Nov 8: Eric Deeds, University of California at Los Angeles
"The evolution of cellular individuality"

Nov 15: Daniel Merkle, University of Southern Denmark
"Graph rewriting and chemistry"

Nov 22: Jean Krivine, IRIF, Université de Paris
"From molecules to systems: the problem of knowledge representation in molecular biology"

Nov 29: Eric Smith, Earth Life Sciences Institute, Tokyo
“Easy and Hard in the Origin of Life"

Dec 13: Yarden Katz, Harvard Medical School, Boston
"Cells as cognitive creatures"

Jan 10: Massimiliano Esposito, University of Luxembourg
"Thermodynamics of Open Chemical Reaction Networks: Theory and Applications"

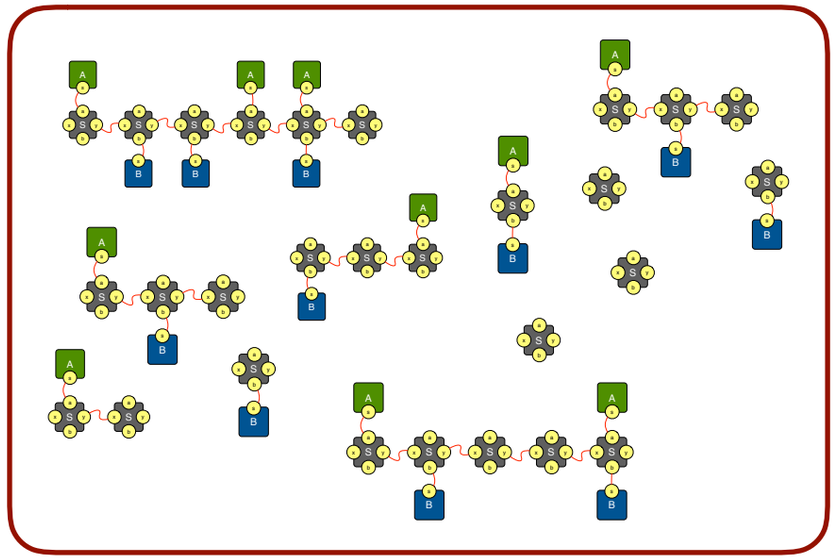
Jan 17: Aleksandra Walczak, ENS Paris
"Prediction in immune repertoires"

Jan 24: Tommy Kirchhausen, Harvard Medical School
"Imaging sub-cellular dynamics from molecules to multicellular organisms"

Generalizing Michaelis-Menten with Scaffolds

$$\mathrm{A} + \mathrm{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{AB} \xrightarrow{k_{cat}} \mathrm{P} + \ldots$$

