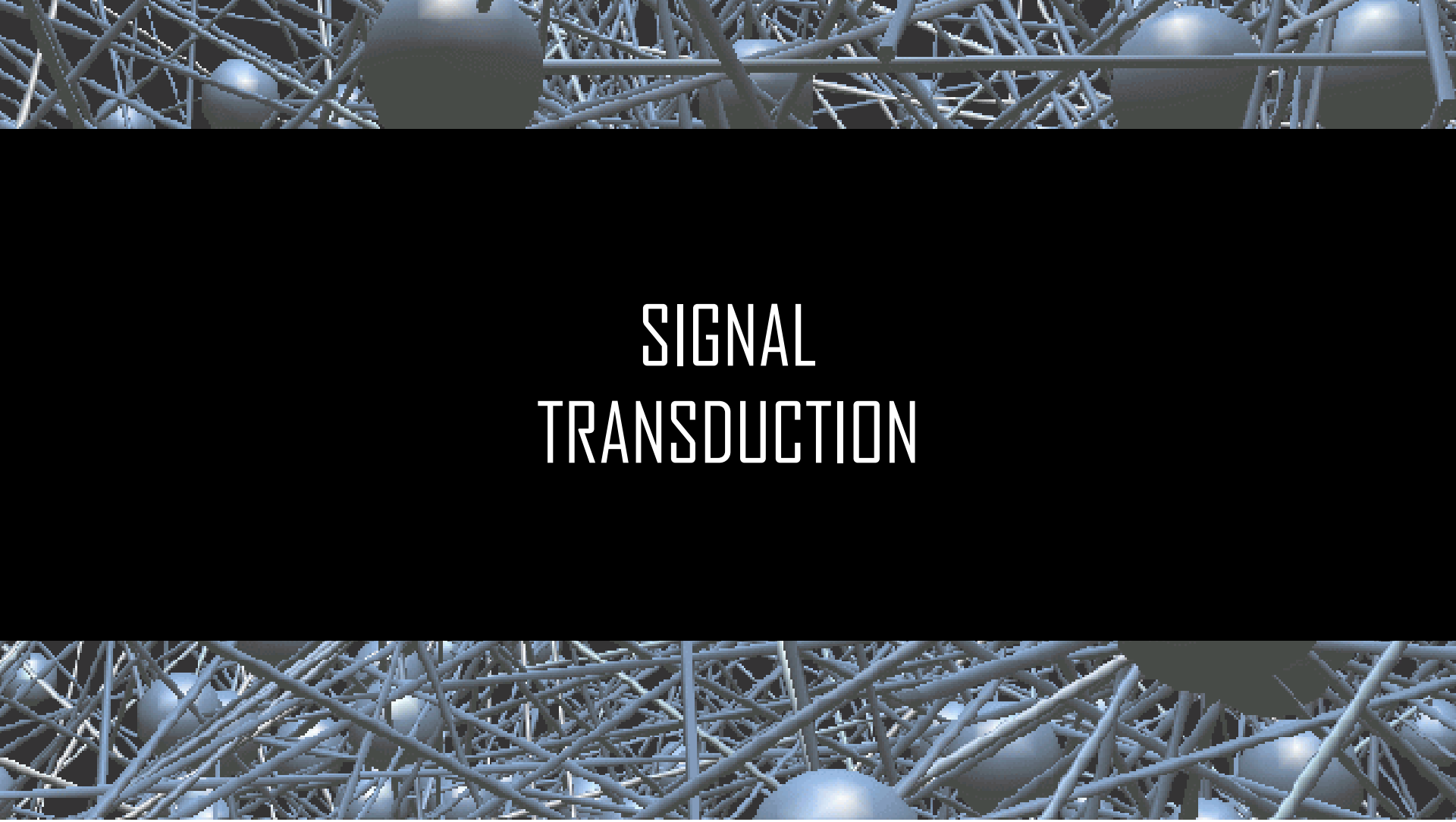


SIGNAL TRANSDUCTION

Principles and Applications of Systems Biology

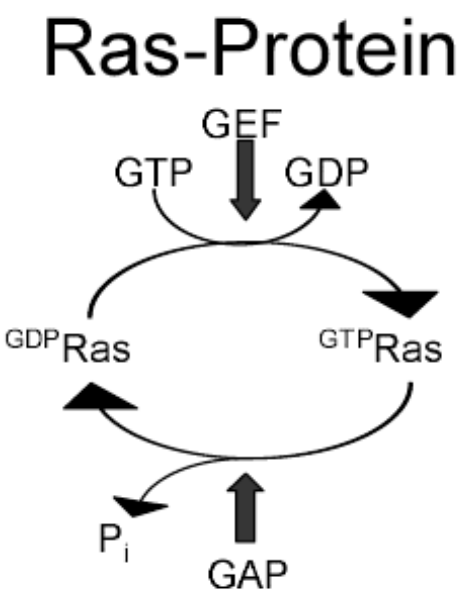
EPFL

Vassily Hatzimanikatis

November 2025

Introduction to signaling

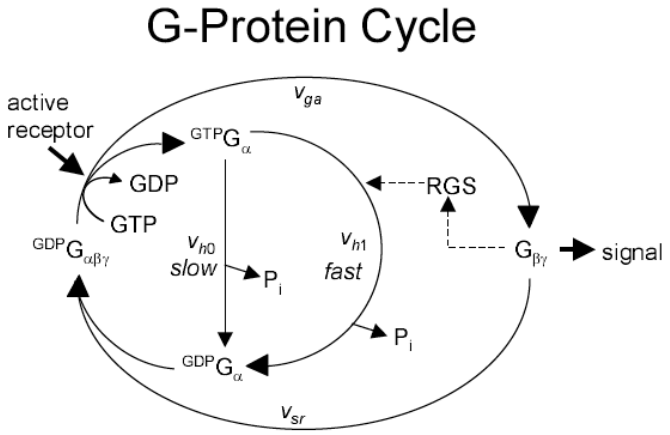
RAS Proteins



The Ras activation cycle. GEF supports the transition from GDP-bound to GTP-bound states to activate Ras, while GAP induces hydrolysis of the bound GTP, resulting in Ras deactivation.

- Monomeric G-proteins
- Biological timers
- Initiate and terminate specific cell functions and determine the periods of time

G-Protein Cycle



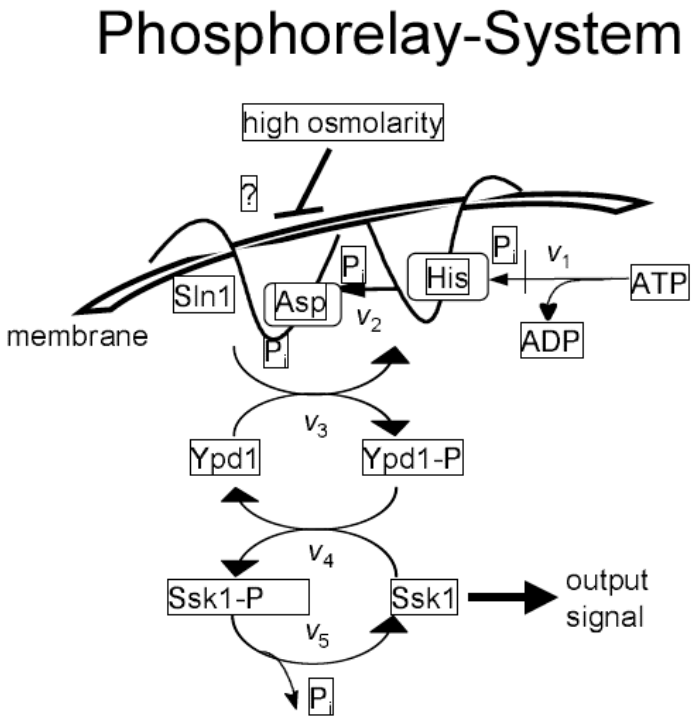
Activation cycle of G protein. Without activation, the heterotrimeric G protein is bound to GPD. Upon activation by the activated receptor, an exchange of GDP with GTP occurs and the G protein is divided into GTP-bound G and the heterodimer G. G-bound GTP is hydrolyzed, either slowly in reaction vh0 or fast in reaction vh1, supported by the RGS protein. GDP-bound G can reassociate with G (reaction vsr).

- They bind the guanine nucleotides GDP and GTP
- Associated to cell surface receptors (G protein–coupled receptors (GPCR)).
- Important cascades: (1) GPCR, (2) an associated G protein, and (3) an intracellular effector that produces a second messenger

They mediate responses to:

- light, flavors, odors, numerous hormones, neurotransmitters (in human)
- cell division, cell-cell fusion (mating), morphogenesis, chemotaxis (in eukaryotes)

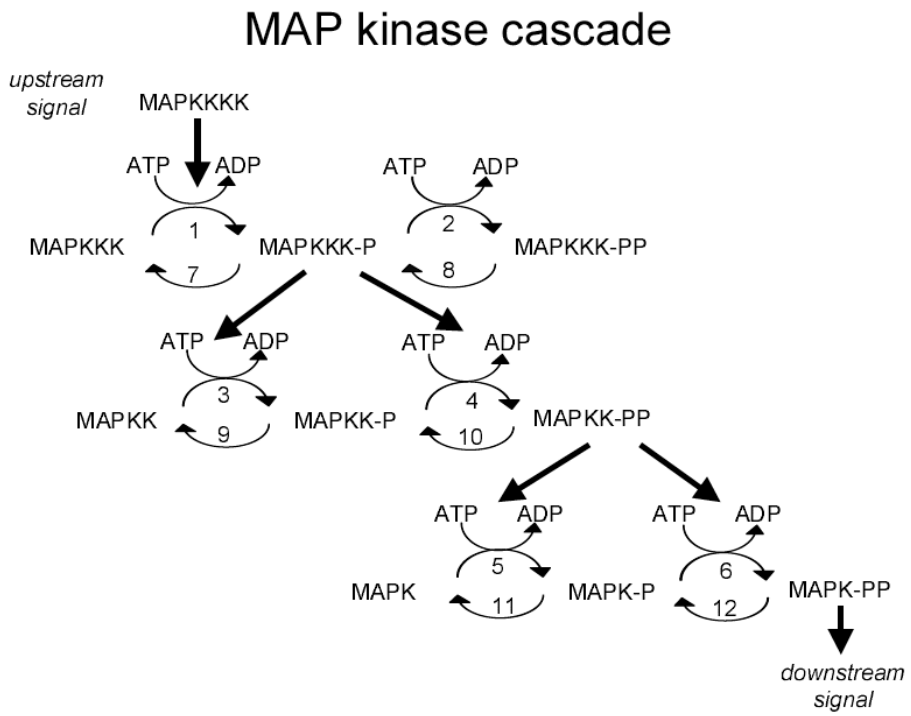
Phosphorelay-System



Schematic representation of a phosphorelay system. (a) Phosphorelay system belonging to the Sln1-branch of the HOG pathway in yeast. (b) General scheme of phosphorylation and dephosphorylation

- Initial phosphorylation using ATP (or another phosphate donor)
- Transfer of the phosphate group directly onto the next protein
- No further use of phosphate donor

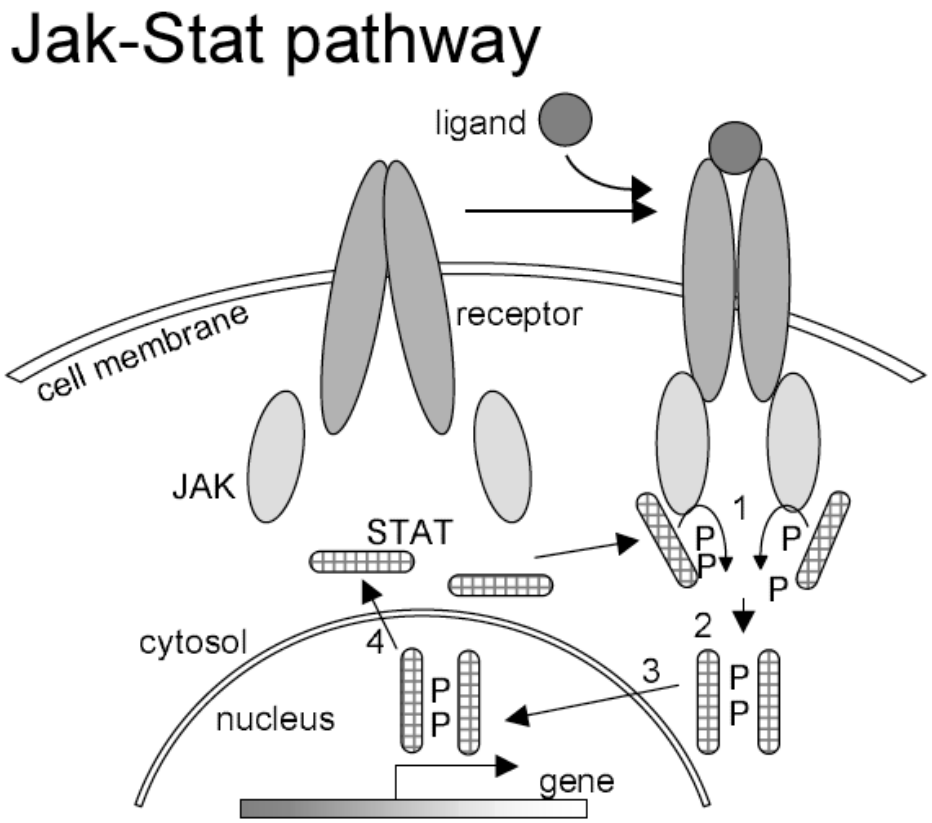
MAP kinase cascades



Schematic representation of the MAP kinase cascade. An upstream signal (often by a further kinase called MAP kinase kinase kinase kinase) causes phosphorylation of the MAPKKK. The phosphorylated MAPKKK in turn phosphorylates the protein at the next level. Dephosphorylation is assumed to occur continuously by phosphatases or autodephosphorylation.

- Family of serine/threonine kinases
- Transduce signals from the cell membrane to the nucleus
- Control of:
  - cell growth
  - differentiation, transformation
  - apoptosis
- Conserved from yeast to mammals

Jak-Stat pathway



- Regulation of

  immune responses

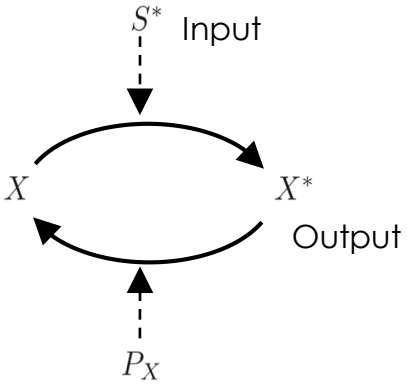
  cellular homeostasis

- Activated by cytokines (a large family of extracellular ligands)

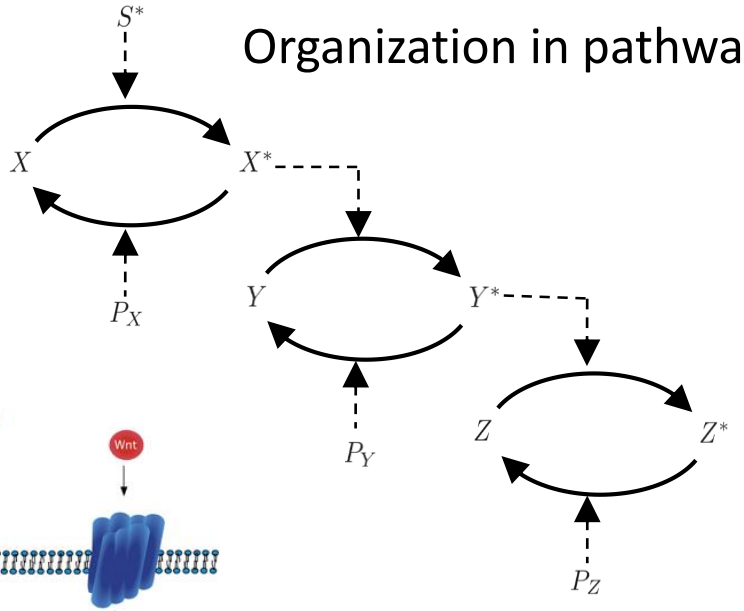
The Jak-Stat signaling pathway. Upon ligand binding, receptor-associated Jaks become activated and mediate phosphorylation of specific receptor tyrosine residues. This leads to the recruitment of specific Stats, which are then also tyrosinephosphorylated. Activated Stats are released from the receptor, dimerize, translocate to the nucleus, and bind to enhancers.

Signaling networks

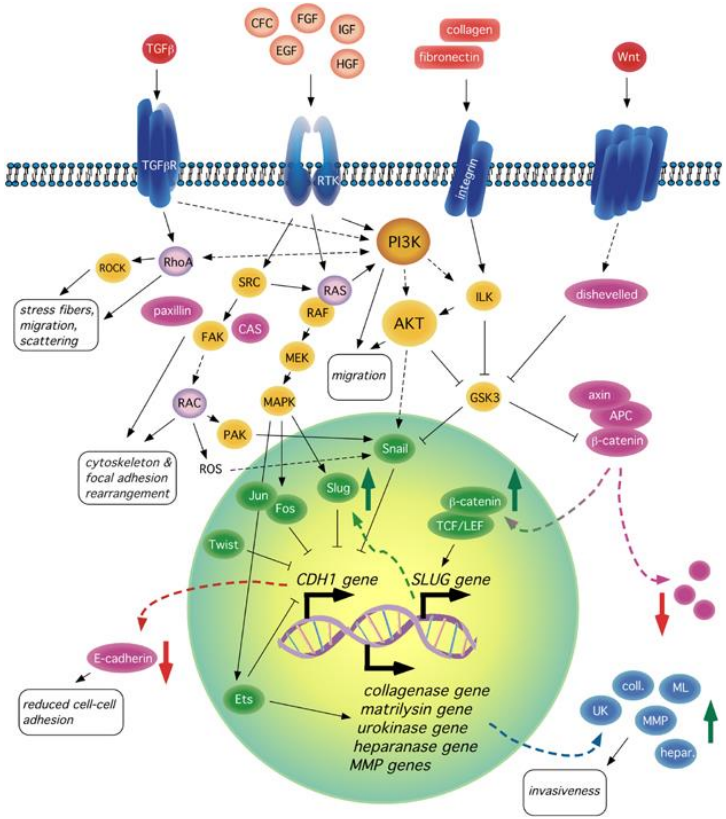
Signaling cycle



Organization in pathways



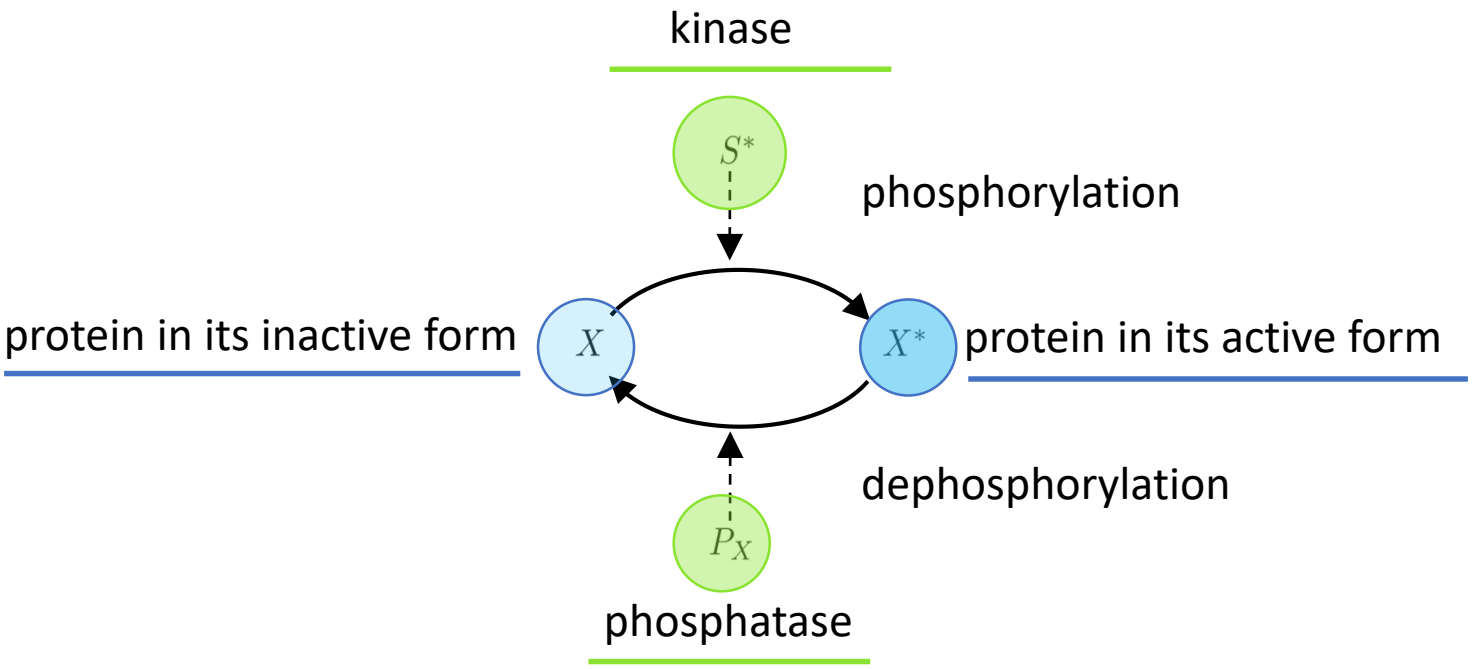
Signaling networks



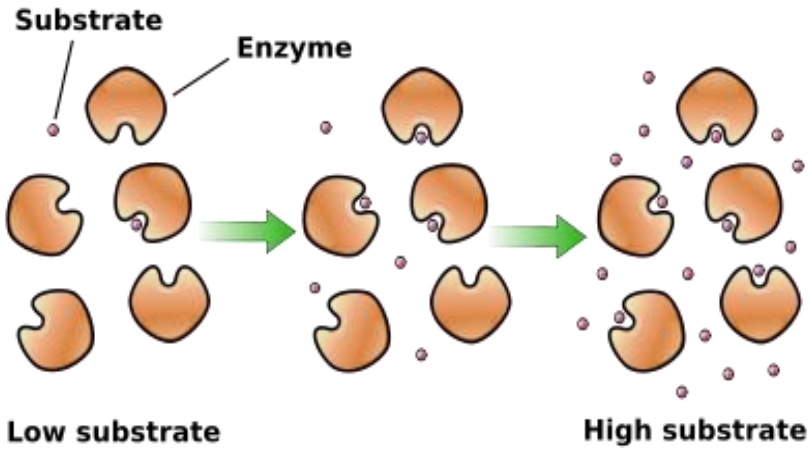
http://www.nature.com/onc/journal/v24/n50/full/1209091a.html

Kinase cascades

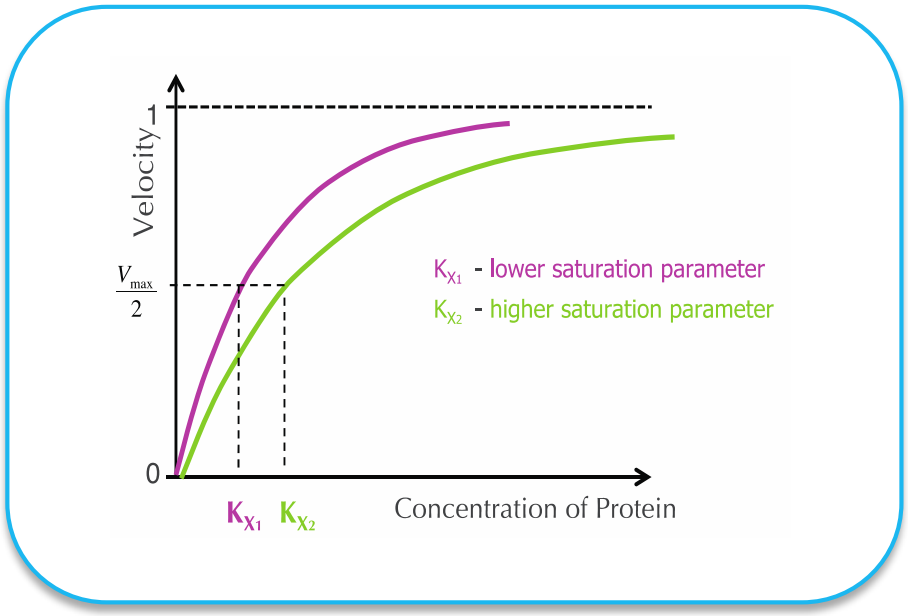
Monocyclic cascade

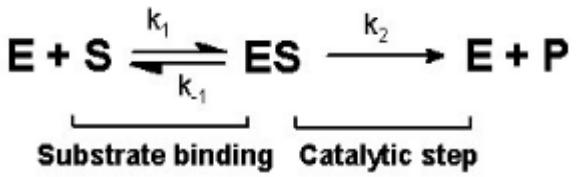


Kinase cascades



The rate of reaction will increase as substrate concentration increases, eventually becoming saturated at very high concentrations of substrate.





$$K_m \overset{\text{def}}{=} \frac{k_2 + k_{-1}}{k_1} \approx \frac{[\mathrm{E}][\mathrm{S}]}{[\mathrm{ES}]}$$

K_m - Michaelis constant

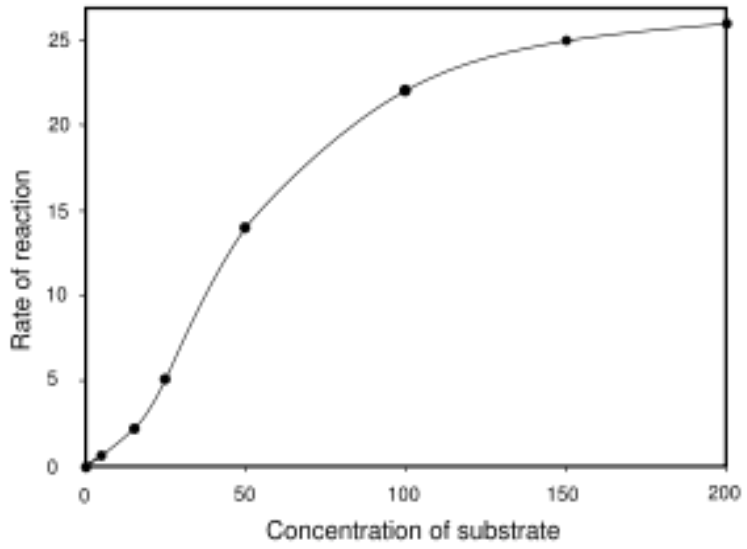
$$v = \frac{V_{\max}[\mathrm{S}]}{K_m + [\mathrm{S}]}$$

Cooperativity

Sigmoidal kinetics *v* by [S] can indicate cooperativity

Positive cooperativity occurs when binding of the first substrate molecule **increases** the affinity of the other active sites for substrate.

Negative cooperativity occurs when binding of the first substrate **decreases** the affinity of the enzyme for other substrate molecules.



Saturation curve for an enzyme reaction showing sigmoid kinetics.

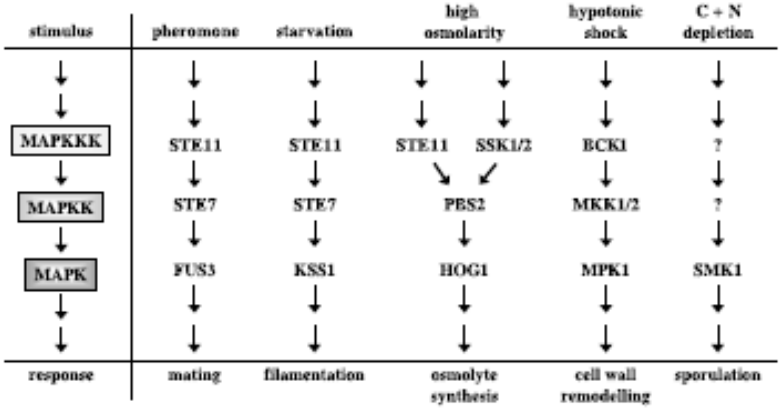
$$v = V_{max} Y = \frac{V_{max} K_B S^n}{1 + K_B S^n} \ .$$

- **Hill Kinetics** are often used to quantitatively describe the degree of cooperativity in non-Michaelis–Menten kinetics.
- The derived Hill coefficient *n* is a measure of how much the binding of substrate affects the binding of another substrate.

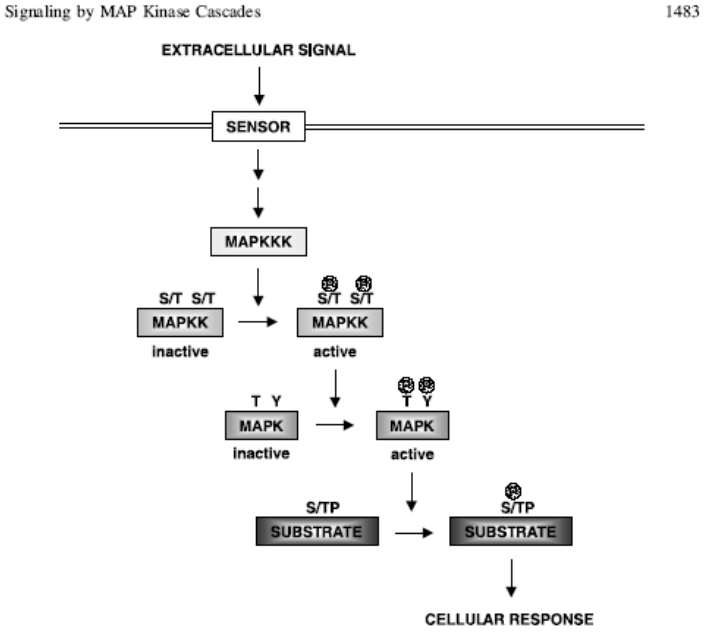
Investigating the design principles of MAPK cascades

Mitogen-Activated Protein Kinase Cascades

- Ubiquitous signal transduction pathway
- Regulates cell growth, differentiation, and proliferation in many eukaryotes



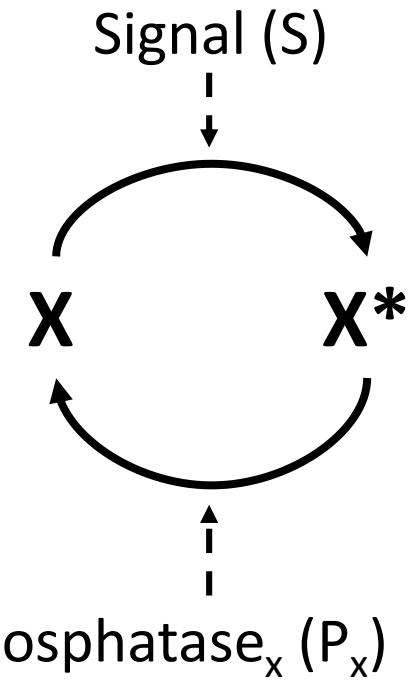
Jonak and Hirt. *Monatshefte für Chemie*. 2003



- Considered **a prototypical system** for studying regulation by phosphorylation
- Conceptual models vary, but always contain the **interconvertible enzyme cascade**

An Interconvertible Enzyme Cascade

Single Enzyme Module



Reactions

$$X \underset{k_{b,x}}{\overset{k_{f,x}}{\rightleftharpoons}} X{:}S \xrightarrow{k_{c,x}} X^*$$

$$X^* \underset{k_{b,x^*}}{\overset{k_{f,x^*}}{\rightleftharpoons}} X^*{:}P_x \xrightarrow{k_{c,x^*}} X$$

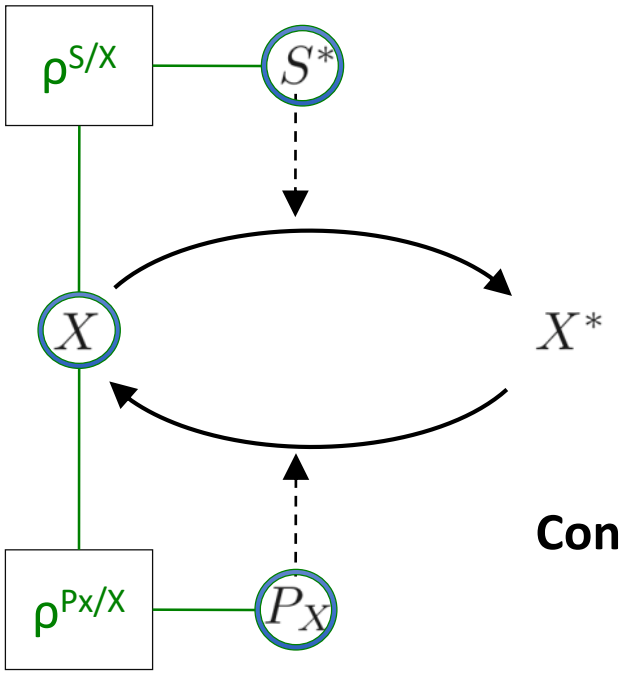
Mass Conservations

$$[X]_{tot} = [X] + [X^*] + [X:S] + [X:P_x]$$

$$[S]_{tot} = [S] + [X:S]$$

$$[P_x]_{tot} = [P_x] + [X^*:P_x]$$

Steady State Dimensionless Parameters



Dimensionless Michaelis-Menten Constants

$$k_{m,x} = \frac{k_{b,x} + k_{c,x}}{k_{f,x} \cdot [X]_{tot}} \qquad k_{m,x^*} = \frac{k_{b,x^*} + k_{c,x^*}}{k_{f,x^*} \cdot [X]_{tot}}$$

Measure the affinity of the kinase/phosphatase

Concentration Ratios

$$\rho_s = \frac{[S]_{tot}}{[X]_{tot}}$$

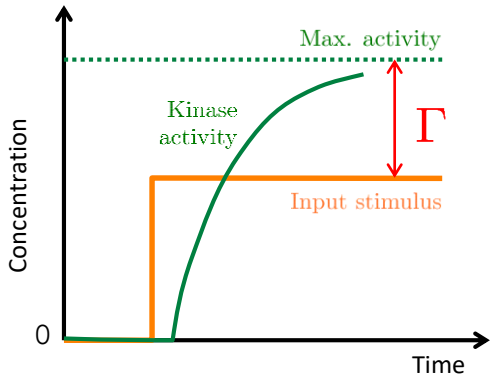
$$\rho_{p_x} = \frac{[P_x]_{tot}}{[X]_{tot}}$$

Cascade Activation

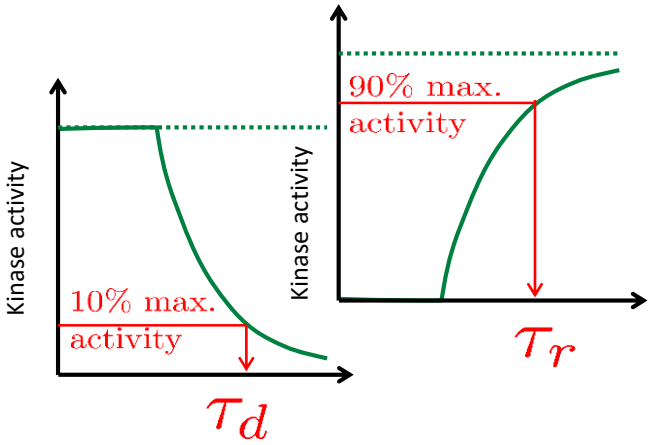
$$\alpha = \frac{k_{c,x} \cdot [S]_{tot}}{k_{c,x^*} \cdot [P_x]_{tot}}$$

System responses

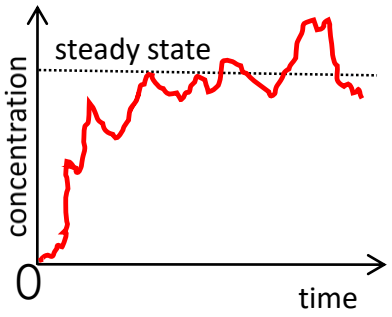
Amplification



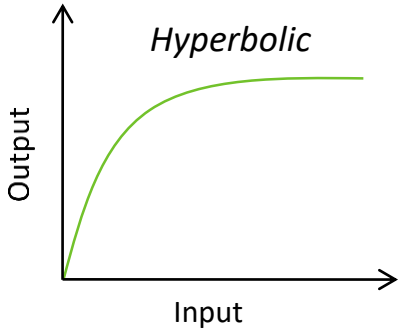
Transduction speed

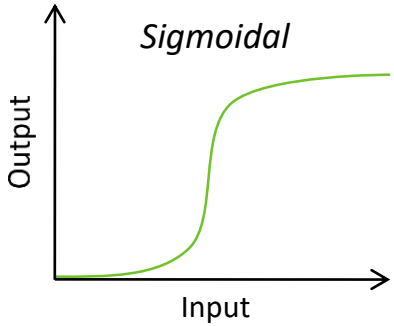


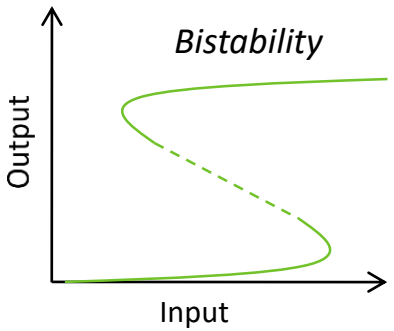
Noise



Different kind of responses

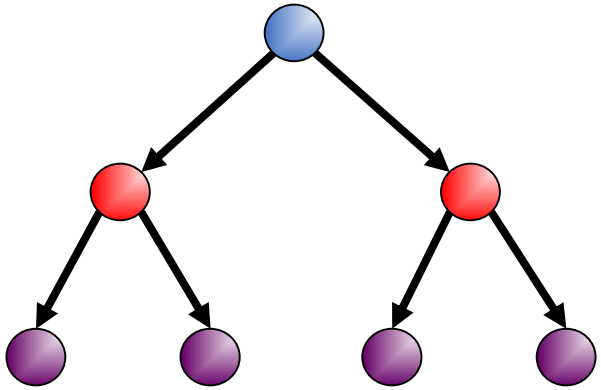




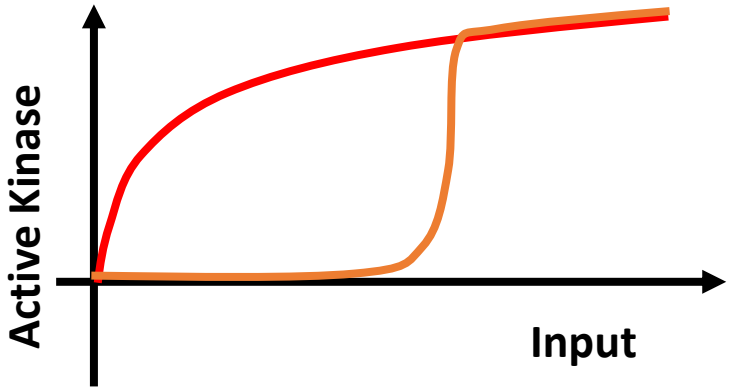


Design characteristics

Amplification – Dramatic increase in active kinase concentration

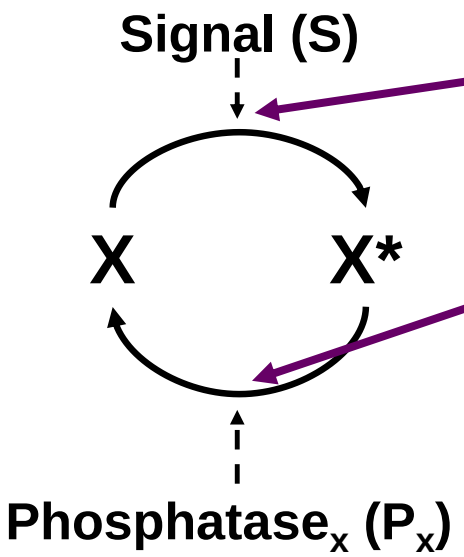


Switch-like threshold – Regulation of activation



Ferrell. *TiBS*. 1996

Threshold Characteristics

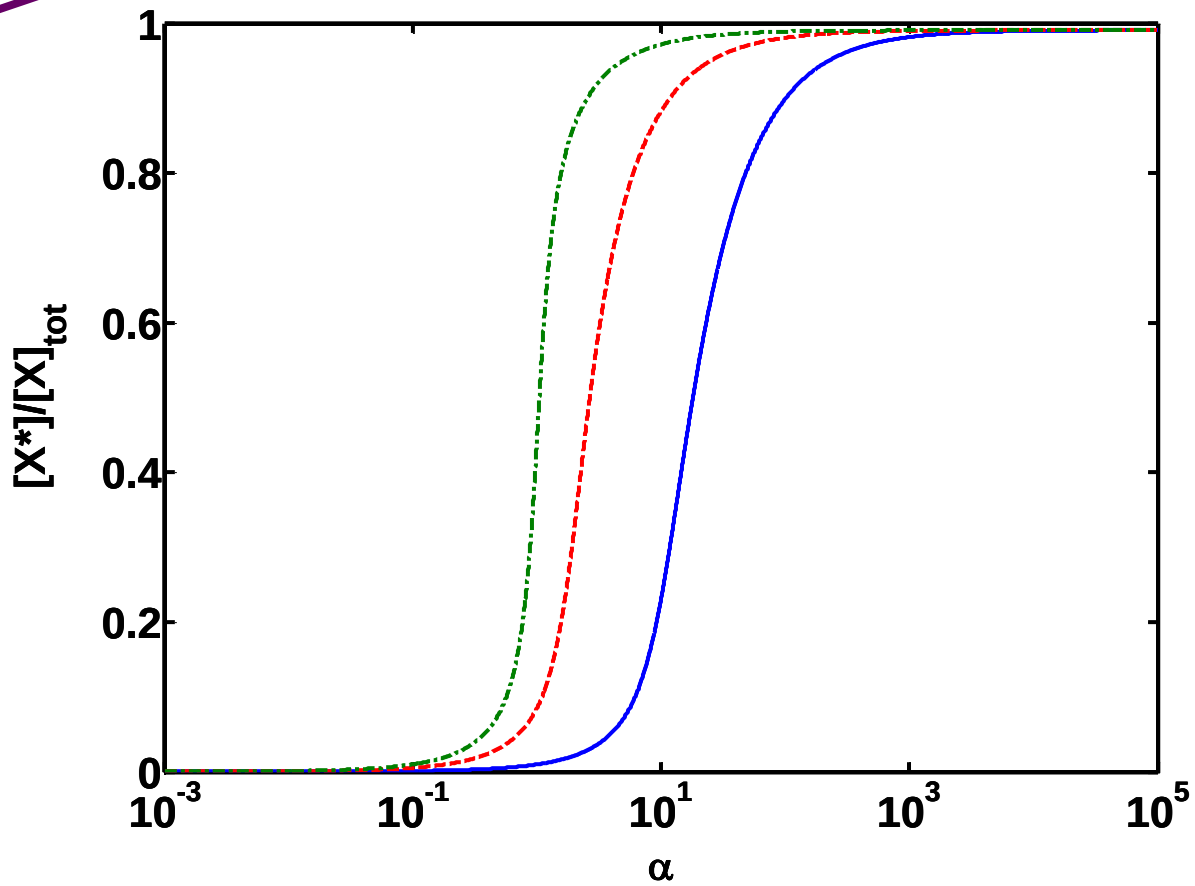


$$\rho_s = \frac{[S]_{tot}}{[X]_{tot}} = 0.1 \quad \rho_{p_x} = \frac{[P_x]_{tot}}{[X]_{tot}} = 0.01, \quad k_{m,x^*} = 0.1$$

