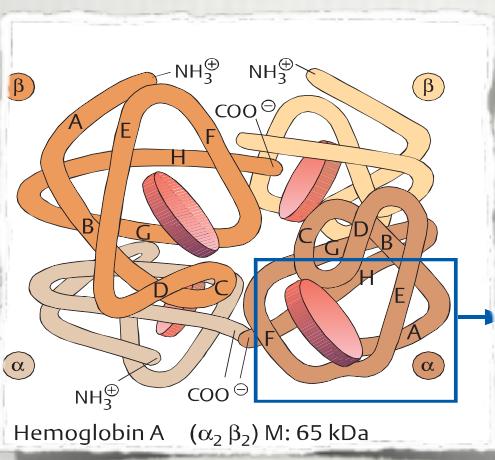
1) Linear



fluxes and concentrations are non-negative quantities

$$x, y \geq 0, v \geq 0$$

2) Bi-linear



EXAMPLE: HEMOGLOBIN

ACTUAL



LUMPED



SPECIAL CASE

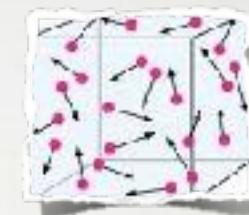


DIMERIZATION



Mass Action Kinetics

$$\left(\begin{array}{l} \text{rate of} \\ \text{reaction} \end{array} \right) \propto \text{collision frequency}$$



Continuum assumption:

Collision frequency \propto concentration

Linear: $v = kx$

Bi-linear: $v = kxy$

Restricted Geometry (rarely used)

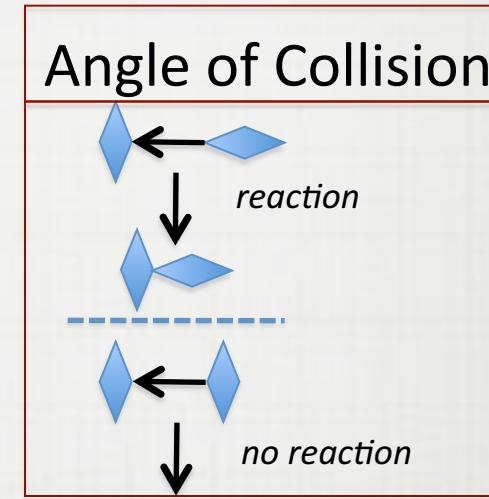
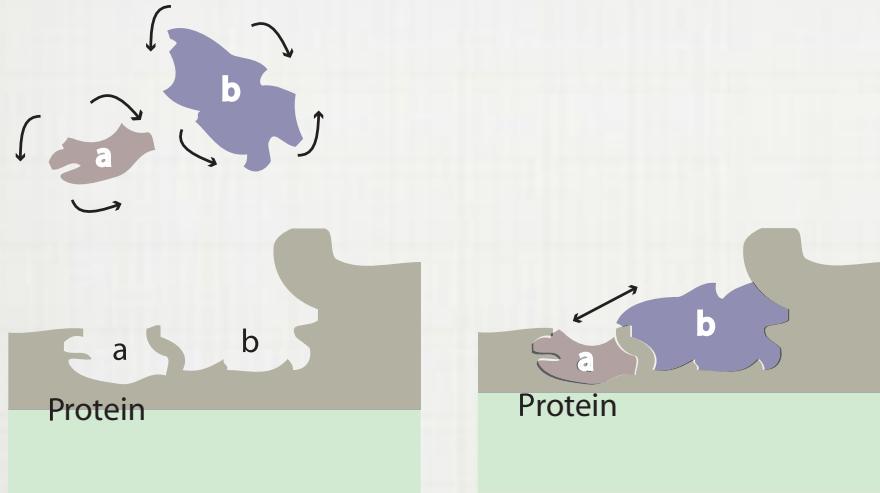
$$v = kx^a$$

$a < 1$ if collision frequency is hampered by geometry

$$v = kx^a y^b$$

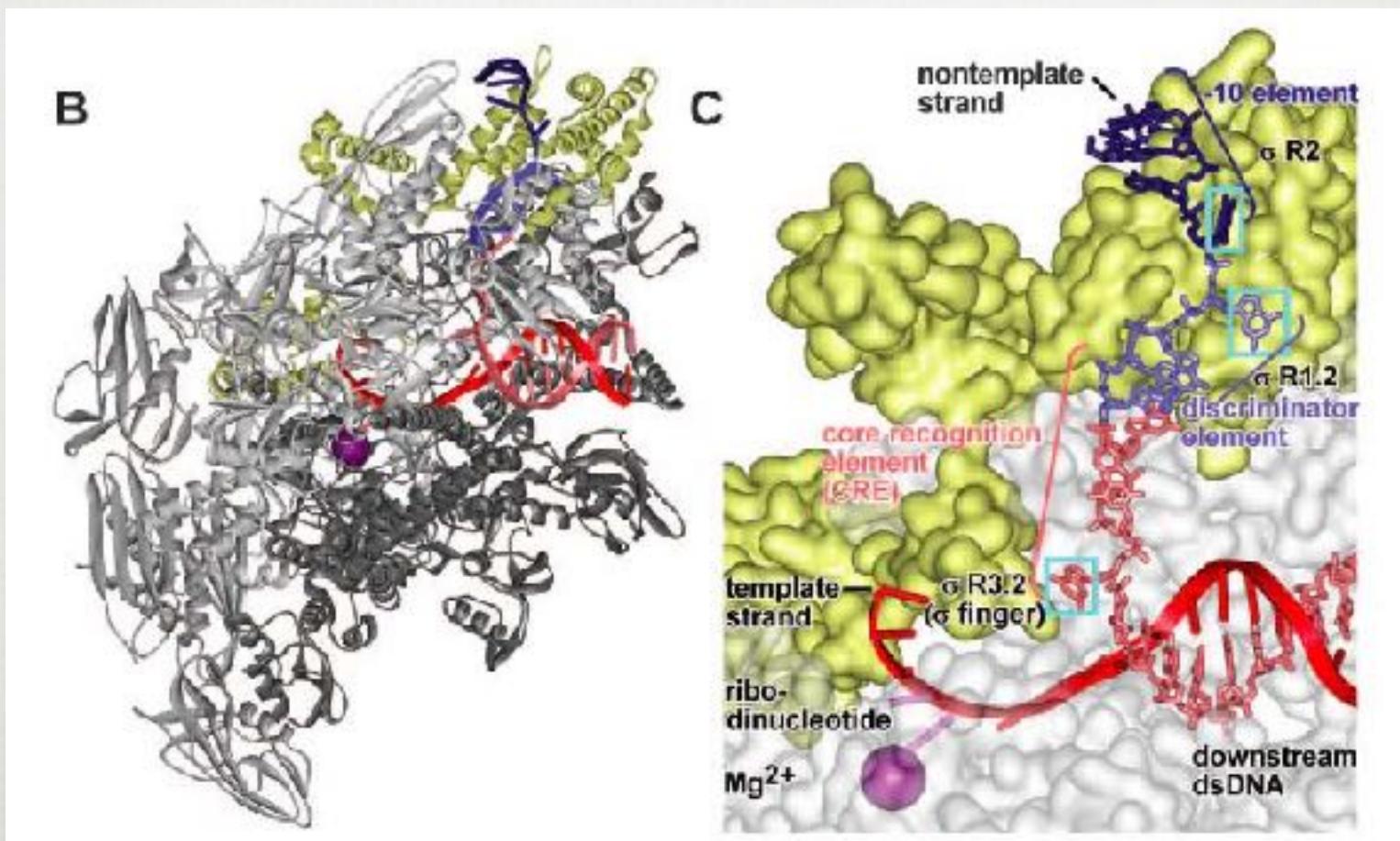
$a > 1$ opposite case or $b > 1$

Kinetic Constants are Biological Design Variables



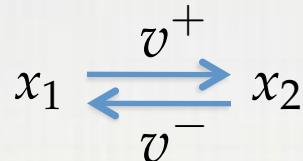
- What determines the numerical value of a rate constant?
- Right collision angle;
 - enzymes are templates for the “right” orientation
- k is a **biologically determined** variable.
 - Genetic basis, evolutionary origin