polymerizing scaffold

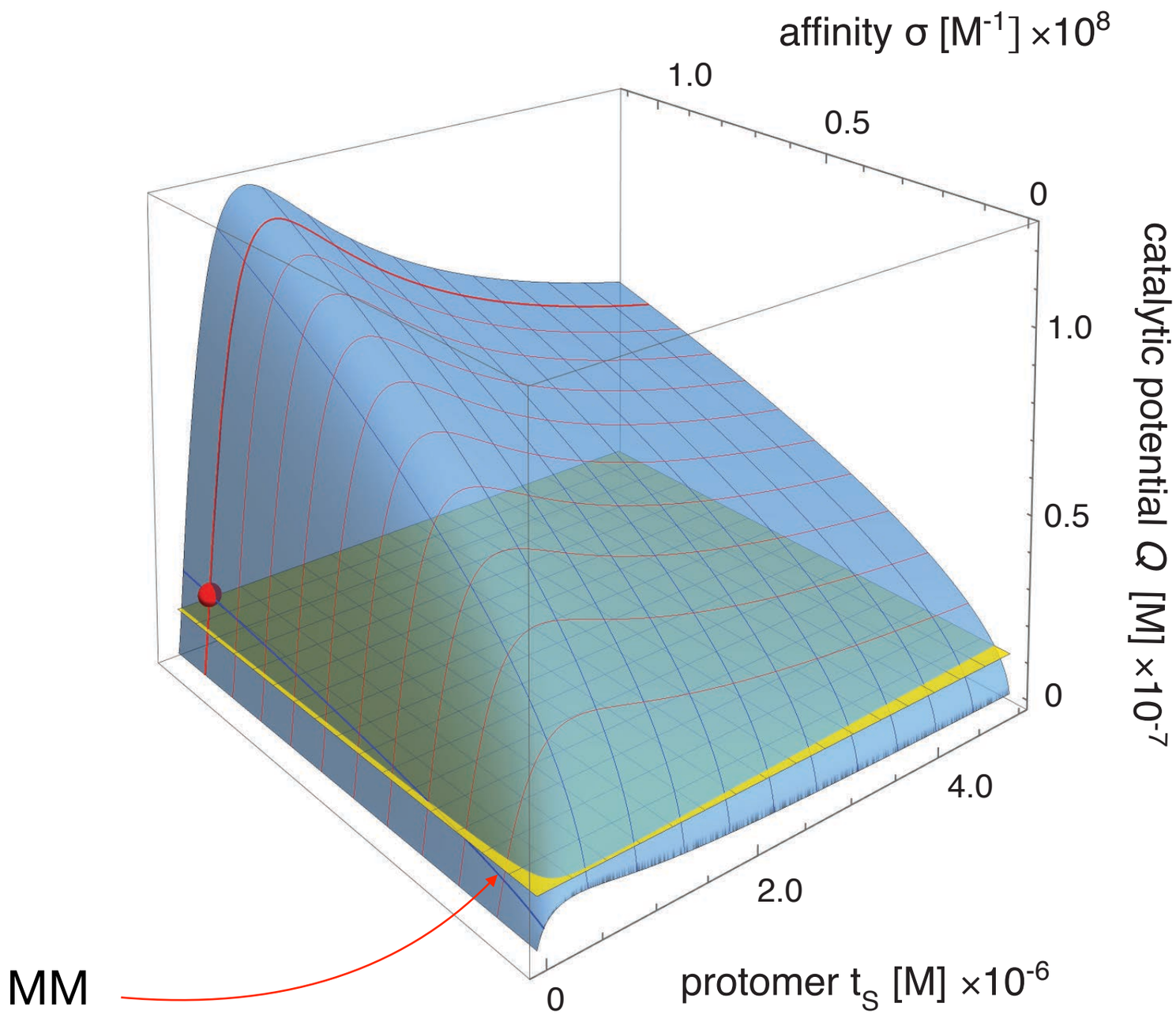


$\xrightarrow{k_{cat}} \mathrm{P} + \ldots$

a *pleiomorphic* ensemble

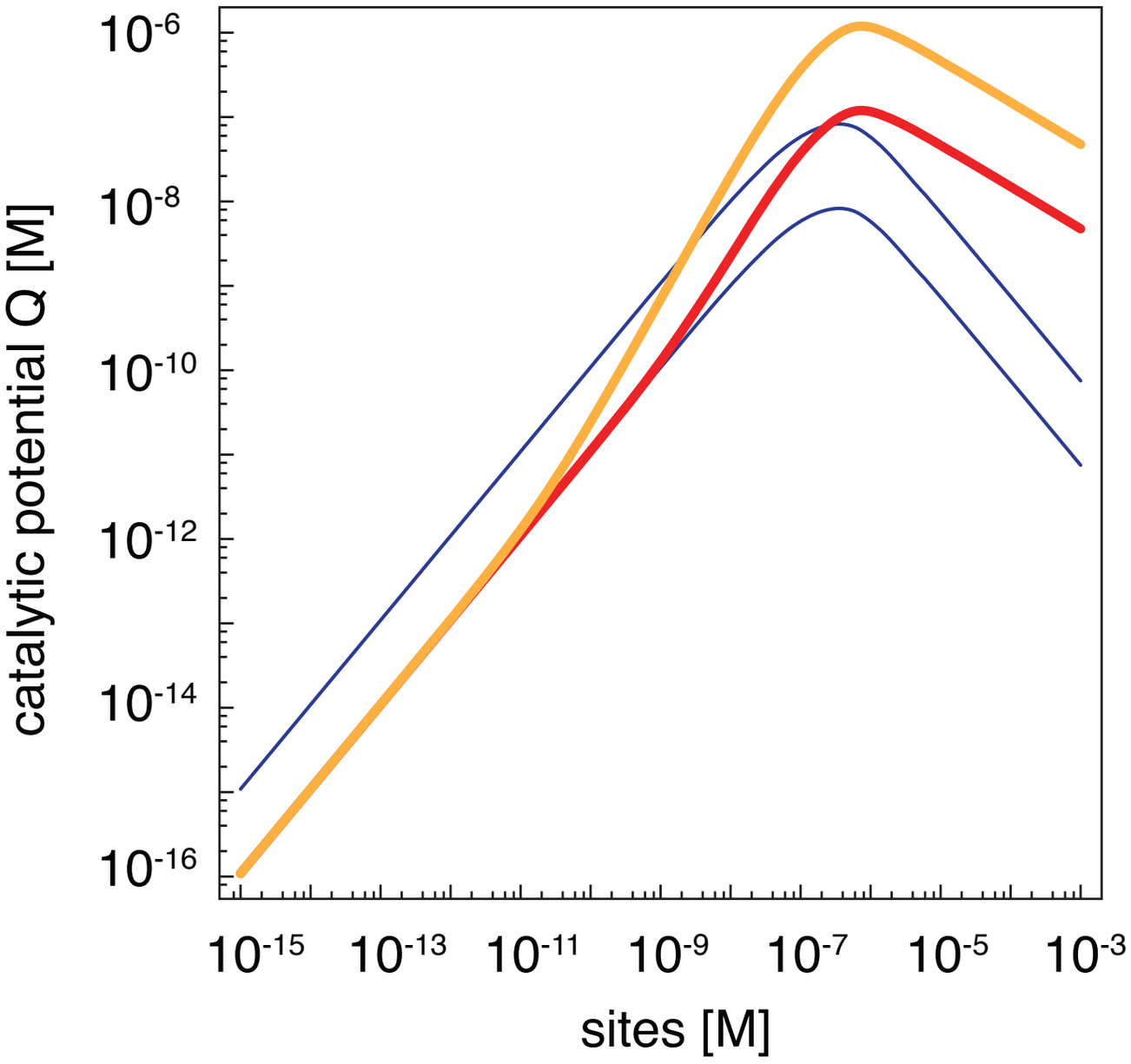
major assumption: the contents of the box are in equilibrium