$k_{m,x}$ = 10

$k_{m,x}$ = 1

$k_{m,x}$ = 0.1



Hill Coefficient

$k_{m,x} = 10$

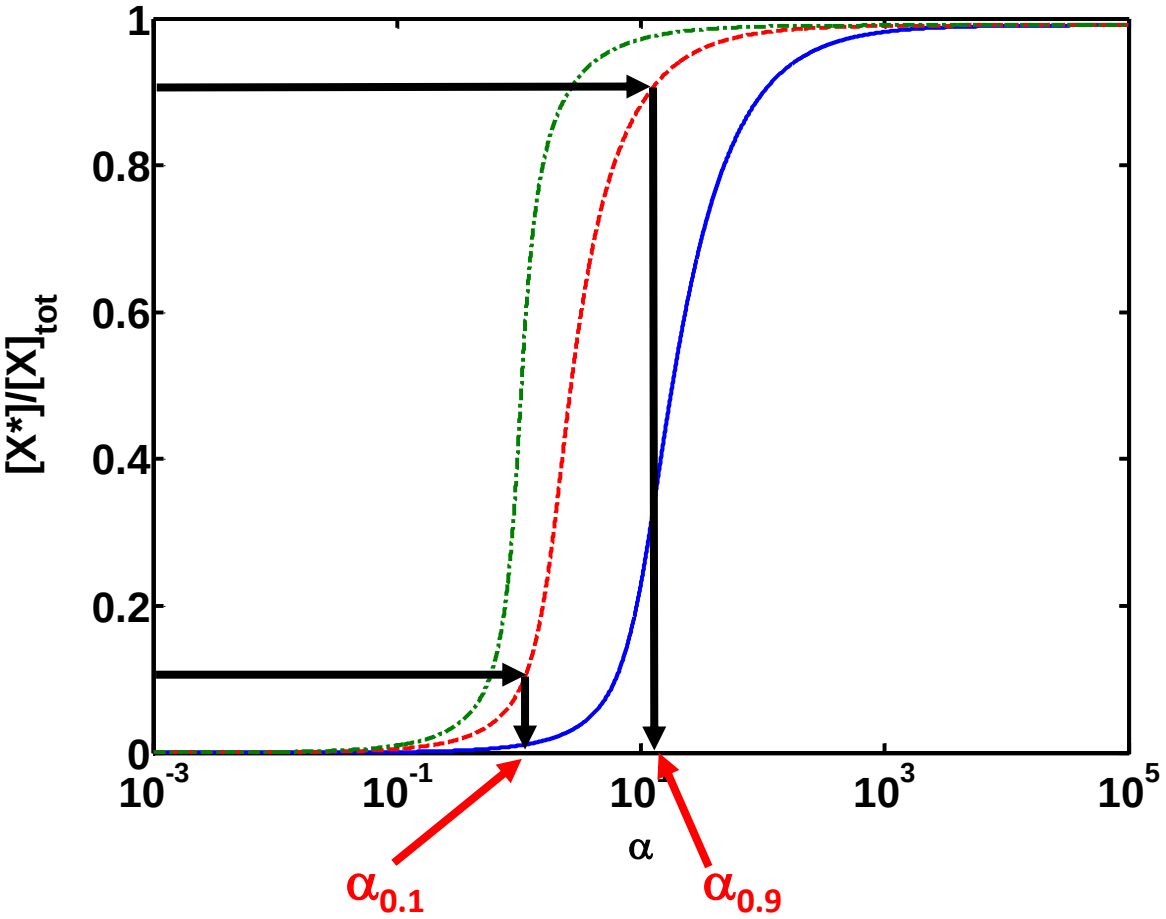
$k_{m,x} = 1$

$k_{m,x} = 0.1$

$n = 1.6$

$n = 1.9$

$n = 3.0$

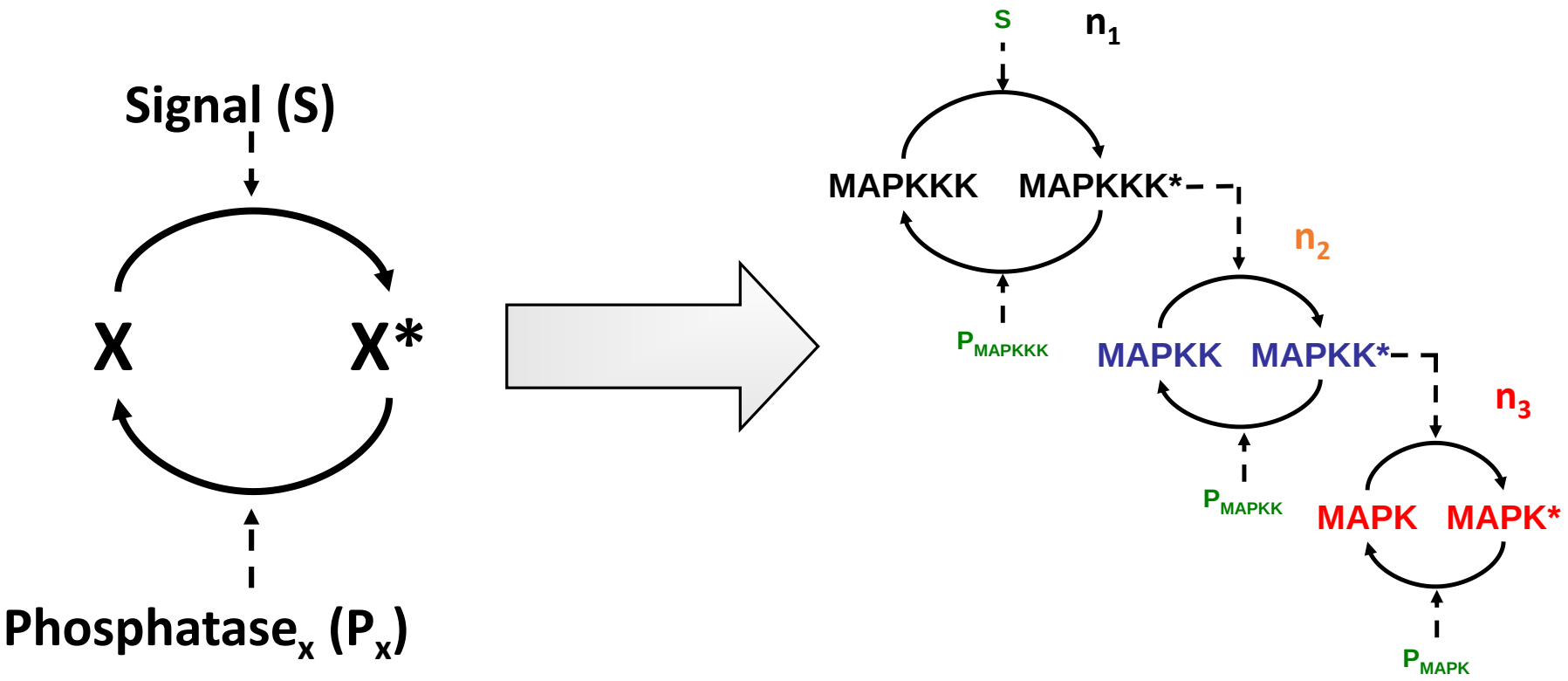


$$x^* = x^*_{\max} \frac{\alpha^n}{k_m^n + \alpha^n}$$

Effective Hill Coefficient:

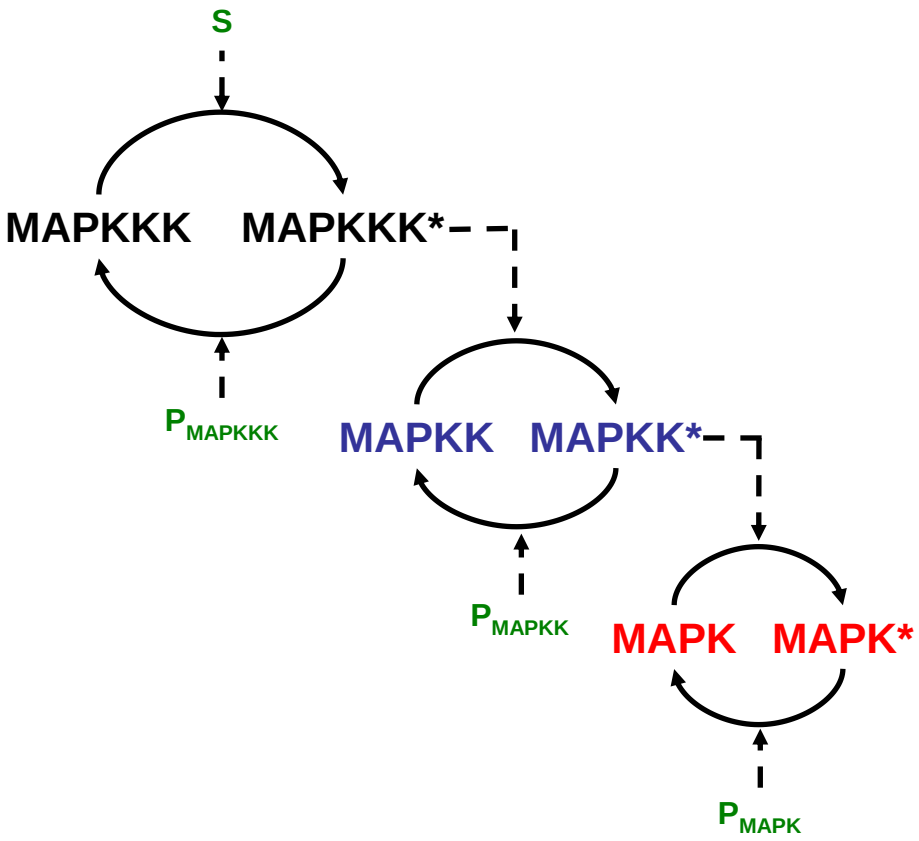
$$n = \frac{\ln(81)}{\ln\left(\frac{\alpha_{0.9}}{\alpha_{0.1}}\right)}$$

Modeling Larger Cascade Networks



$$n_{cascade} \propto n_1 \times n_2 \times n_3$$

Network Complexity: Concentration Regimes

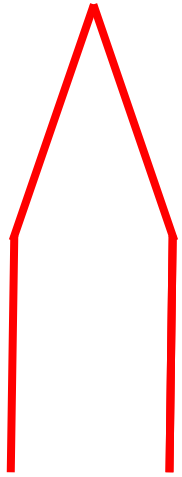


Huang and Ferrell. *PNAS*. 1996

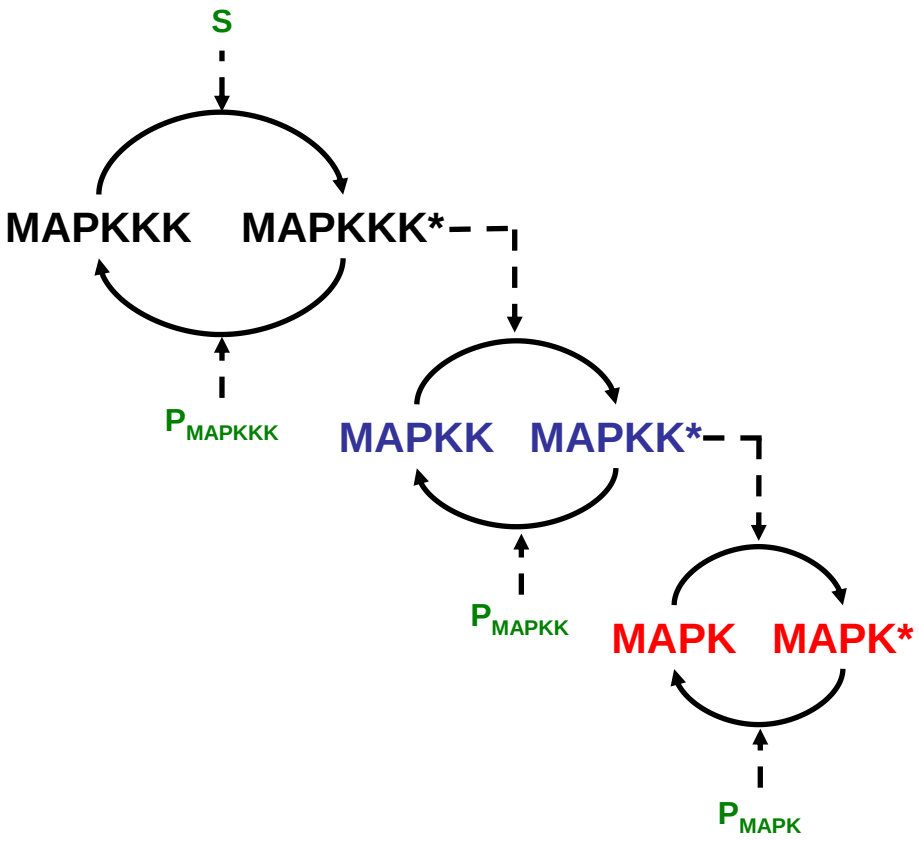
$[MAPKKK]_{tot} = 3\times10^{-9}$ M

$[MAPKK]_{tot} = 1.2\times10^{-6}$ M

$[MAPK]_{tot} = 1.2\times10^{-6}$ M



Network Complexity: Concentration Regimes

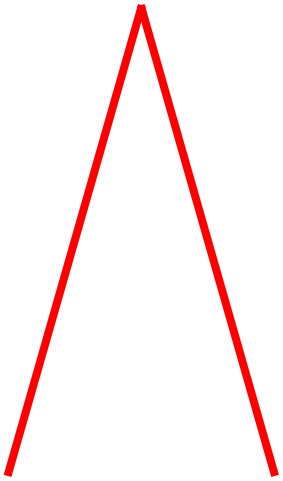


Asthagiri and Lauffenburger.
***Biotech & Bioeng*. 2001.**

$[MAPKKK]_{tot} = 3\times10^{-9}$ M

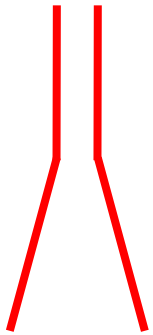
$[MAPKK]_{tot} = 1.7\times10^{-8}$ M

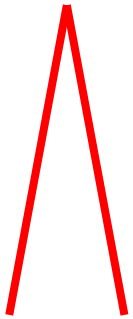
$[MAPK]_{tot} = 1.2\times10^{-6}$ M

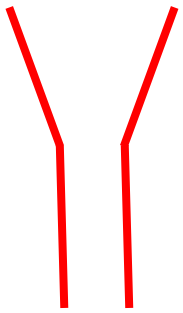


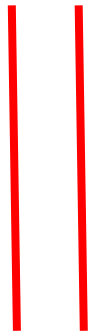
Network Complexity: Concentration Regimes

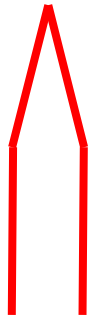
1. 

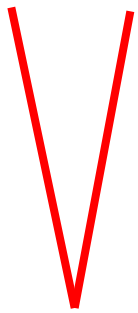
2. 

3. 

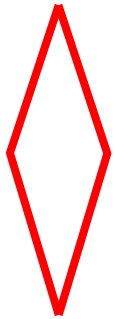
4. 

5. 

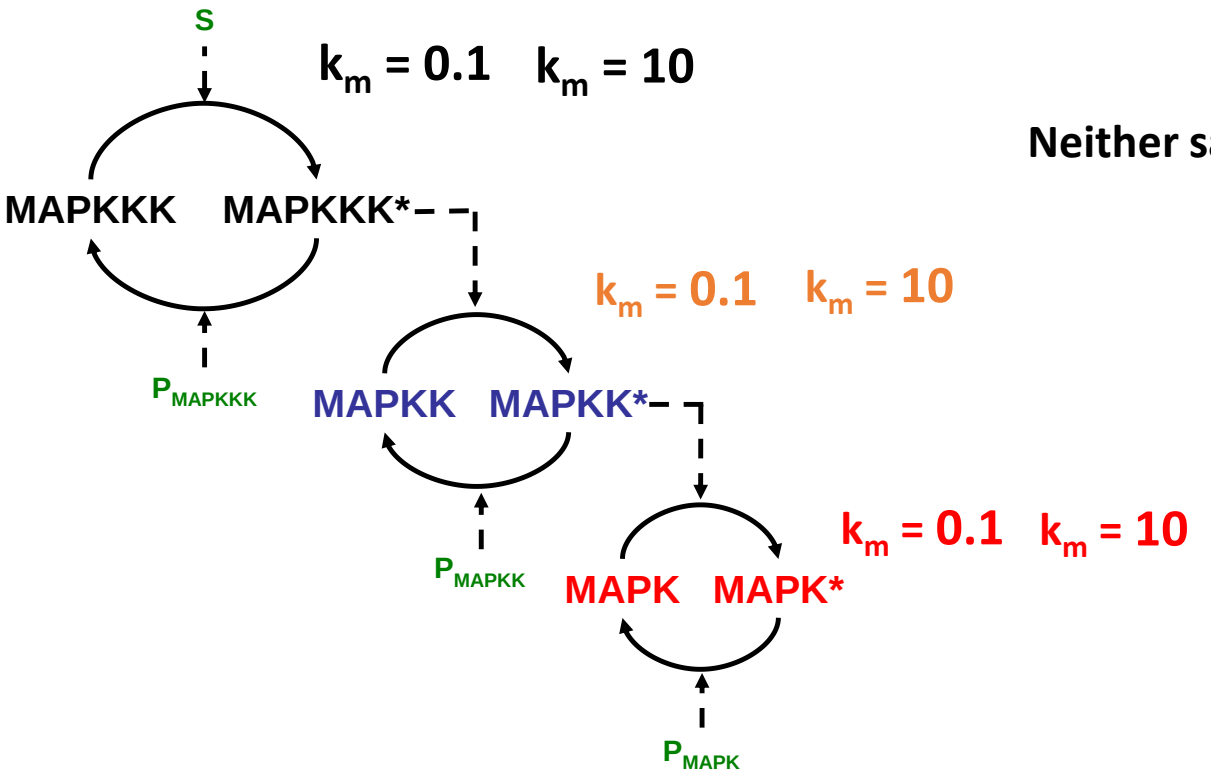
6. 

7. 

8. 

9. 

Network Complexity: k_m configuration



Each kinase of the cascade can be either saturated:

k_m = 0.1

Neither saturated nor unsaturated:

k_m = 1

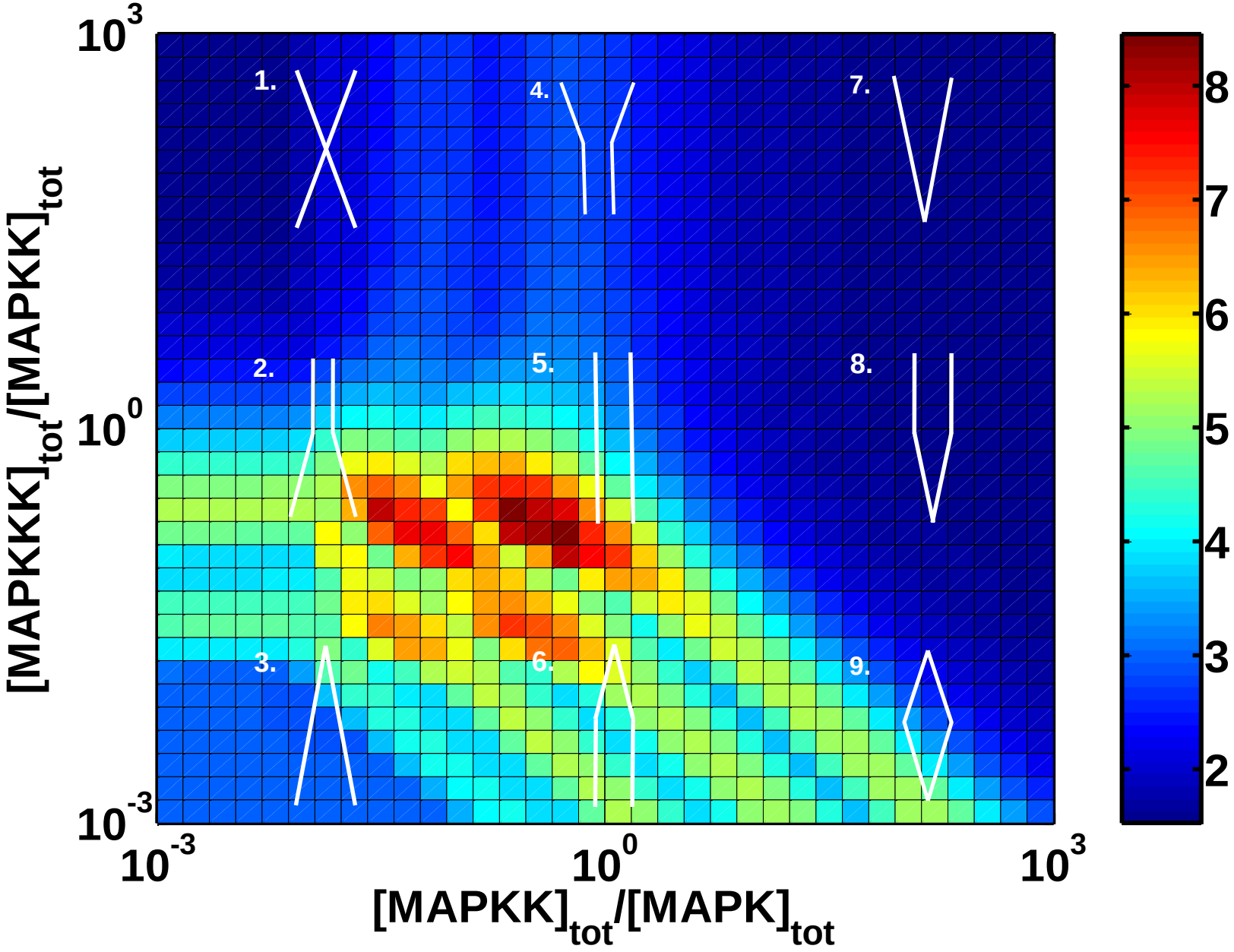
Or unsaturated:

k_m = 10

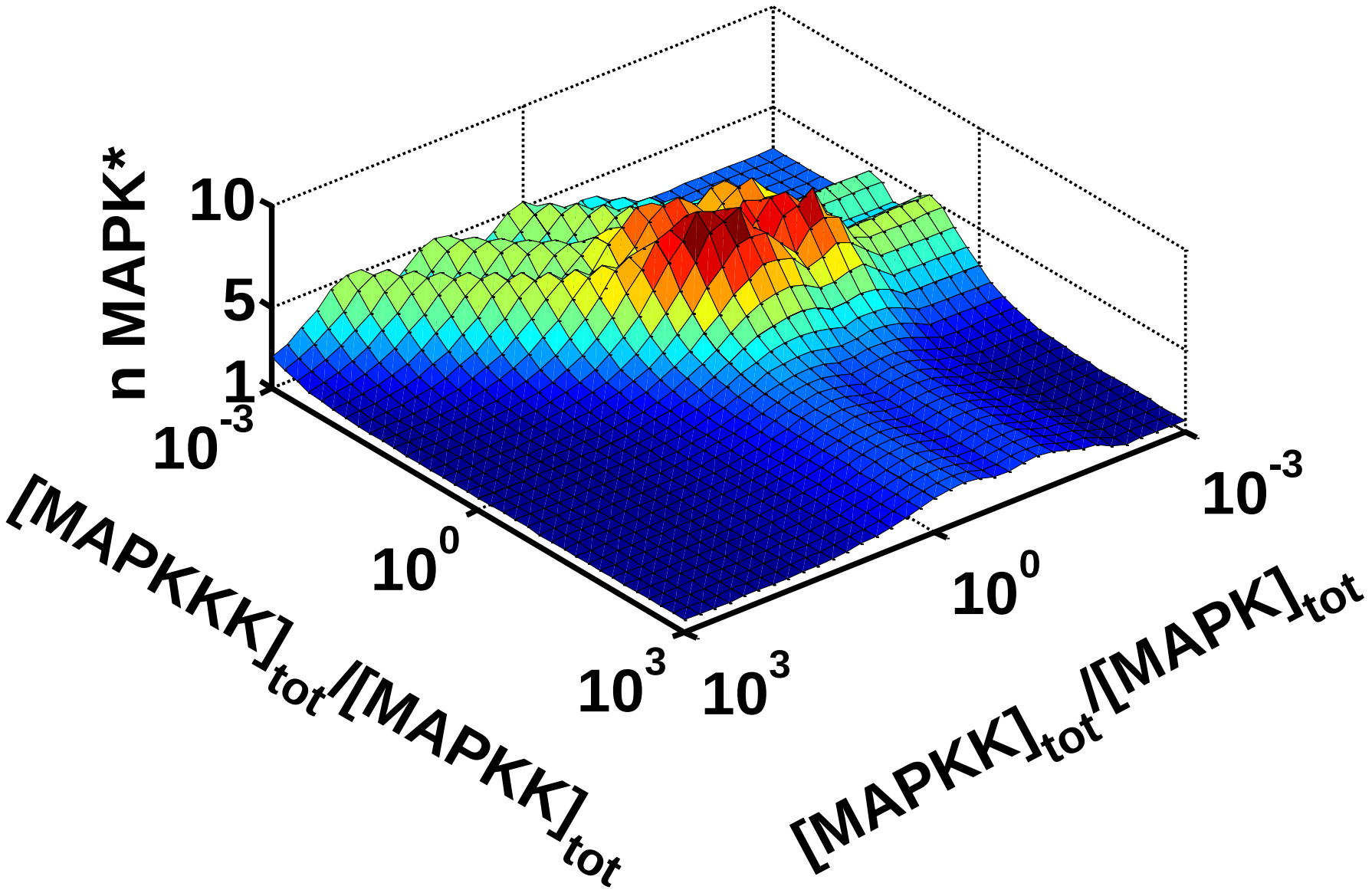
Fixed $[S]_{tot}/[MAPKKK]_{tot}$ = 0.1
Fixed $[P_{MAPX}]_{tot}/[MAPX]_{tot}$ = 0.01
Fixed Phosphatase k_m = 0.1 (saturated)

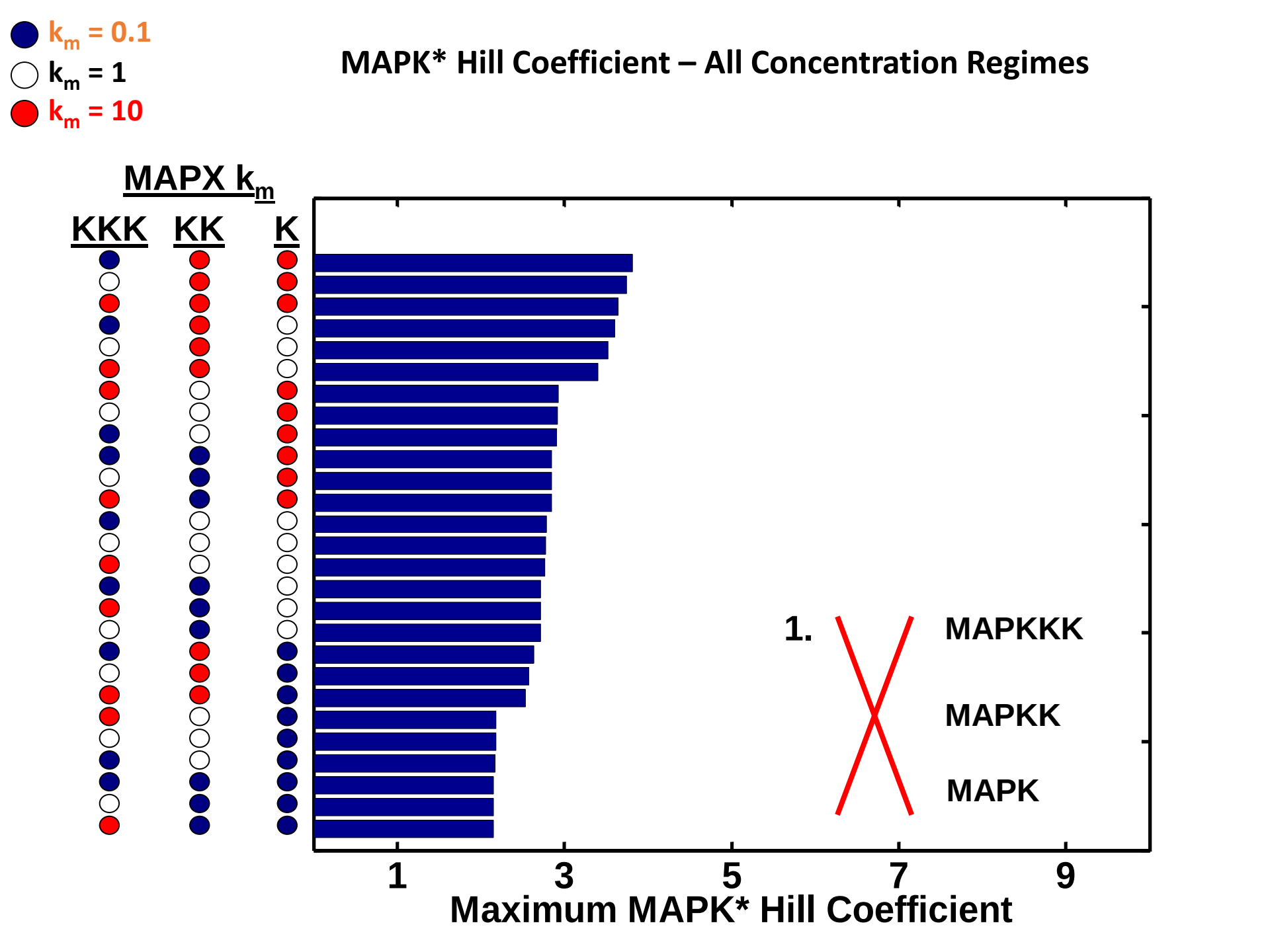
For each k_m configuration (27):

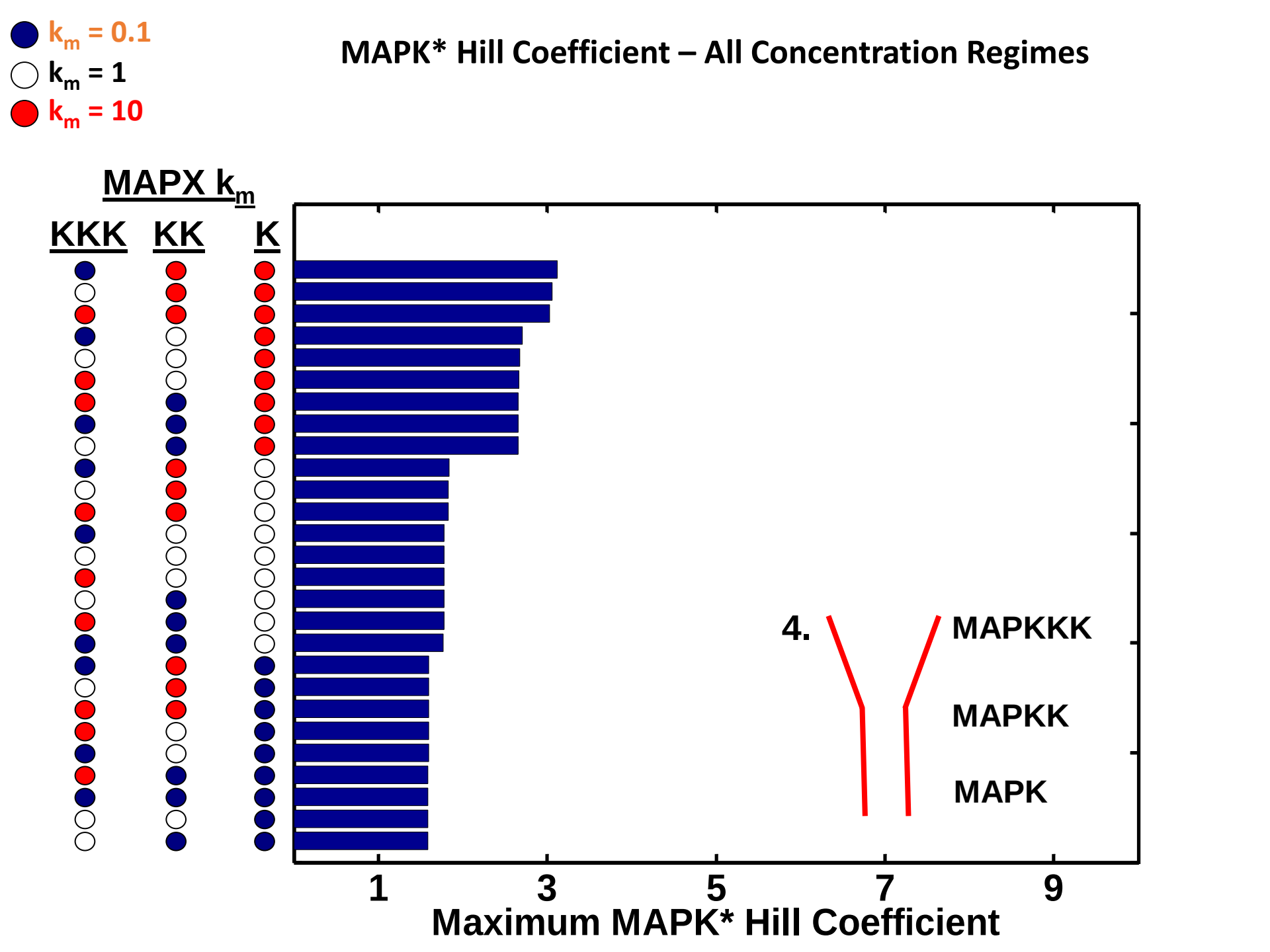
1. **Simulate all 9 concentration regimes**
2. **Determine the Hill coefficient for MAPK***

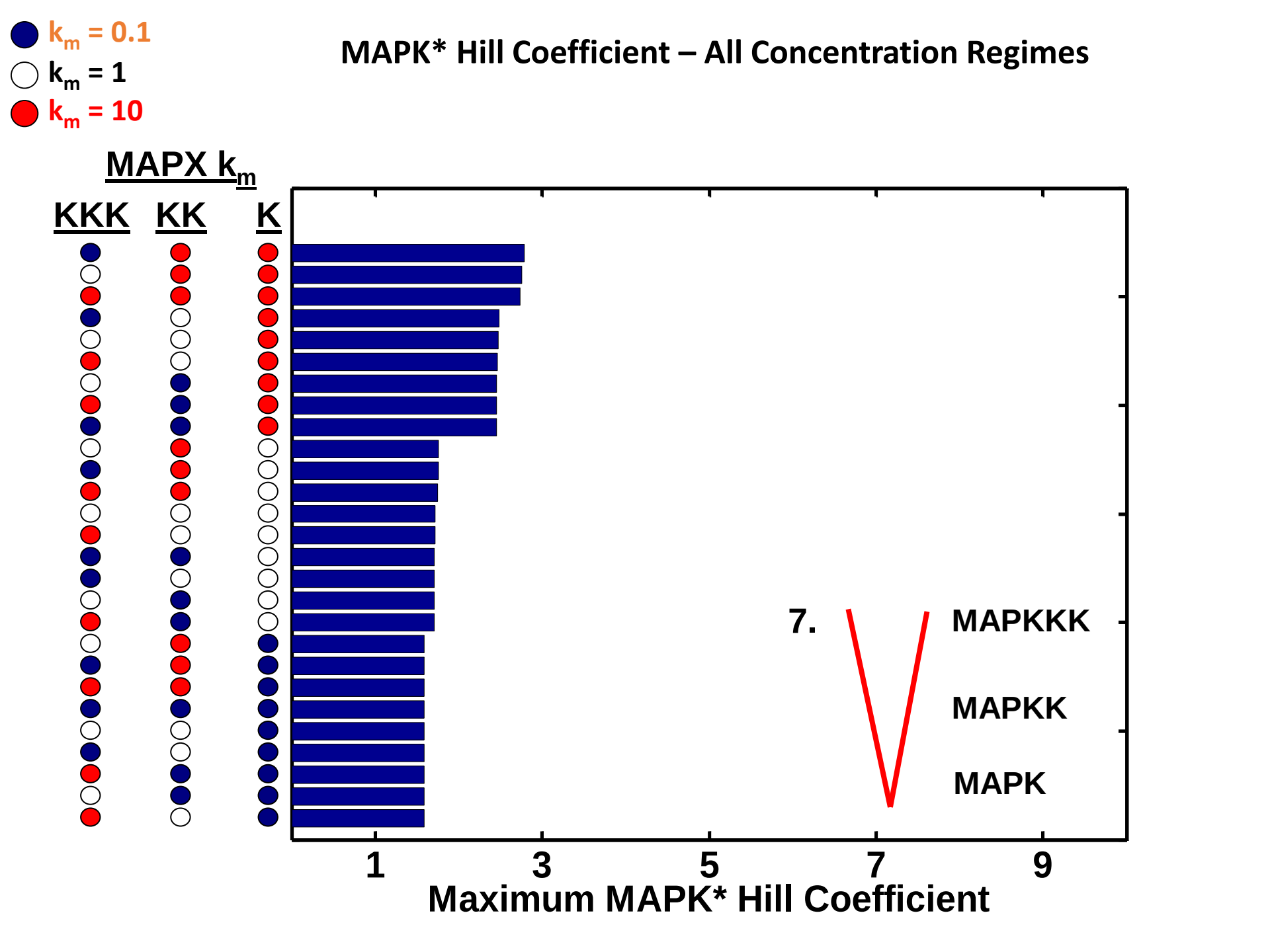

Maximum Possible MAPK* Hill Coefficient – All 27 k_m Configurations
10^3
10^0
10^{-3}
10^{-3}
10^0
10^3
$[MAPKK]_{tot}/[MAPK]_{tot}$
$[MAPKKK]_{tot}/[MAPKK]_{tot}$
1.
2.
3.
4.
5.
6.
7.
8.
9.
8
7
6
5
4
3
2