Detailed and Complicated Example: RNA Polymerase



Combining Elementary Reactions

Reversible reactions



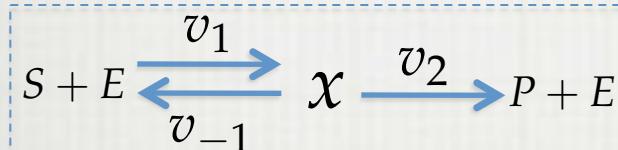
$$v_{net} > 0 \rightarrow$$

$$v_{net} < 0 \leftarrow$$

$$v_{net} = 0 \text{ equil}$$

Equilibrium constant, K_{eq} , is a physico-chemical quantity

Convert a reaction mechanism into a rate law:



$$\xrightarrow{\text{qssa or qea}} v(s) = \frac{V_m s}{K_m + s}$$

$$\begin{aligned} V_m &= k_2 e_{tot} \\ K_m &= (k_{-1} + k_2)/k_1 \end{aligned}$$

mechanism

assumption

rate law

Mass action ratio (Γ)



closed system

$$K_{eq} \frac{[F6P]_{eq}}{[G6P]_{eq}}$$

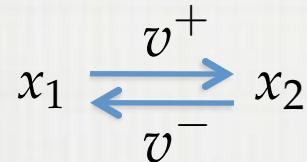
open system

$$\Gamma = \frac{[F6P]_{ss}}{[G6P]_{ss}}$$

$$\frac{\Gamma}{K_{eq}}$$

Distance from ‘equilibrium’ and the basis for forming a pool

Reversible reactions



$$v_{net} > 0 \rightarrow$$

$$v_{net} < 0 \leftarrow$$

$$v_{net} = 0 \text{ equil}$$

$$v_{net} = k_1 x_1 - k_{-1} x_2 = k_1 (x_1 - k_{-1} x_2 / k_1) = k_1 (x_1 - x_2 / K_{eq})$$

k_1 : *speed of the reaction*

$(x_1 - x_2 / K_{eq})$: *distance from equilibrium*;

=0 in equilibrium

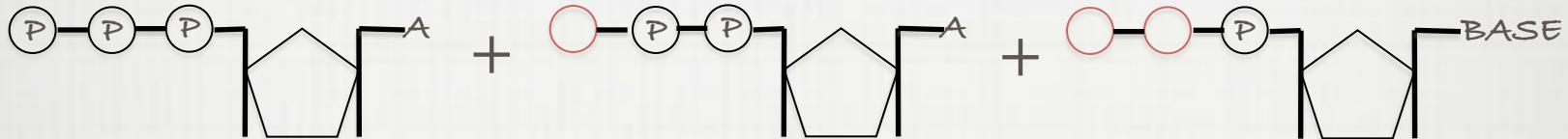
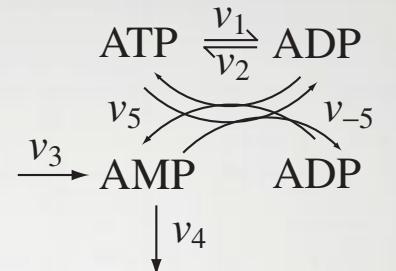
can be viewed as an aggregate variable or ‘pool’

Temporal decomposition and ‘physiologically meaningful’ pools

MULTI-SCALE DYNAMIC MODELS

Example of pools:

High energy phosphate bond trafficking in cells



$$\text{CAPACITY: } = 2(\text{ATP} + \text{ADP} + \text{AMP})$$

$$\text{OCCUPANCY: } 2\text{ATP} + 1\text{ADP} + 0\text{AMP}$$

$$EC = \frac{\text{OCCUPANCY}}{\text{CAPACITY}} \sim [0.85-0.90]$$

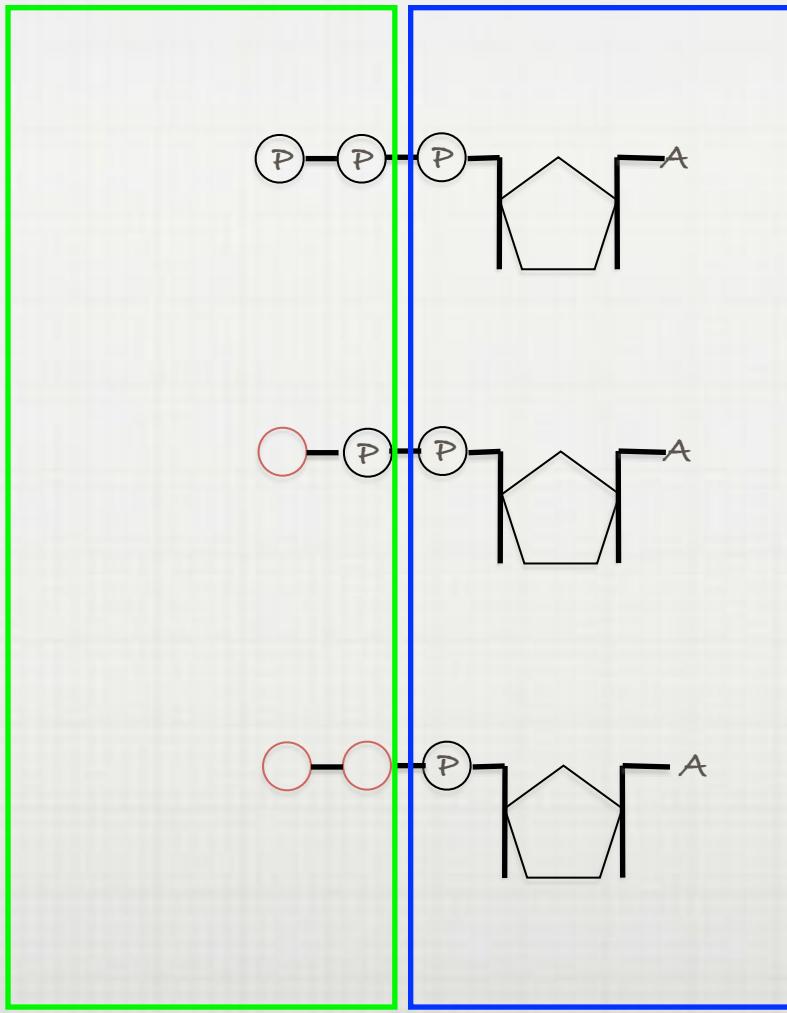
EXAMPLE:

$$\text{ATP} = 10, \text{ADP} = 5, \text{AMP} = 2$$

$$\left. \begin{array}{l} \text{OCCUPANCY} = 2 \cdot 10 + 5 = 25 \\ \text{CAPACITY} = 2(10 + 5 + 2) = 34 \end{array} \right\} EC = \frac{25}{34}$$