The Equilibrium Q-surface (Continuum Case)



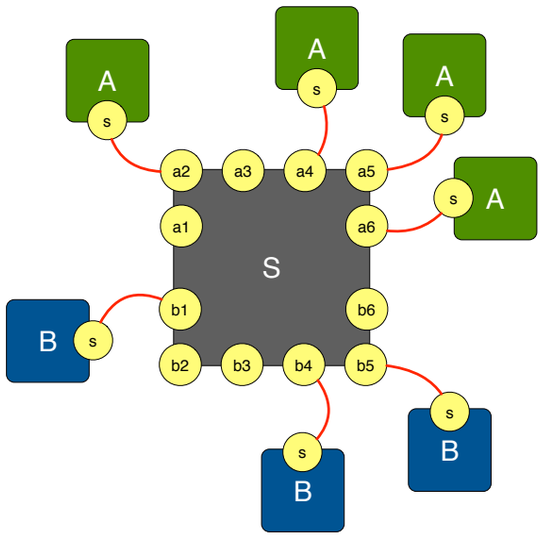
$\alpha = \beta = 10^7\ \mathrm{M}^{-1}$, $t_A = 15 \cdot 10^{-9}\ \mathrm{M}$, and $\sigma = 10^8\ \mathrm{M}^{-1}$