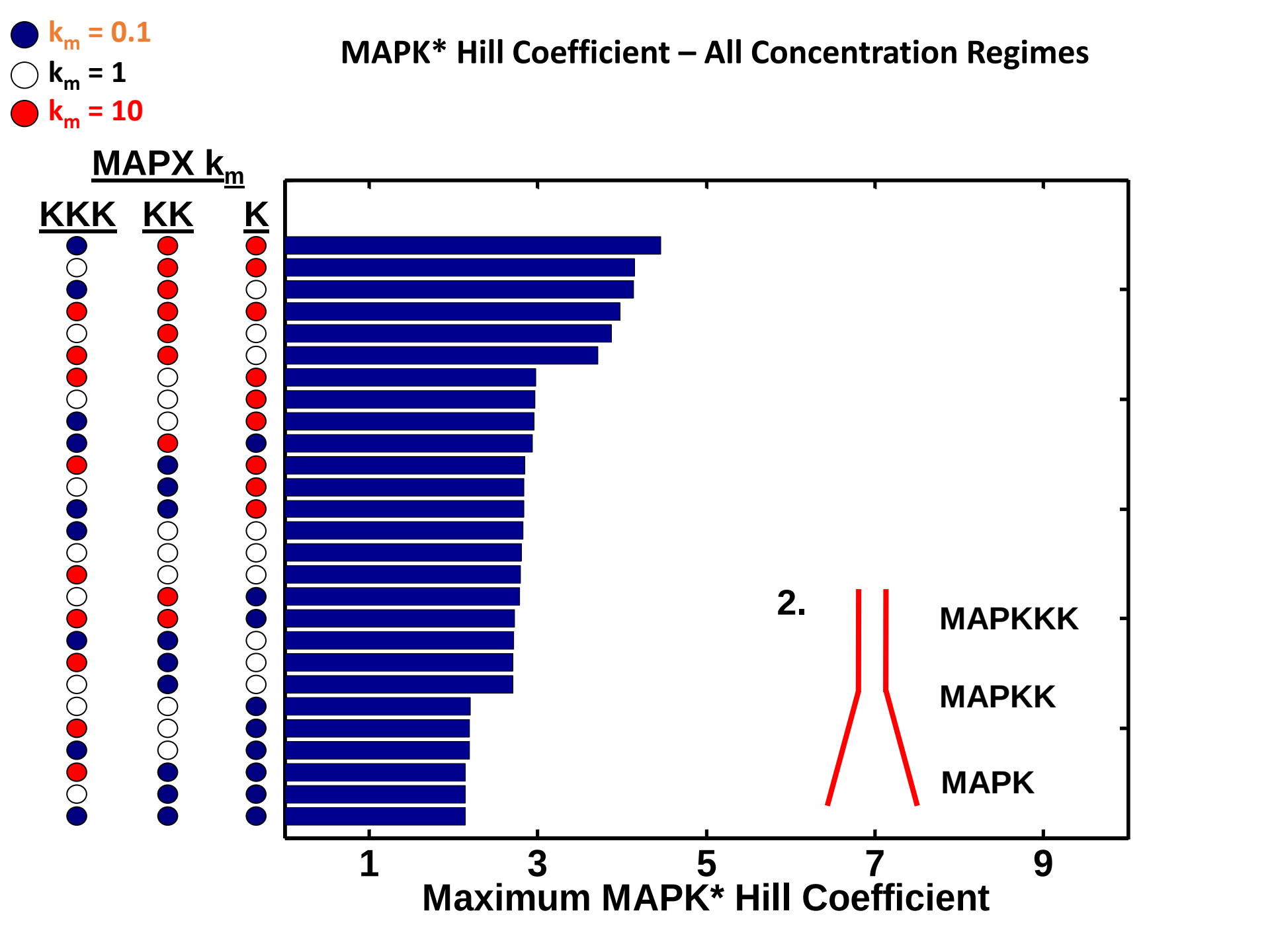
Maximum Possible MAPK* Hill Coefficient – All 27 k_m Configurations

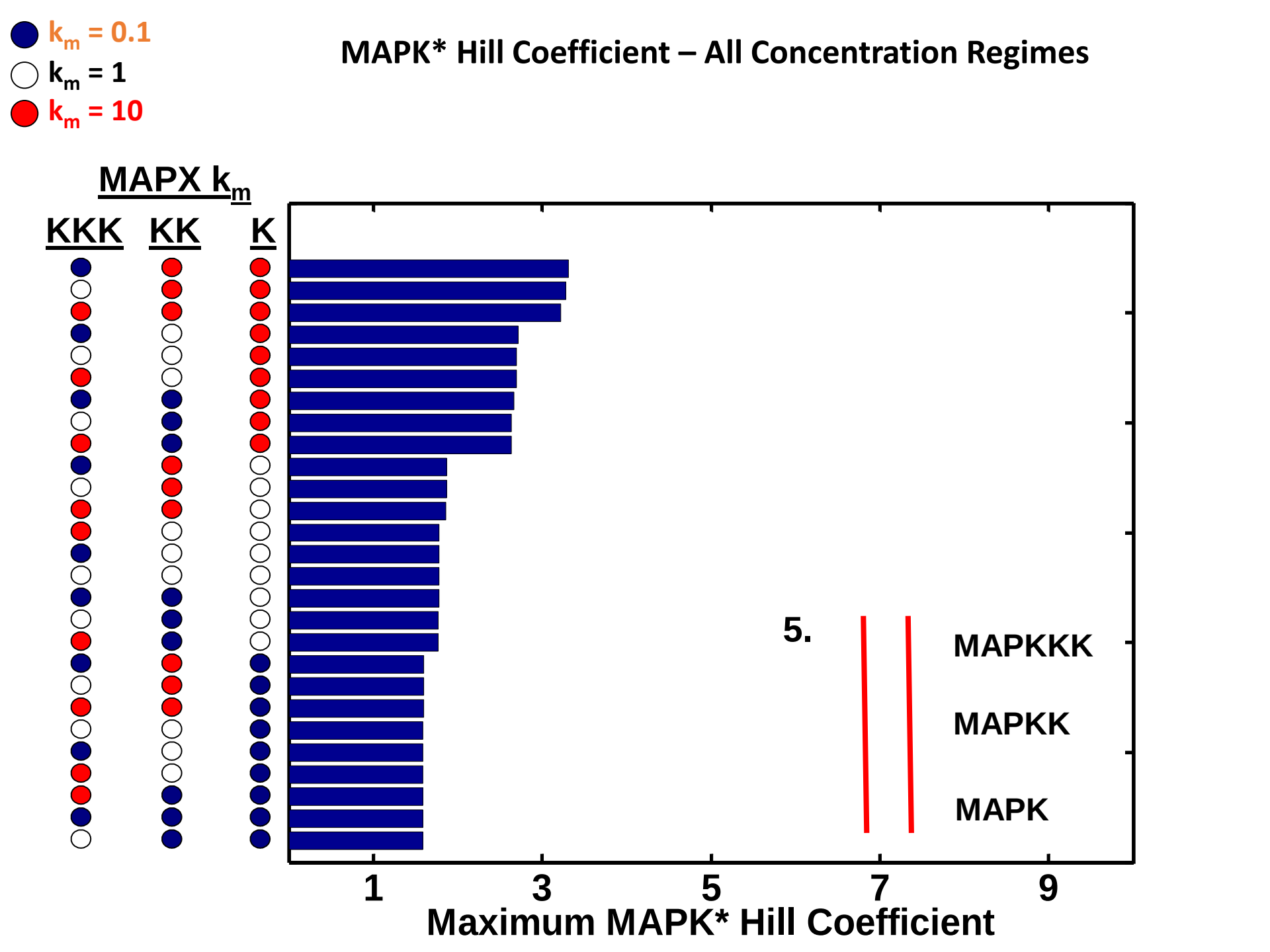


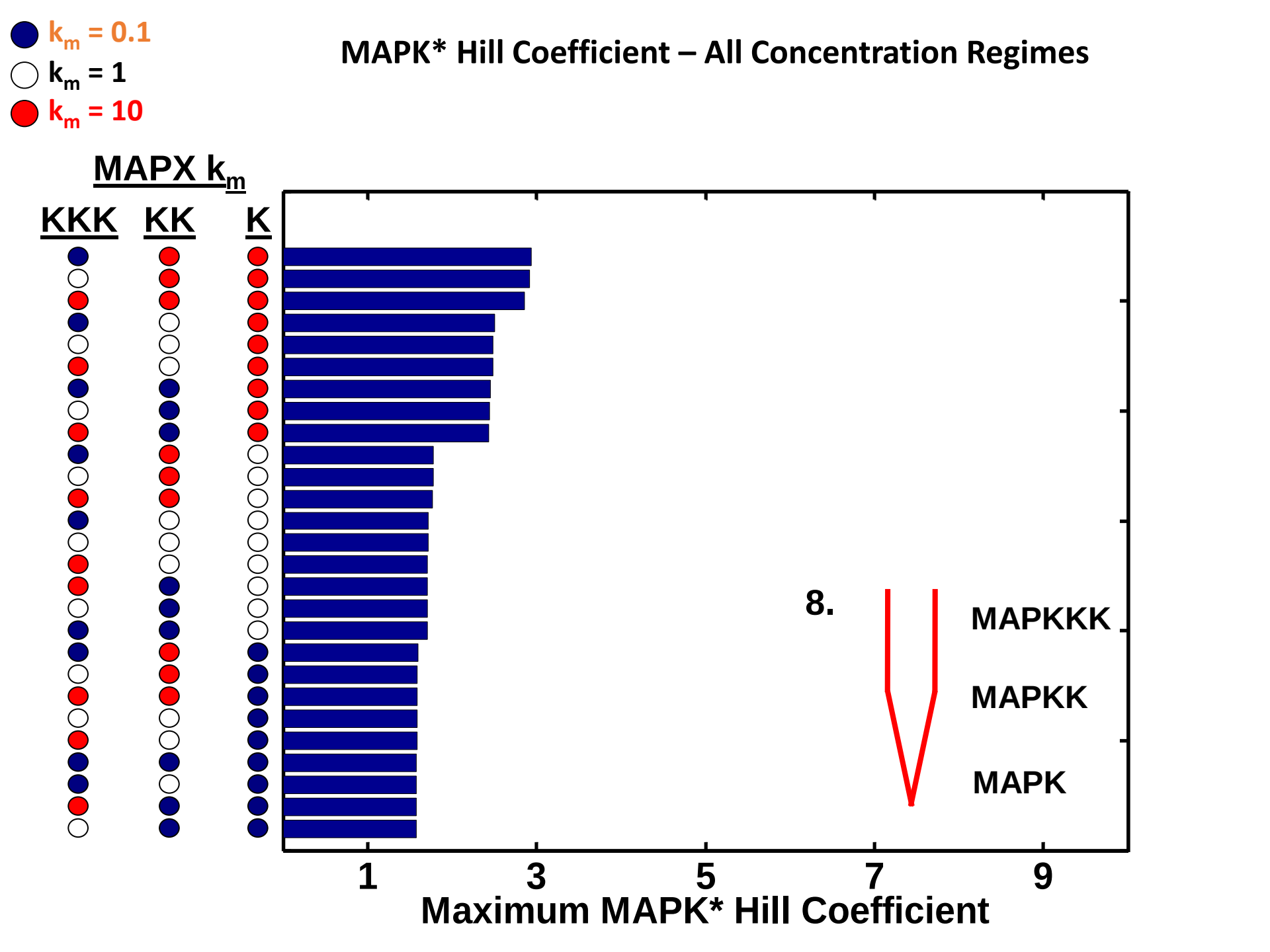

k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
1.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient

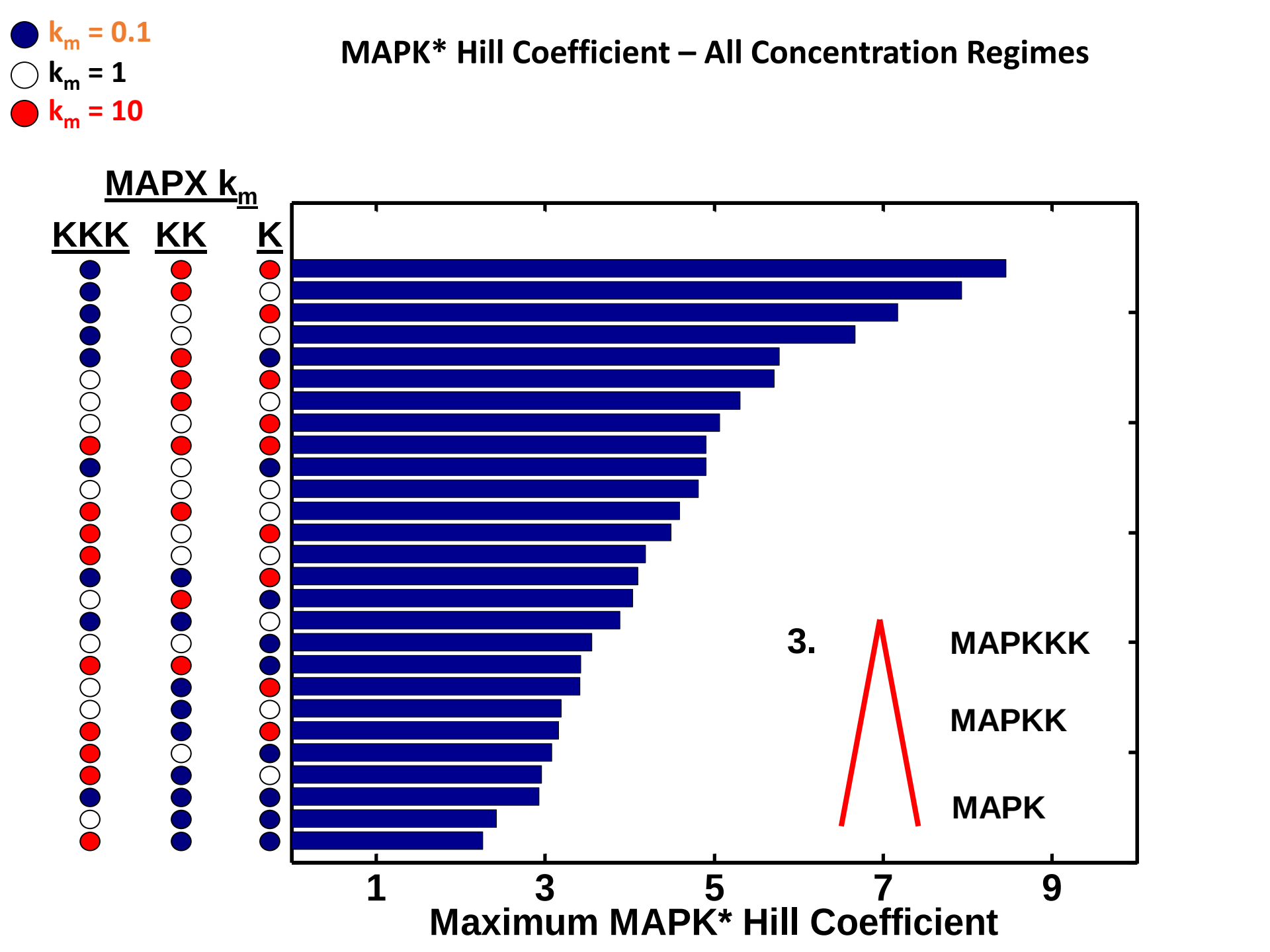

k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
4.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient

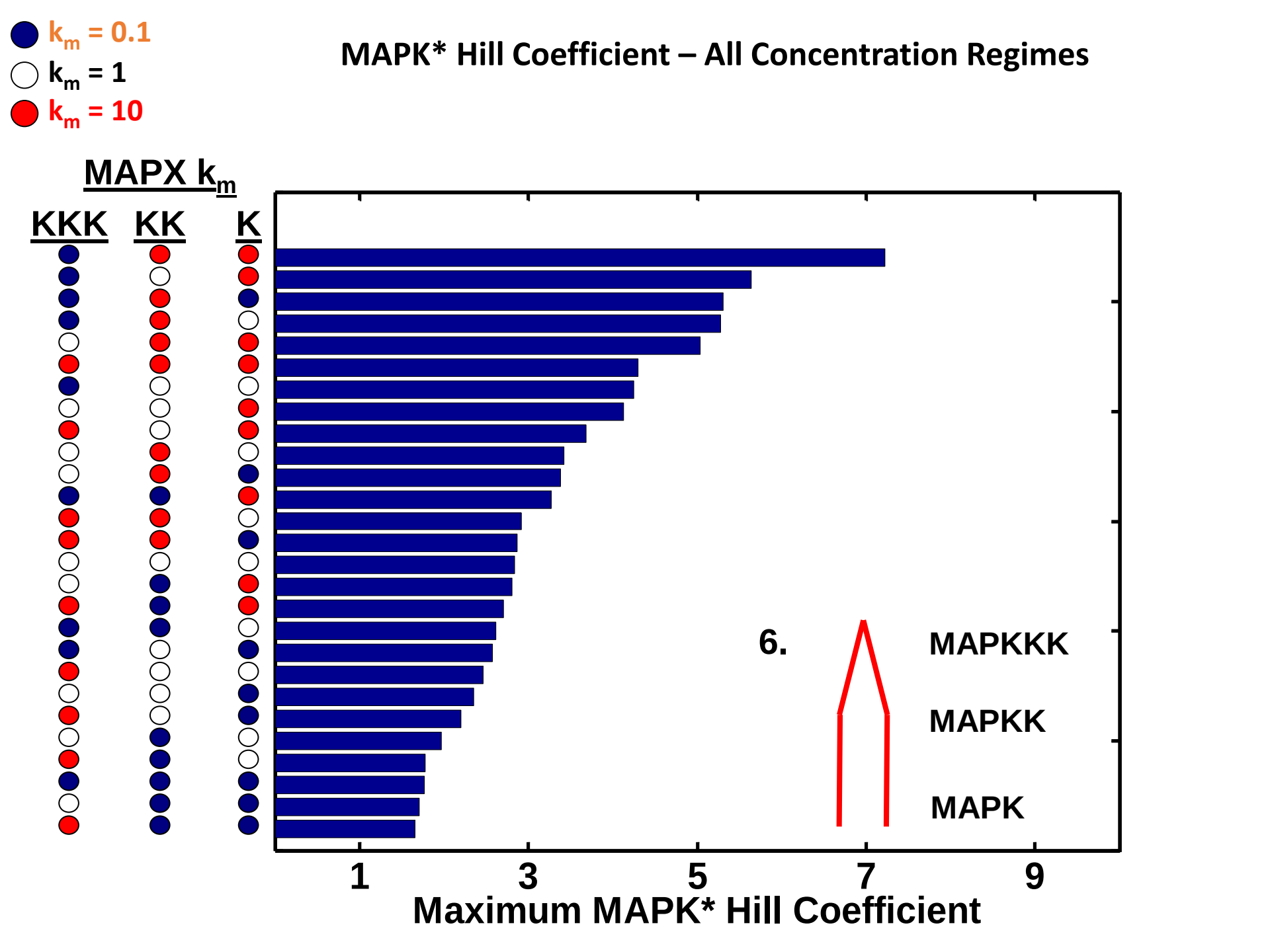

k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
7.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient

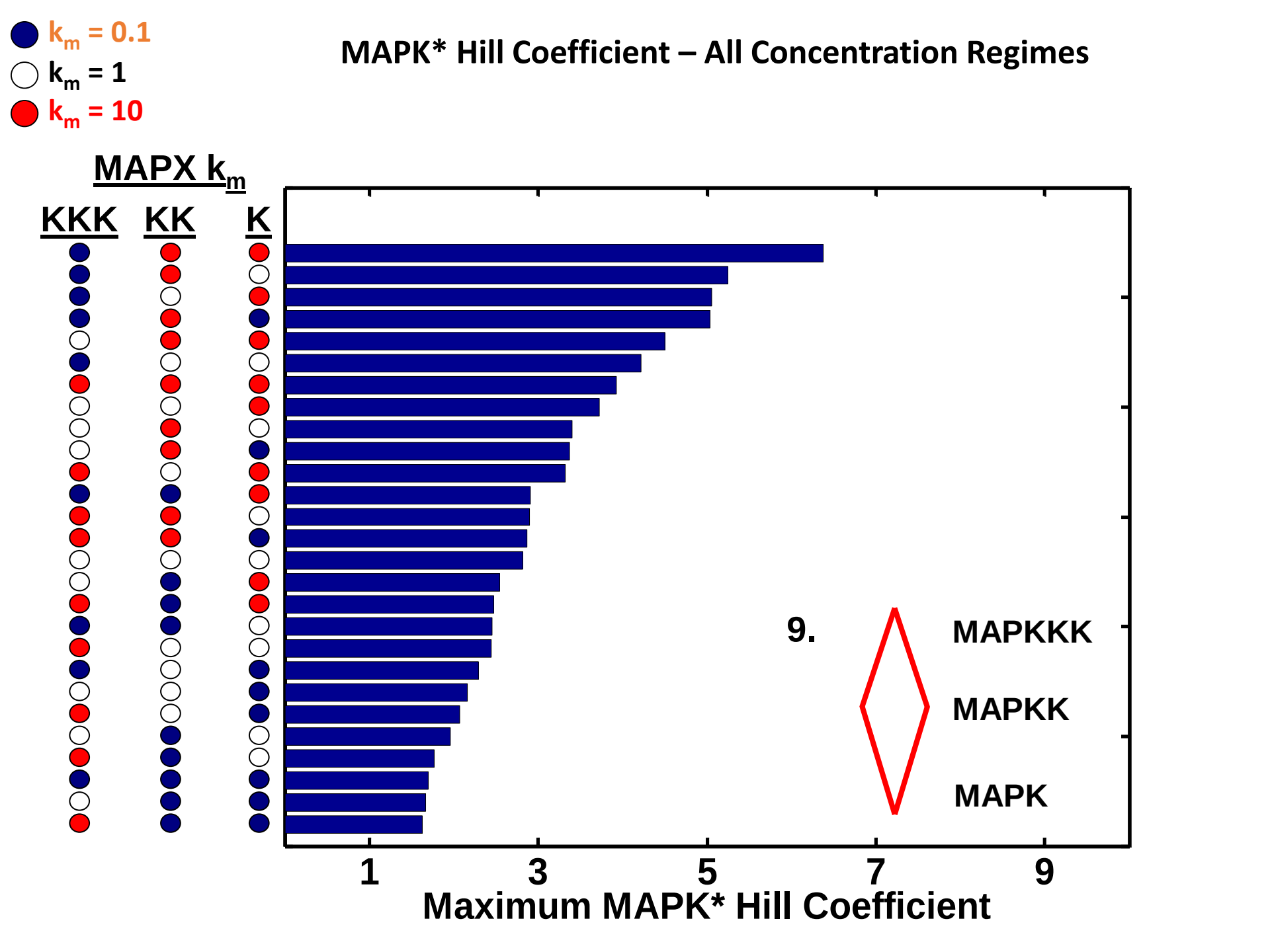

k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
2.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient


k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
5.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient


k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
8.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient


k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
3.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient


k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
6.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient

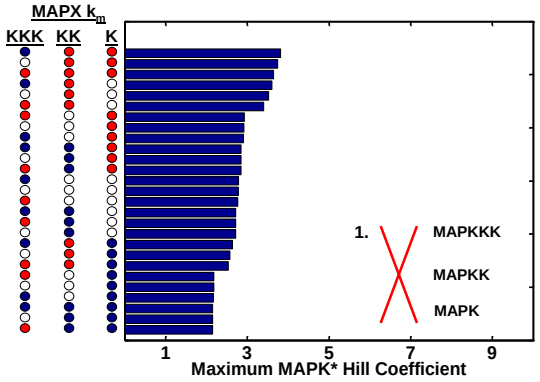

k_m = 0.1
k_m = 1
k_m = 10
MAPK* Hill Coefficient – All Concentration Regimes
MAPX k_m
KKK
KK
K
9.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
Maximum MAPK* Hill Coefficient

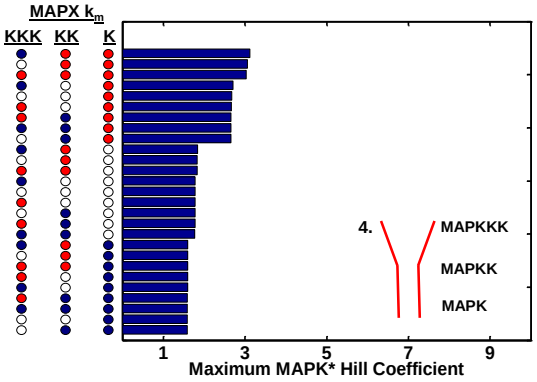
$k_m = 0.1$

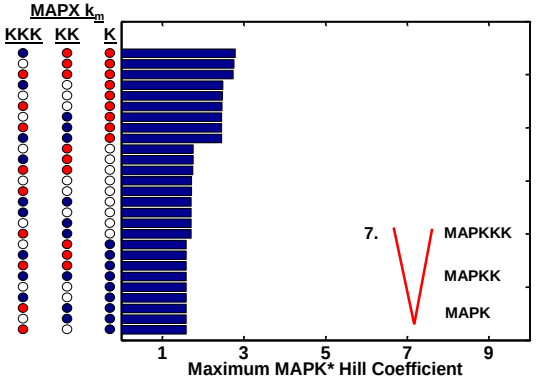
$k_m = 1$

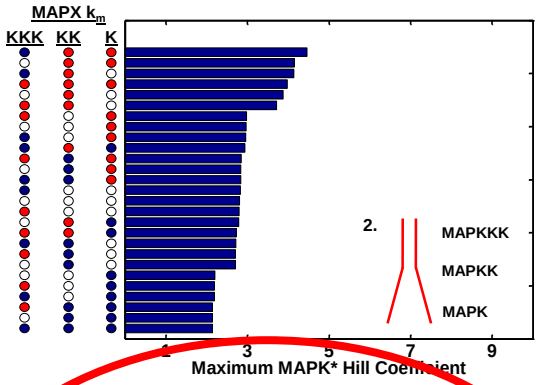
$k_m = 10$

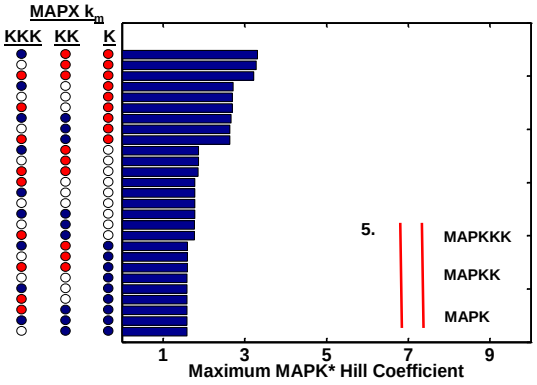
MAPK* Hill Coefficient – All Concentration Regimes

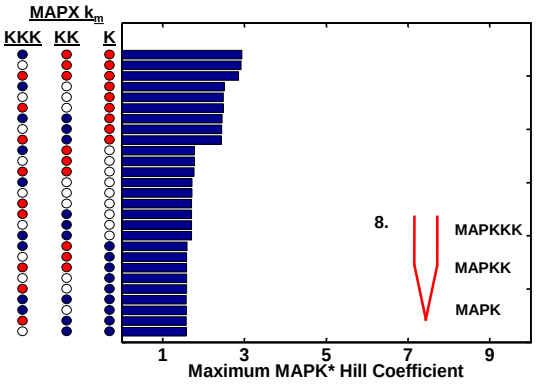


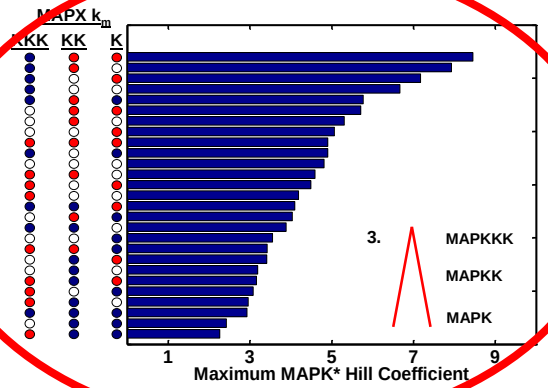


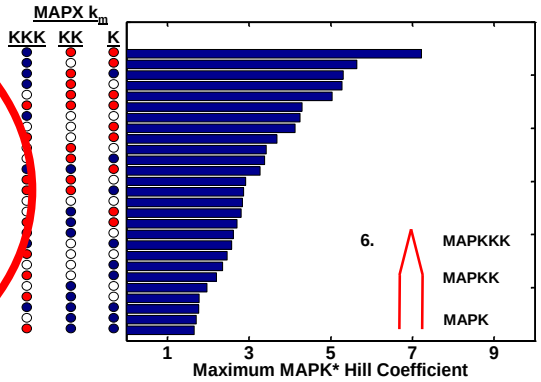


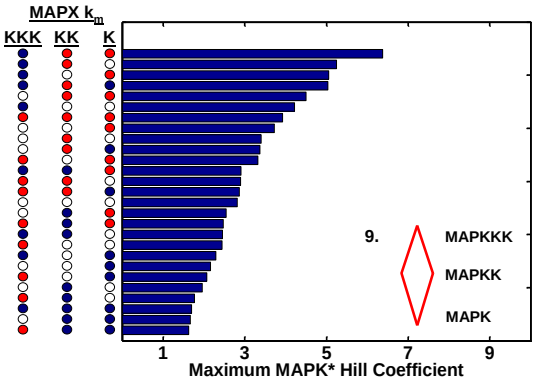


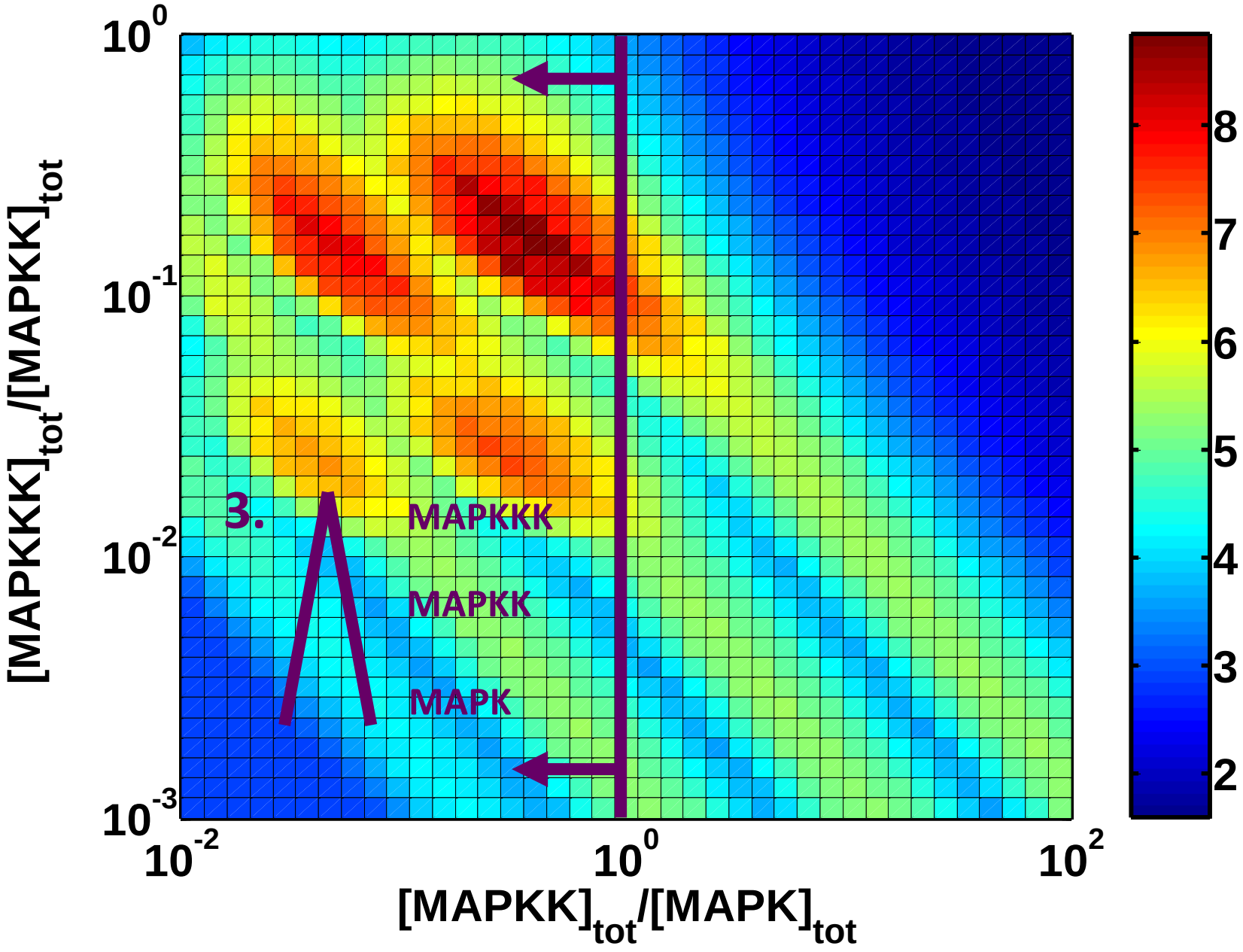




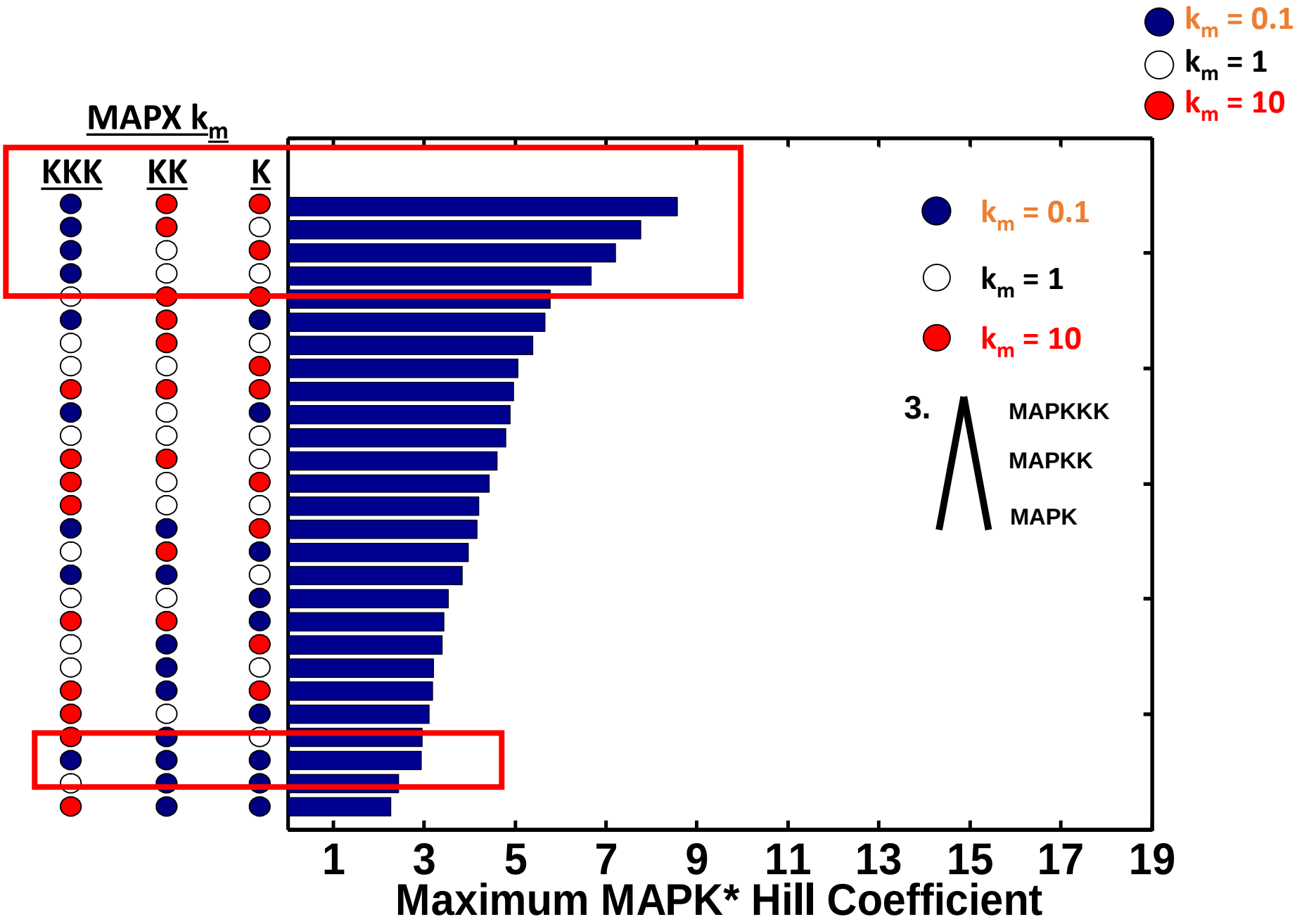




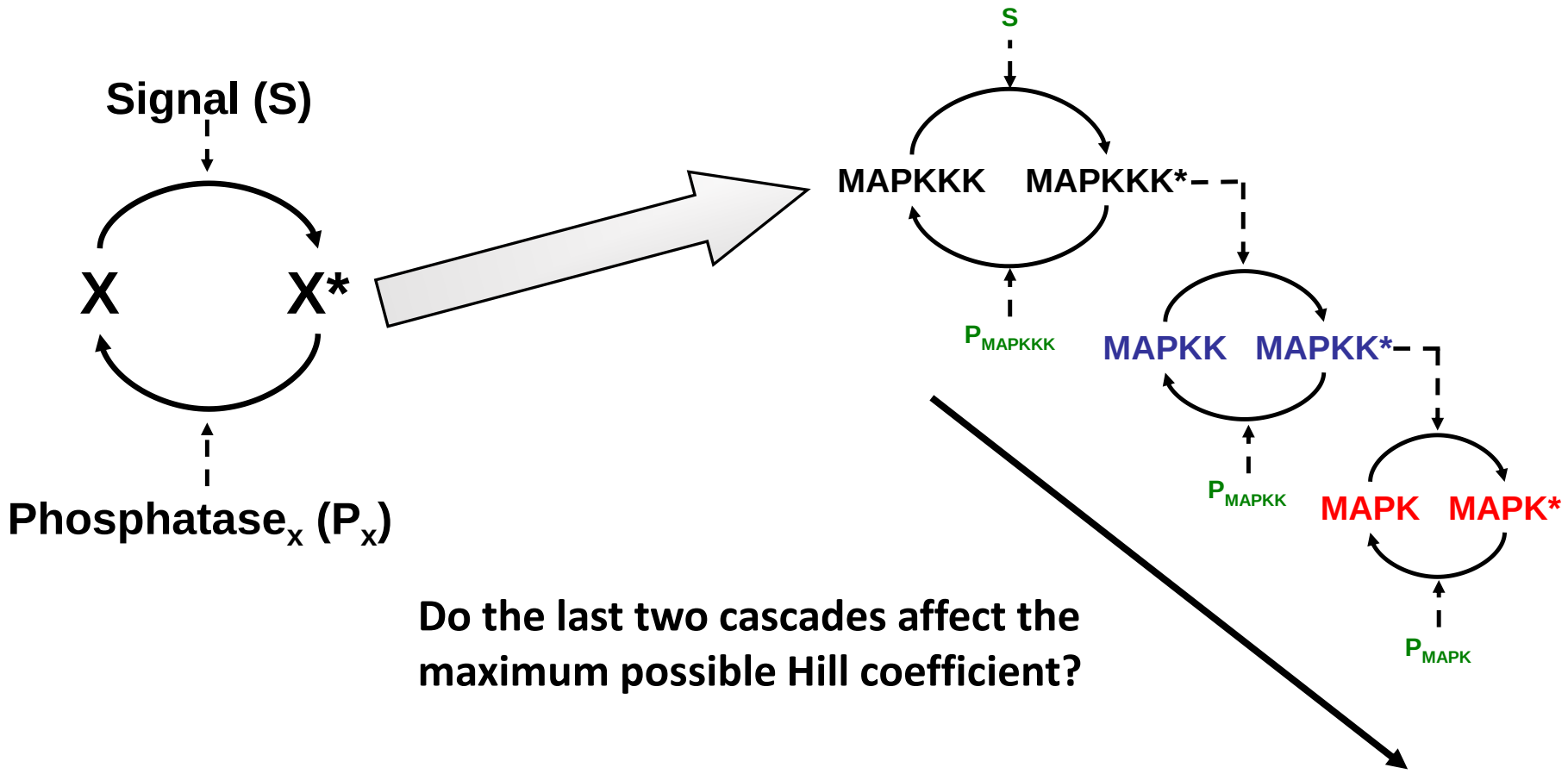



Maximum Possible MAPK* Hill Coefficient – All 27 k_m Configurations
10^0
10^{-1}
10^{-2}
10^{-3}
$[MAPKK]_{tot}/[MAPKK]_{tot}$
3.
MAPKKK
MAPKK
MAPK
10^{-2}
10^0
10^2
$[MAPKK]_{tot}/[MAPK]_{tot}$
8
7
6
5
4
3
2

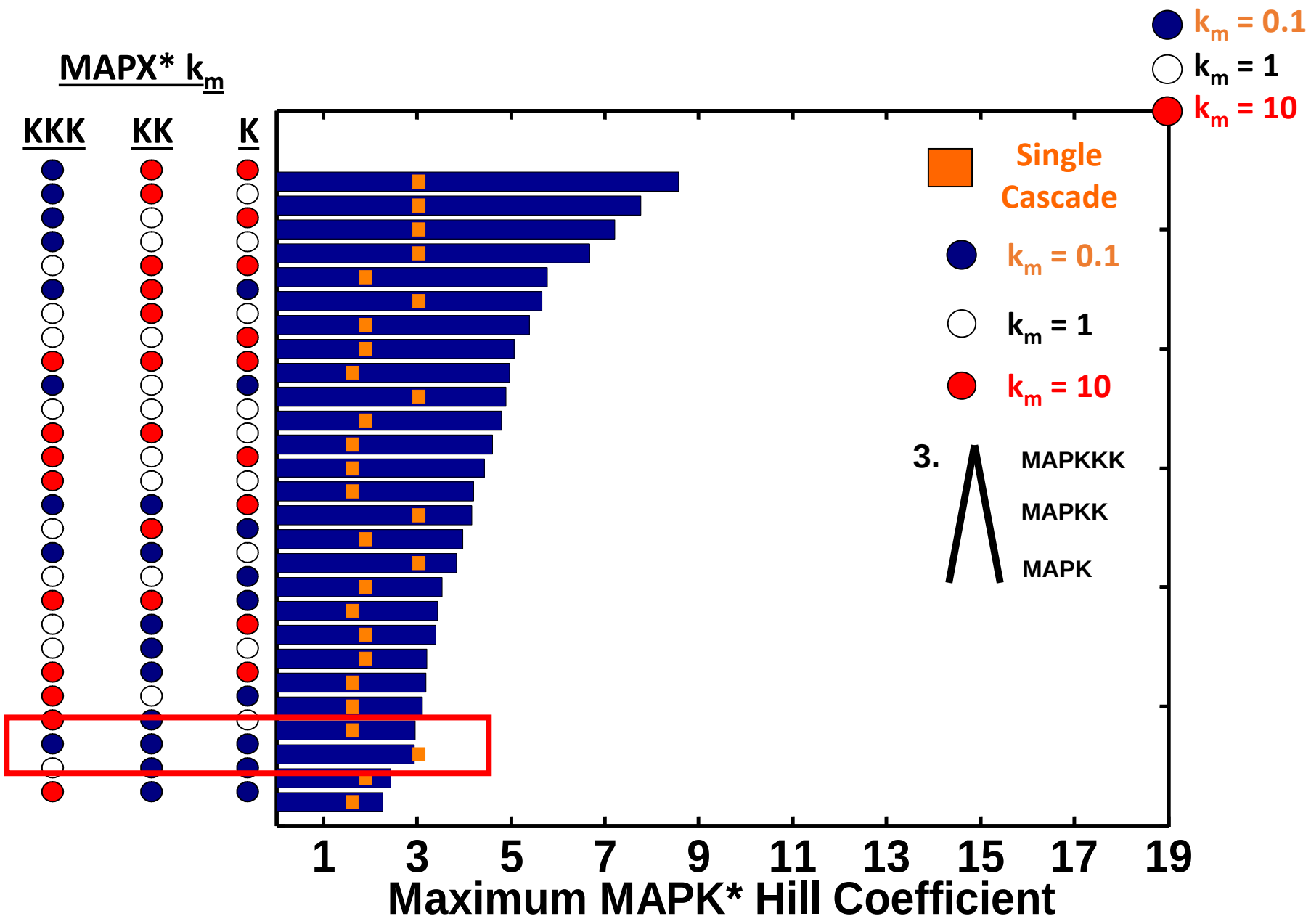
Saturated MAPKKK k_m's Produce the Highest Hill Coefficients



Single Cascades Compared to Networks



Do the last two cascades affect the maximum possible Hill coefficient?