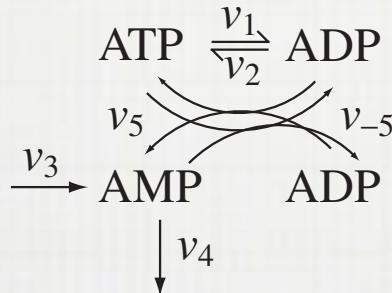
Visualization of pools using chemical structures

OCCUPANCY: $2ATP + 1ADP + OAMP$



CAPACITY: $2(ATP + ADP + AMP)$

Kinetic Description



$$\begin{aligned}\frac{dATP}{dt} &= -v_1 + v_2 & +v_{5,net} \\ \frac{dADP}{dt} &= +v_1 - v_2 & -2v_{5,net} \\ \frac{dAMP}{dt} &= v_3 - v_4 & +v_{5,net}\end{aligned}$$

pooling:

$$\frac{d(ATP+ADP+AMP)}{dt} = v_3 - v_4 \quad \text{Slow}$$

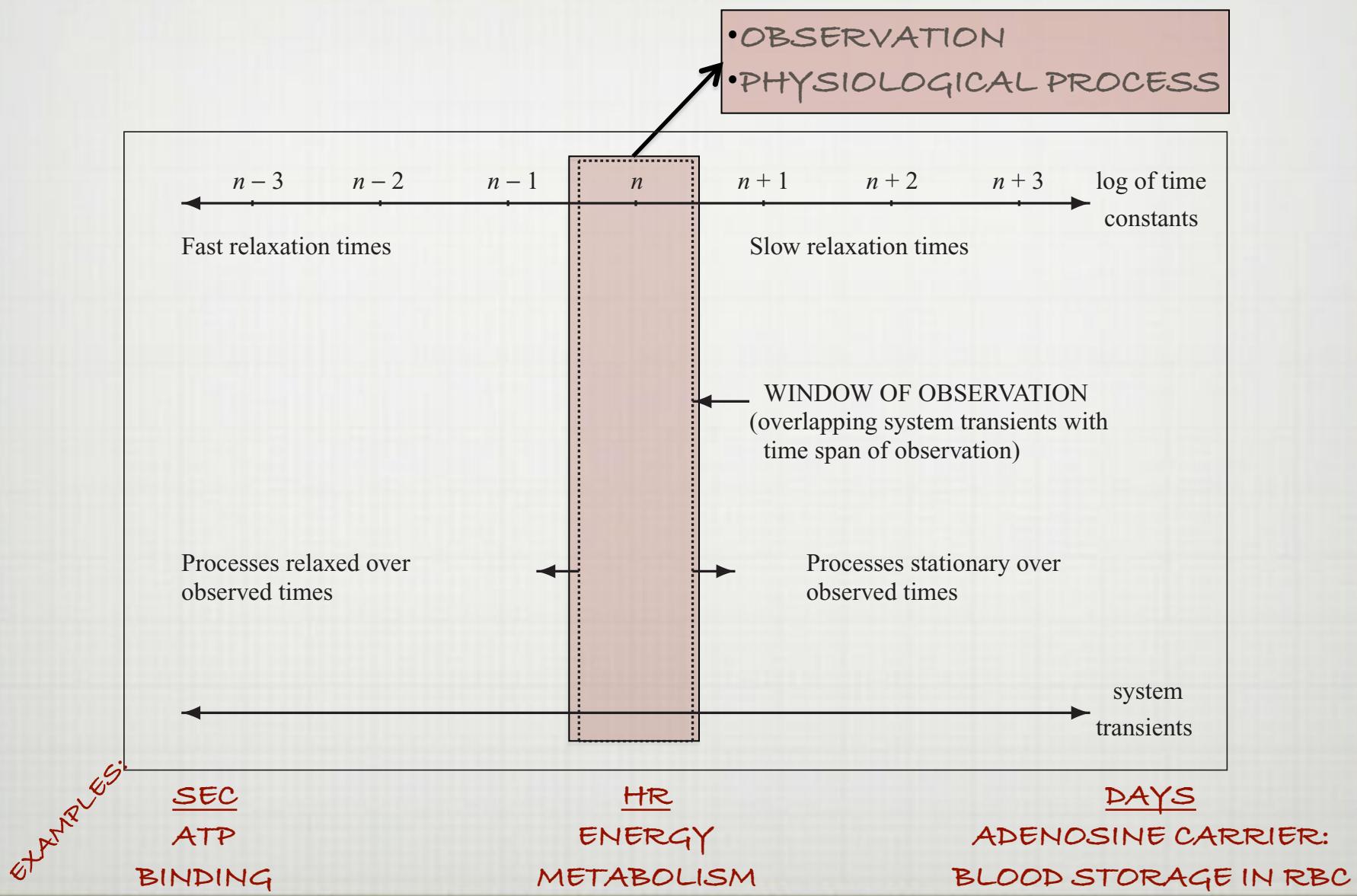
$$ATP+ADP+AMP=A_{\text{tot}}$$

$$\frac{d(2ATP+ADP)}{dt} = -v_1 + v_2 \quad \text{Intermediate}$$

total
inventory
of ~P

$$\frac{d(ATP+ADP)}{dt} = -v_{5,net} \quad \text{Fast}$$