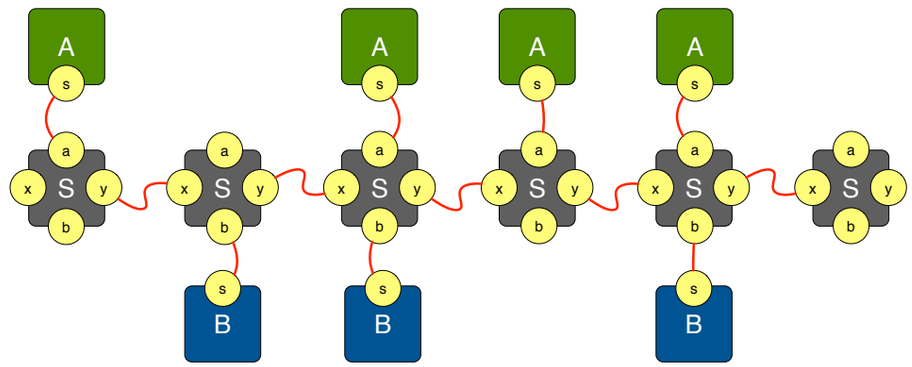
Multivalent Scaffolds and Poly-Scaffold



$\alpha = \beta = 10^7\ \mathrm{M}^{-1}, \sigma = 10^8\ \mathrm{M}^{-1}, t_A = 15 \cdot 10^{-9}\ \mathrm{M}, t_B = 0.5 \cdot 10^{-6}\ \mathrm{M}$

Multivalent Scaffolds as Stepping Stones





$$Q = \underbrace{p(t_{\mathrm{sit}}, t_A, \alpha) p(t_{\mathrm{sit}}, t_B, \beta)}_{I} \underbrace{Q_{\max}(\vec{t}_S)}_{II}$$

not dependent on partitioning of sites
only dependent on ligand binding

not dependent on ligand binding
only dependent on partitioning of sites

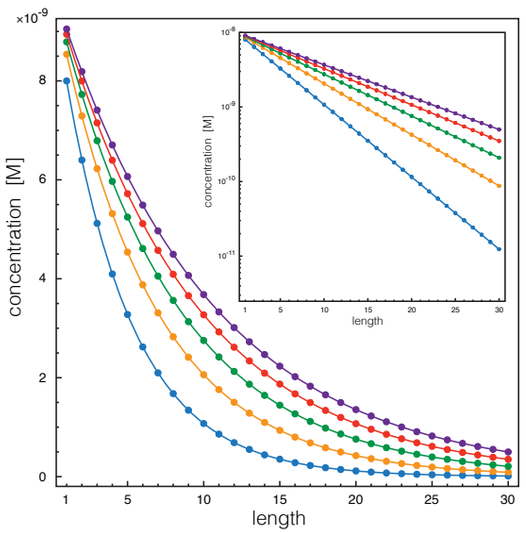
with $$p(t_{\mathrm{sit}}, t_X, \gamma) = \frac{\gamma t_X - \gamma t_{\mathrm{sit}} - 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\mathrm{sit}} - 1)^2}}{\gamma t_X - \gamma t_{\mathrm{sit}} + 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\mathrm{sit}} - 1)^2}}$$

$$Q_{\mathrm{poly}} = p(t_S, t_A, \alpha) p(t_S, t_B, \beta) \sum_{n=1}^{\infty} n^2 \sigma^{n-1} s^n = p(t_S, t_A, \alpha) p(t_S, t_B, \beta) \frac{s(1+\sigma s)}{(1-\sigma s)^3}$$