Enhancement Above the Single Cascade is Possible Except When All k_m = 0.1
MAPX* k_m
KKK
KK
K
k_m = 0.1
k_m = 1
k_m = 10
Single Cascade
k_m = 0.1
k_m = 1
k_m = 10
3.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
11
13
15
17
19
Maximum MAPK* Hill Coefficient

Michaelis-Menten vs. Mass Action

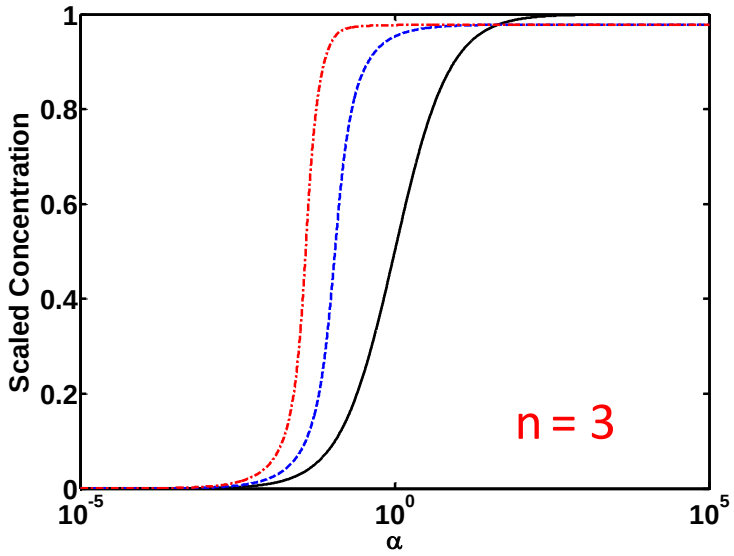
Modeling assumptions affect the effective Hill coefficient of the network

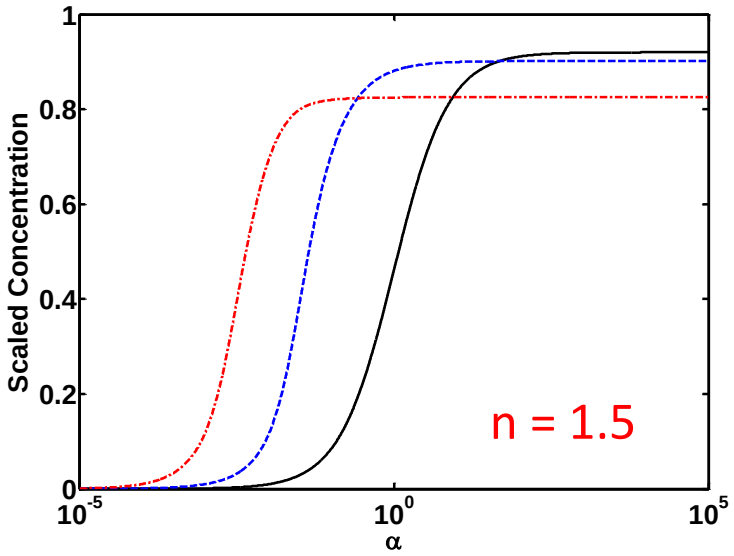
Michaelis-Menten

- Concentration of enzyme-substrate complexes assumed negligible
- Quasi-steady state approximation for enzyme complexes

Mass-Action

- Explicit inclusion of enzyme complexes
- No time scale assumptions



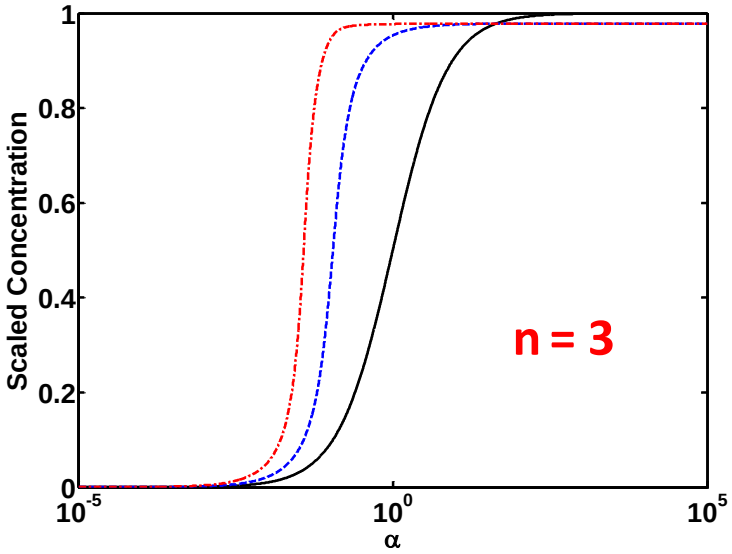


$[MAPKKK^*]/[MAPKKK]_{tot}$ $[MAPKK^*]/[MAPKK]_{tot}$ $[MAPK^*]/[MAPK]_{tot}$

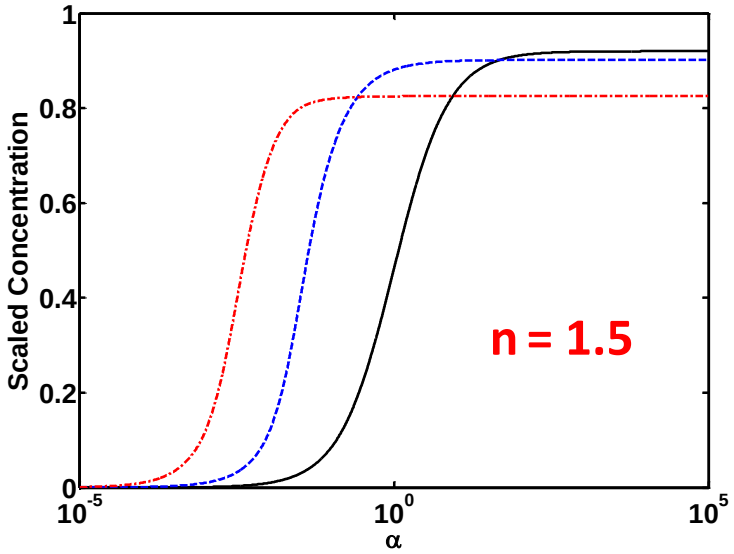
Parameters from Huang and Ferrell. *PNAS*. 1996

Michaelis-Menten vs. Mass Action

Michaelis-Menten



Mass-Action

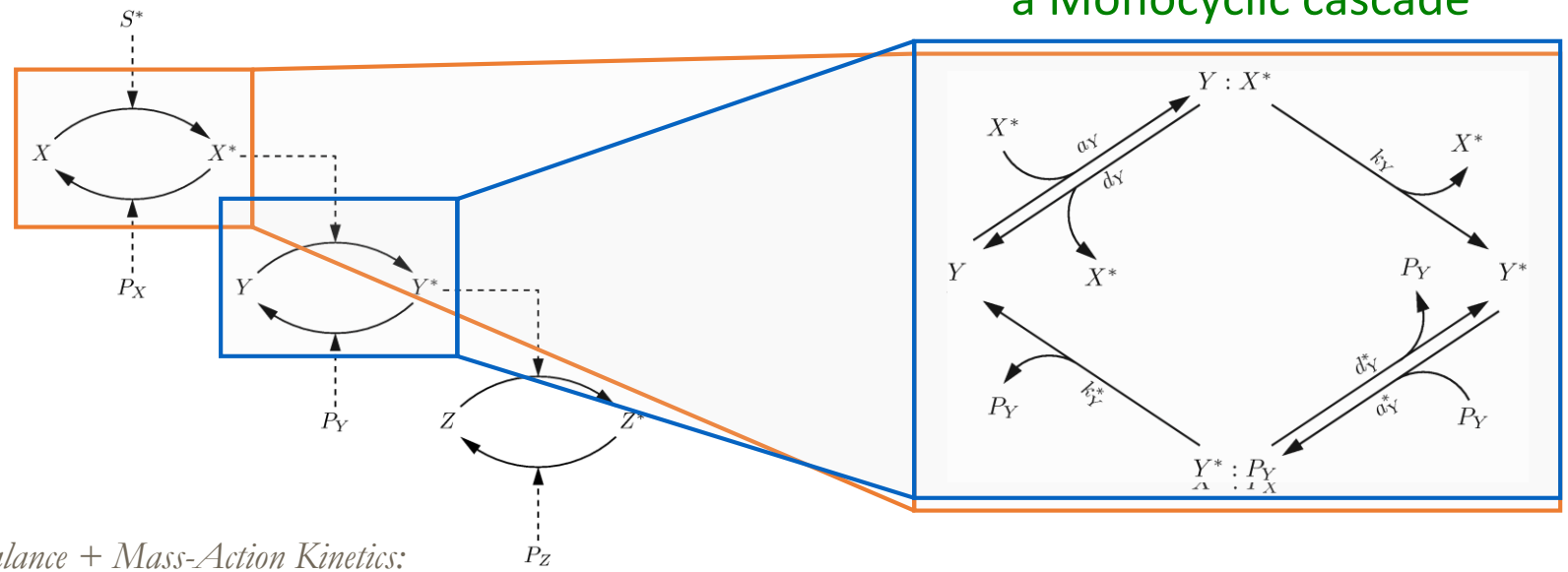


Do networks modeled using Michaelis-Menten kinetics **always over-predict the Hill coefficient**, compared to mass action kinetics?

Do both mathematical formulations achieve maximal Hill coefficient for the same k_m configurations?

A full mass action model

Prototypical tricyclic cascade:



Elementary steps of a Monocyclic cascade

Mass-Balance + Mass-Action Kinetics:

$$\frac{\mathrm{d}[X^*]}{\mathrm{d}t} = -a_X^*[X^*][P_X] + k_X[X:S^*] + d_X^*[X^*:P_X]$$

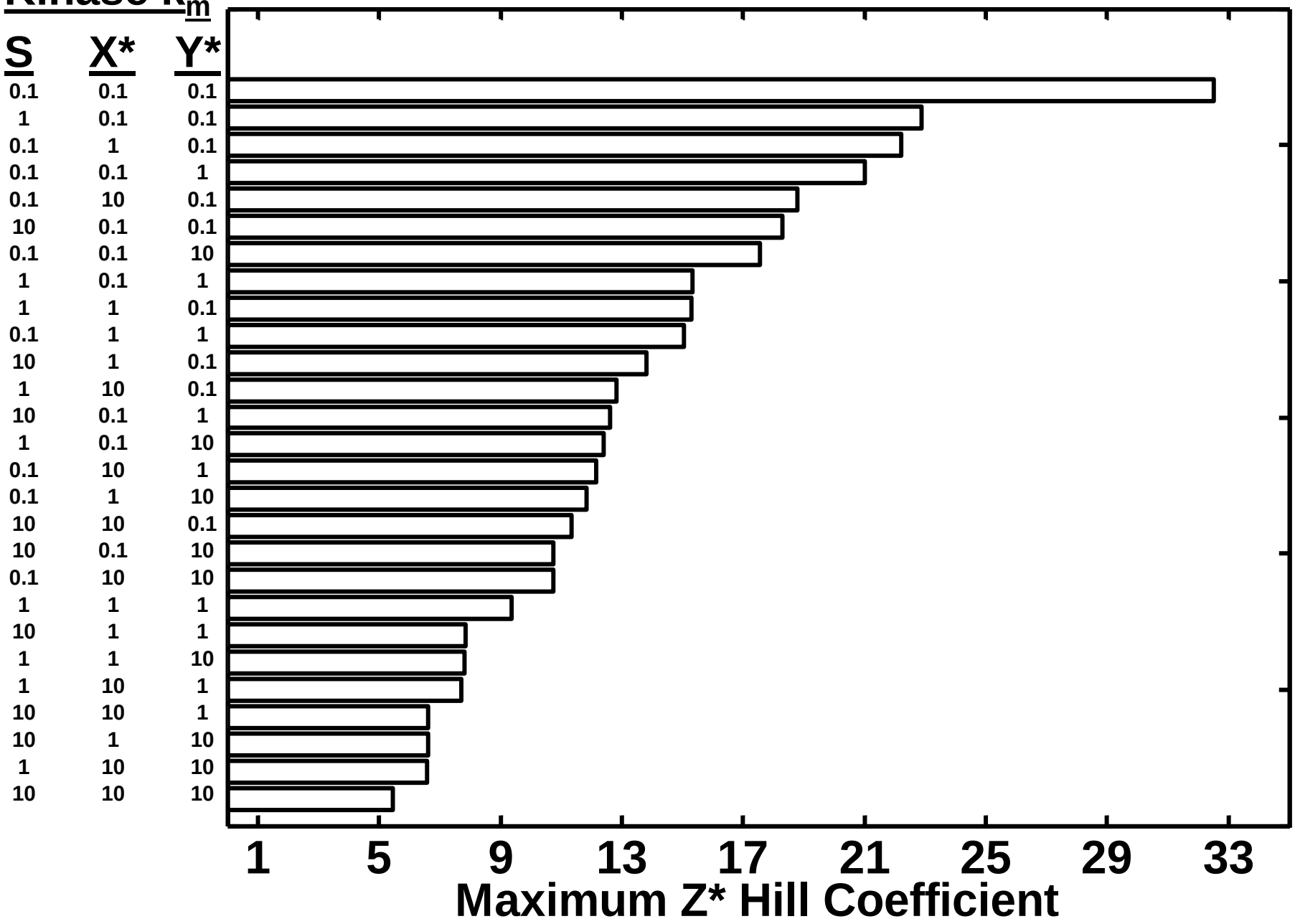
$$\frac{\mathrm{d}[X:S^*]}{\mathrm{d}t} = a_X[X][S^*] - (k_X + d_X)[X:S^*]$$

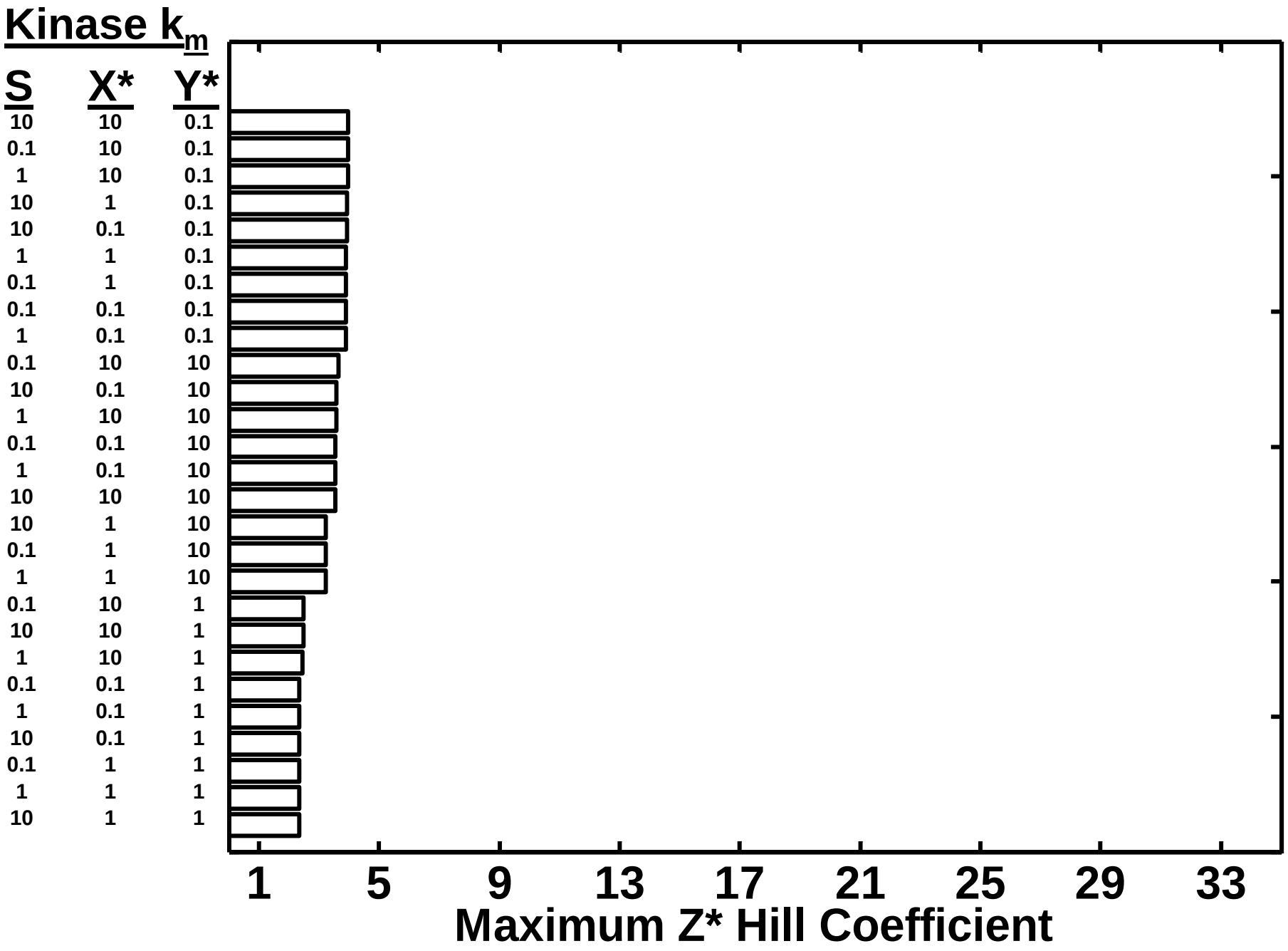
$$\frac{\mathrm{d}[X^*:P_X]}{\mathrm{d}t} = a_X^*[X^*][P_X] - (k_X^* + d_X^*)[X^*:P_X]$$

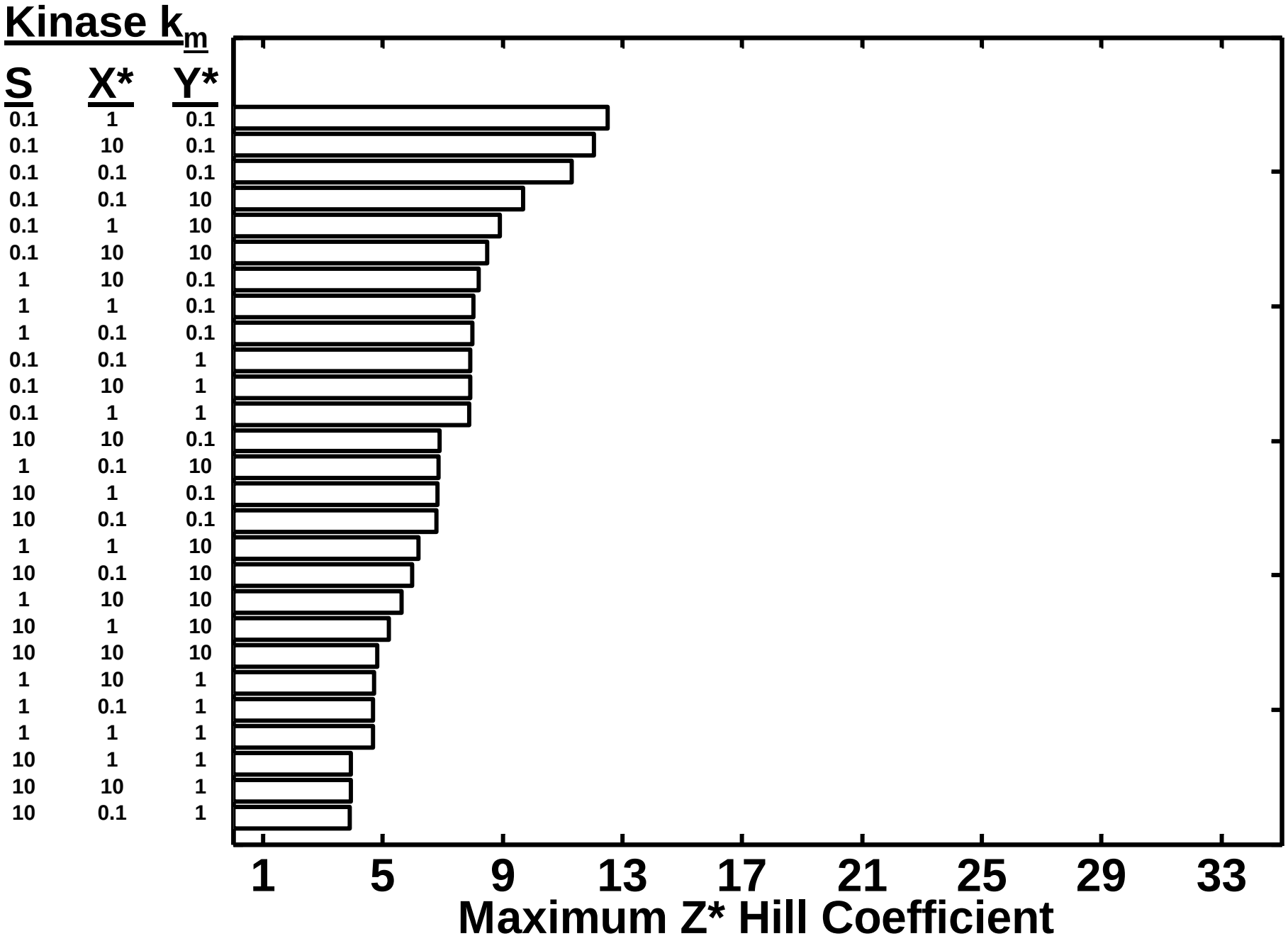
$$[X]_{\mathrm{tot}} = [X] + [X^*] + [X:S^*] + [X^*:P_X]$$

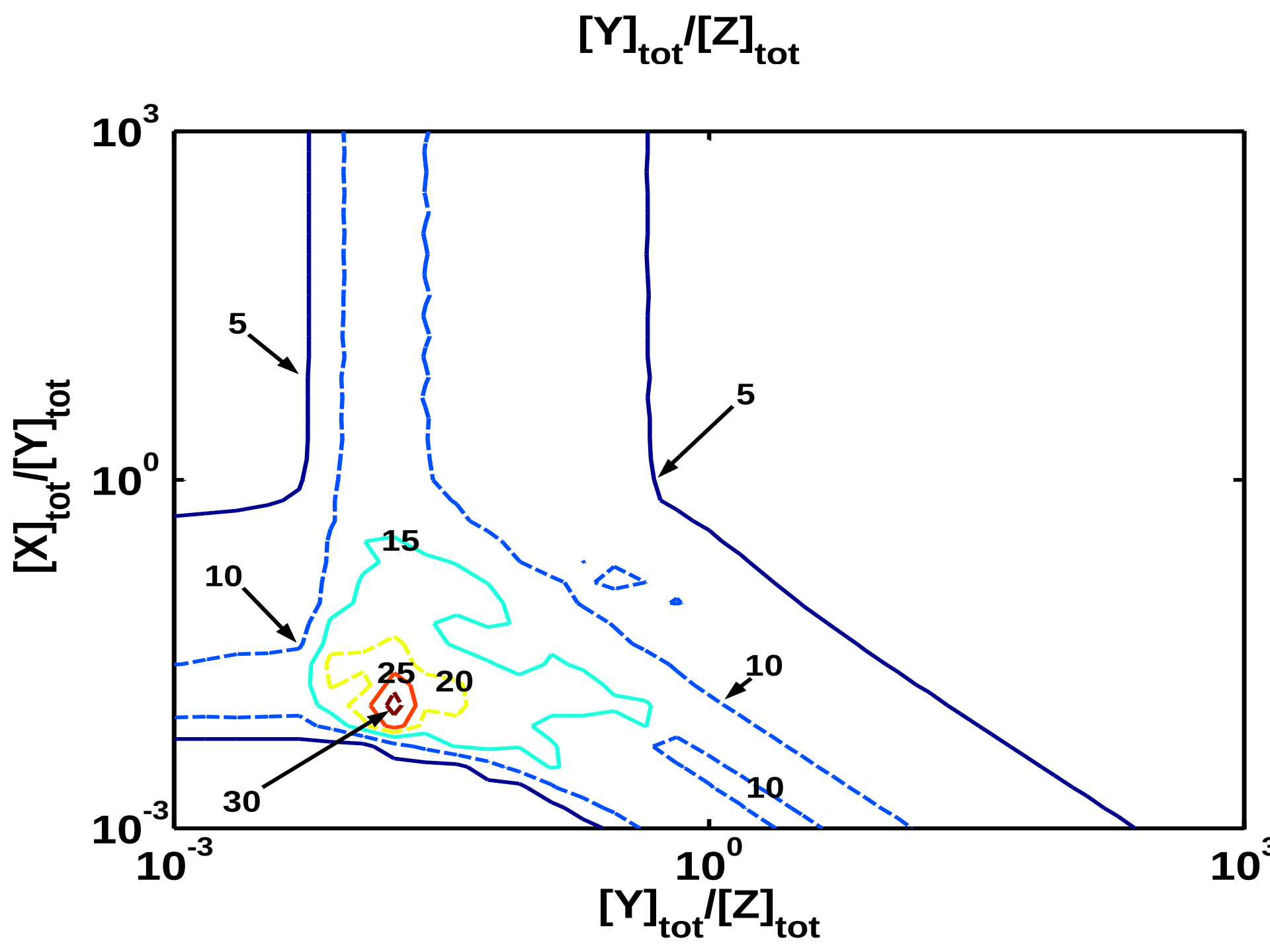
$$[S]_{\mathrm{tot}} = [S] + [S^*] + [X:S^*]$$

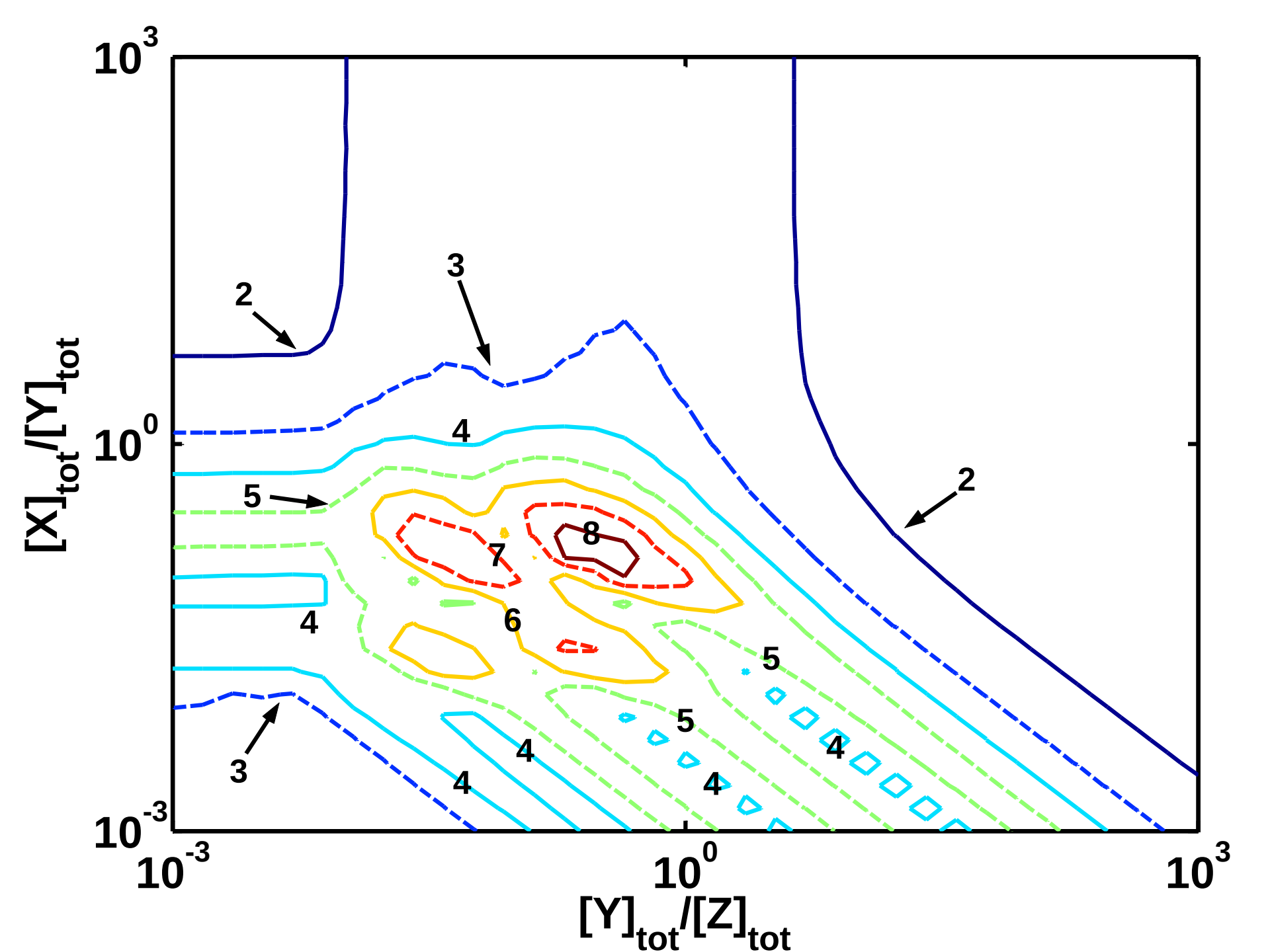
$$[P_X]_{\mathrm{tot}} = [P_X] + [X^*:P_X]$$


Kinase k_m
S
X*
Y*
0.1 0.1 0.1
1 0.1 0.1
0.1 1 0.1
0.1 0.1 1
0.1 10 0.1
10 0.1 0.1
0.1 0.1 10
1 0.1 1
1 1 0.1
0.1 1 1
10 1 0.1
1 10 0.1
10 0.1 1
1 0.1 10
0.1 10 1
0.1 1 10
10 10 0.1
10 0.1 10
0.1 10 10
1 1 1
10 1 1
1 1 10
1 10 1
10 10 1
10 1 10
1 10 10
10 10 10
1
5
9
13
17
21
25
29
33
Maximum Z* Hill Coefficient


Kinase k_m
S
X*
Y*
10 10 0.1
0.1 10 0.1
1 10 0.1
10 1 0.1
10 0.1 0.1
1 1 0.1
0.1 1 0.1
0.1 0.1 0.1
1 0.1 0.1
0.1 10 10
10 0.1 10
1 10 10
0.1 0.1 10
1 0.1 10
10 10 10
10 1 10
0.1 1 10
1 1 10
0.1 10 1
10 10 1
1 10 1
0.1 0.1 1
1 0.1 1
10 0.1 1
0.1 1 1
1 1 1
10 1 1
1
5
9
13
17
21
25
29
33
Maximum Z* Hill Coefficient


Kinase k_m
S X* Y*
0.1 1 0.1
0.1 10 0.1
0.1 0.1 0.1
0.1 0.1 10
0.1 1 10
0.1 10 10
1 10 0.1
1 1 0.1
1 0.1 0.1
0.1 0.1 1
0.1 10 1
0.1 1 1
10 10 0.1
1 0.1 10
10 1 0.1
10 0.1 0.1
1 1 10
10 0.1 10
1 10 10
10 1 10
10 10 10
1 10 1
1 0.1 1
1 1 1
10 1 1
10 10 1
10 0.1 1
1 5 9 13 17 21 25 29 33
Maximum Z* Hill Coefficient

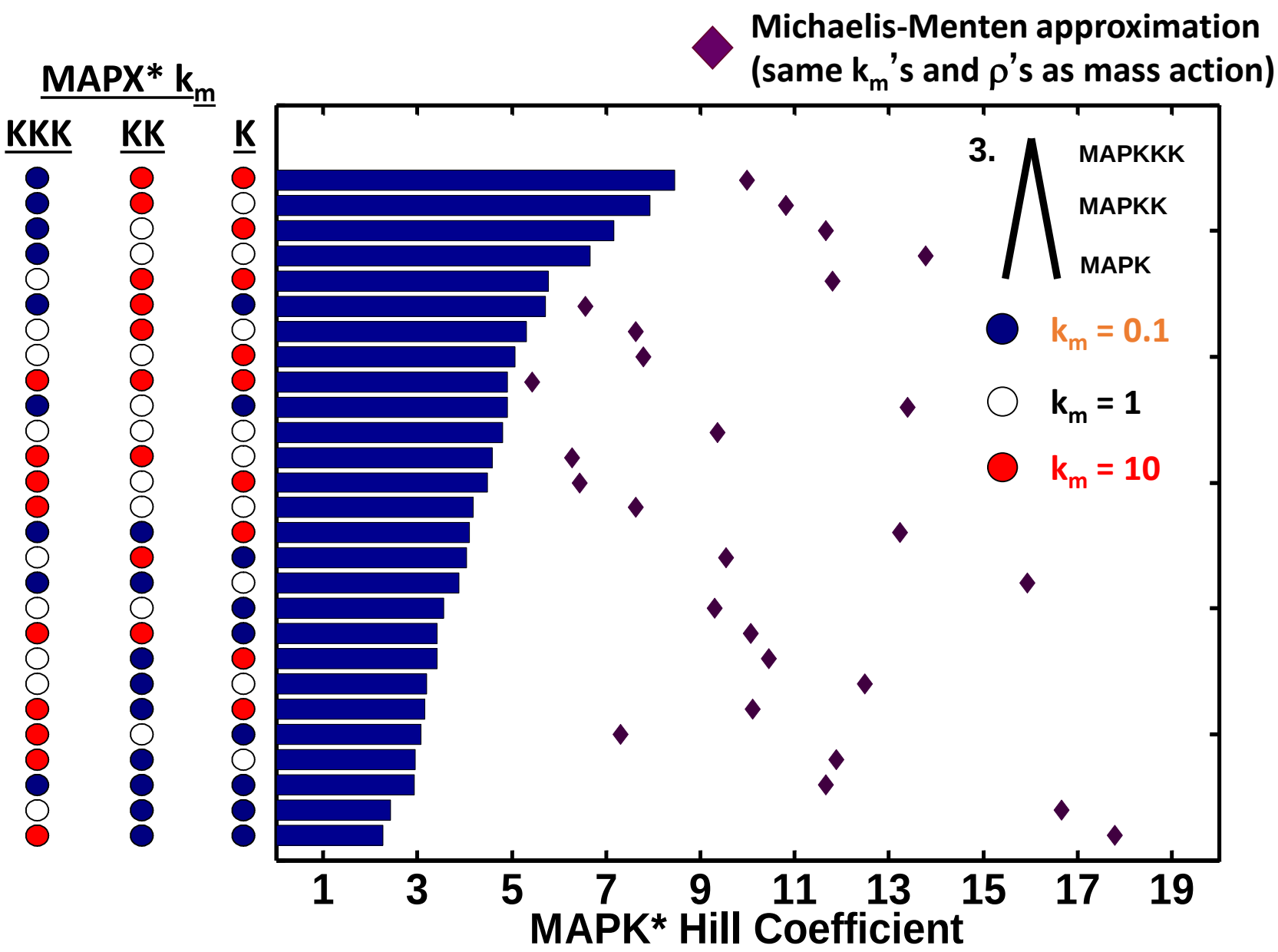

[Y]tot/[Z]tot
10^3
10^0
10^-3
[X]tot/[Y]tot
5
5
15
10
25
20
10
30
10
10^-3
10^0
[Y]tot/[Z]tot

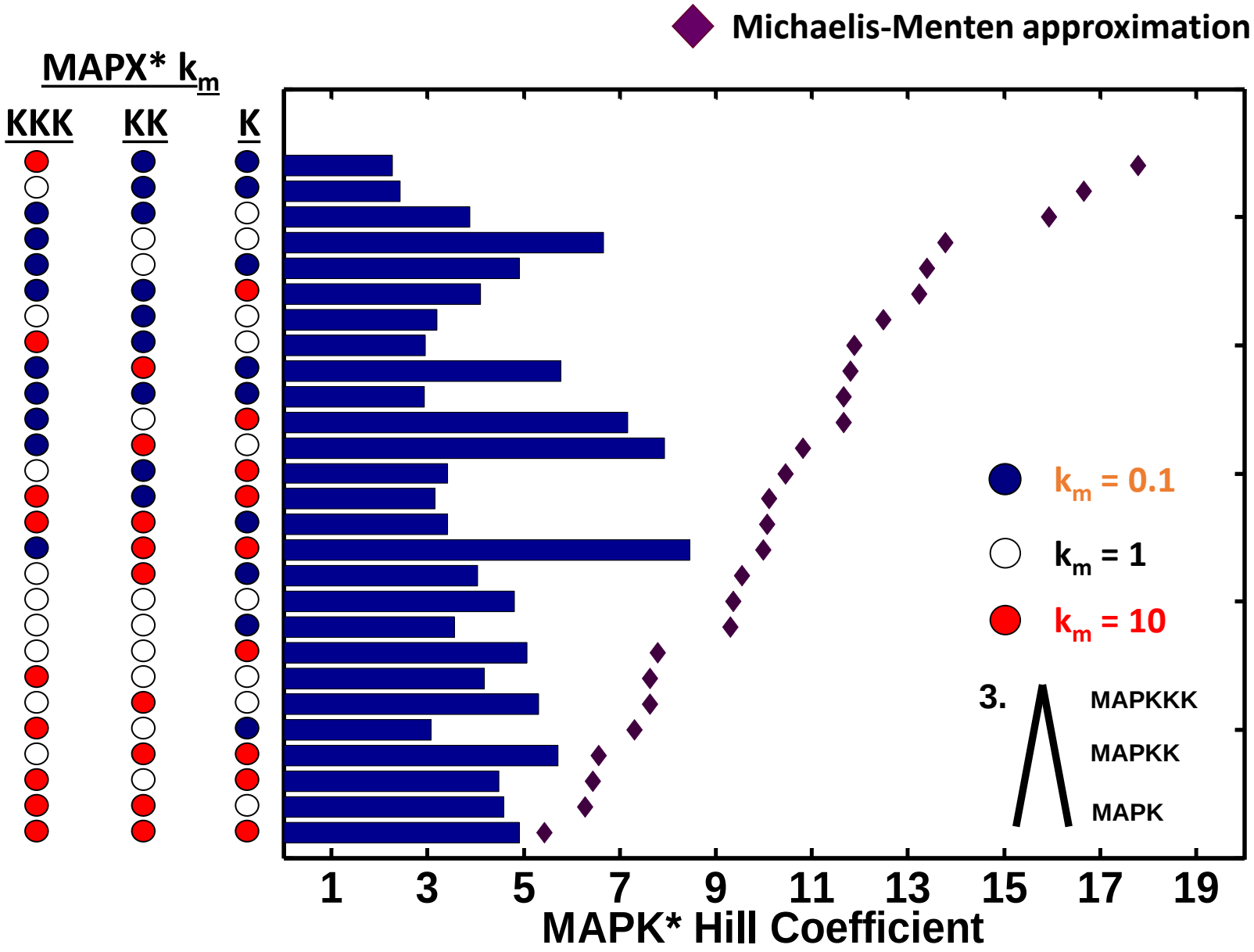

10^3
10^0
10^{-3}
$[X]_{tot}/[Y]_{tot}$
10^{-3}
10^0
10^3
$[Y]_{tot}/[Z]_{tot}$
2
3
4
5
6
7
8
2
3
4
4
4
4
5
5
5
4
4

Hill Coefficient from Michaelis-Menten

vs.