Time Scale Hierarchy



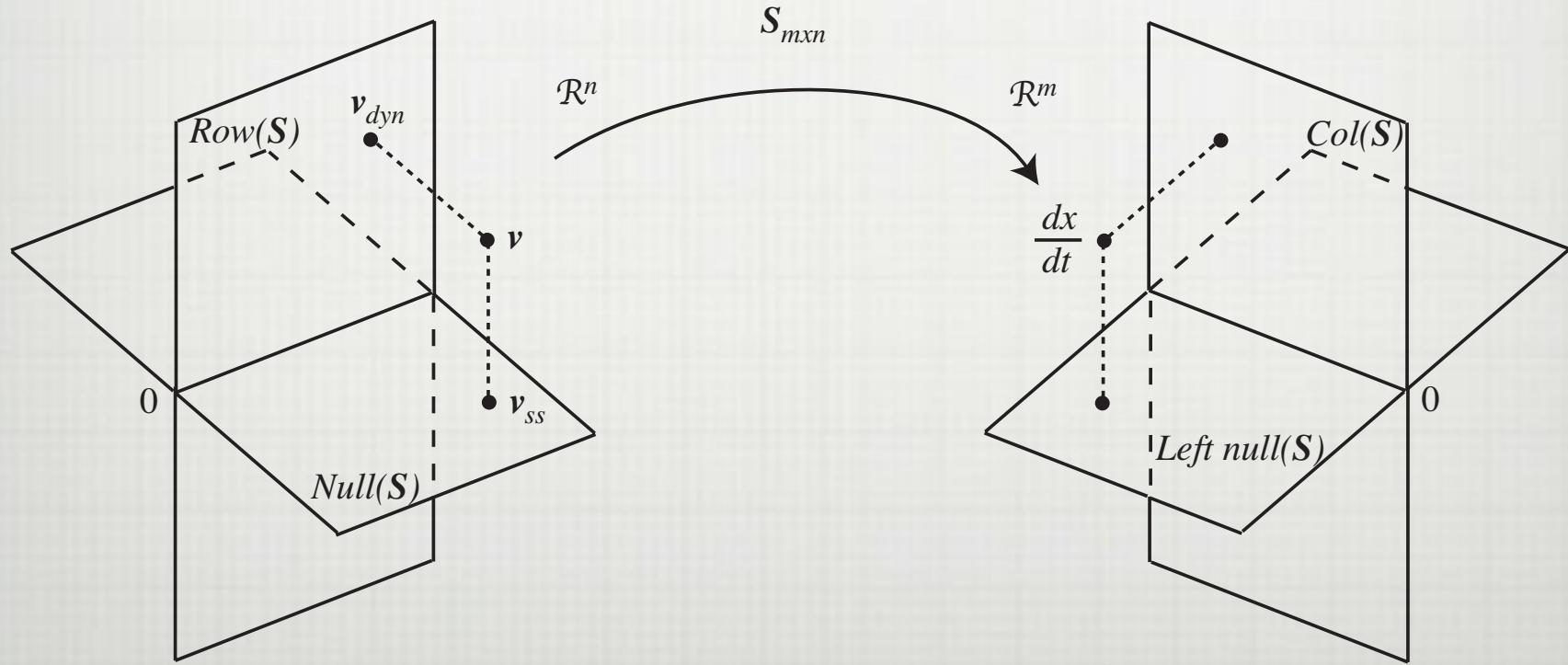
Some fundamental properties

THE STOICHIOMETRIC MATRIX

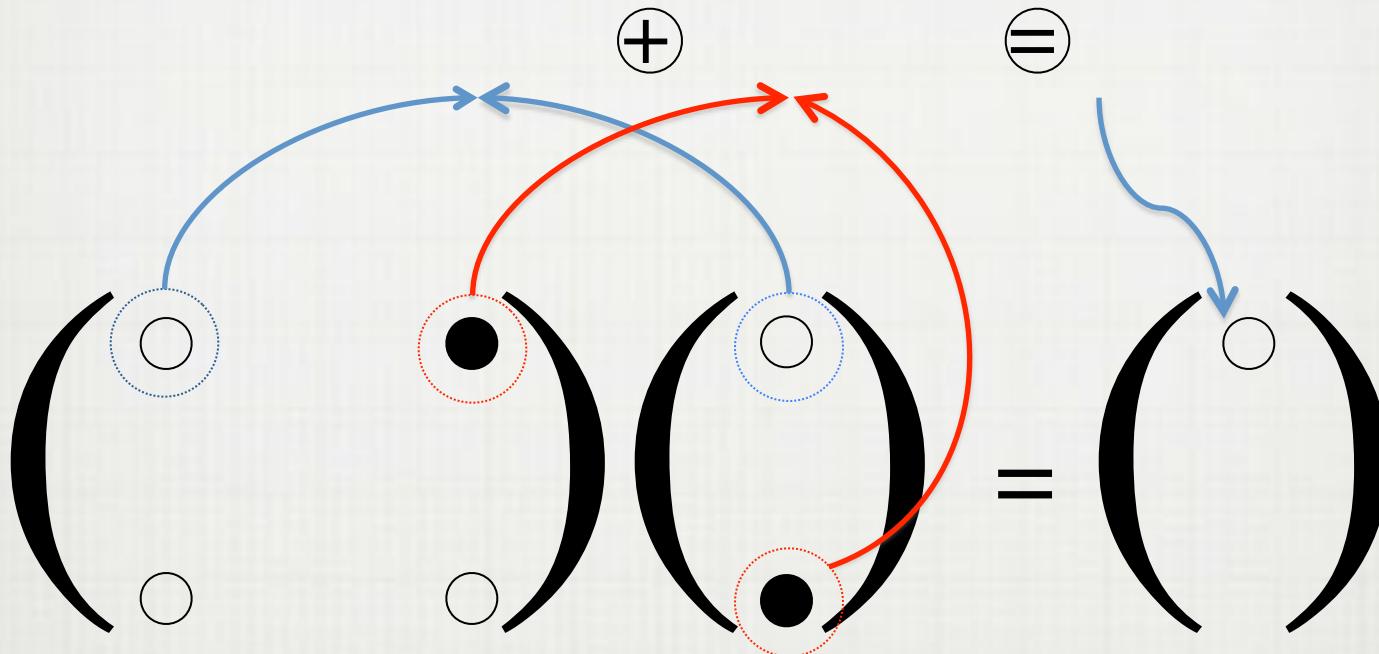
\mathbf{S} represents a mapping operation

$$\frac{dx}{dt} = \dot{x} = x' = \mathbf{S} \cdot \mathbf{v} \quad ;$$

$$\begin{matrix} \mathbf{V} \\ (n \times 1) \end{matrix} \xrightarrow[m \times n]{\mathbf{S}} \begin{matrix} \dot{x} \\ (m \times 1) \end{matrix}$$



Matrix Multiplication: refresher



$$s_{11} \cdot v_1 + s_{12} \cdot v_2 = dx_1/dt$$

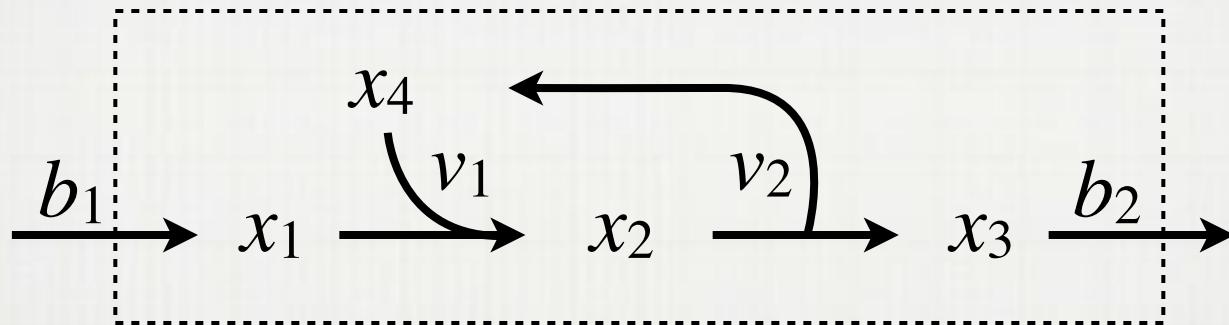
What is in the null spaces?