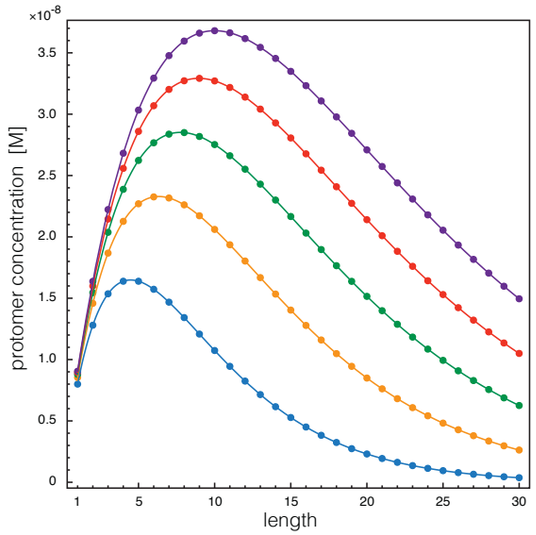
Polymerization Overview

as a function of t_S

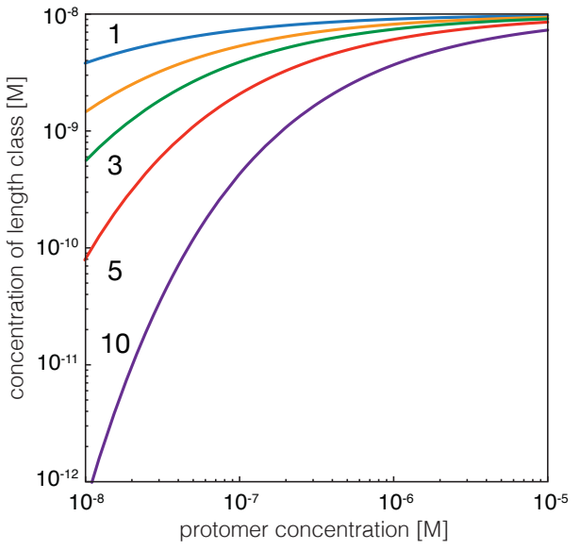
distribution of sizes



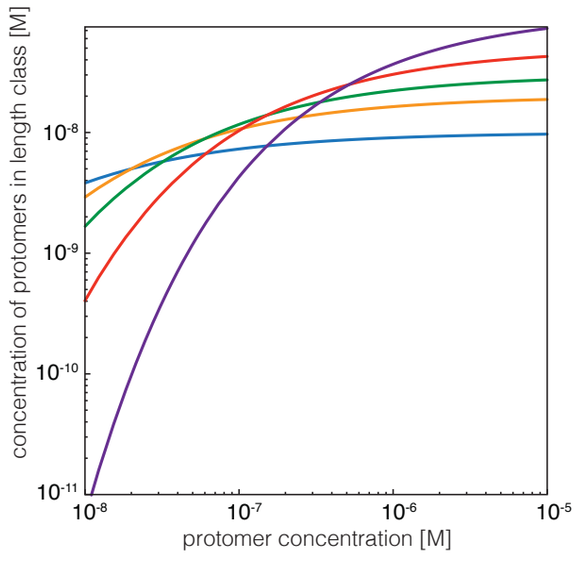
distribution of mass



concentration of sizes



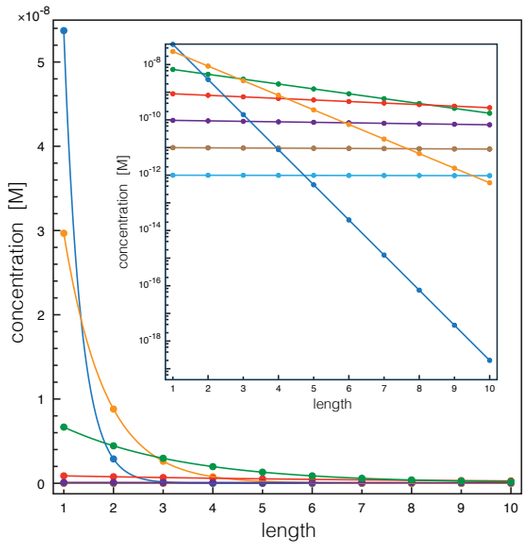
concentration of mass



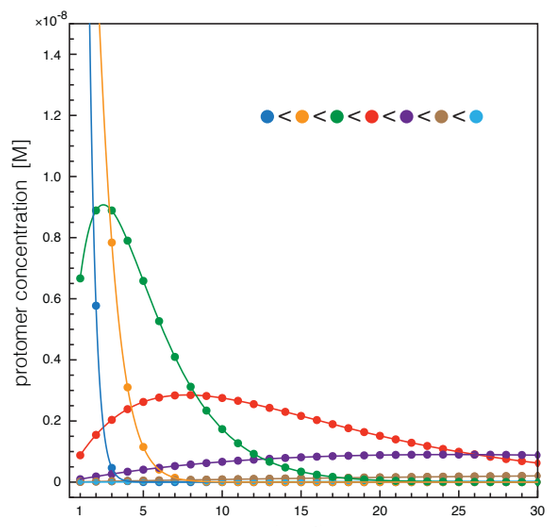
$$s_n \to \frac{1}{\sigma} \quad \text{in the limit} \quad t_S \to \infty$$