Maximum Hill Coefficient from Mass Action




Different k_m Conclusions from Michaelis-Menten Kinetics
(Data sorted by *Michaelis-Menten* Hill Coefficient)
Michaelis-Menten approximation
MAPX* k_m
KKK
KK
K
k_m = 0.1
k_m = 1
k_m = 10
3.
MAPKKK
MAPKK
MAPK
1
3
5
7
9
11
13
15
17
19
MAPK* Hill Coefficient

Summary

- For almost any value of k_m or concentration ratio, cascade networks can enhance the Hill coefficient, compared to a single cascade
- However, multiplicative Hill coefficients are never observed

- Conditions for enhancement of the **Hill coefficient differ** based on the mathematical formulation chosen

  - **Mass action – Highest Hill coefficients with saturated 1st cascade, and unsaturated 2nd and 3rd cascades**

  - Michaelis-Menten – 2nd and 3rd cascades should be saturated for maximum Hill coefficients

STOCHASTIC AND SPATIAL EFFECTS ON THE INTRACELLULAR LEVEL

Principles and Applications of Systems Biology

EPFL

Vassily Hatzimanikatis

October 2025

Stochastic Models

When size matters…

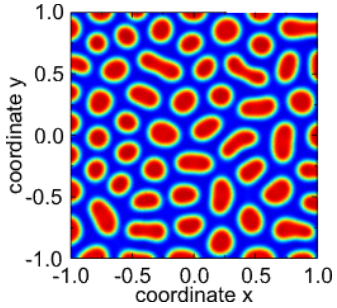
When does stochasticity become important?

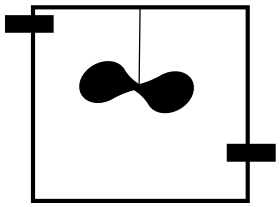
Time scale

Length scale

Spatial deterministic models:

- Many molecules
- Locally well mixed

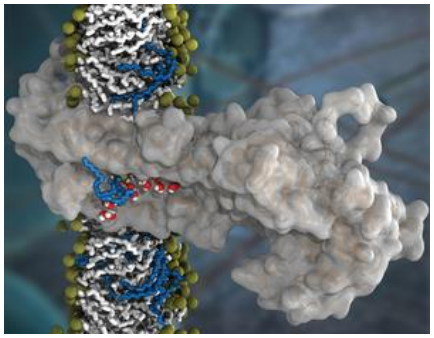




Deterministic models:

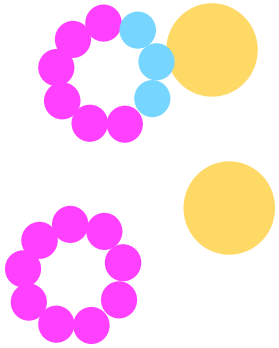
- Many molecules
- well mixed

Vestergaard, Anna L., et al. *PNAS* 111.14 (2014)



Molecular dynamics

- Classical physics
- Interaction via forces



Particle reaction diffusion:

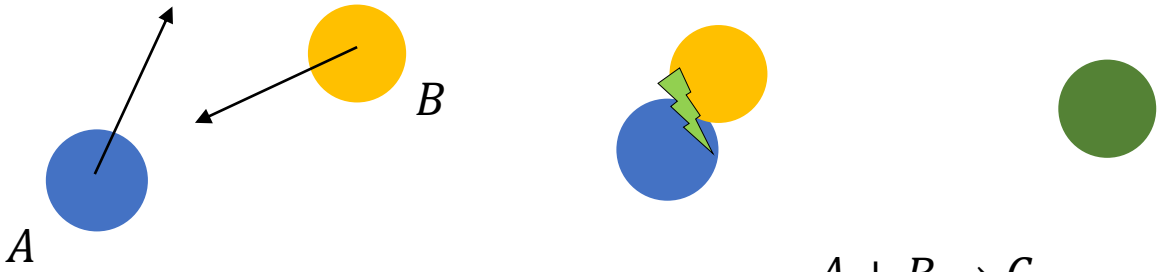
- Particles as spheres
- Reaction upon collision

Stochastic models:

- well mixed
- Little number molecules

Chemical reactions

Boltzmann collision theory:



$A + B \rightarrow C$

Collision frequency of all A molecules with B

$$f_A = N_A r_{AB}^2 k(T) \sqrt{\frac{8k_b T}{\mu_{AB}}} [A][B]$$

Concentrations of A and B

Only valid if the number of molecules is very big!!!

$r_{AB} = r_A + r_B$

Term from kinetic theory of gases $\langle v^2 \rangle \propto T$

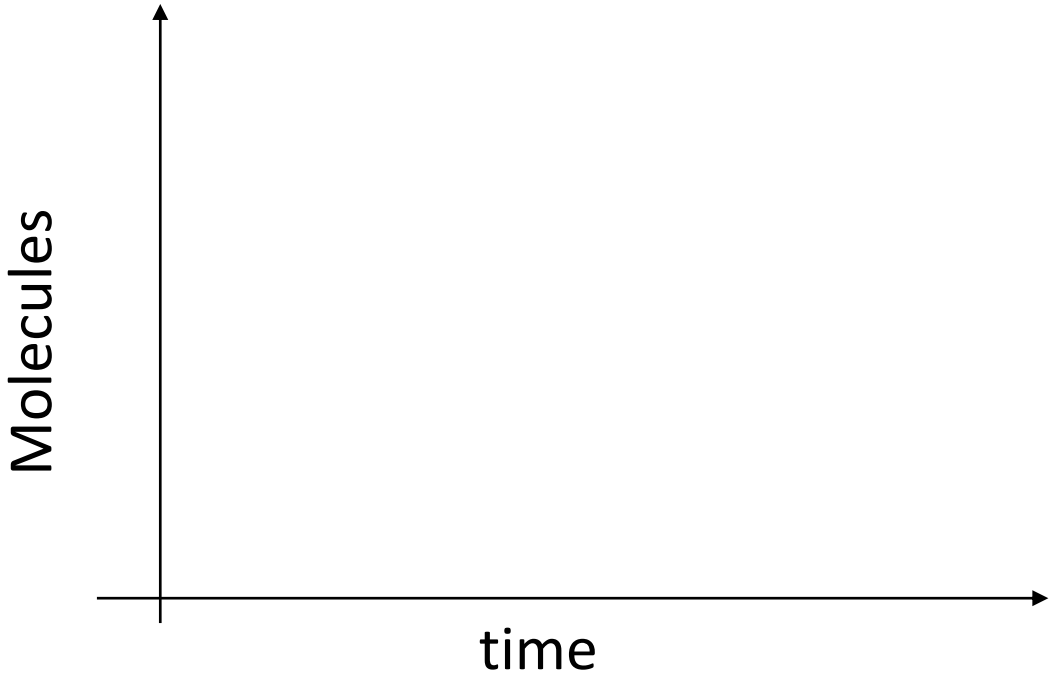
Probability distributions

Describe the concentrations of each species with the time development of a probability distribution

$A \rightarrow B$

$[A](t)$, $[B](t)$ Deterministic description for the concentrations $[A]$ and $[B]$

#A(t), #B(t) Number of molecules A, B at a time t



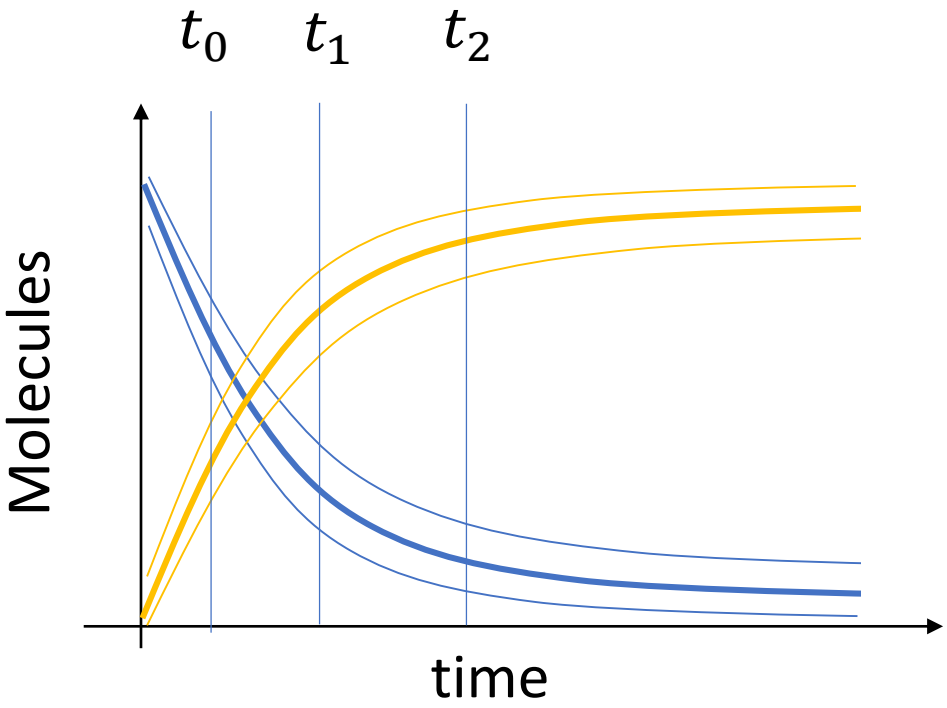
Probability distributions

Describe the concentrations of each species with the time development of a probability distribution

$A \rightarrow B$

$[A](t), [B](t)$ Deterministic description for the concentrations $[A]$ and $[B]$

$P(A, B, t)$ Probability for number of molecules A, B at a time t



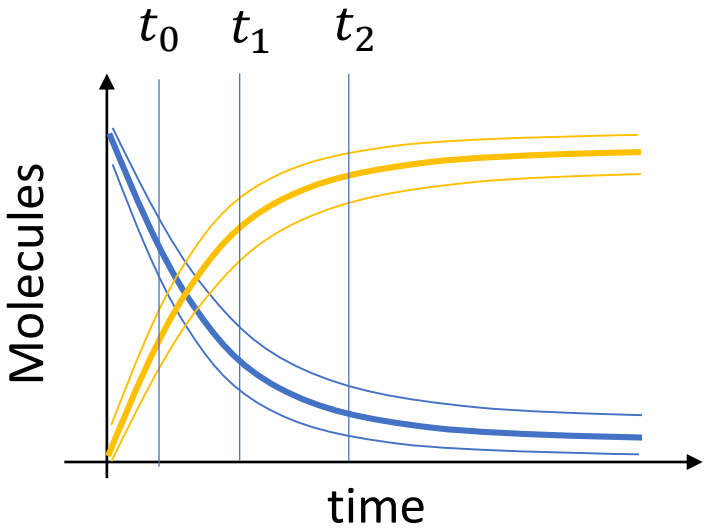
Probability distributions

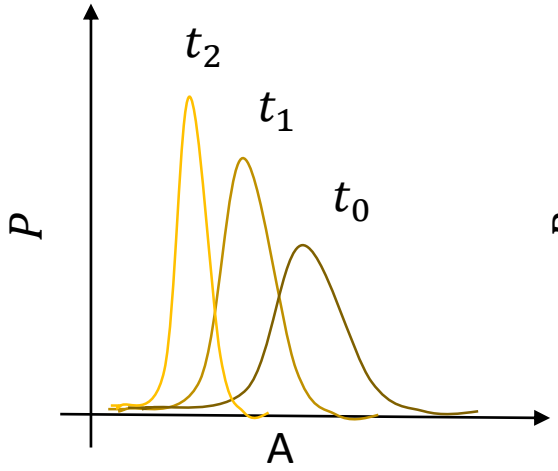
Describe the concentrations of each species with the time development of a probability distribution

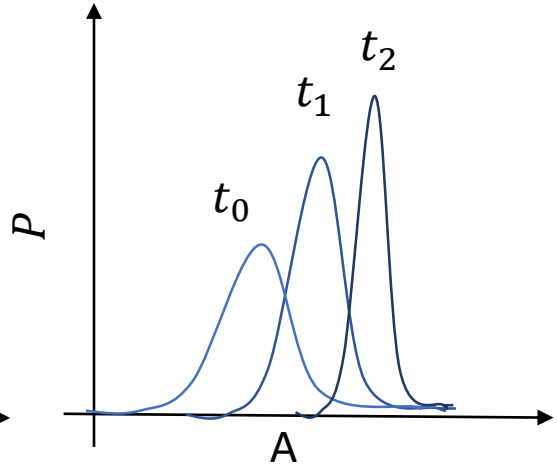
$A \rightarrow B$

$[A](t), [B](t)$ Deterministic description for the concentrations $[A]$ and $[B]$

$P(A, B, t)$ Probability for number of molecules A, B at a time t







Chemical Master Equation

Chemical master equation

Chemical master equation:

$$\frac{dP(\vec{X},t)}{dt} = \sum_{j=1}^{M} a_j(\vec{X} - \vec{s}_j)P(\vec{X} - \vec{s}_j, t) - P(\vec{X},t)\sum_{j=1}^{M} a_j(\vec{X})$$

$\vec{X} \quad (X_1, X_2 \dots)$	Vector describing the state of the system
$\vec{s}_j$	Transition vector, describing the state transition given a reaction
$a_j(\vec{X})$	Propensity: The probability per unit time reaction j happens
$P(\vec{X},t)$	Probability of the system to be in state $\vec{X}$

Chemical master equation

Transition probabilities:

- Probability to go from a state with X_i molecules of species to a state with X_k molecules of species. (**Changes occur according to stoichiometry of the reaction**.)

- Assume that **all molecules react independently** within a time interval dt with the **probability per time c_j**

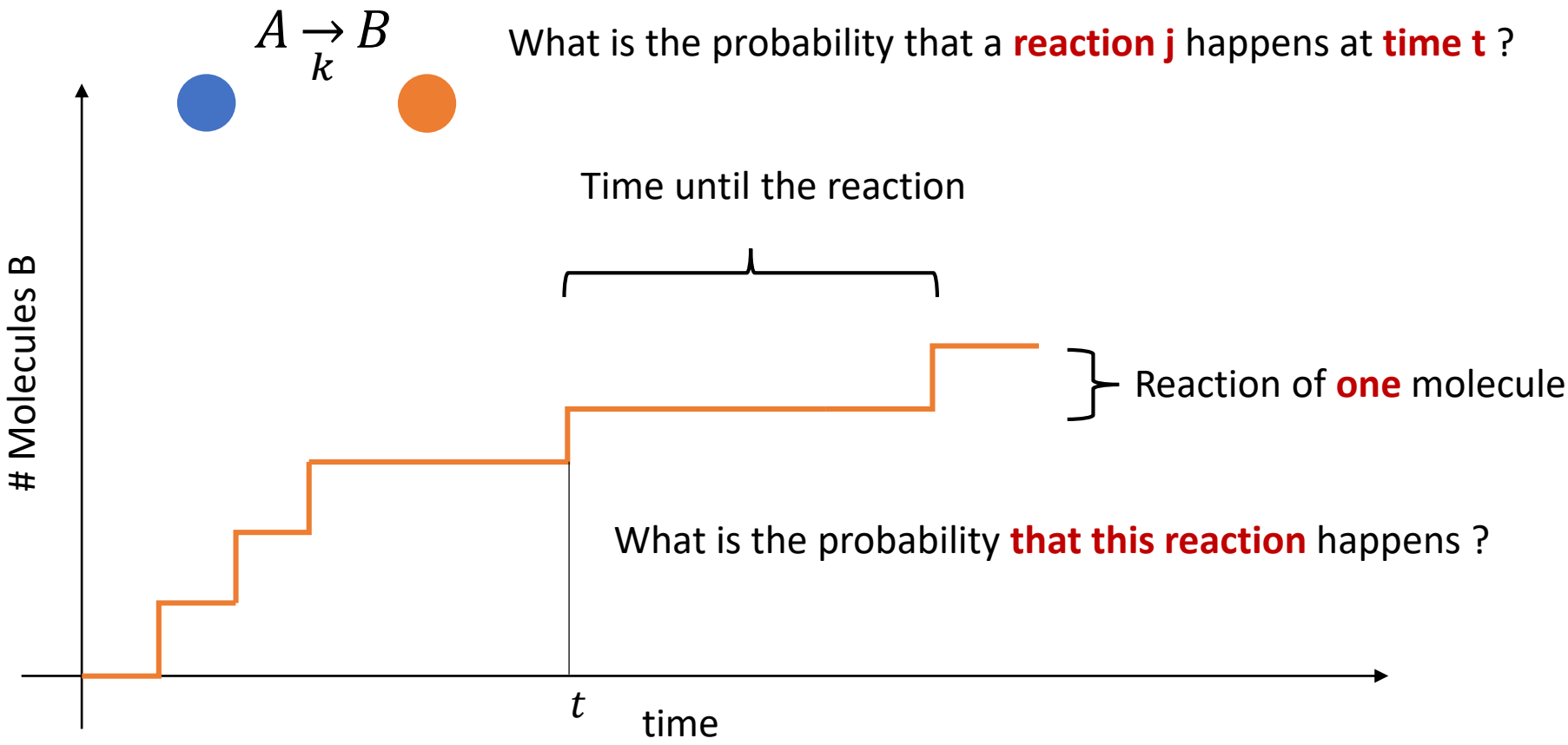
- Hence, the probability that one molecule reacts within an infinitesimal time interval dt is:

$$a_j\, dt = \sum_{i=1}^{n} c_j dt = n c_j dt \qquad \text{for} \qquad A \rightarrow B$$

with c_j reaction probability per time

Stochastic Simulation Algorithm

Stochastic Simulation Algorithm

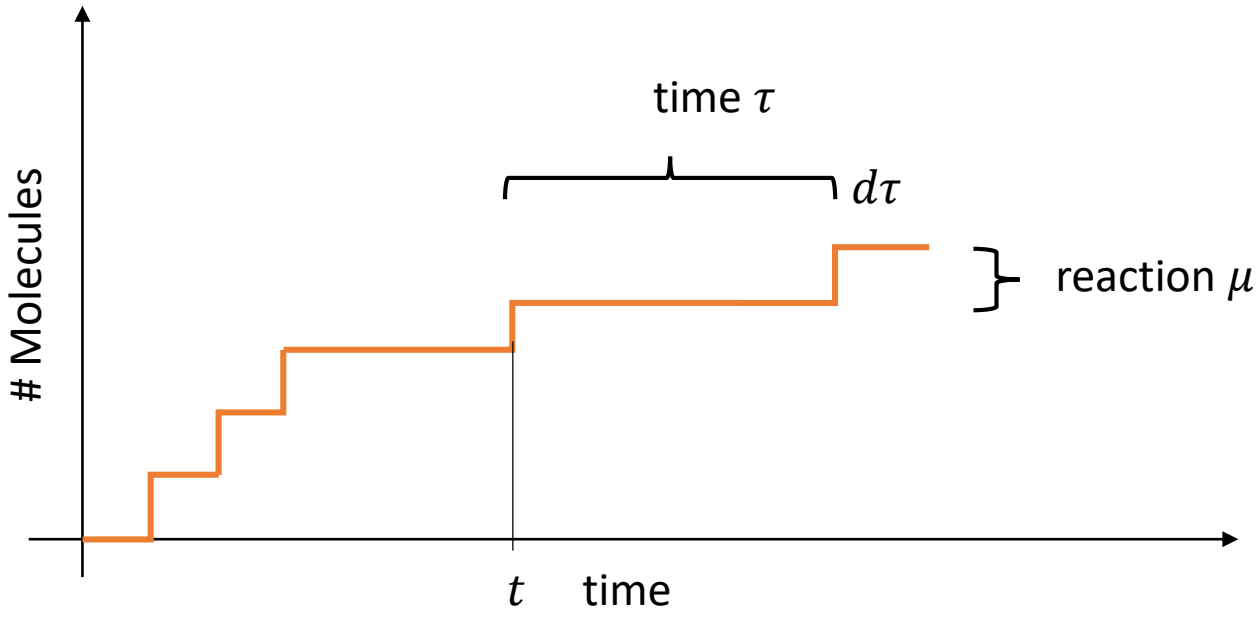


Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Derivation of the probability density function

Introduce the reaction probability density function: $\mathrm{P}(\tau, \mu)$

$\mathrm{P}(\tau, \mu)d\tau =$ Probablity that, given the state $(X_1, \ldots, X_N)$ at time t, the next reaction μ in V will occur in the time interval $[t + \tau, t + \tau + d\tau]$



Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Derivation of the probability density function

Consider a system:

With the states as the number of molecules: $(X_1, X_2, \dots)$

These molecules participate in M reactions R_μ

From the master equation we have the transition probability for a single molecule as:

$a_\mu \, d\tau$ = Probablity that the reaction R_μ will occur in a volume V within the time interval $(t, t + d\tau)$, given that the system is in the state $(X_1, X_2, \dots)$ at time t $(\mu = 1, \dots M)$

We calculate $\mathrm{P}(\tau, \mu)d\tau$ as product of the probability **that no reaction occurs** within the time interval $(t, t + \tau)$ and **that the reaction μ occurs within** $(t, t + \tau + d\tau)$

$$\mathrm{P}(\tau, \mu)d\tau = P_0(\tau) \times a_\mu d\tau$$

Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

The probability that no reaction occurs within the time interval $(t', t' + \tau' + d\tau)$ is

$$P_0(\tau' + d\tau') = P_0(\tau')\left[1 - \underbrace{\sum_{\nu}^{M} a_\nu \, d\tau'}\right]$$

probability that one reaction occurs

$$P_0(\tau) = \exp\left(-\sum_{\nu}^{M} a_\nu \, \tau\right)$$

$$P(\tau, \mu) = a_\mu \exp\left(-\sum_{\nu}^{M} a_\nu \, \tau\right)$$

Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

Python:

OPEN ACCESS Freely available online

PLOS ONE

StochPy: A Comprehensive, User-Friendly Tool for Simulating Stochastic Biological Processes

Timo R. Maarleveld[1,2,3], Brett G. Olivier[1], Frank J. Bruggeman[1,4]*

1 Systems Bioinformatics, Amsterdam Institute for Molecules Medicines and Systems, VU University Amsterdam, Amsterdam, The Netherlands, **2** Life Sciences, Centrum Wiskunde & Informatica, Amsterdam, The Netherlands, **3** BioSolar Cells, Wageningen, The Netherlands, **4** Kluyver Centre for Genomics of Industrial Fermentation, Delft, The Netherlands

http://stochpy.sourceforge.net/html/userguide_doc.html

MATLAB®:

https://ch.mathworks.com/matlabcentral/fileexchange/34707-gillespie-stochastic-simulation-algorithm

It's a noisy business!

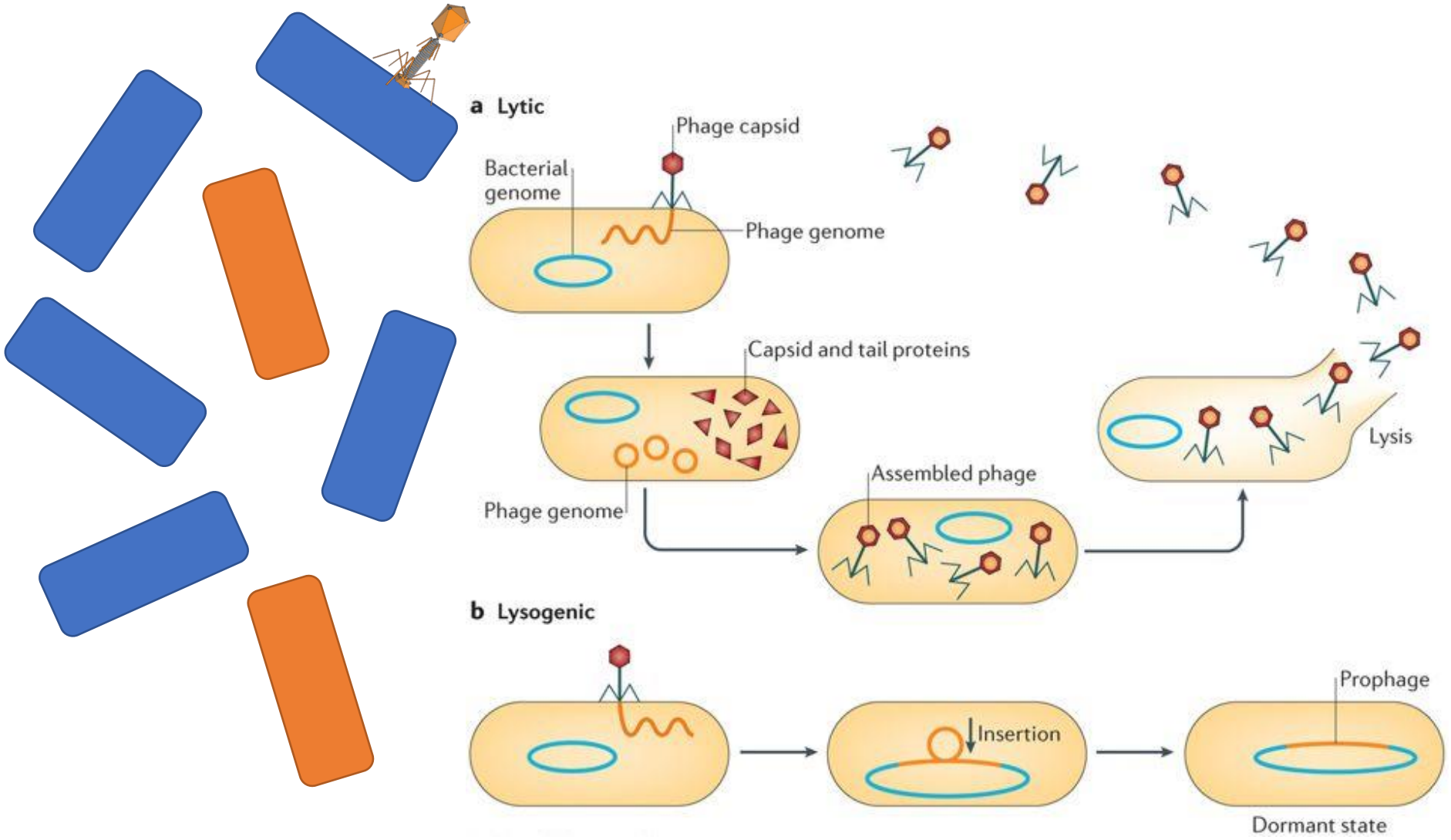
Genetic regulation at the nanomolar scale

Many molecules that control genetic regulatory circuits act at extremely low intracellular concentrations. Resultant fluctuations (noise) in reaction rates cause large random variation in rates of development, morphology and the instantaneous concentration of each molecular species in each cell. To achieve regulatory reliability in spite of this noise, cells use redundancy in genes as well as redundancy and extensive feedback in regulatory pathways. However, some regulatory mechanisms exploit this noise to randomize outcomes where variability is advantageous.

Application of stochastic models

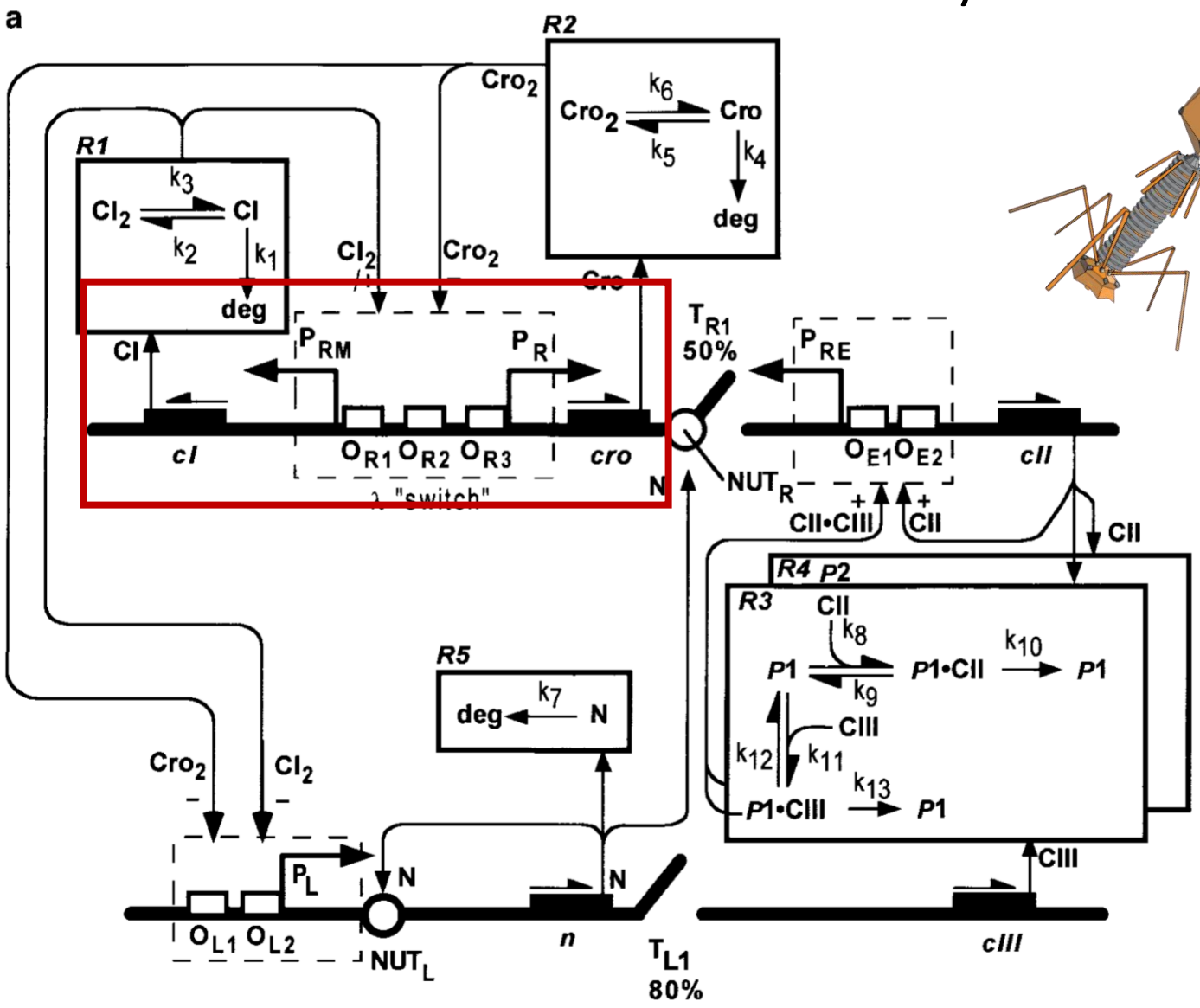
… a noisy business

Bi-stable circuits to create diversity



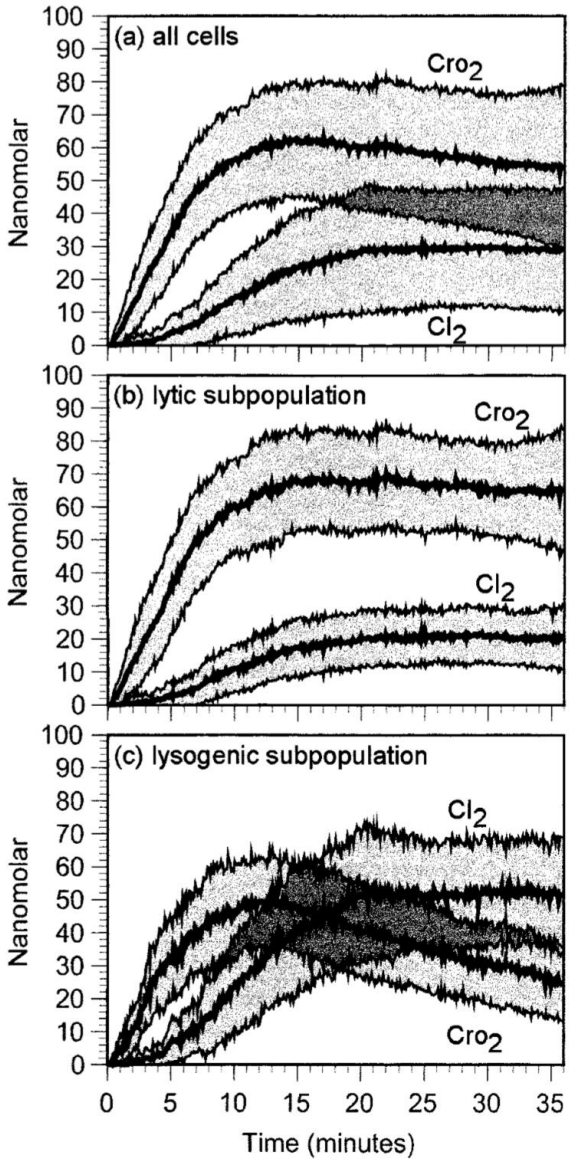
Arkin, A., Ross, J. and McAdams, H.H., 1998. *Genetics*, *149*(4), pp.1633-1648.
Feiner, R., Argov, T., Rabinovich, L., Sigal, N., Borovok, I. and Herskovits, A.A., 2015. *Nature Reviews Microbiology*, *13*(10), pp.641-650.

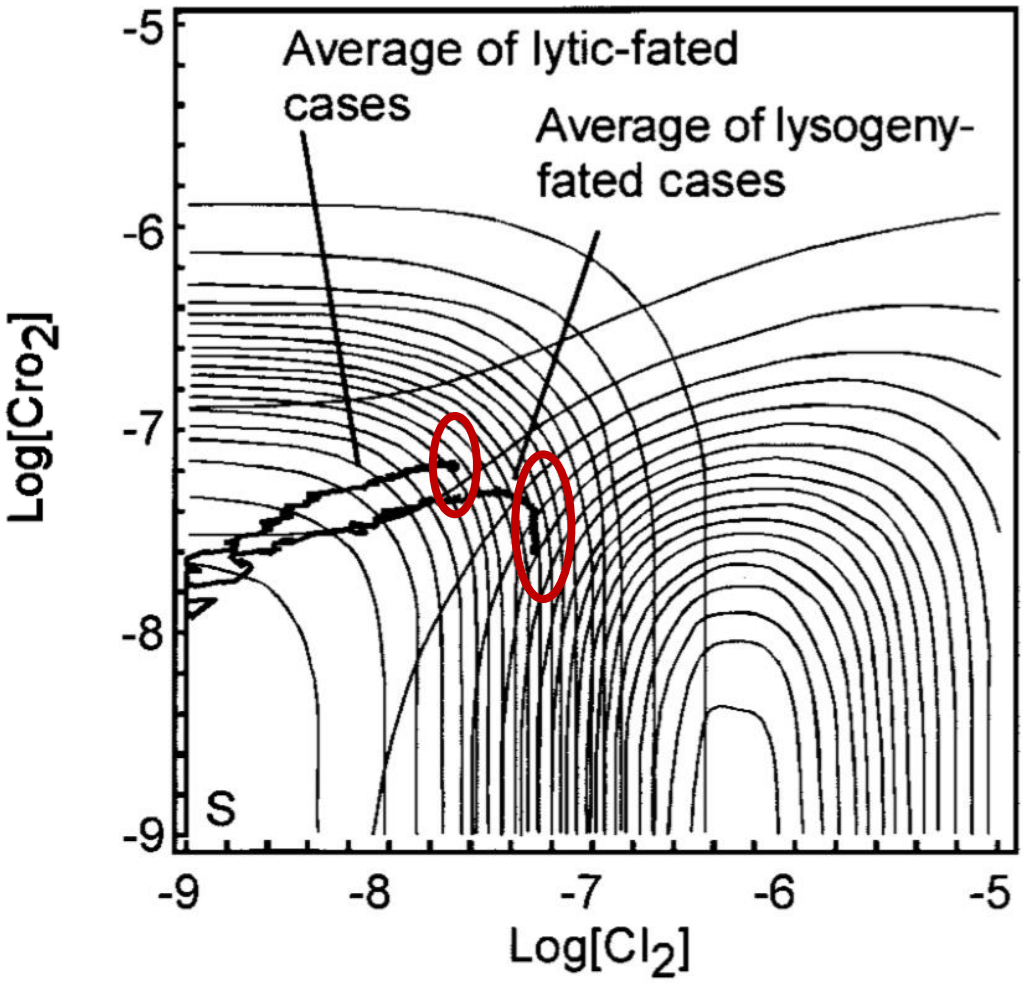
Bi-stable circuits to create diversity



Arkin, A., Ross, J. and McAdams, H.H., 1998. *Genetics*, *149*(4), pp.1633-1648.