- (right) null space
 - $0 = \mathbf{S} \bullet \mathbf{v}$; all steady state solutions
 - left null space
 - $0 = \mathbf{l} \bullet \mathbf{S}$; time invariants
-

$$\mathbf{l} \cdot \frac{dx}{dt} = \mathbf{l} \cdot \mathbf{S} \cdot \mathbf{v} = 0$$

$$0 = \mathbf{l} \cdot \frac{dx}{dt} = \frac{d}{dt} \langle \mathbf{l} \cdot \mathbf{x} \rangle ; \langle \mathbf{l} \cdot \mathbf{x} \rangle = \text{const}$$

What is in the Null Space of S?



$$S = \begin{pmatrix} v_1 & v_2 & b_1 & b_2 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & 0 & -1 \\ -1 & 1 & 0 & 0 \end{pmatrix} \quad \begin{array}{ll} x_1 & n=4, m=4, r=3 \\ x_2 & \dim(\text{Null}(S)) = 4-3=1 \\ x_3 & \dim(\text{Left Null}(S)) = 4-3=1 \\ x_4 & \end{array}$$

Null space spanned by $(1,1,1,1)^T$, a pathway composed of all the reactions

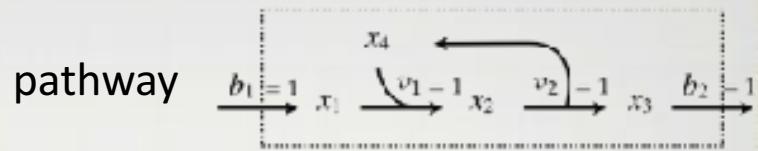
Left Null space spanned by $(0,1,0,1)$, a pool of $x_2 + x_4$

right null

$$\mathbf{S} \cdot \mathbf{v} = 0$$

$$\boxed{\quad} = 0$$

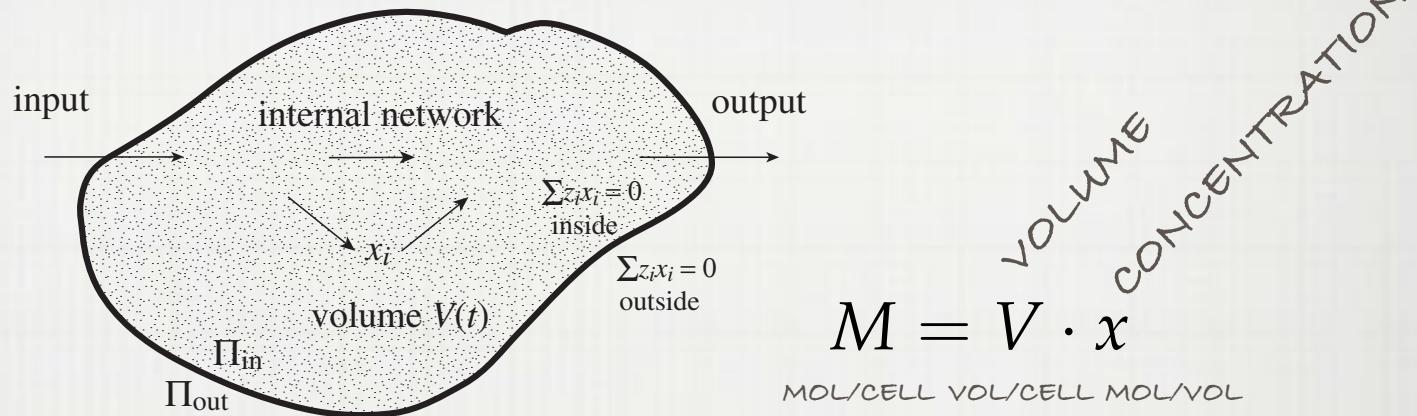
$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & 0 & -1 \\ -1 & 1 & 0 & 0 \end{pmatrix} \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix} = 0$$



For the ‘expert’

IMPORTANT ASSUMPTIONS

The Constant Volume Assumption



$$M = V \cdot x$$

MOL/CELL VOL/CELL MOL/VOL

**TOTAL MASS
BALANCE**

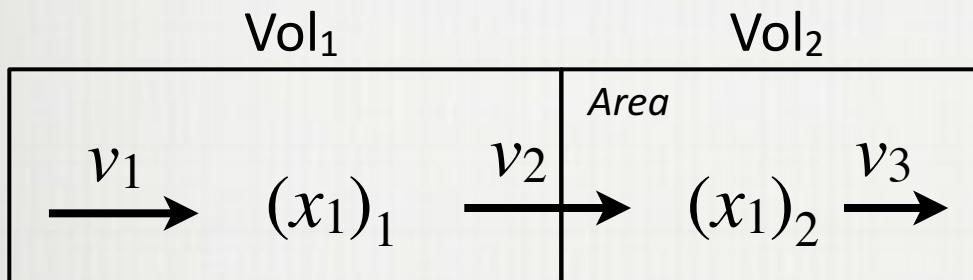
$$\frac{dM}{dt} = \sum v_f - \sum v_d \rightarrow \boxed{\text{MOL/CELL/TIME}}$$

f = formation, d = degradation

$$\frac{dM}{dt} = V \frac{dx}{dt} + \boxed{x \frac{dV}{dt}} \rightarrow \boxed{= 0 \text{ IF } V(t) = \text{CONST}}$$

$$\frac{dx}{dt} = \frac{1}{V} \left[\sum v_f - \sum v_d \right] = \sum \frac{v_f}{V} - \sum \frac{v_d}{V} \rightarrow \boxed{\text{MOL/VOL/TIME}}$$

Beware of surface-to-volume ratios in multi-compartmental models!



v_1 : mol/vol/time
 v_2 : mol/Area/time

Total Mass Balances:

$$\frac{d(\text{Vol}_1(x_1)_1)}{dt} = (\text{Vol}_1)v_1 - (\text{Area})v_2 \quad \text{Compartment 1}$$

$$\frac{d(\text{Vol}_2(x_1)_2)}{dt} = (\text{Area})v_2 - (\text{Vol}_2)v_3 \quad \text{Compartment 2}$$

Volumetric Mass Balances:

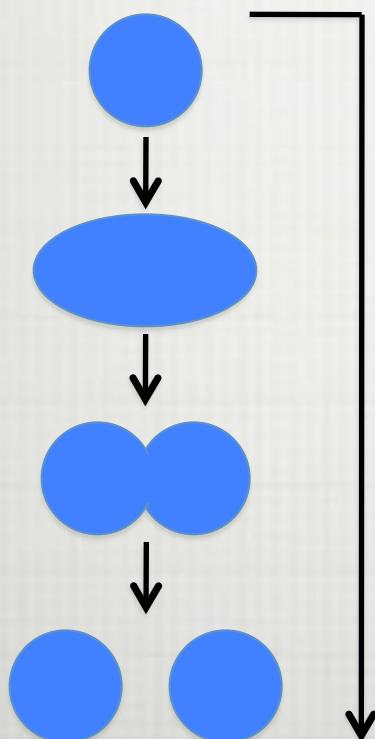
Not the same!

$$\frac{d(x_1)_1}{dt} = v_1 - (\text{Area}/\text{Vol}_1)v_2 \quad \text{Compartment 1}$$

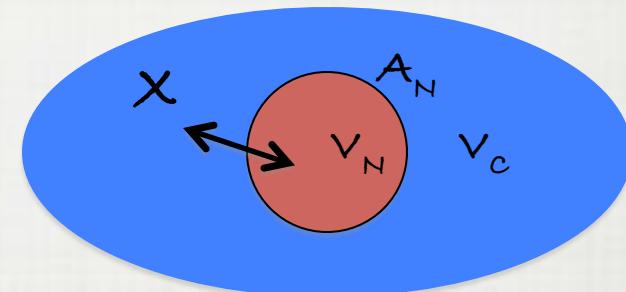
$$\frac{d(x_1)_2}{dt} = v_1 - (\text{Area}/\text{Vol}_2)v_2 - v_3 \quad \text{Compartment 2}$$

Two Historical Examples of Bad Assumptions

1. Cell volume doubling during division
2. Nuclear translocation



MODELING THE
PROCESS OF CELL
DIVISION
BUT
VOLUME
ASSUMED TO
BE CONSTANT



$$\frac{dx}{dt} = \dots - (A_N/V_C) V_{\text{TRANSLOCATION}}$$

$$\frac{dx}{dt} = \dots + (A_N/V_N) V_{\text{TRANSLOCATION}}$$

MISSING (A/V) PARAMETERS MAKE
MASS LOST DURING TRANSLOCATION

Hypotheses/Theories can be right or wrong...