as a function of σ

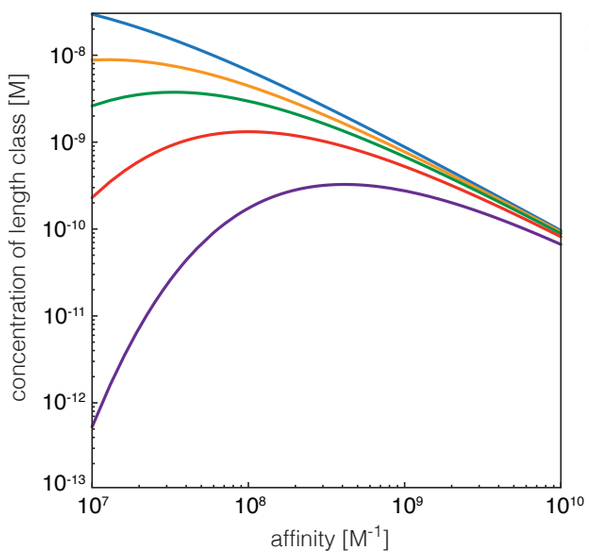
distribution of sizes



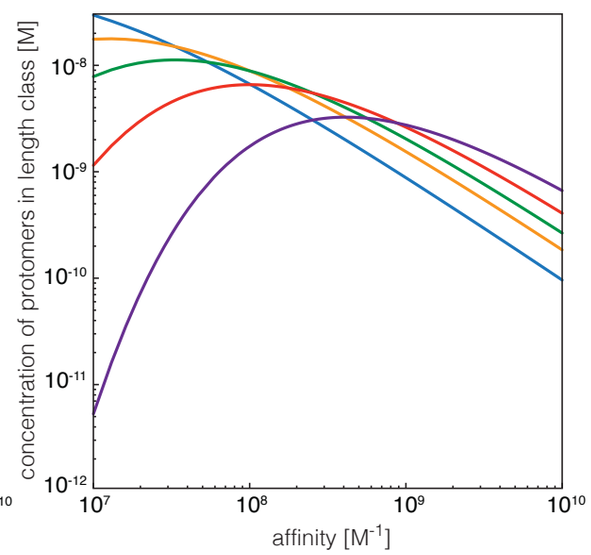
distribution of mass



concentration of sizes



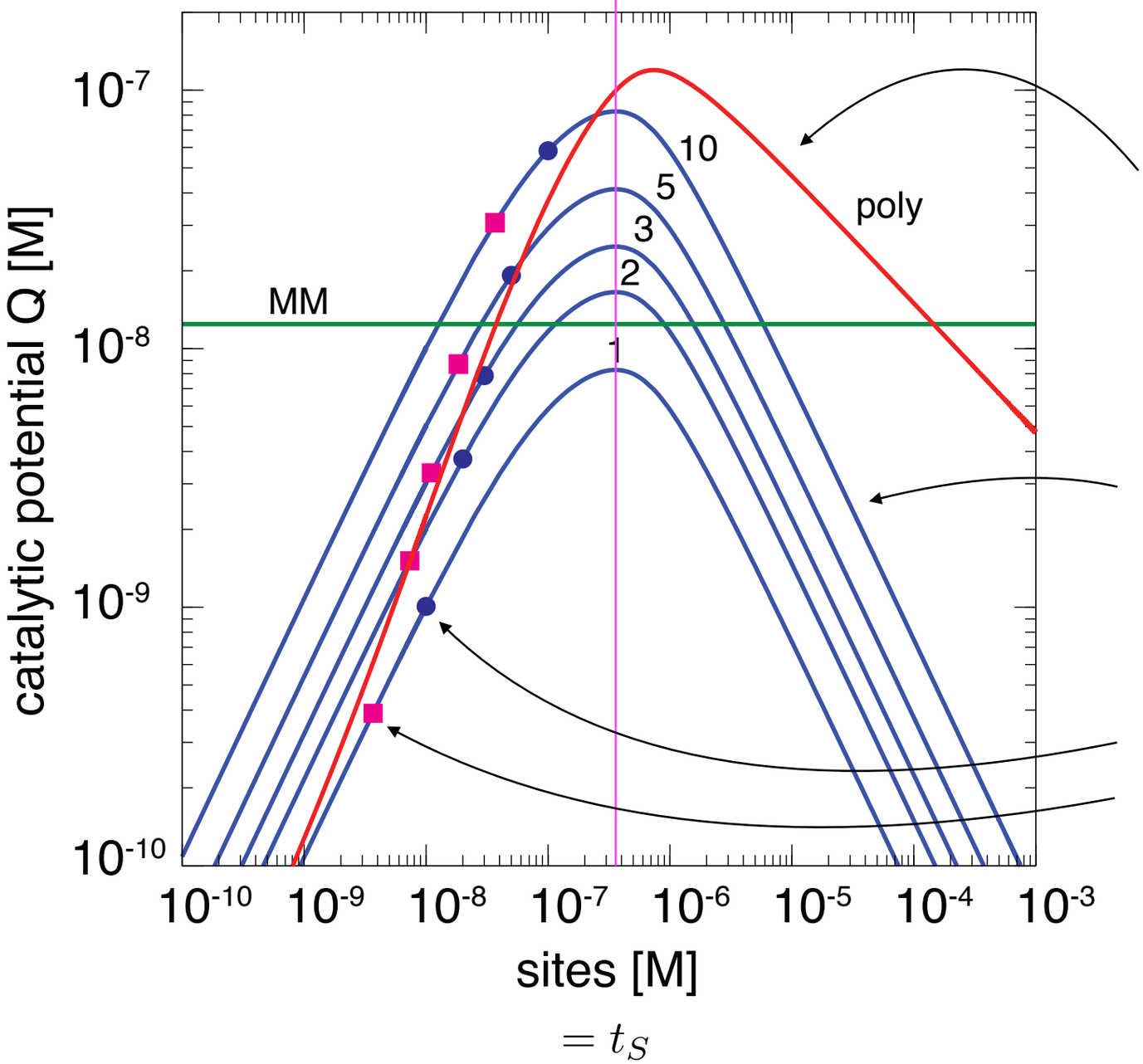
concentration of mass



$$s_n \to 0 \quad \text{in the limit} \quad \sigma \to \infty$$

Multivalent Scaffolds and Poly-Scaffold

$$t_{S_{(k)}} = \frac{1}{k}\left(\frac{1}{\alpha} + \frac{t_A + t_B}{2}\right)$$



$$Q_{\text{poly}} = p(t_S, t_A, \alpha)p(t_S, t_B, \beta)\frac{s(1+\sigma s)}{(1-\sigma s)^3}$$

$$Q_{\text{multi}} = p(kt_{S_{(k)}}, t_A, \alpha)p(kt_{S_{(k)}}, t_B, \beta)k^2\, t_{S_{(k)}}$$