Bi-stable circuits to create diversity





Molecular particle models

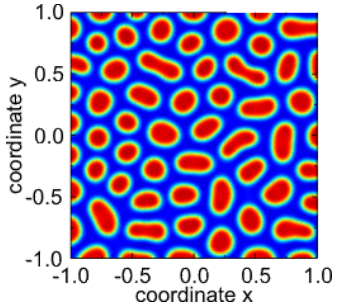
Molecular particle models

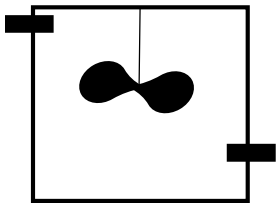
Time scale

Length scale

Spatial deterministic models:

- Many molecules
- Locally well mixed

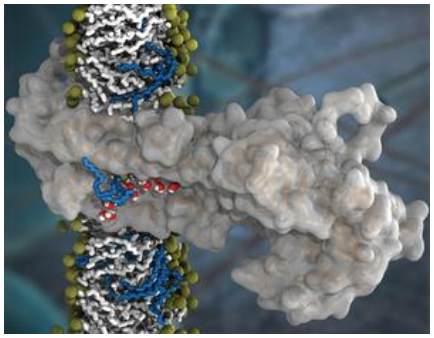




Deterministic models:

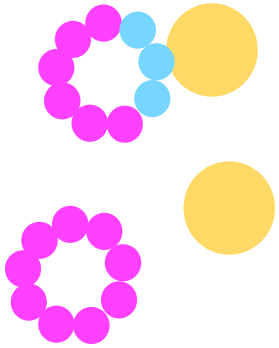
- Many molecules
- well mixed

Vestergaard, Anna L., et al. *PNAS* 111.14 (2014)



Molecular dynamics

- Classical physics
- Interaction via forces



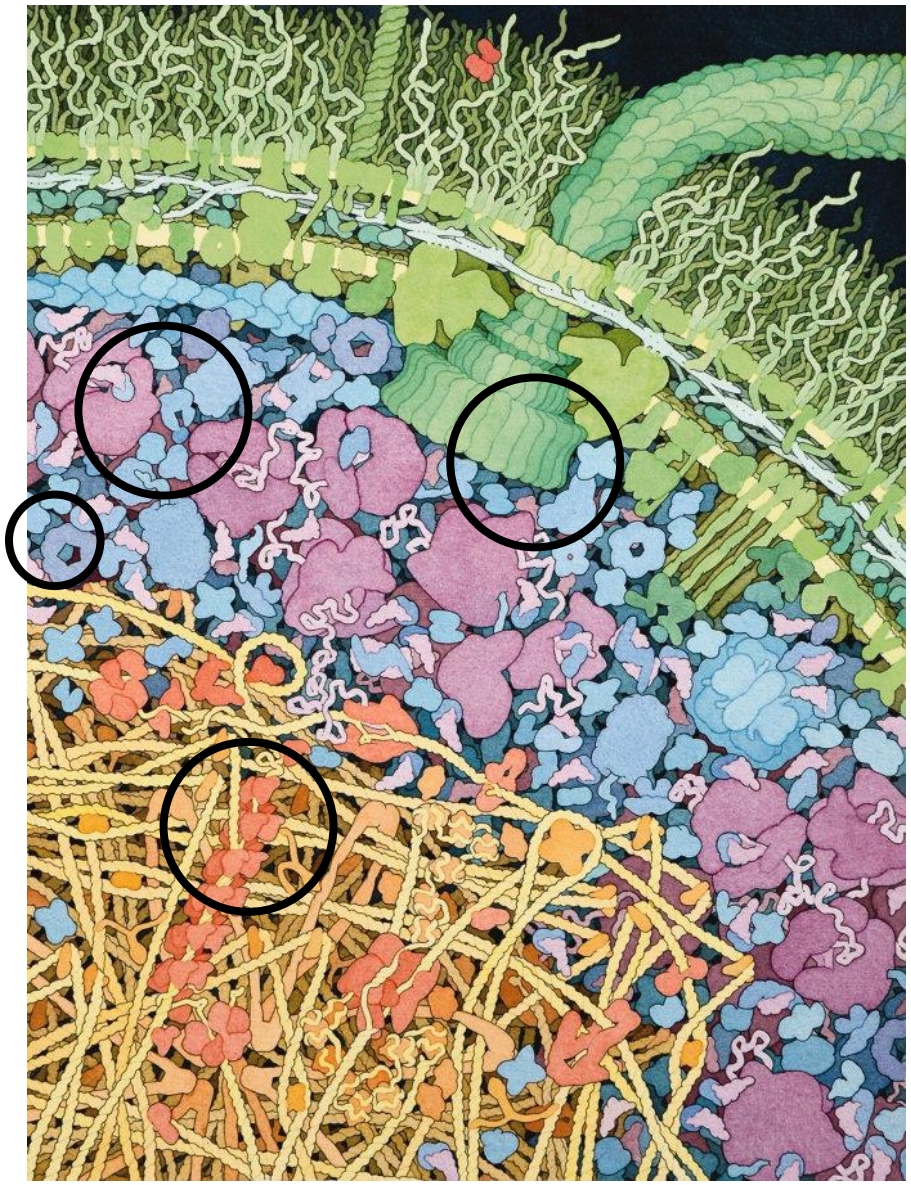
Particle reaction diffusion:

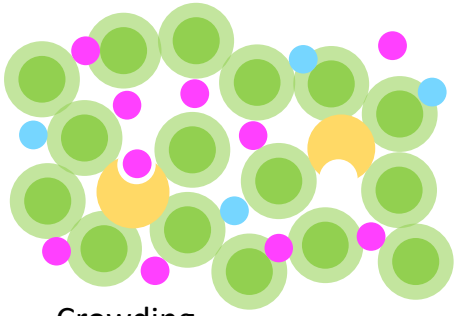
- Particles as spheres
- Reaction upon collision

Stochastic models:

- well mixed
- Little number molecules

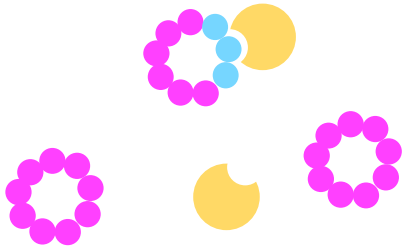
Molecular particle models

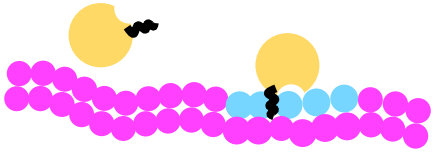




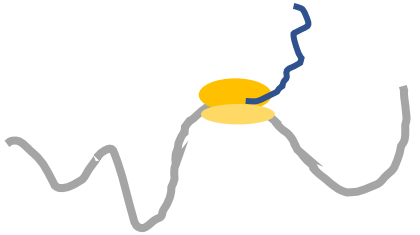
Crowding

Micelles, Liposomes





Membranes

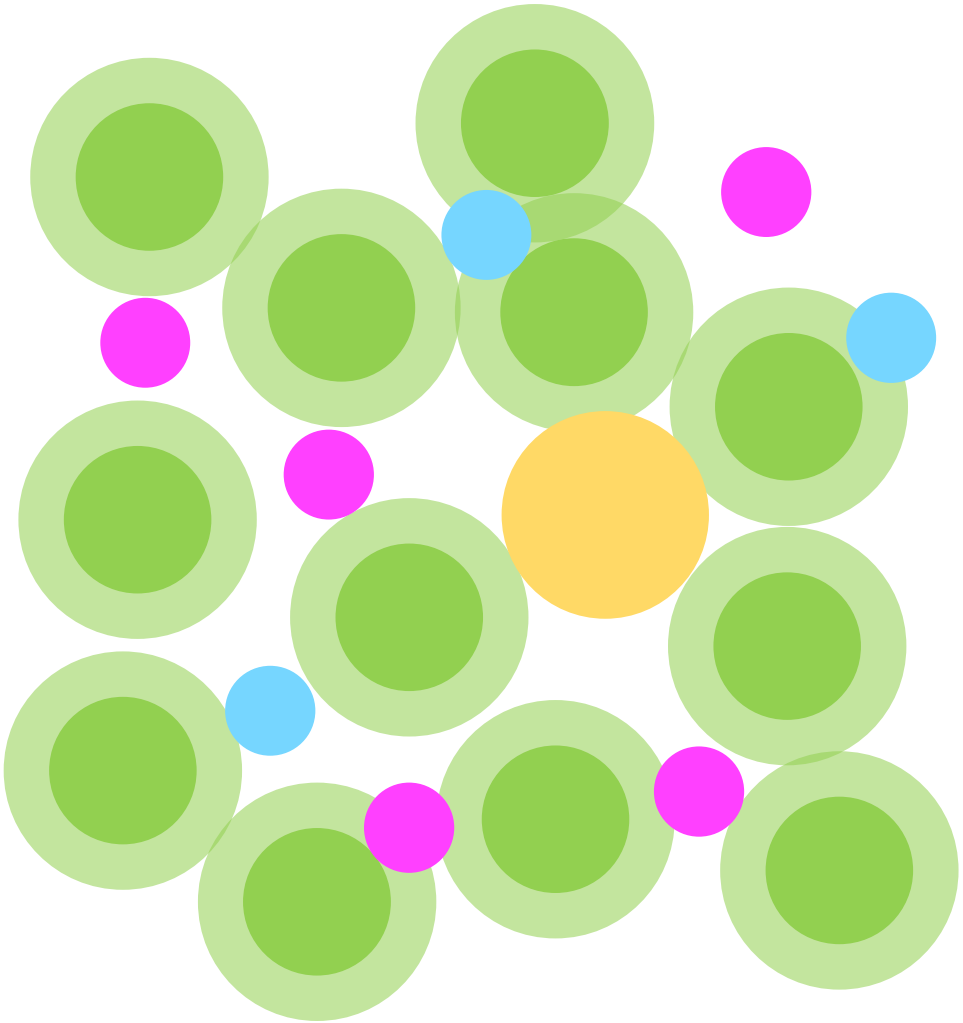


DNA

Goodsell, D.S., *Biochemistry and Molecular Biology Education*, **2009**. 37(6)

Molecular particle models

Why use molecular particle models?



Key assumption for mass-action kinetics:

- ~~Well mixed system~~
- ~~Free diffusion (3D collisions)~~

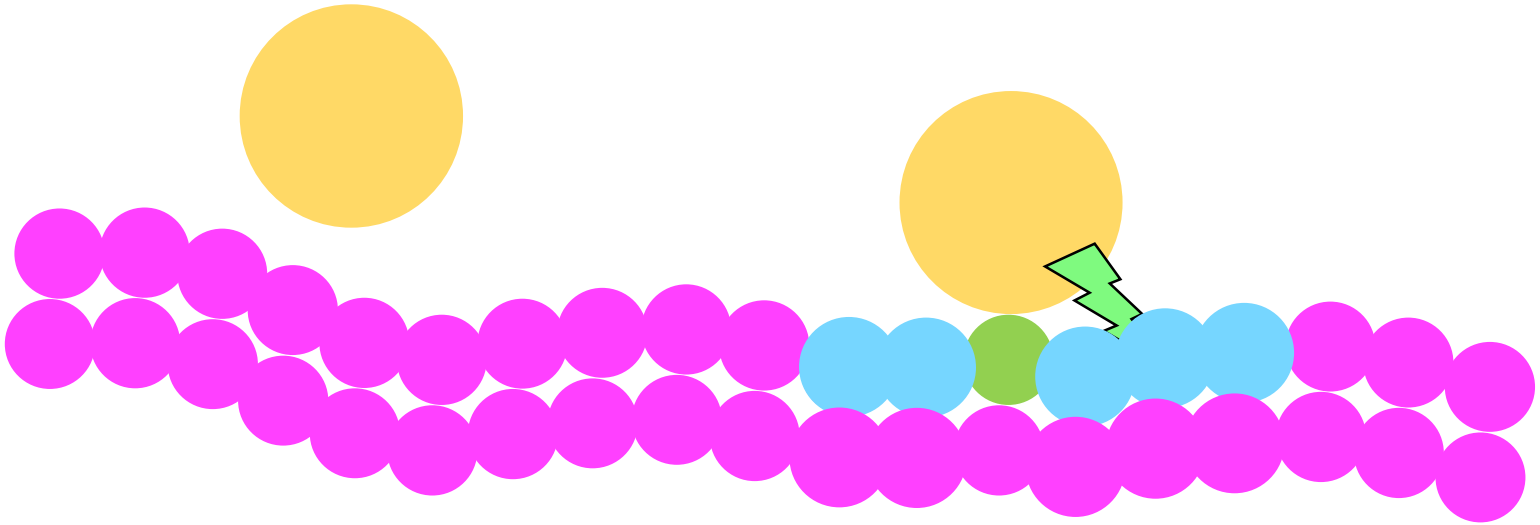
Large molecule that does not participate in the reaction (crowding agent)

Molecular particle models

Why use molecular particle models?

Key assumption for mass-action kinetics:

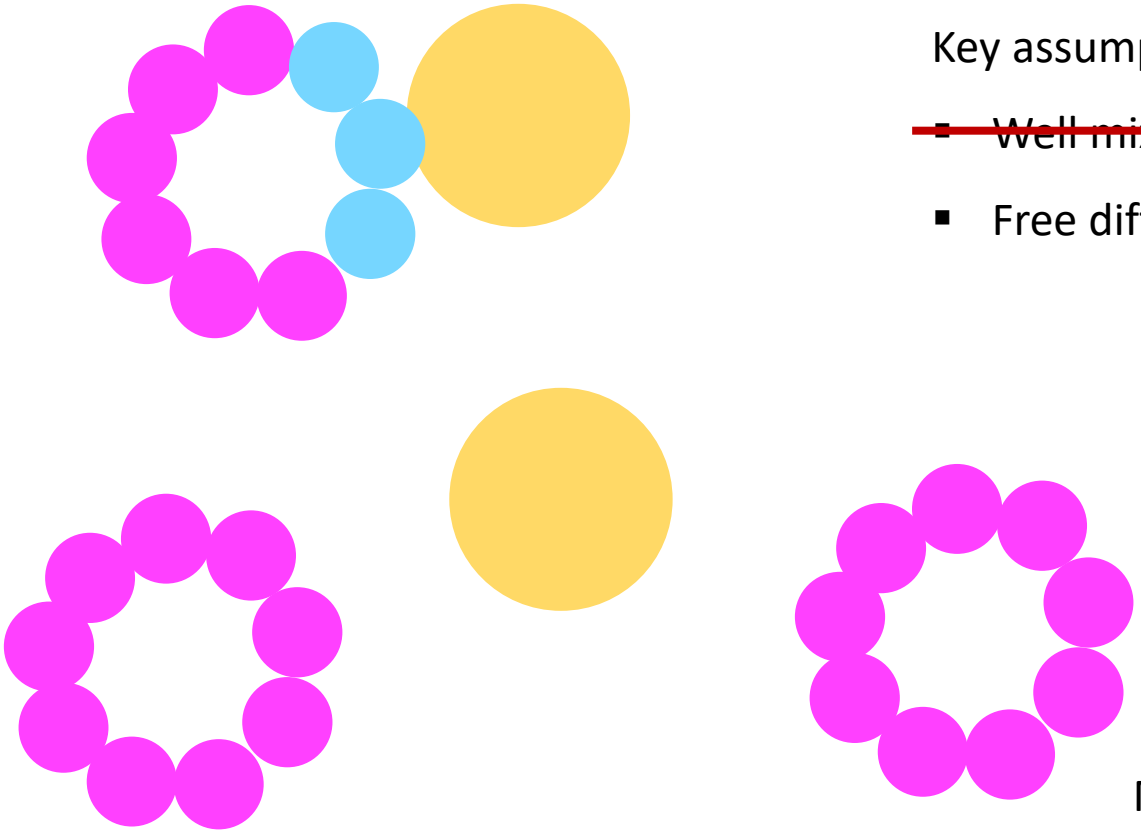
- Well mixed system
- ~~Free diffusion (3D collisions)~~



Lipid Bilayer

Molecular particle models

Why use molecular particle models?



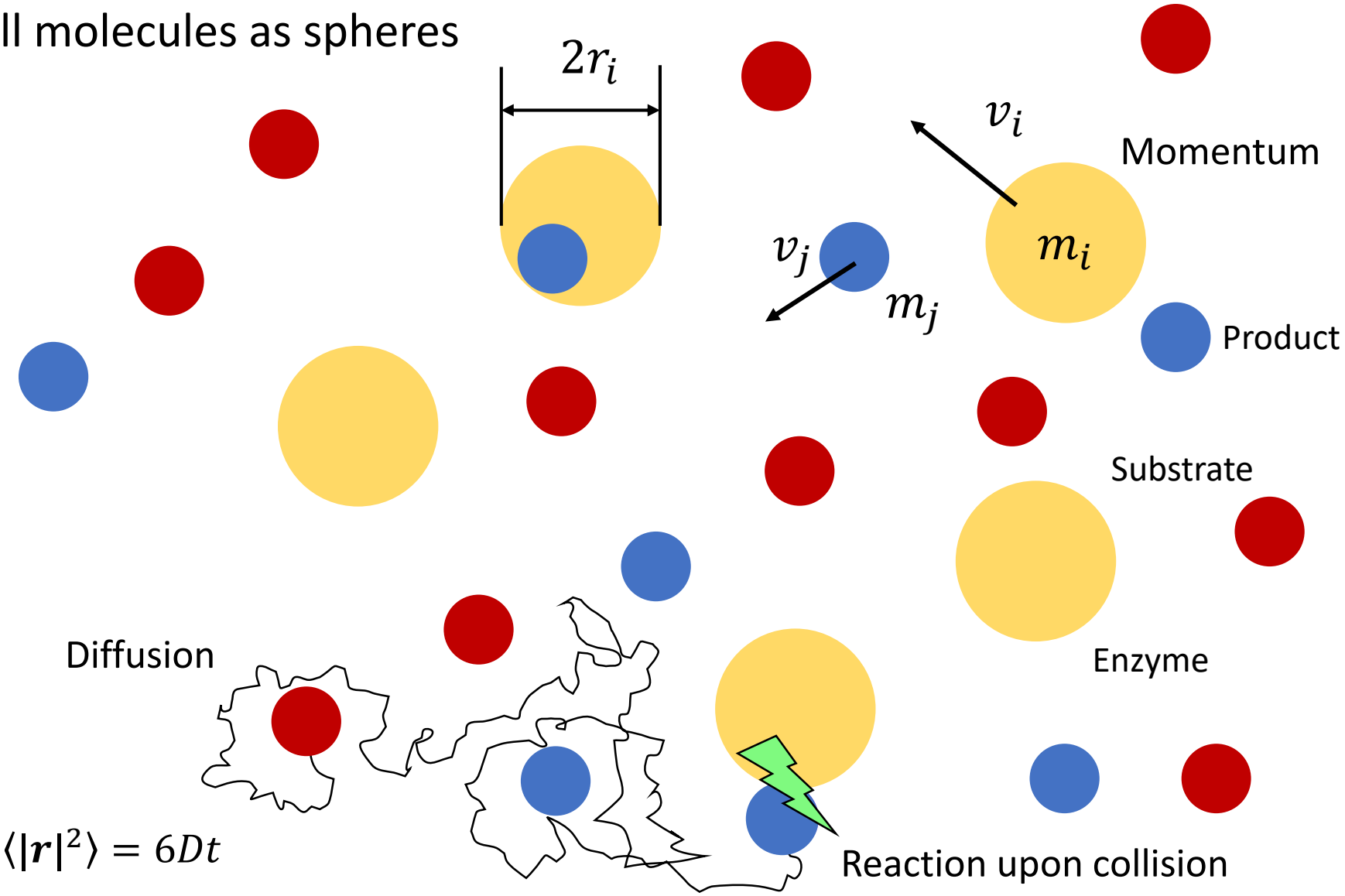
Key assumption for mass-action kinetics:

- ~~Well mixed system~~
- Free diffusion (3D collisions)

Micelles, or lipid droplets

Particle model

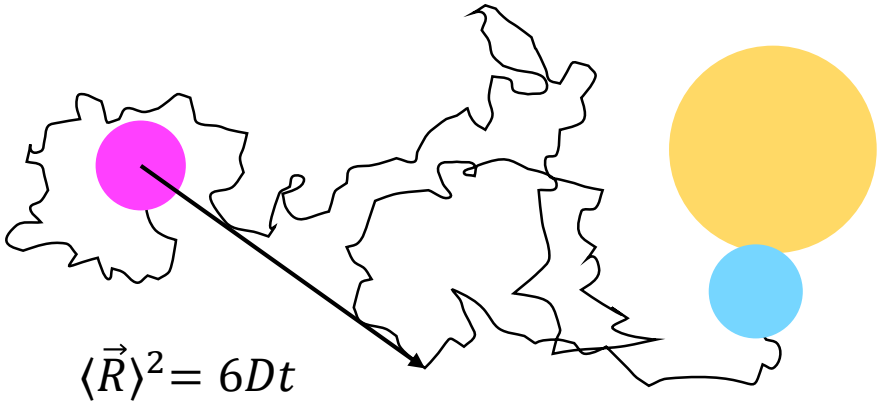
All molecules as spheres

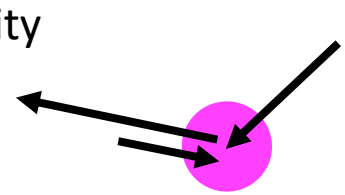


Diffusion

Brownian motion:

The random motion of a particle
in a viscous medium
(microscopic definition of diffusion)





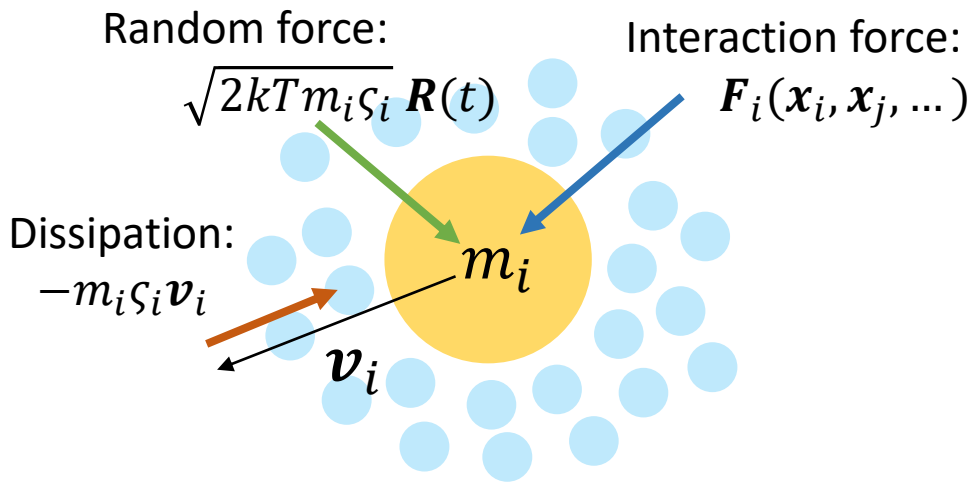
Relation between collision forces
and drag force is the diffusion coefficient
D

Diffusion

Brownian dynamics

$$\frac{d\boldsymbol{x}_i}{dt} = \boldsymbol{F}_i(\boldsymbol{x}_i, \boldsymbol{x}_j, \dots)\frac{k_B T}{D_i} - \sqrt{2D_i}\boldsymbol{R}(t)$$

$$D_i = \frac{k_B T}{m_i \varsigma_i} \quad \frac{\text{Thermal Exitiation}}{\text{Local dissipation}}$$



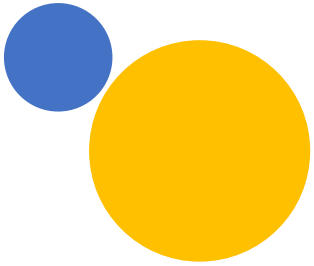
[3] A. Brünger et al., 1984, 105 (5) 495-500.

Enzyme Substrate binding

Unsuccessful collision

Successful collision

Only a part of the collisions is successful



How do can we account for this?

Enzyme Substrate binding

a) Monte Carlo Step for the reaction

$$p \leq 1 - e^{\frac{k_{micro}\Delta t}{C(\Delta t, D_{ij}, R_{ij})}}$$

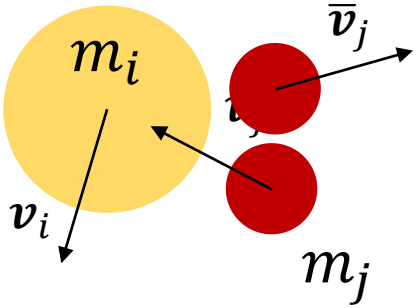
k_{micro} transition rate in contact

$C(\Delta t, D_{ij}, R_{ij})$ Correction factor for all possible contacts in Δt

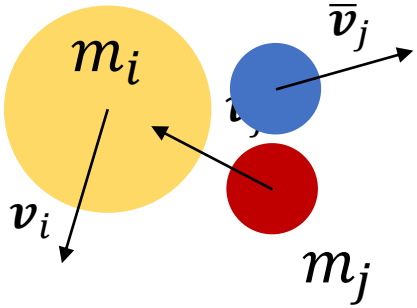
b) Momentum conserving collision in case unsuccessful:

$$\boldsymbol{v}_i m_i + \boldsymbol{v}_j m_j = \bar{\boldsymbol{v}}_i m_i + \bar{\boldsymbol{v}}_j m_j$$
$$\boldsymbol{v}_i^2 m_i + \boldsymbol{v}_j^2 m_j = \bar{\boldsymbol{v}}_i^2 m_i + \bar{\boldsymbol{v}}_j^2 m_j$$

b)



a) + b)



Application: Macromolecular Crowding in enzyme kinetics

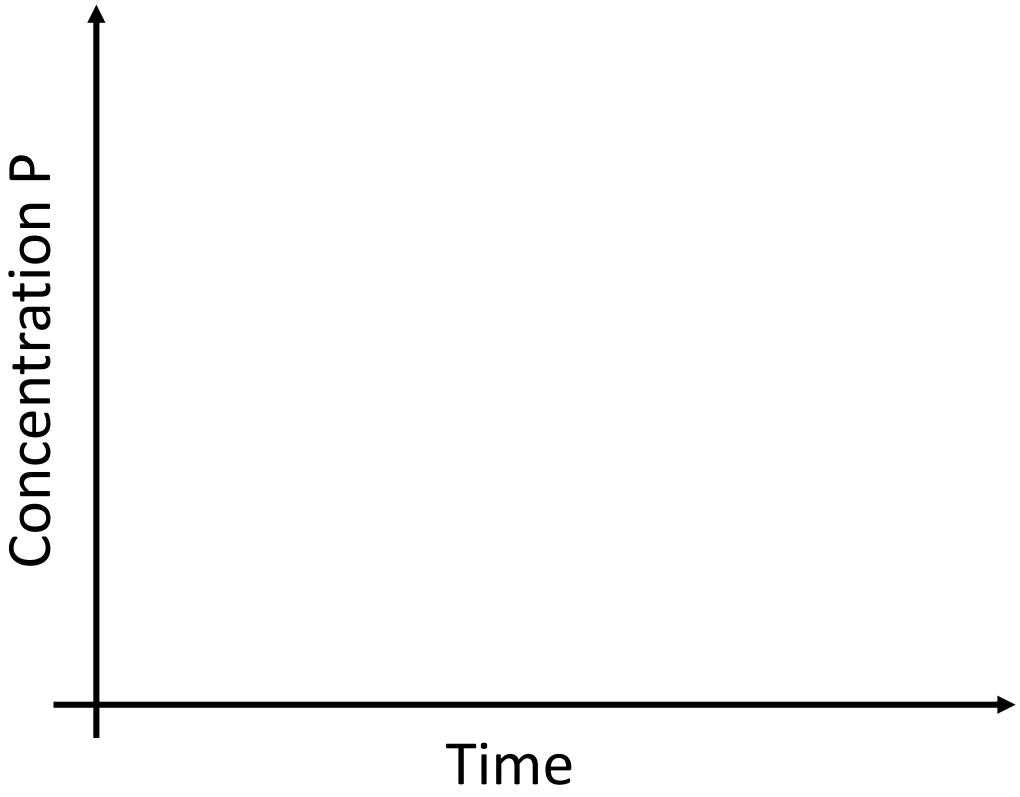
Enzyme kinetics

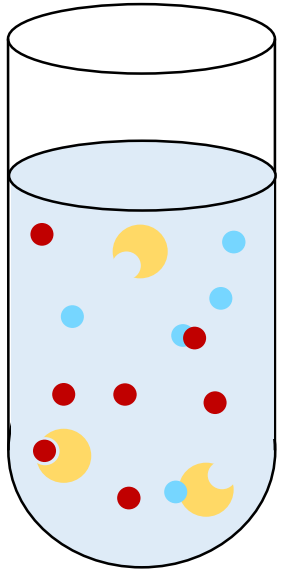
Phosphoglycerate isomerase

Glycerate-3-phosphate ⟶ Glycerate-2-phosphate

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Initial rate experiment





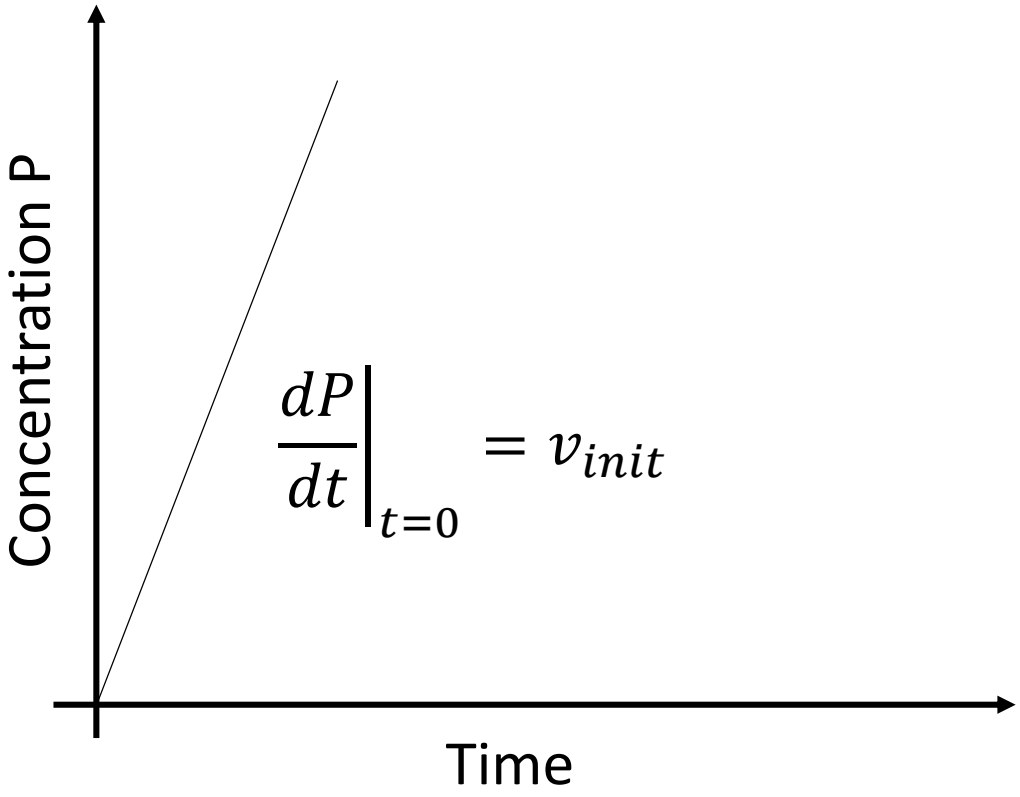
Enzyme kinetics

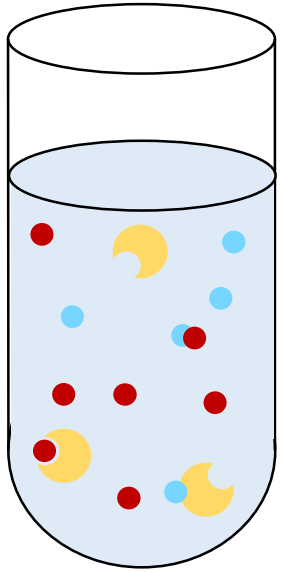
Phosphoglycerate isomerase

Glycerate-3-phosphate ⟶ Glycerate-2-phosphate

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Initial rate experiment





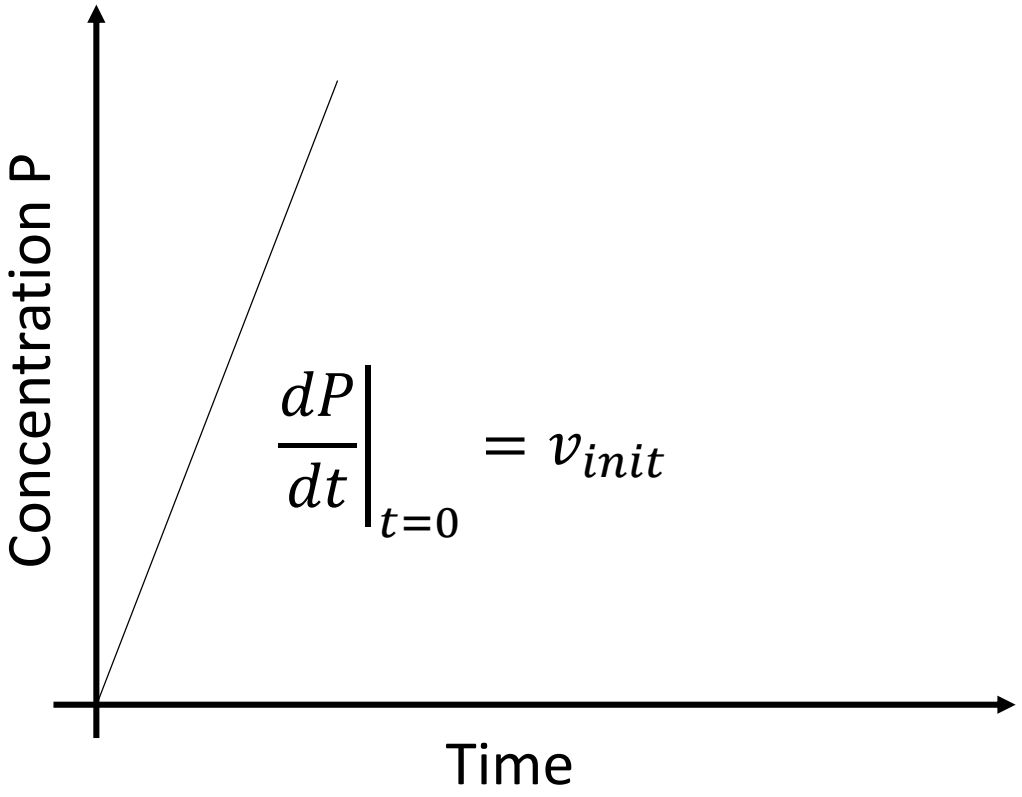
Enzyme kinetics

Phosphoglycerate isomerase

Glycerate-3-phosphate ⟶ Glycerate-2-phosphate

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Initial rate experiment



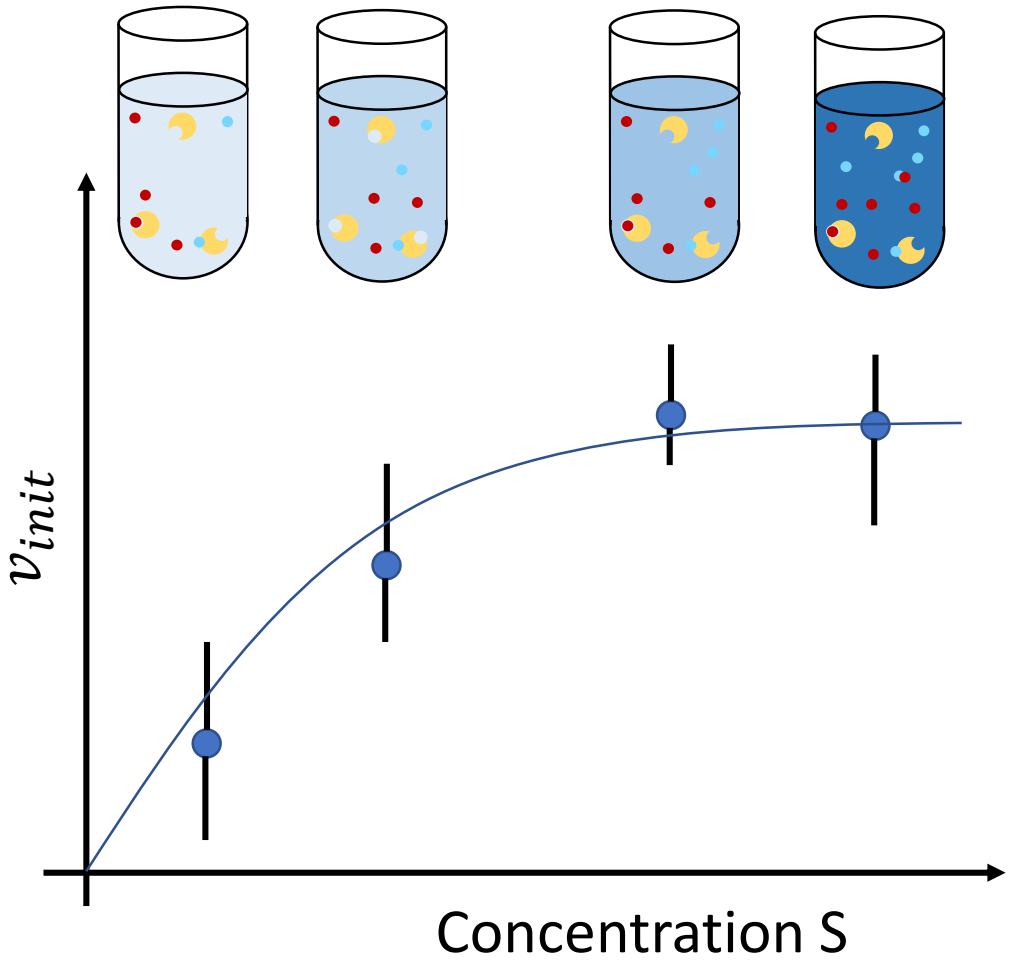
Increasing substrate concentration

Enzyme kinetics

Phosphoglycerate isomerase

Glycerate-3-phosphate ⟶ Glycerate-2-phosphate

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$



$$v = V_{max} \frac{\frac{S}{K_{M,S}}\left(1 - \frac{1}{K_{eq}}\frac{P}{S}\right)}{1 + \frac{S}{K_{M,S}} + \frac{P}{K_{M,P}}}$$

for $[P] = 0$

Introduce in vitro measured parameters?