*Models have a third possibility;
they can be *irrelevant**

--*Manfred Eigen*

Also see:

http://www.numberwatch.co.uk/computer_modelling.htm

Summary

- τ_i is a key quantity
- Spectrum of $\tau_i \rightarrow$ time scale separation \rightarrow temporal decomposition
- Multiple time scales lead to aggregate variables
- Elimination of a $\tau_i \rightarrow$ reduction in dim from $m \rightarrow m-1$
 - one aggregate or pooled variable,
 - one simplifying assumption (qssa or qea) applied
- Elementary reactions; $v = kx, v = kxy, v \geq 0, x \geq 0$
- Understand the assumptions that lead to $\frac{dx}{dt} = Sv(x; k)$

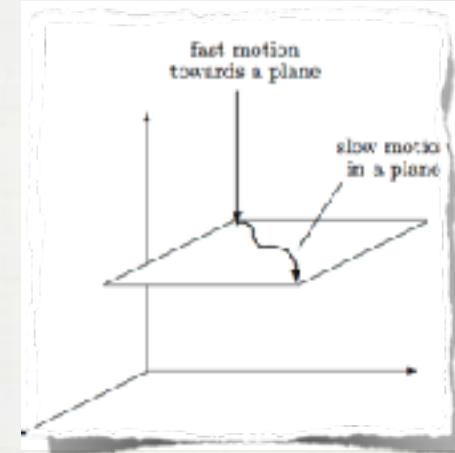
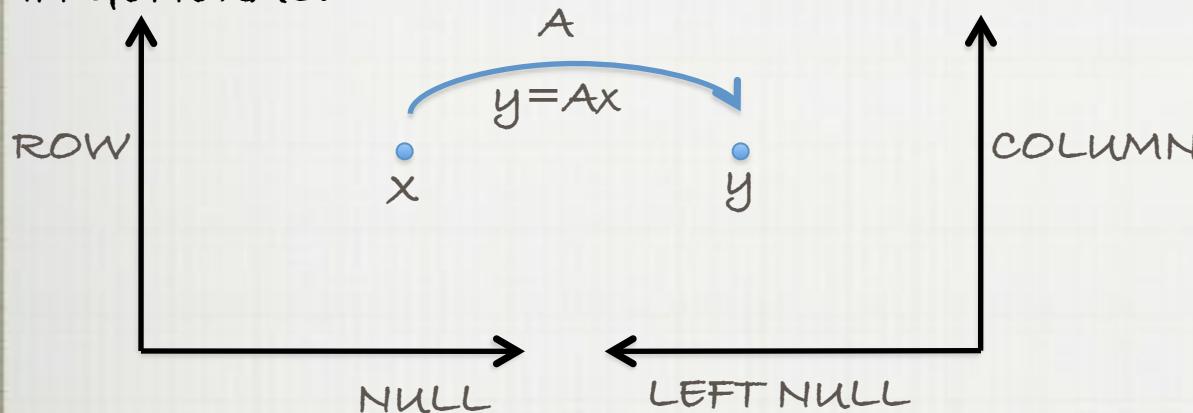
Extra topics

Some mathematics

TIME SCALE DECOMPOSITION

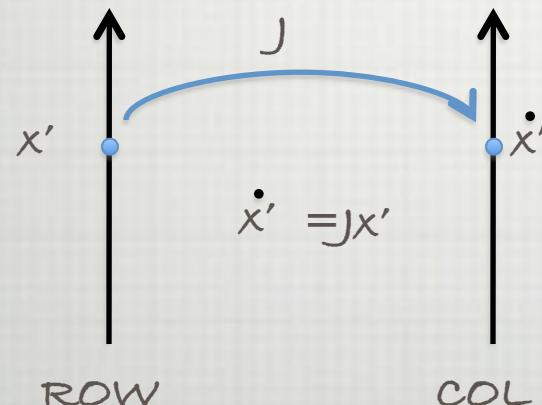
(Dynamic Simplification) = (Reduction in Dimensionality)

IN GENERAL:

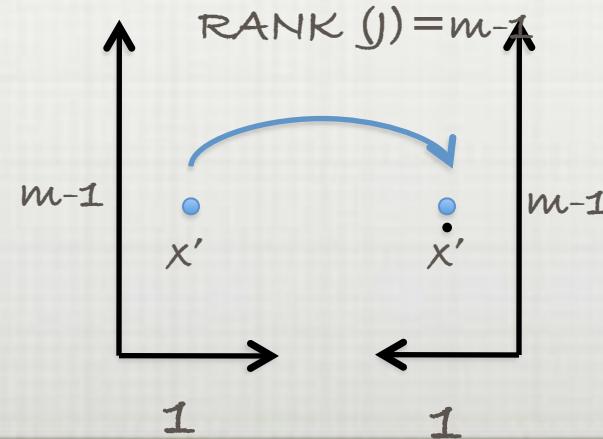


JACOBIAN

FULL RANK J ; $r=m$



ELIMINATE A TIME SCALE



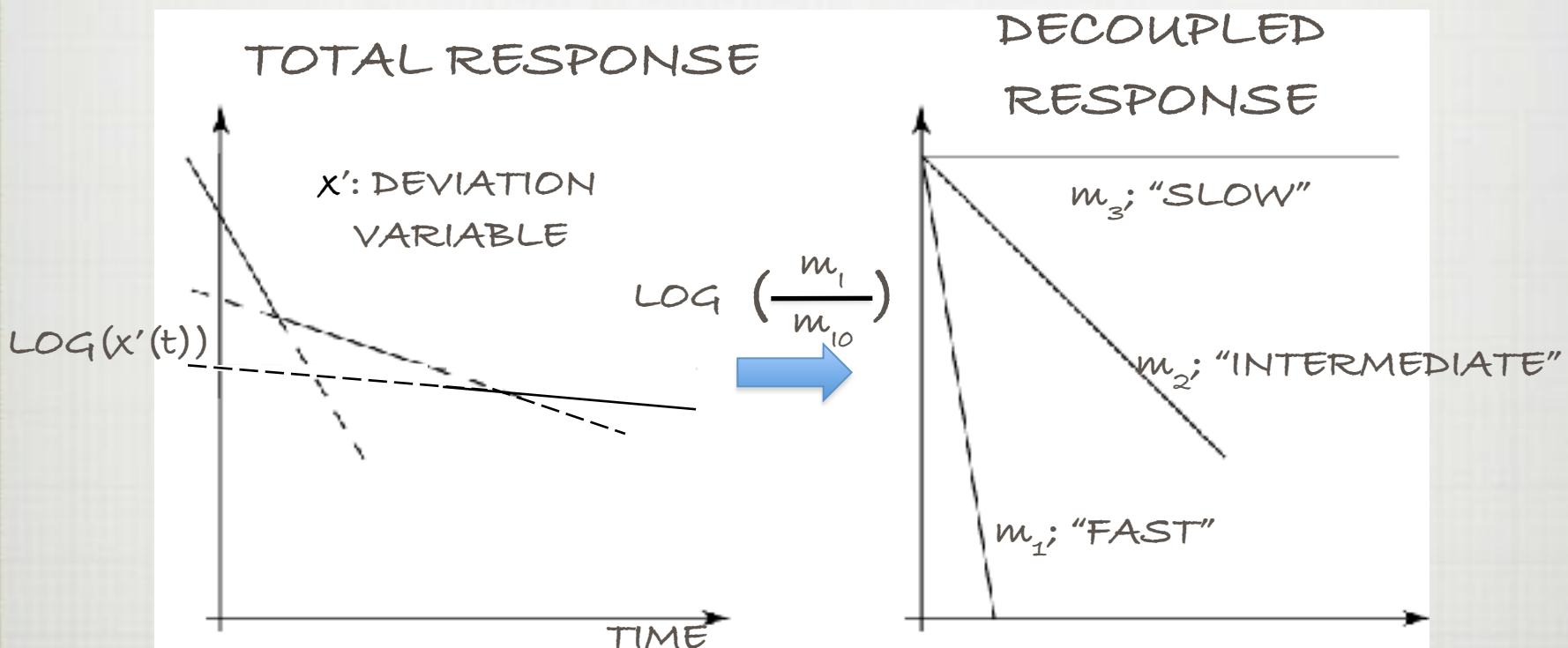
$J_p = 0$
i.e., ONE QSSA OR QEA

$J = 0$
 $I_{x'} = 0$
CONSERVATION=POOL

Untangling dynamic response:

Approximate: pooling matrix $p = Px'$;

Exact: modal analysis $m = M^{-1}x'$



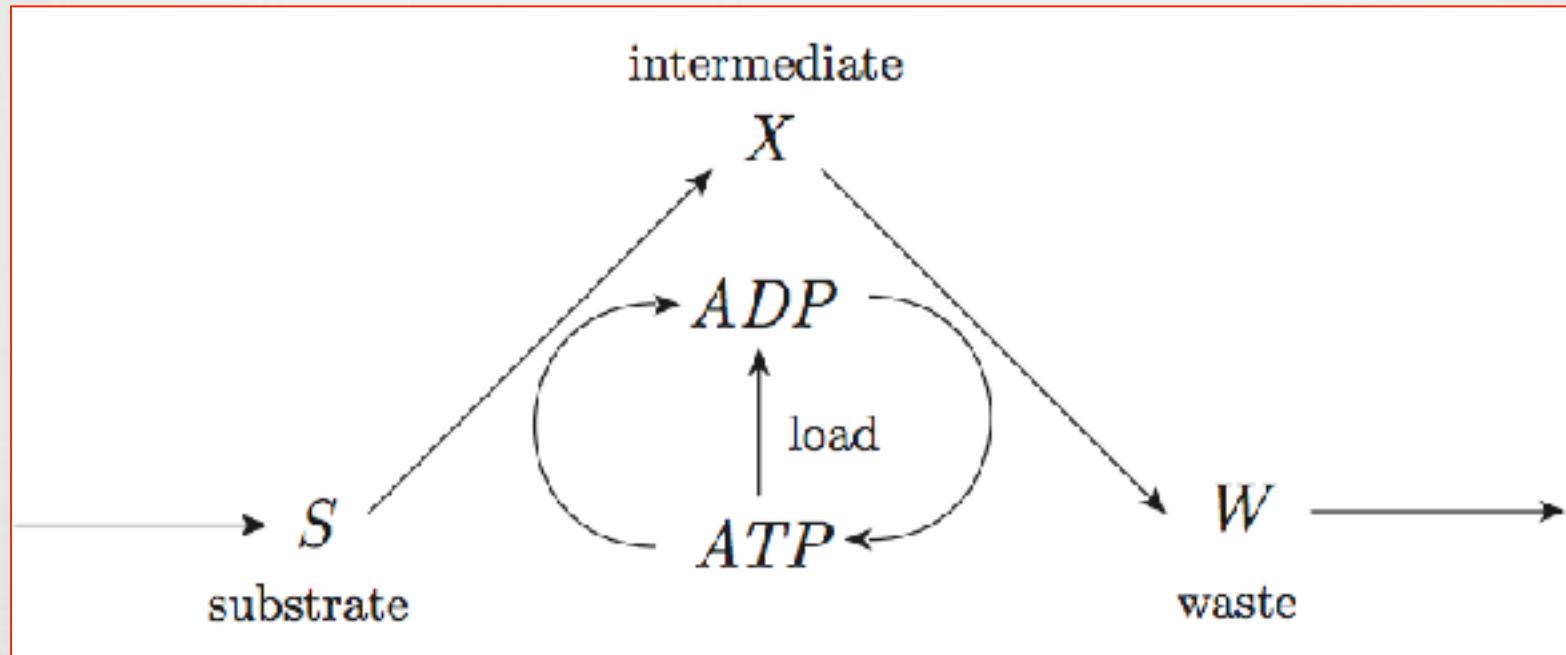
EXAMPLE:

$$p(t) = \begin{pmatrix} 1 & 1 & 0 \\ 2 & 1 & 0 \\ 1 & 1 & 1 \end{pmatrix} \begin{pmatrix} ATP \\ ADP \\ AMP \end{pmatrix} = \begin{pmatrix} ATP + ADP \\ 2ATP + ADP \\ ATP + ADP + AMP \end{pmatrix} = \begin{pmatrix} p_1 \\ p_2 \\ p_3 \end{pmatrix}$$

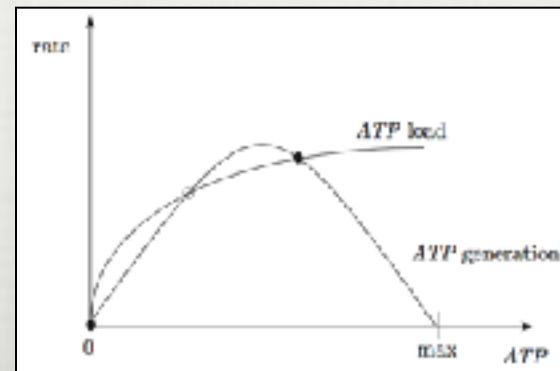
The fundamental ‘structure vs. function’ theme from molecular biology