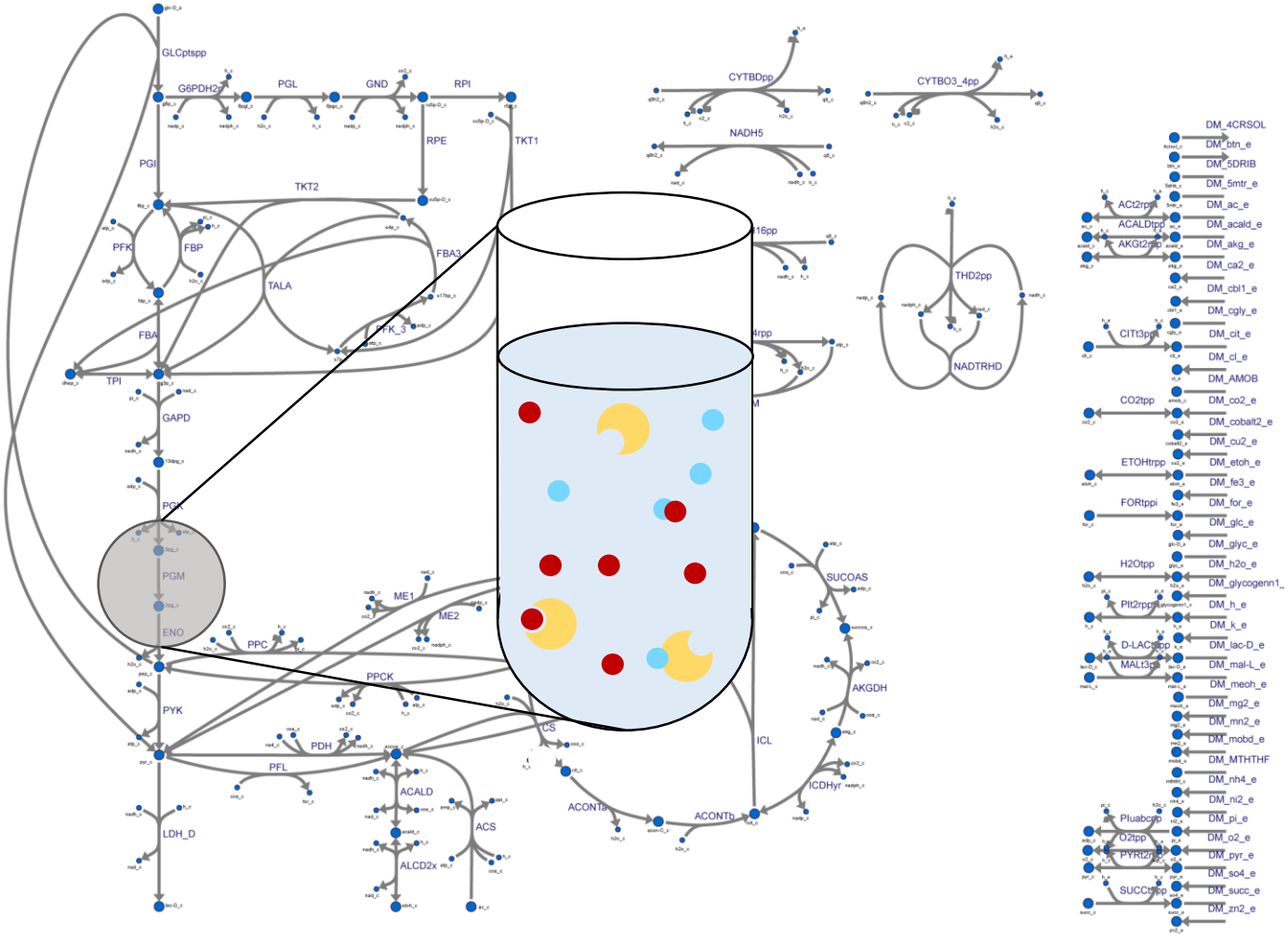
$$\frac{d\boldsymbol{x}}{dt} = N\,\boldsymbol{v}(\boldsymbol{x},\boldsymbol{p})$$

$\boldsymbol{x}$ Concentrations

$\boldsymbol{v}$ Enzyme fluxes

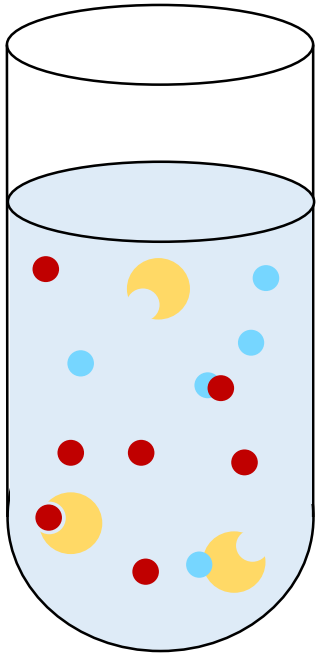
N Stoichiometry

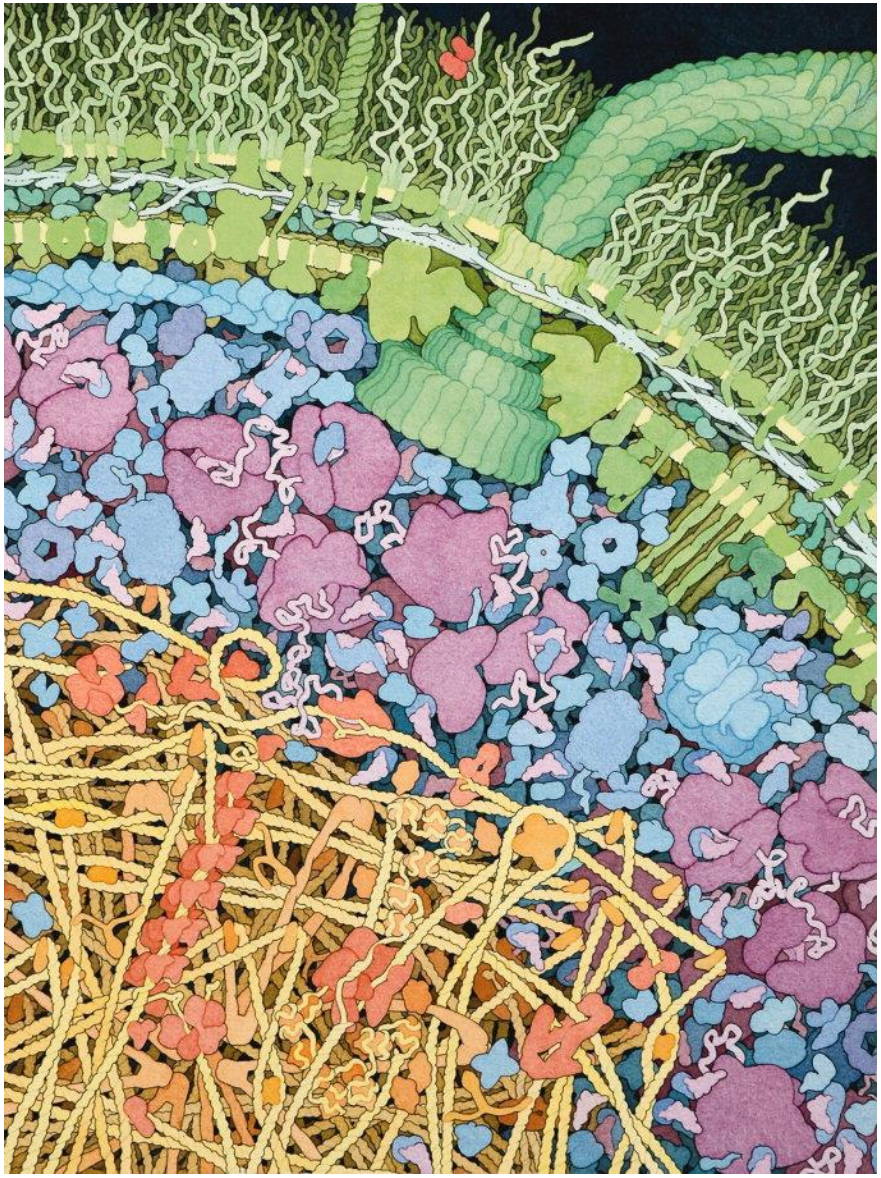
$\boldsymbol{p}$ Parameters



In vivo environment

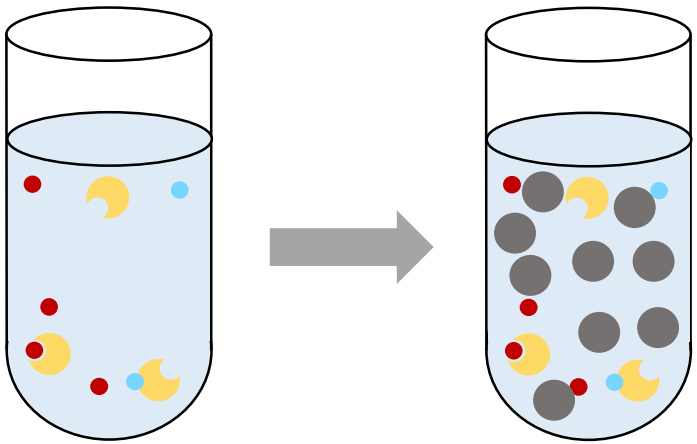
$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

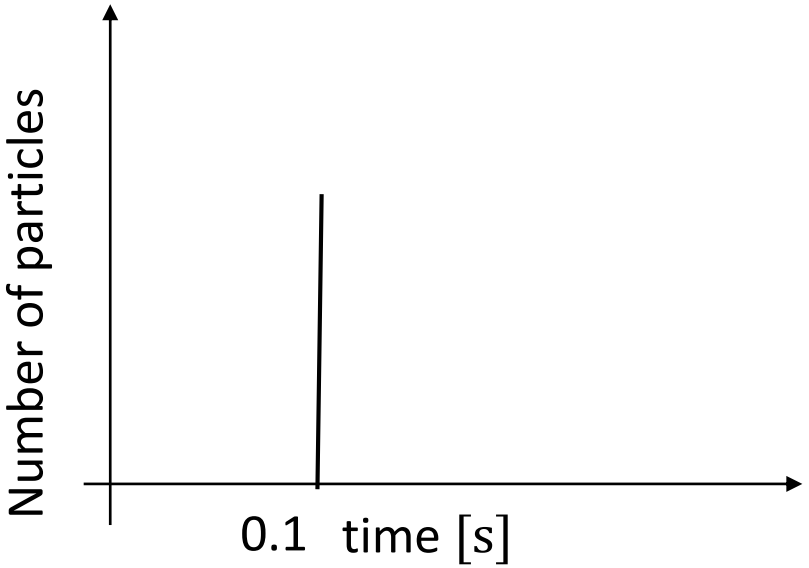




Goodsell, D.S., *Biochemistry and Molecular Biology Education*, **2009**. 37(6)

Timescale differences

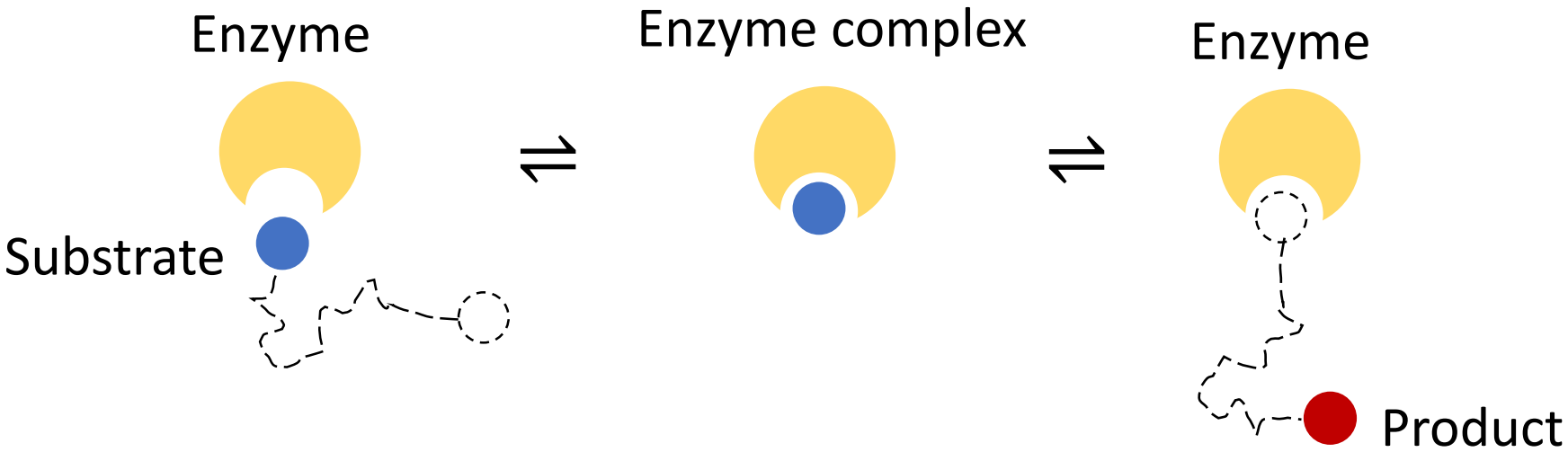




- Time scales for metabolic reactions 0.1 s
  Collision time scales 1 ns

- Large molecule numbers – **Stochastic effects negligible**

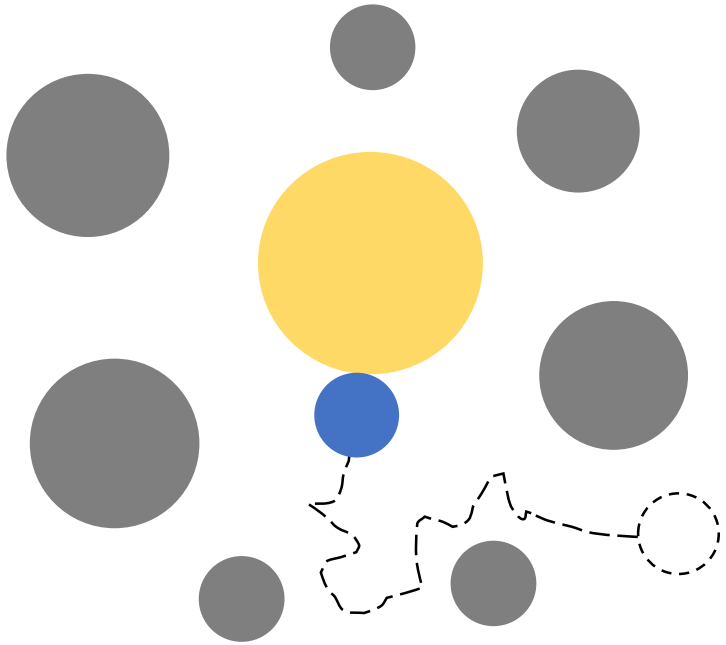
Crowded enzyme kinetics



$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Crowded enzyme kinetics

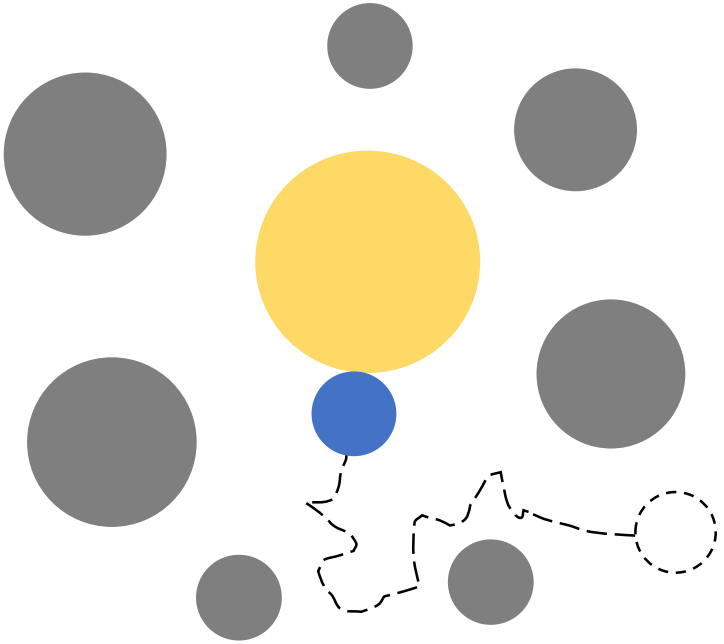
Altered collision dynamics



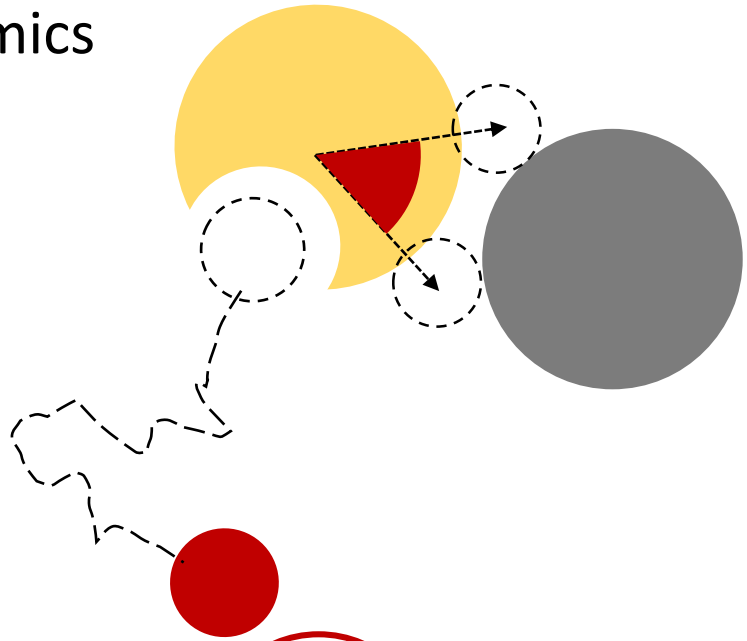
$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Crowded enzyme kinetics

Altered collision dynamics



Altered dissociation dynamics

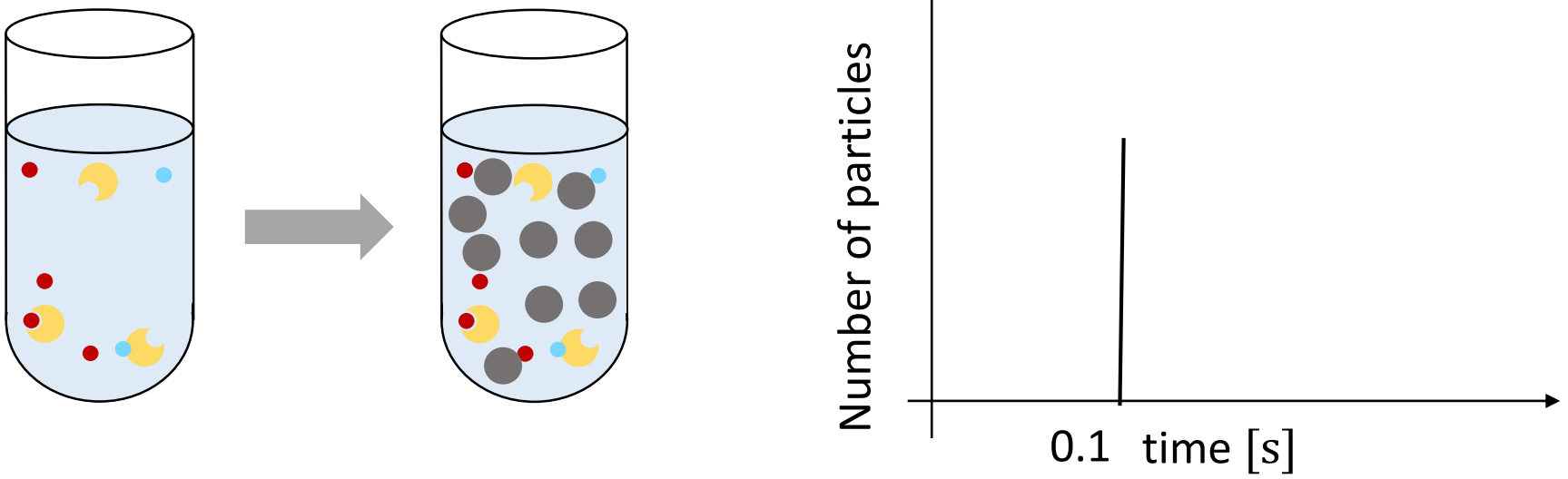


$k_{1,f}$ $k_{2,f}$

$$S + E \rightleftharpoons ES \rightleftharpoons E + P$$

Change in effective rate constant

Timescale differences



- Relaxation time metabolic reactions ≈ 0.1 s
- Average time of substrate and enzyme collisions ≈1 ns

- For metabolism **mean changes are of interest** due to large molecule number

Modeling the average effects

Ordinary differential equations (ODEs) that account for the **average crowding effects**!

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

CORRECTED DUE TO CROWDING

$$k_{j,eff}(\boldsymbol{X}, \phi) = k_{i,0} e^{\beta_j} \prod_{i=1}^{M} \left(\frac{[X_i]}{[X_i]_{ref}} \right)^{\alpha_{i,j}}$$

Savageau, M. A. 1969. *Journal of theoretical biology* **25**(3):370-379.
Savageau, M. A. 1970. *Journal of theoretical biology* **26**(2):215-226.

Elementary rate constants

… **effective** functions of concentrations due to crowding

$$\mathrm{S} + \mathrm{E} \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} \mathrm{ES} \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} \mathrm{E} + \mathrm{P}$$

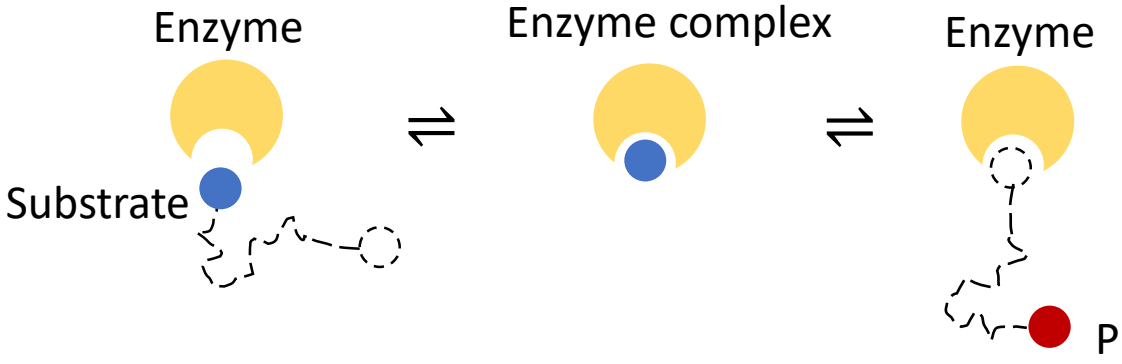
$$\frac{d[P]}{dt} = v_{2,f} - v_{2,v}$$

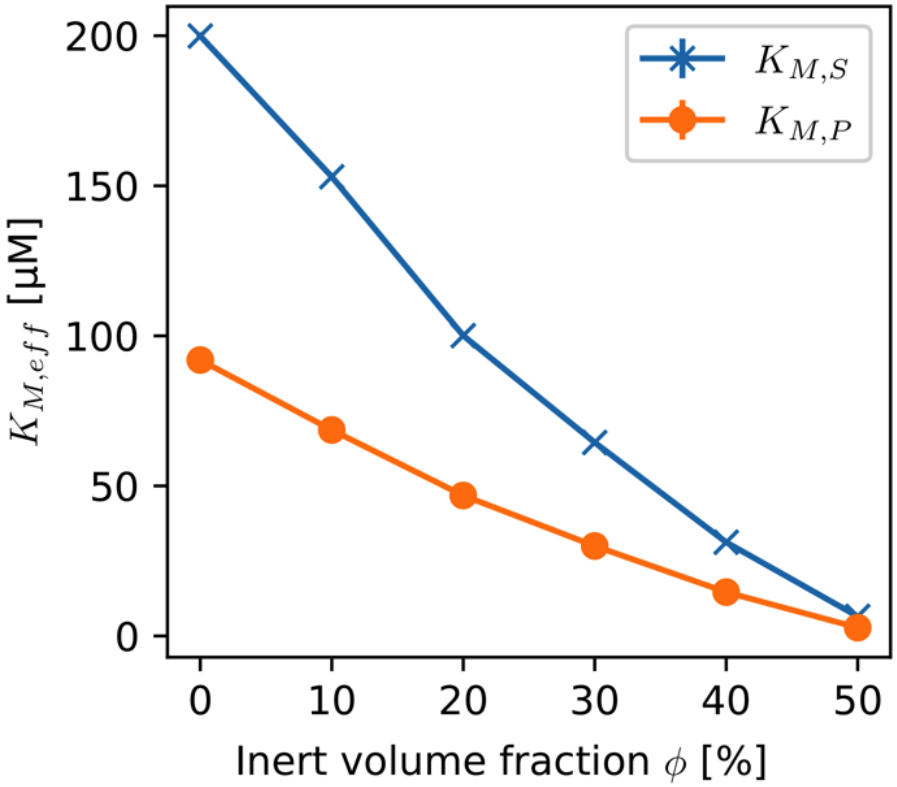
$$= k_{2,f}[ES] - k_{2,b}[E][P]$$

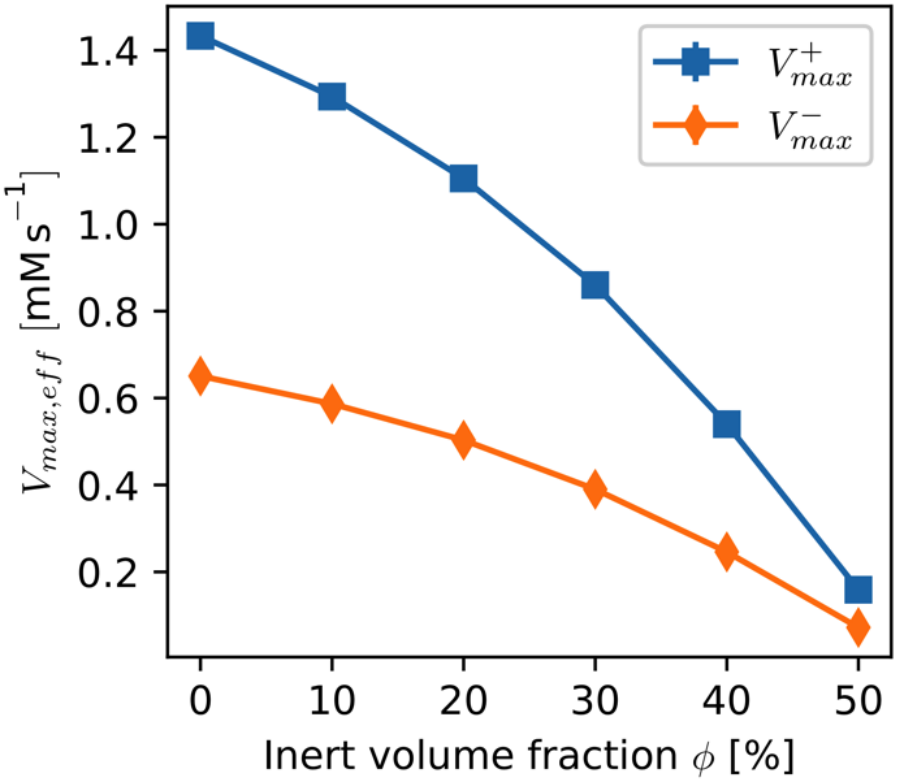
$$= \left\{ k_{2,f,0} \exp \beta_j \left(\frac{[\mathrm{ES}]}{[\mathrm{ES}]_0}\right)^{\alpha_{\mathrm{ES},2,f}} \left(\frac{[\mathrm{E}]}{[\mathrm{E}]_0}\right)^{\alpha_{\mathrm{E},2,f}} \left(\frac{[\mathrm{S}]}{[\mathrm{S}]_0}\right)^{\alpha_{\mathrm{S},2,f}} \left(\frac{[\mathrm{P}]}{[\mathrm{P}]_0}\right)^{\alpha_{\mathrm{P},2,f}} \right\} [ES]$$

$$- \left\{ k_{2,b,0} \exp \beta_j \left(\frac{[\mathrm{ES}]}{[\mathrm{ES}]_0}\right)^{\alpha_{\mathrm{ES},2,b}} \left(\frac{[\mathrm{E}]}{[\mathrm{E}]_0}\right)^{\alpha_{\mathrm{E},2,b}} \left(\frac{[\mathrm{S}]}{[\mathrm{S}]_0}\right)^{\alpha_{\mathrm{S},2,b}} \left(\frac{[\mathrm{P}]}{[\mathrm{P}]_0}\right)^{\alpha_{\mathrm{P},2,f}} \right\} [E][P]$$

Effect of CROWDING on *in vivo* Kinetics

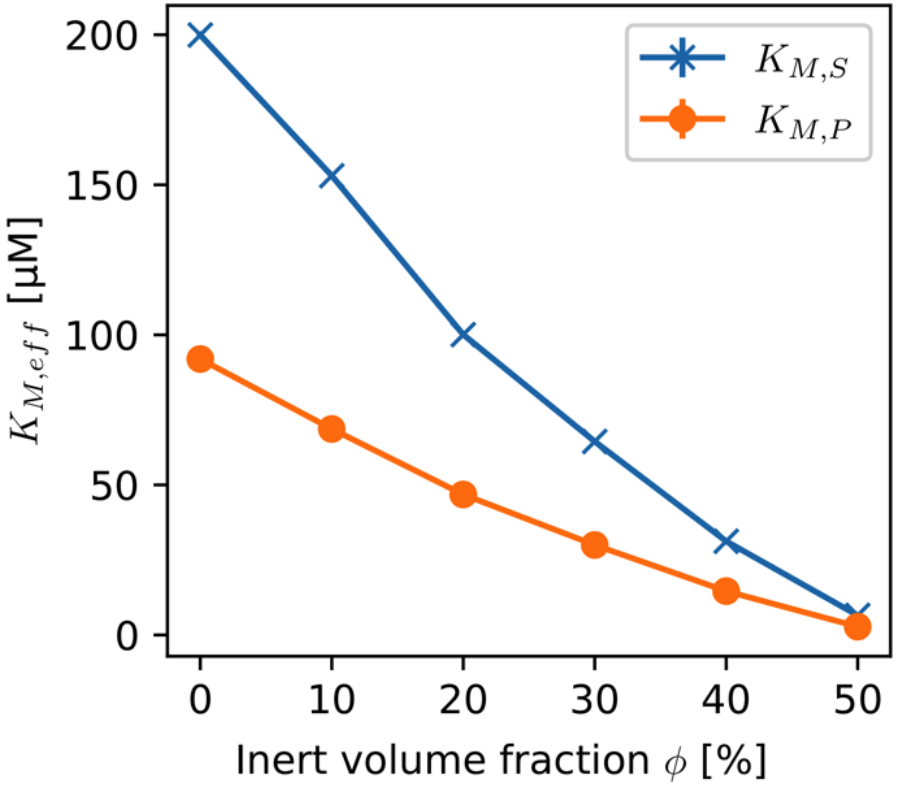


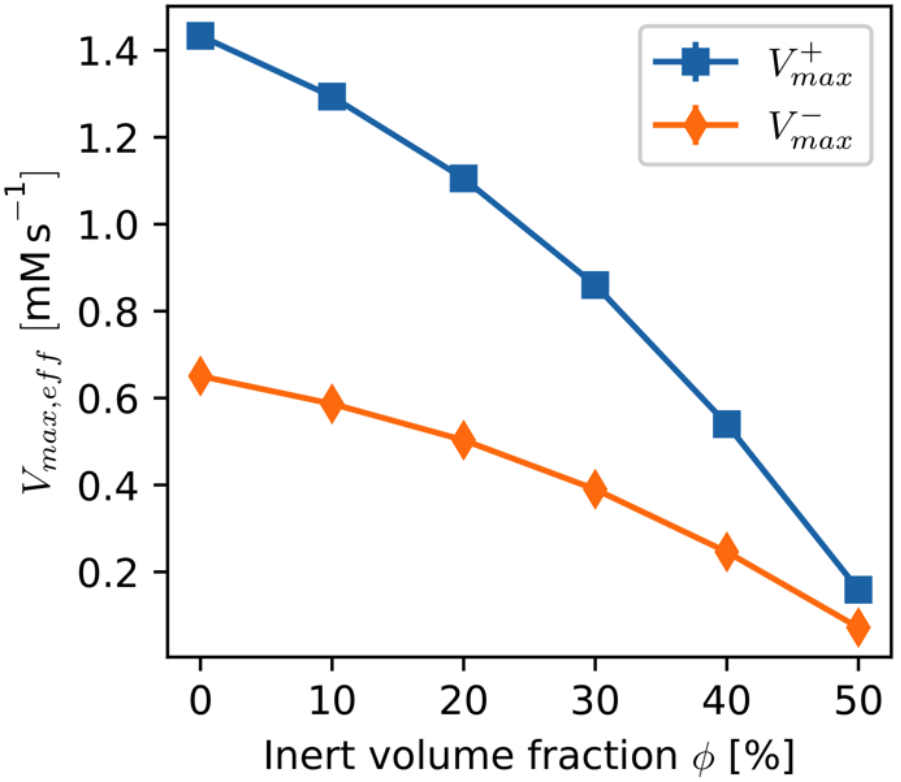




Weilandt, D. R., & Hatzimanikatis, V. (2019). *Biophysical Journal*.

Effect of CROWDING on *in vivo* Kinetics





Increasing volume fraction **decreases** apparent V_{max} and K_M

Weilandt, D. R., & Hatzimanikatis, V. (2019). *Biophysical Journal*.

Crowding effect

Satellite at 8h30 on a Thursday

Image source: https://ofcampuslausanne.ch/stamm-sat/

Crowding effect

Satellite at 18h30 on a Thursday

Image source: https://ofcampuslausanne.ch/stamm-sat/

Thank you for your attention

Chemical master equation

Transition probabilities:

1st order reactions: $A \rightarrow \cdots$

- Consider c_j to be the reaction probability for every molecule A_i per unit time
- The probability for a molecule A_i to react is then $c_j dt$
- The transition probability from a state with N_A molecules is therefore:

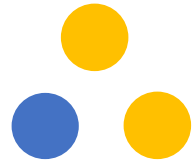
$$\mathrm{a}_j = c_j N_A$$

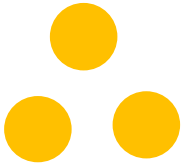
2nd order reactions: $A + B \rightarrow \cdots$

- Consider c_j to be the reaction probability a pair A_i , B_i
- For A and B molecules there are $N_A \times N_B$ pairs of molecules

$$\mathrm{a}_j = c_j N_A N_B$$

- **Attention: $2A_i \rightarrow \cdots$ gives only $N_A(N_A - 1)$ pairs**

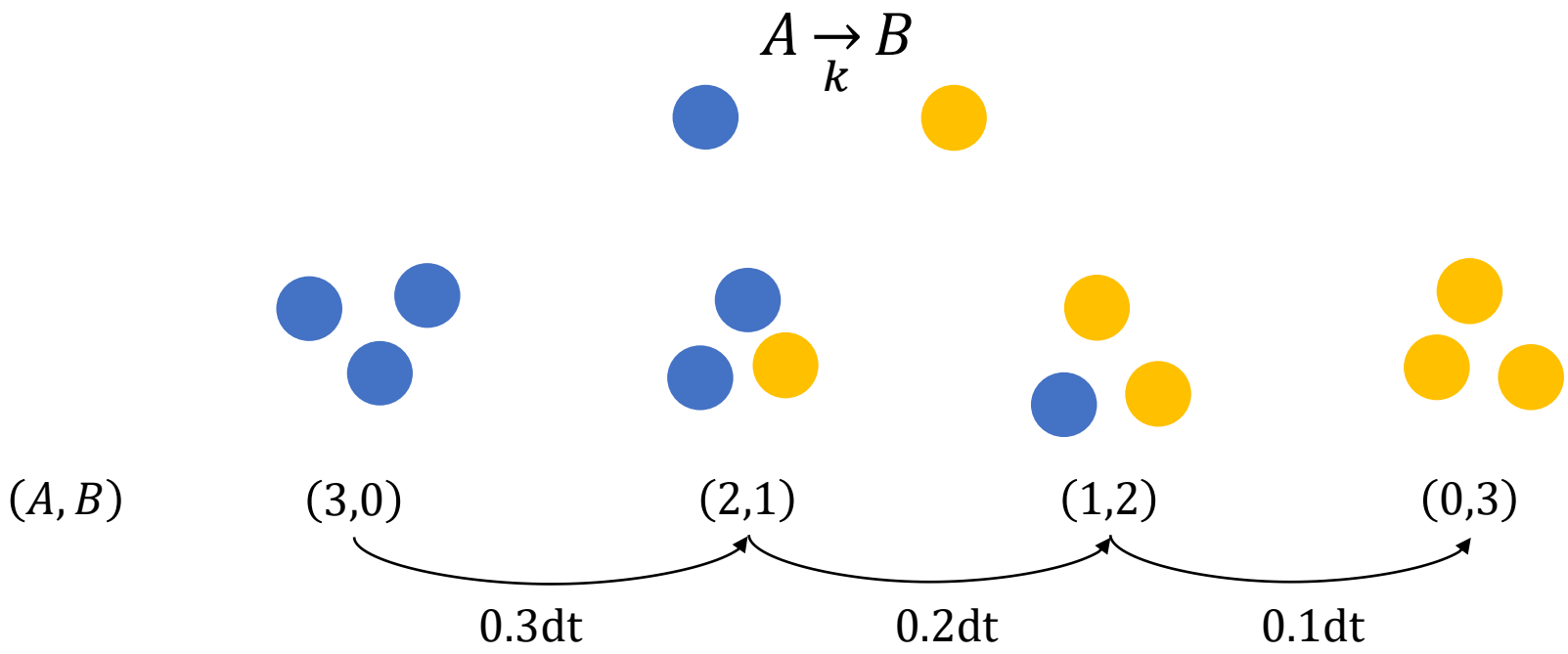




Chemical master equation

Consider a **1st order reaction** with $N = 3$ **molecules**

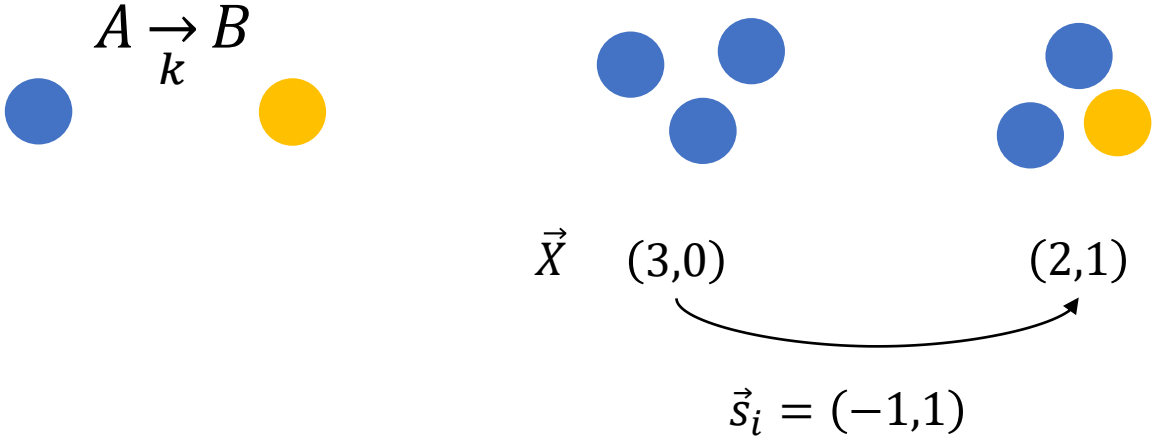
and a **transition probability of** $c_1 = 0.1$:



Possible transitions and their probabilities for an infinitely small time interval dt

Chemical master equation

For the 1st Order reaction and total number molecules $N = 3$:



Probability to remain in state $\vec{X}$ in dt

$$\frac{dP(\vec{X},t)}{dt} = \sum_{i=1}^{M} a_i(\vec{X}+\vec{s}_i)P(\vec{X}+\vec{s}_i,t) - P(\vec{X},t)\sum_{i=1}^{M} a_i(\vec{X})$$

Probability for **any** transition $\vec{s}_i$ in dt

Chemical master equation

General solution for 1st order reactions: $A \rightarrow B$

We assume that we have N molecules of A at $t = 0$ c reaction probability per time

From the master equation for A we know the probability a reaction :

$$s_j = -1 \quad a_j = c(n - s_j)$$

$$\frac{dP_n}{dt} = c(n-1)P_{n+1} - cn\,P_n \qquad P_n(t=0) = 0$$

And the probability that there was **no** reaction is:

$$\frac{dP_n}{dt} = -cN\,P_n \qquad P_n(t=0) = 1$$

Chemical master equation

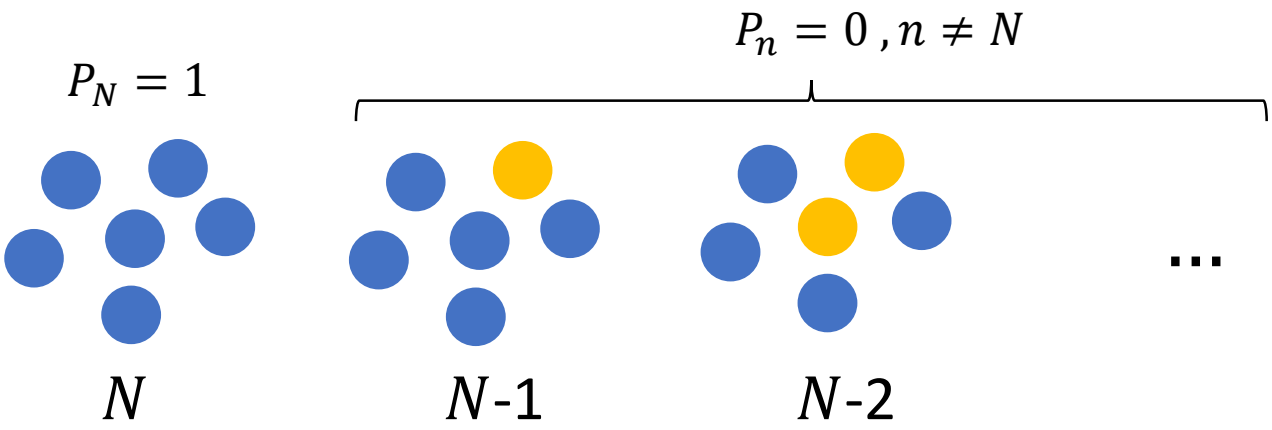
General solution for irreversible 1st order reactions: $A \rightarrow B$

$$\frac{dP_N}{dt} = -cN\,P_N \qquad P_N(t=0) = 1$$

$$\frac{dP_{N-1}}{dt} = cN\,P_N - c(N-1)\,P_{N-1} \qquad P_{N-1}(t=0) = 0$$

$$\frac{dP_{N-2}}{dt} = c(N-1)\,P_{N-1} - c(N-2)\,P_{N-2} \qquad P_{N-2}(t=0) = 0$$

$t = 0$



Chemical master equation

General solution for irreversible 1st order reactions: $A \rightarrow B$

$$\frac{dP_N}{dt} = -cN\,P_N \qquad P_N(t=0) = 1 \qquad \rightarrow \qquad P_N = e^{-cNt}$$

$$\frac{dP_{N-1}}{dt} = cN\,P_N - c(N-1)\,P_{N-1} \qquad P_{N-1}(t=0) = 0$$

$$\frac{dP_{N-2}}{dt} = c(N-1)\,P_{N-1} - c(N-2)\,P_{N-2} \qquad P_{N-2}(t=0) = 0$$

...