STOICHIOMETRY VS. DYNAMICS

Dominant Effects of Stoichiometry on Network Dynamics



Steady states on ATP →

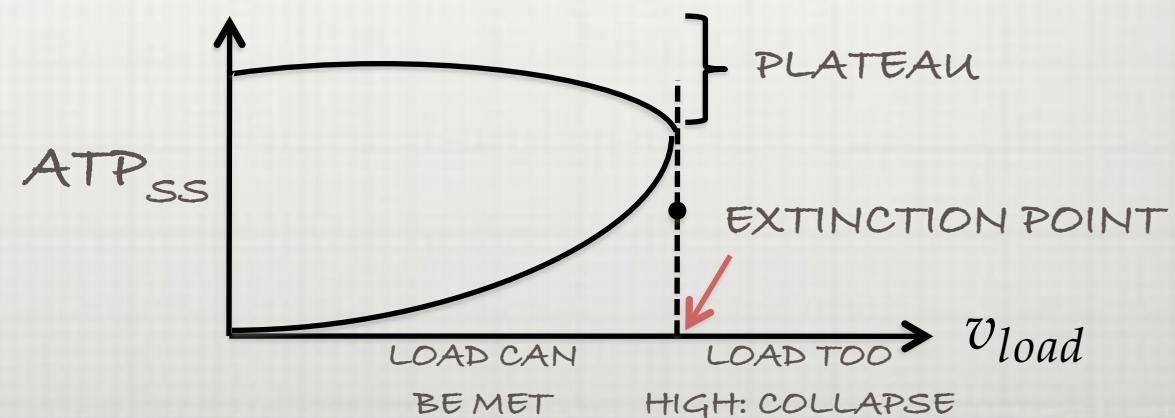
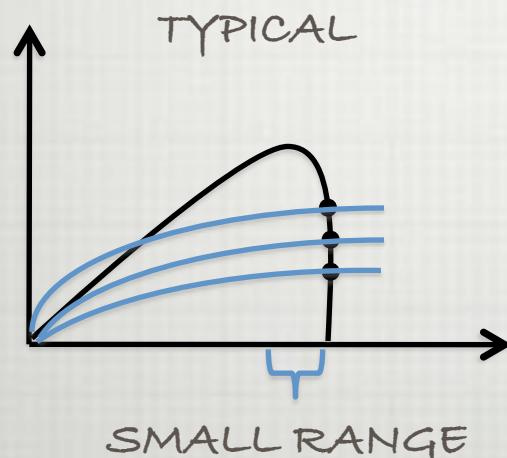
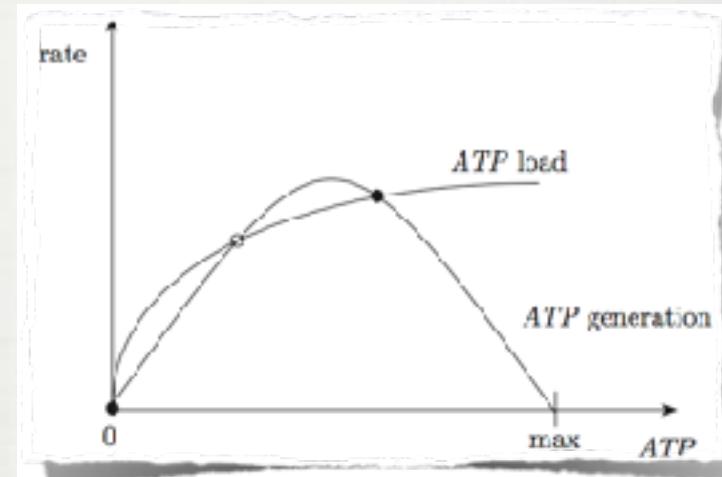


Dynamic Balance at Steady State

Key Concepts:

1. Stability of steady state
2. Capacity limitations
3. Robustness

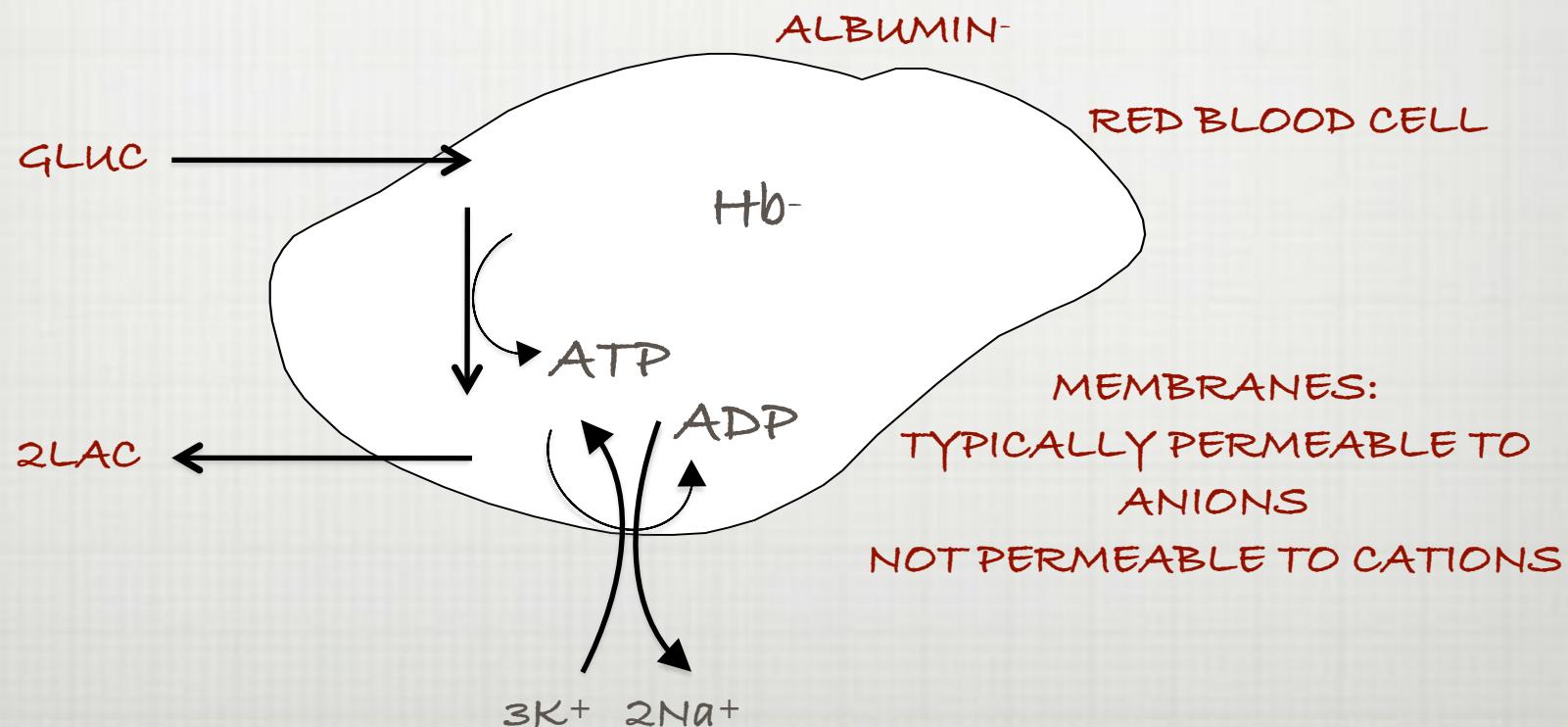
$$v_{\text{generation}} = v_{\text{load}} @ \text{STST}$$



Fundamental physical constraints

Osmotic balance: $\Pi_{in} = \Pi_{out}$; $\Pi_{in} = RT\Phi \Pi_i X_i$

Electro-neutrality: $\sum_i Z_i X^{Z_i} = 0$



The end