Solving leads to:

$$P_n(t) = \binom{N}{n}(e^{-ct})^n(1-e^{-ct})^{N-n}$$

$$p_k(t) = \binom{n}{k}p^k(1-p)^{n-k}$$

Binomial distribution

Chemical master equation

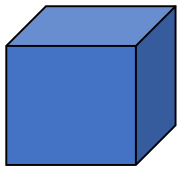
General solution for irreversible 1st order reactions: $A \rightarrow B$

$$P_n(t) = \binom{N}{n} (e^{-ct})^n (1 - e^{-ct})^{N-n}$$ Binomial distribution

Time evolution of the mean

$$\langle P_n(t) \rangle = N e^{-ct}$$

$$[A]_0 = \frac{N}{V_A}$$



N molecules in volume V

$$[A](t) = [A]_0 e^{-ct}$$

Chemical master equation

General solution for irreversible 1st order reactions: $A \rightarrow B$

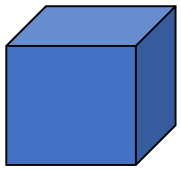
$$P_n(t) = \binom{N}{n} (e^{-ct})^n (1 - e^{-ct})^{N-n}$$

Binomial distribution

Time evolution of the mean

$$\langle P_n(t) \rangle = N e^{-ct}$$

$$[A]_0 = \frac{N}{V_A}$$



N molecules in volume V

$$[A](t) = [A]_0 e^{-ct}$$

Time evolution of deterministic kinetics

$$\frac{d[A]}{dt} = -k[A]$$

Mass action

$$[A](t) = [A]_0 e^{-kt}$$

Relation to the deterministic system

		Reaction rate	**Propensity**
Reaction 1:	$A \xrightarrow{k_1} B$	$v_1 = k_1[A]$	$a_1 = c_1 \, N_\mathrm{A}$

Relation to the deterministic system

		Reaction rate	**Propensity**
Reaction 1:	$A \xrightarrow{k_1} B$	$v_1 = k_1[A]$	$a_1 = c_1 \, N_\mathrm{A}$
Units:		$\frac{mol}{L \, s}$	$\frac{1}{s}$

Relation to the deterministic system

		Reaction rate	**Propensity**
Reaction 1:	$A \xrightarrow{k_1} B$	$v_1 = k_1[A]$	$a_1 = c_1 \, N_\mathrm{A}$
Units:		$\frac{mol}{L \; s}$	$\frac{1}{s}$
Meaning:		$\frac{\#reactions}{volume \; time}$	$\frac{\#reactions}{time}$

Relation to the deterministic system

		Reaction rate	Propensity
Reaction 1:	$A \xrightarrow{k_1} B$	$v_1 = k_1[A]$	$a_1 = c_1 N_A$
Units:		$\frac{mol}{L\,s}$	$\frac{1}{s}$
Meaning:		$\frac{\#reactions}{volume\ time}$	$\frac{\#reactions}{time}$

In average we expect that:

$$v_1 V n_A = a_1$$

$$k_1[A] V n_A = c_1 N_A$$

V volume

n_A Avogadro's number

Relation to the deterministic system

Reaction rate **Propensity**

Reaction 2: $A + B \xrightarrow{k_2} C$ $v_2 = k_2[\mathrm{A}][\mathrm{B}]$ $a_2 = c_2 N_A N_B$

In average we expect that:

$$v_2 V n_A = a_2$$

$$k_2[A][B] V n_A = c_2 N_A N_B$$

$$k_2 \frac{N_A}{V n_A} \frac{N_B}{V n_A} V n_A = c_2 N_A N_B$$

V volume

n_A Avogadro's number

$$c_2 = \frac{k_2}{V n_A} \qquad c_o = \frac{k_o}{(V n_A)^{o-1}}$$

Chemical master equation

General solution for irreversible 1st order reactions: $A \rightarrow B$

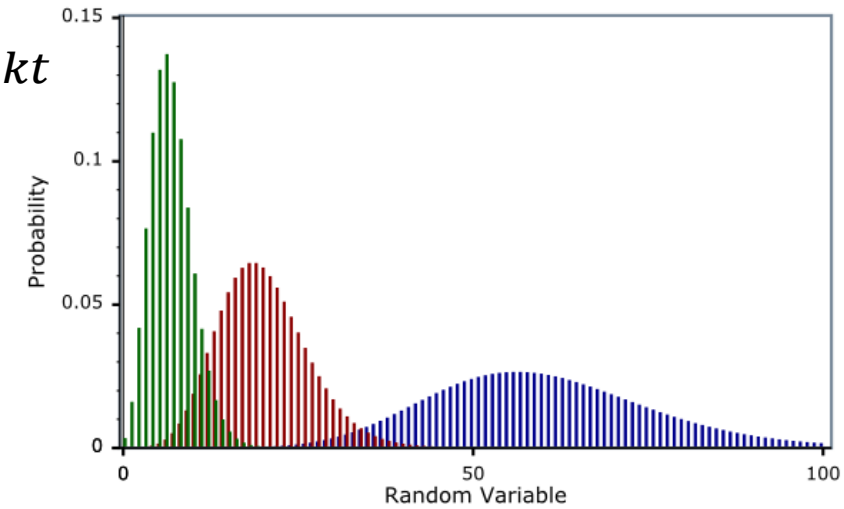
$$P_n(t) = \frac{N!}{n!\,(N-n)!}\left(e^{-kt}\right)^n\left(1-e^{-kt}\right)^{N-n}$$

Binomial distribution

Variance of the distribution quantifies the strength of the fluctuations:

$$\langle (P_n(t) - \langle P_n(t)\rangle)^2\rangle = N\left(1-e^{-kt}\right)e^{-kt}$$

$$\frac{STD\left(P_n(t)\right)}{N} = \frac{\sqrt{N}}{N}\left(1-e^{-kt}\right)e^{-kt}$$



Solution for the master equation ?

For most problems there is no analytical solution for the master equation

Exact Stochastic Simulation of Coupled Chemical Reactions

Daniel T. Gillespie*

Research Department, Naval Weapons Center, China Lake, California 93555 *(Received May 12, 1977)*

Publication costs assisted by the Naval Weapons Center

There are two formalisms for mathematically describing the time behavior of a spatially homogeneous chemical system: The *deterministic approach* regards the time evolution as a continuous, wholly predictable process which is governed by a set of coupled, ordinary differential equations (the "reaction-rate equations"); the *stochastic*

Stochastic Simulation Algorithm

$$P(\tau, \mu) = a_\mu \exp\left(-\sum_{\nu}^{M} a_\nu \, \tau\right)$$

Probability density for reaction times and reactions

Map the probability distribution to random numbers r_1 and r_2 so that:

$$P'(r_1, r_2) = \begin{cases} 1 \; if \;\; 0 \leq r_1 \leq 1 \; and \; 0 \leq r_2 \leq 1 \\ 0 \qquad\qquad otherwise \end{cases}$$

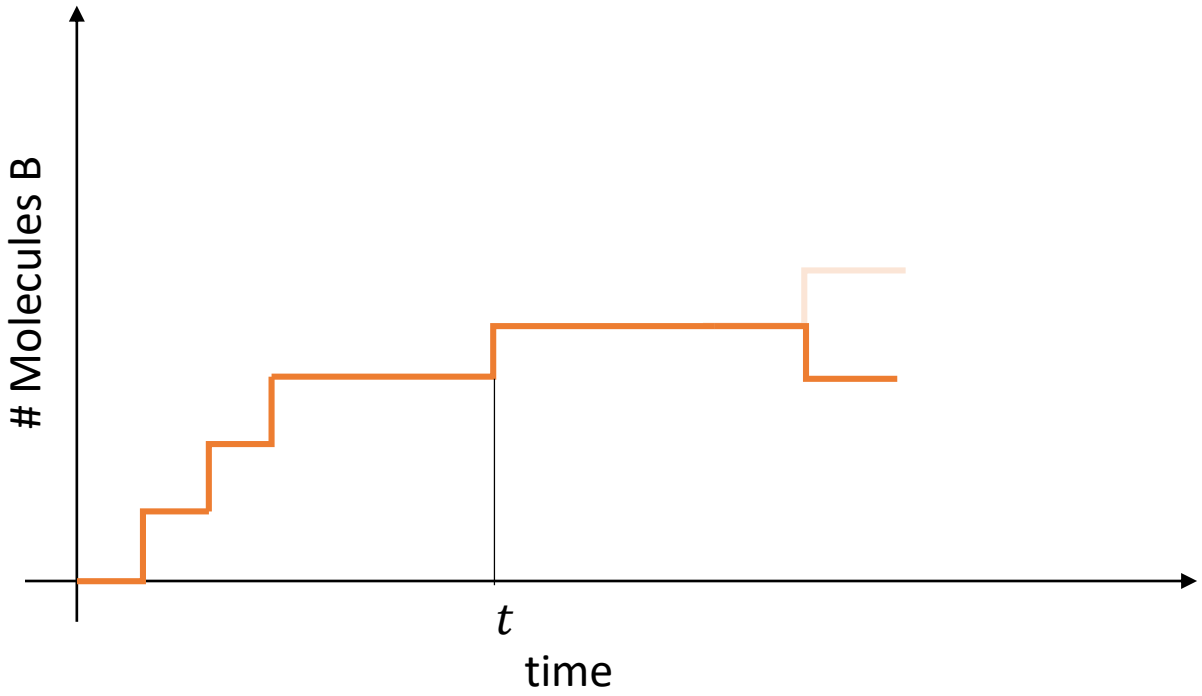
Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

Direct Method

$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B$$

1. Draw two uniformly distributed random numbers r_1 and r_2 from $[0,1]$



Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

Direct Method

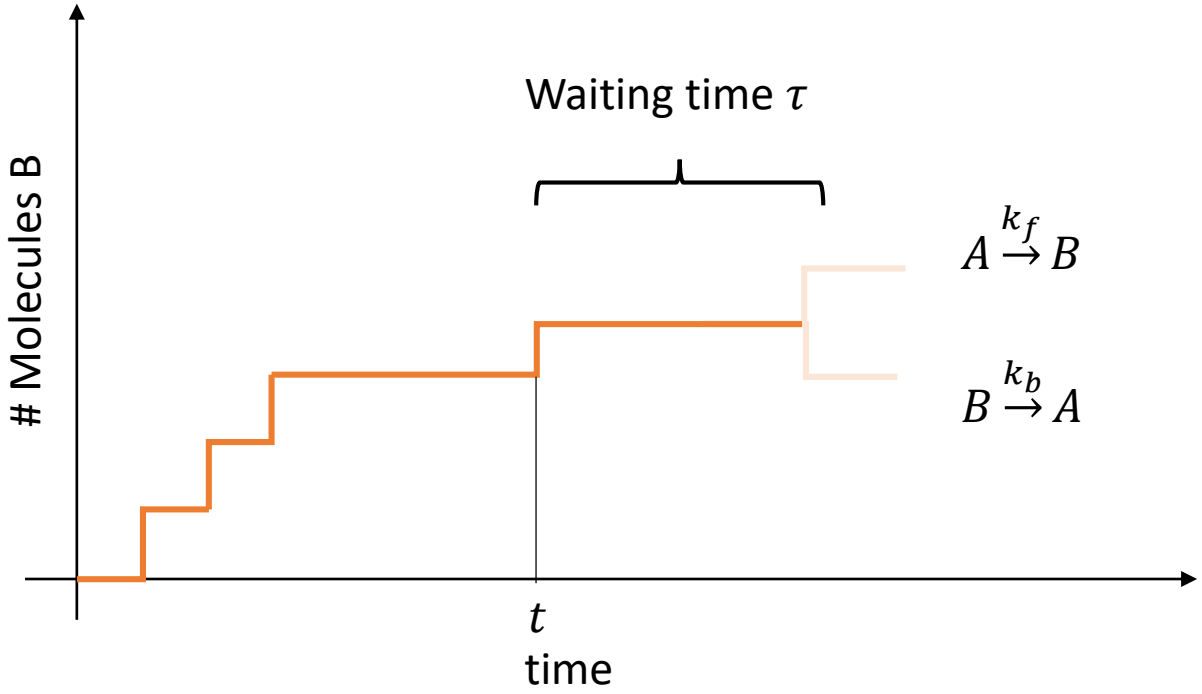
$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B$$

2. The time until the next reaction is then $\tau = \frac{1}{a_0} \ln\left(\frac{1}{r_1}\right)$

$$a_0 = \sum_{\nu}^{M} a_\nu$$

$$a_0 = a_1 + a_2$$

$$a_0 = c_f N_{\mathrm{A}} + c_b N_{\mathrm{B}}$$



Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

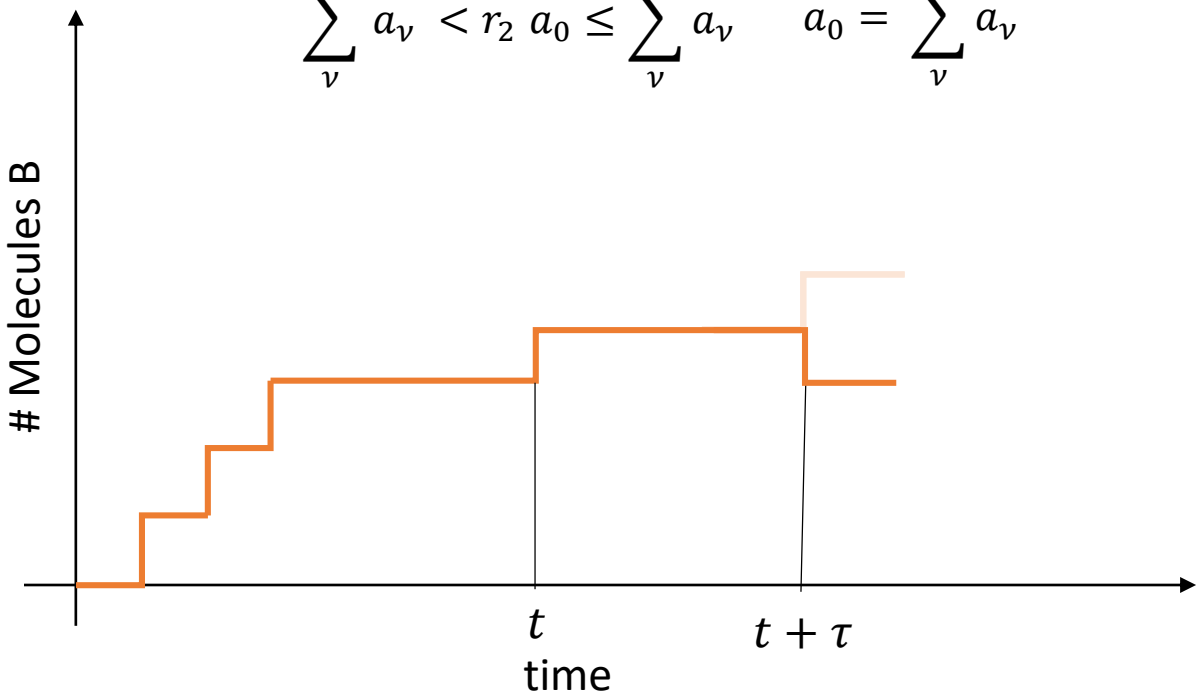
Stochastic Simulation Algorithm

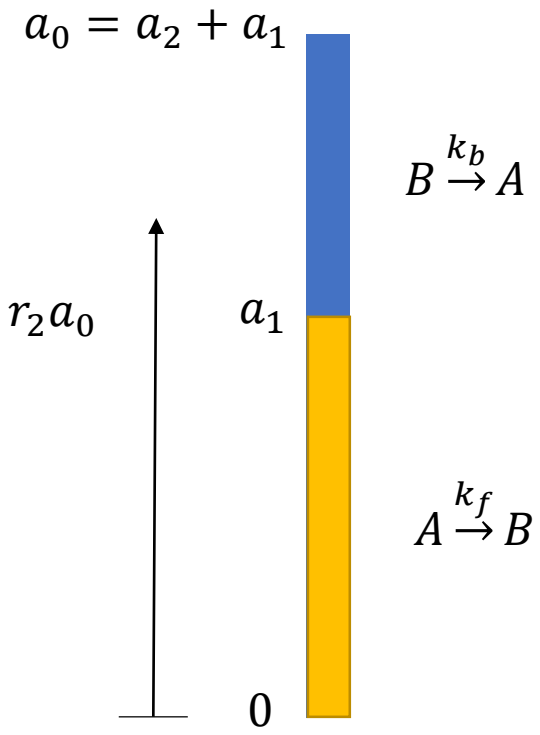
Direct Method

$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B$$

3. Find the reaction μ for which holds:

$$\sum_{\nu}^{\mu-1} a_\nu < r_2\, a_0 \leq \sum_{\nu}^{\mu} a_\nu \qquad a_0 = \sum_{\nu}^{M} a_\nu$$





Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

Direct Method

1. Draw two uniformly distributed random numbers r_1 and r_2 from $[0,1]$

2. The time until the next reaction is then $\tau = \frac{1}{a_0} \ln\left(\frac{1}{r_1}\right)$

3. Find the reaction μ for which holds:

$$\sum_{\nu}^{\mu-1} a_\nu \; < r_2 \; a_0 \leq \sum_{\nu}^{\mu} a_\nu \qquad\qquad a_0 = \sum_{\nu}^{M} a_\nu$$

Gillespie, D. T. (1977). Journal of Physical Chemistry **81**(25): 2340-2361.

Stochastic Simulation Algorithm

Other methods:

- Direct Method
- First Reaction Method

} Gillespie, D. T. (1977). J. Phys. Chem

- Next Reaction Method — Gibson and Bruck, (1999), J. Phys. Chem
- Tau-leap Method — Cao et al. (2006), J. Chem. Phys

Efficient Exact Stochastic Simulation of Chemical Systems with Many Species and Many Channels

Michael A. Gibson * and Jehoshua Bruck
California Institute of Technology, Department of Computation and Neural Systems, Mail Code 136-93, Pasadena, CA 91125

J. Phys. Chem. A, **2000**, *104* (9), pp 1876–1889
DOI: 10.1021/jp993732q
Publication Date (Web): February 15, 2000

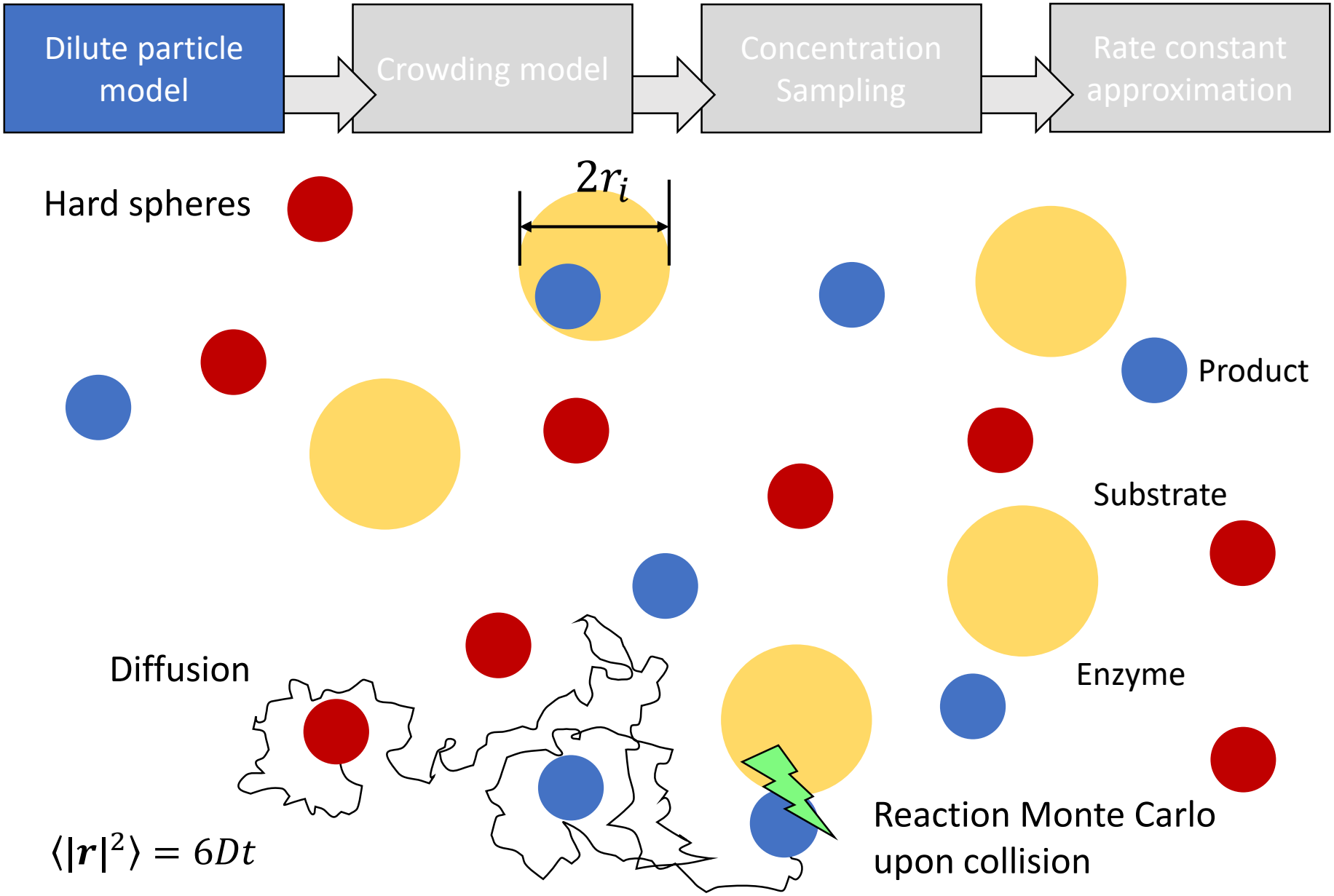
THE JOURNAL OF CHEMICAL PHYSICS **124**, 044109 (2006)

Efficient step size selection for the tau-leaping simulation method

Yang Cao[a)]
Department of Computer Science, Virginia Tech, Blacksburg, Virginia 24061
Daniel T. Gillespie
Dan T. Gillespie Consulting, 30504 Cordoba Place, Castaic, California 91384
Linda R. Petzold
Department of Computer Science, University of California, Santa Barbara, Santa Barbara, California 93106

(Received 3 August 2005; accepted 29 November 2005; published online 30 January 2006)

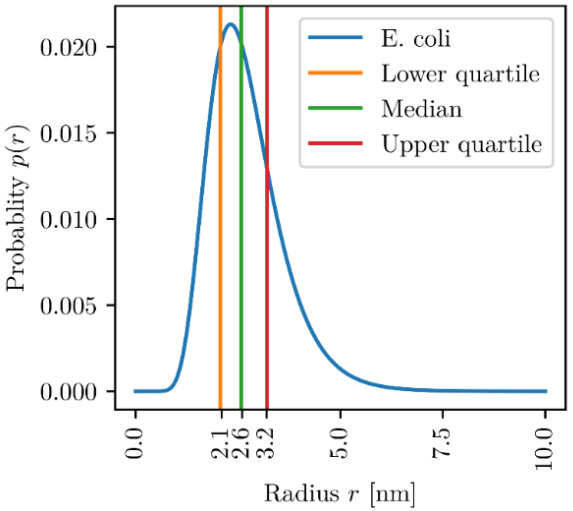
From particles to ODEs



From particles to ODEs

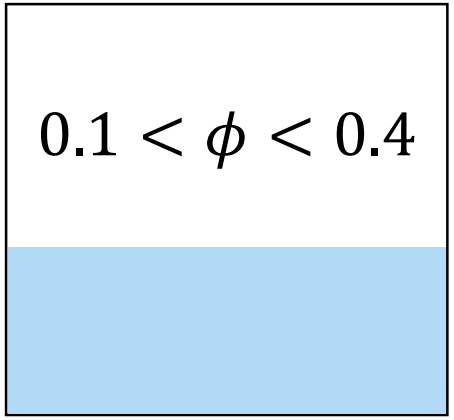
Dilute particle model → **Crowding model** → Concentration Sampling → Rate constant approximation

Size distribution



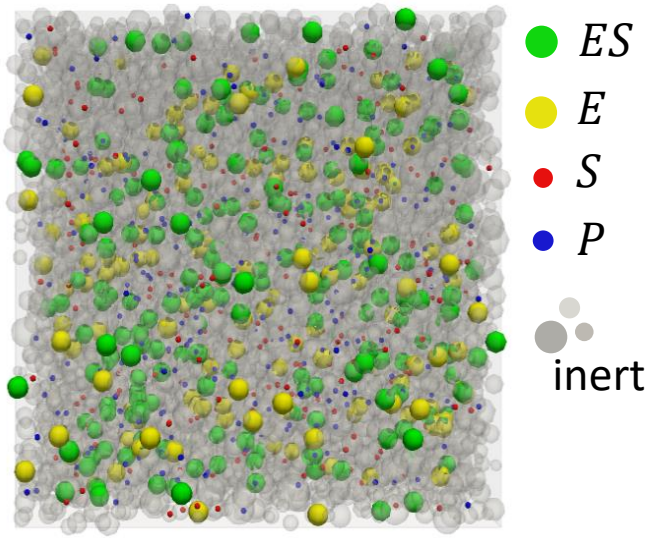
+

Volume occupancy



=

Crowded particle model

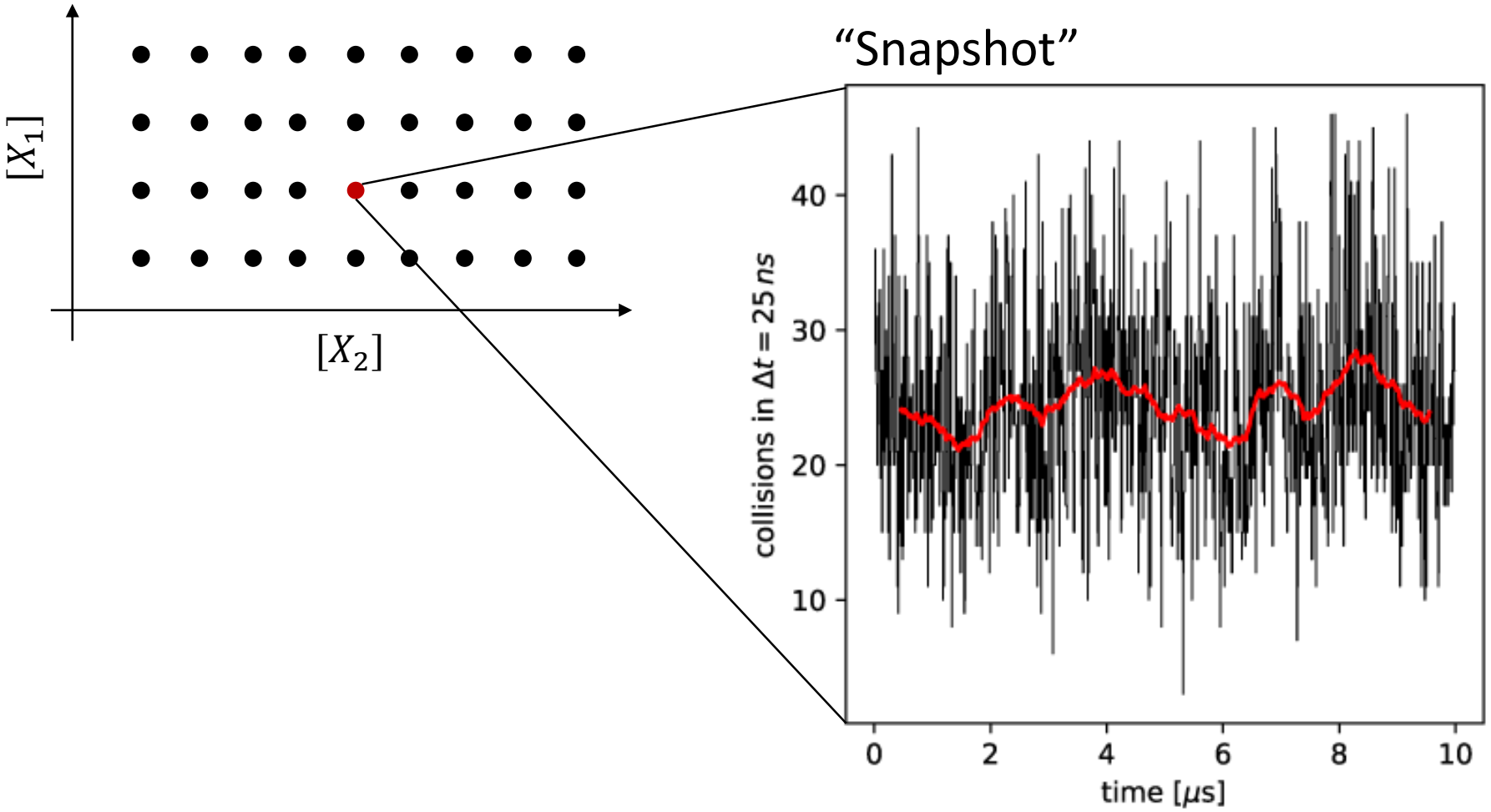


Kalwarczyk et al. 2012 *Bioinformatics,* **28**(22) 2971-2978

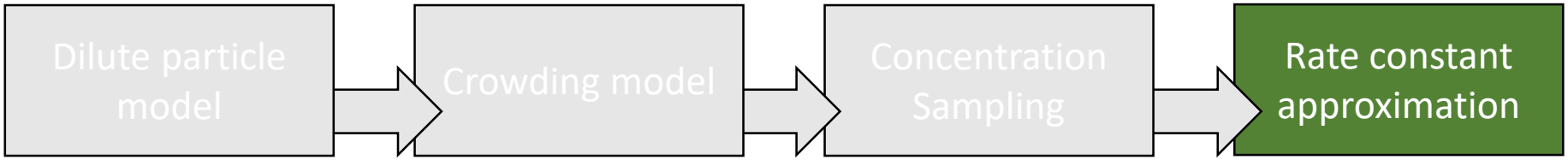
Ellis, R.J., 2001. *Trends in biochemical sciences* **26**(10) 597-604

From particles to ODEs

Dilute particle model → Crowding model → **Concentration Sampling** → Rate constant approximation

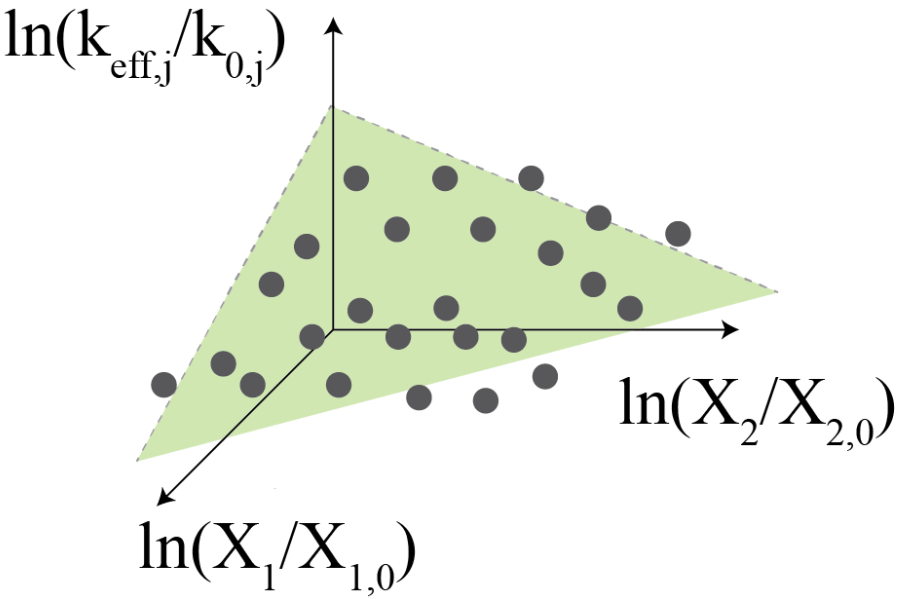


From particles to ODEs



Approximate rate constants:

$$k_{j,eff}(\boldsymbol{X},\phi) = k_{i,0}e^{\beta_j}\prod_{i=1}^{M}\left(\frac{[X_i]}{[X_i]_{ref}}\right)^{\alpha_{i,j}}$$



$$\log\left(\frac{k_{j,eff}}{k_{j,0}}\right) = \sum_{i=1}^{N}\alpha_{i,j}\log\left(\frac{[X_i]}{[X_i]_0}\right) + \beta_j$$

Linear regression

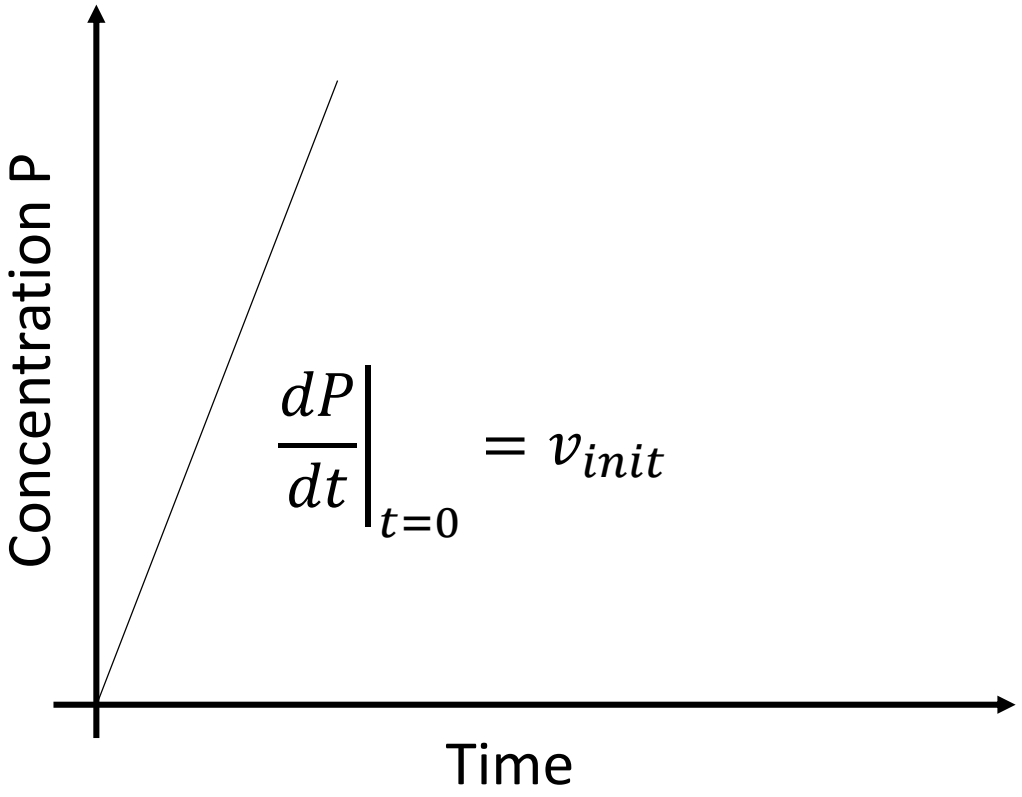
Enzyme kinetics

Phosphoglycerate isomerase

Glycerate-3-phosphate ⟶ Glycerate-2-phosphate

$$S + E \underset{k_{1,b}}{\overset{k_{1,f}}{\rightleftharpoons}} ES \underset{k_{2,b}}{\overset{k_{2,f}}{\rightleftharpoons}} E + P$$

Initial rate experiment



Increasing substrate concentration

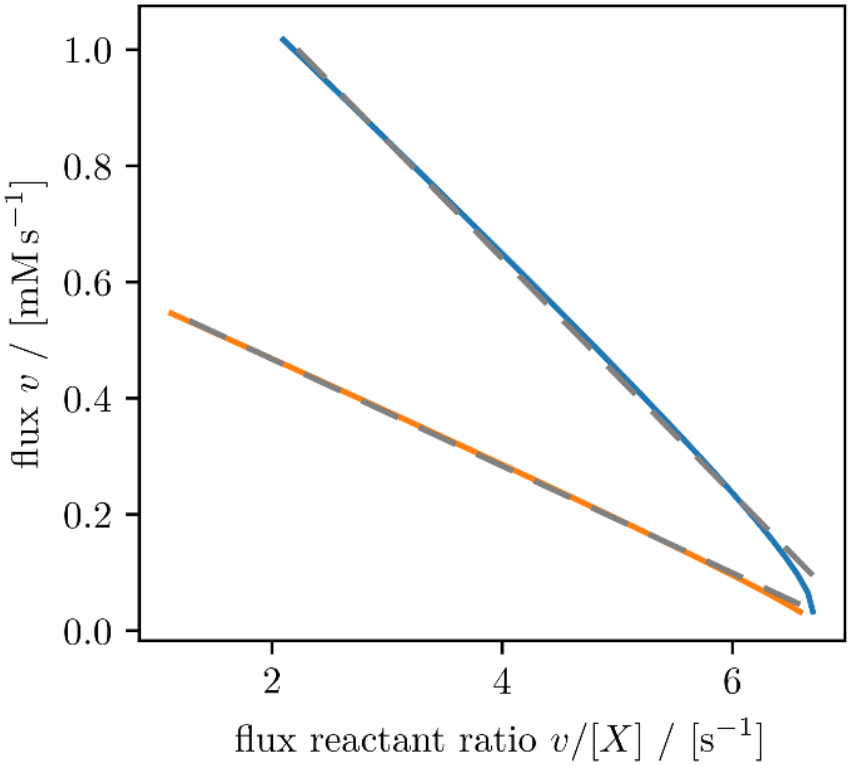
Estimate in vivo MM parameters

from initial-rate simulations

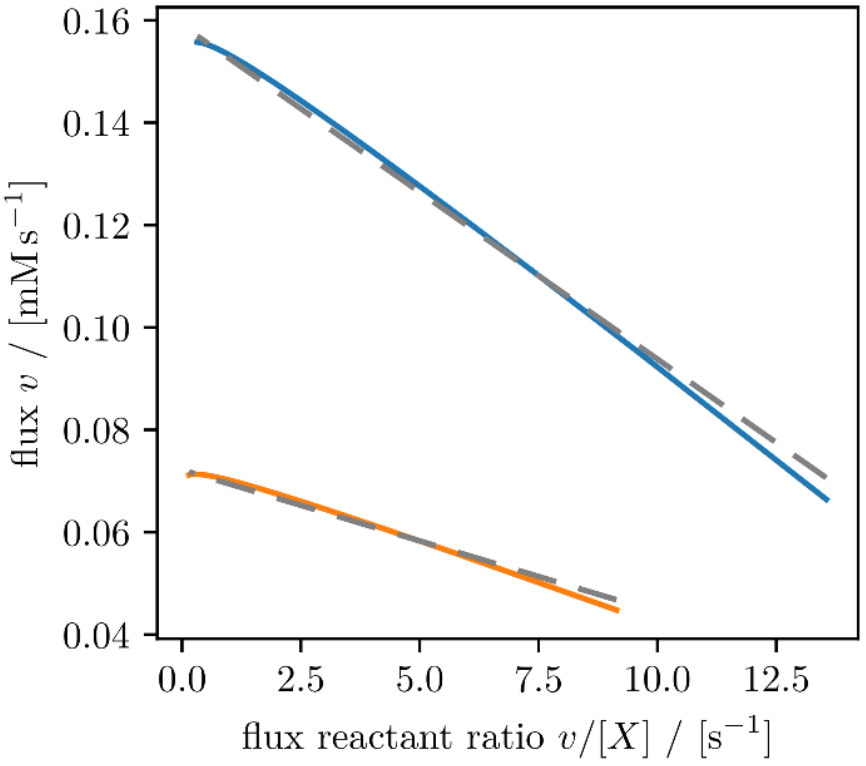
$$v = -K_{m,X}\frac{v}{[X]} + V_{max}$$

Eddi-Hofstee diagrams (see kinetics lecture)

$\phi = 0\ \%$



$\phi = 50\ \%$



Weilandt, D. R., & Hatzimanikatis, V. (2019). *Biophysical Journal*.