$$Q_{\text{multi}} = p(ns_n, t_A, \alpha)p(ns_n, t_B, \beta)n^2\, s_n$$

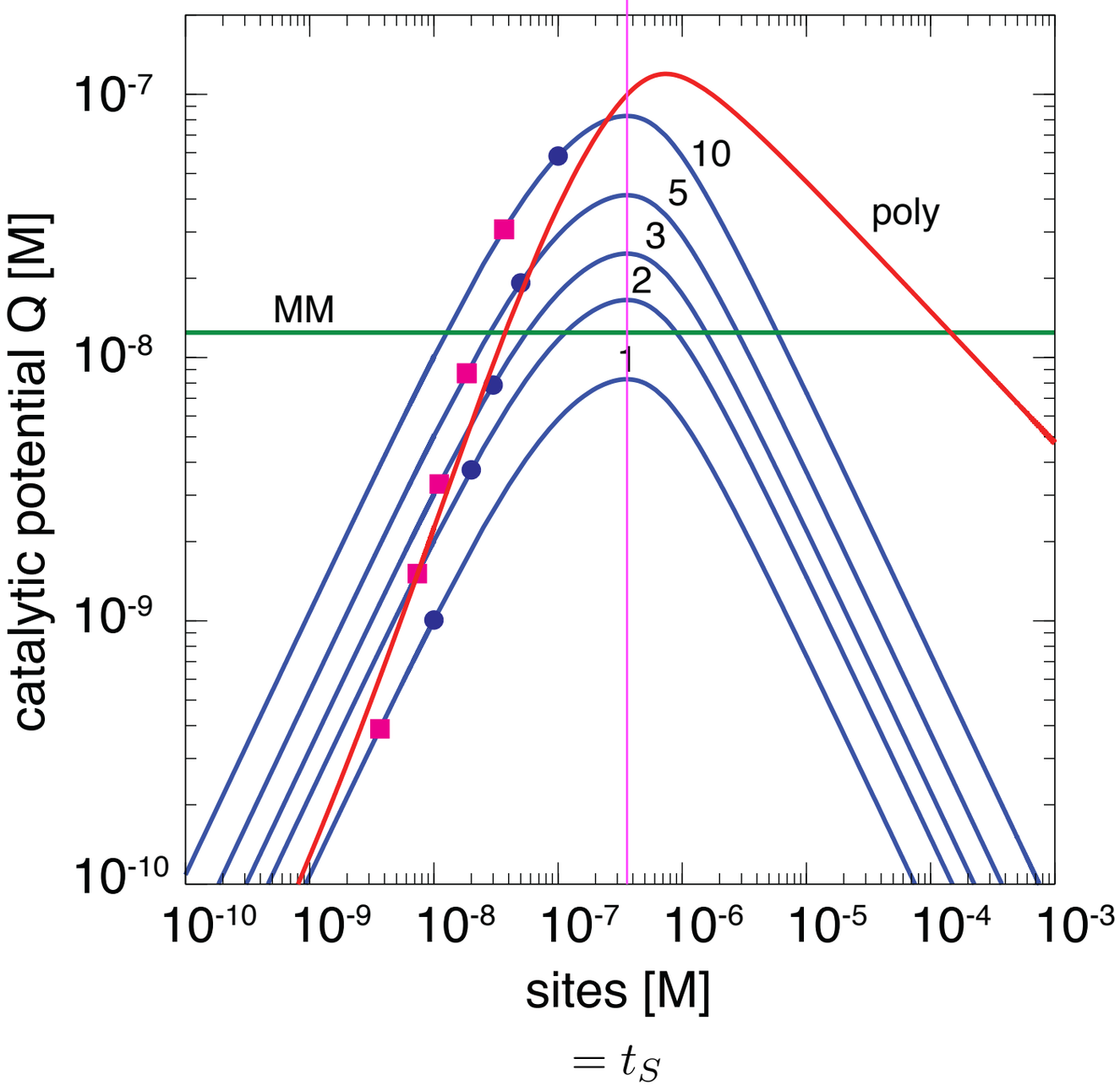
at maximum value of s_n

at maximum dominance of s_n

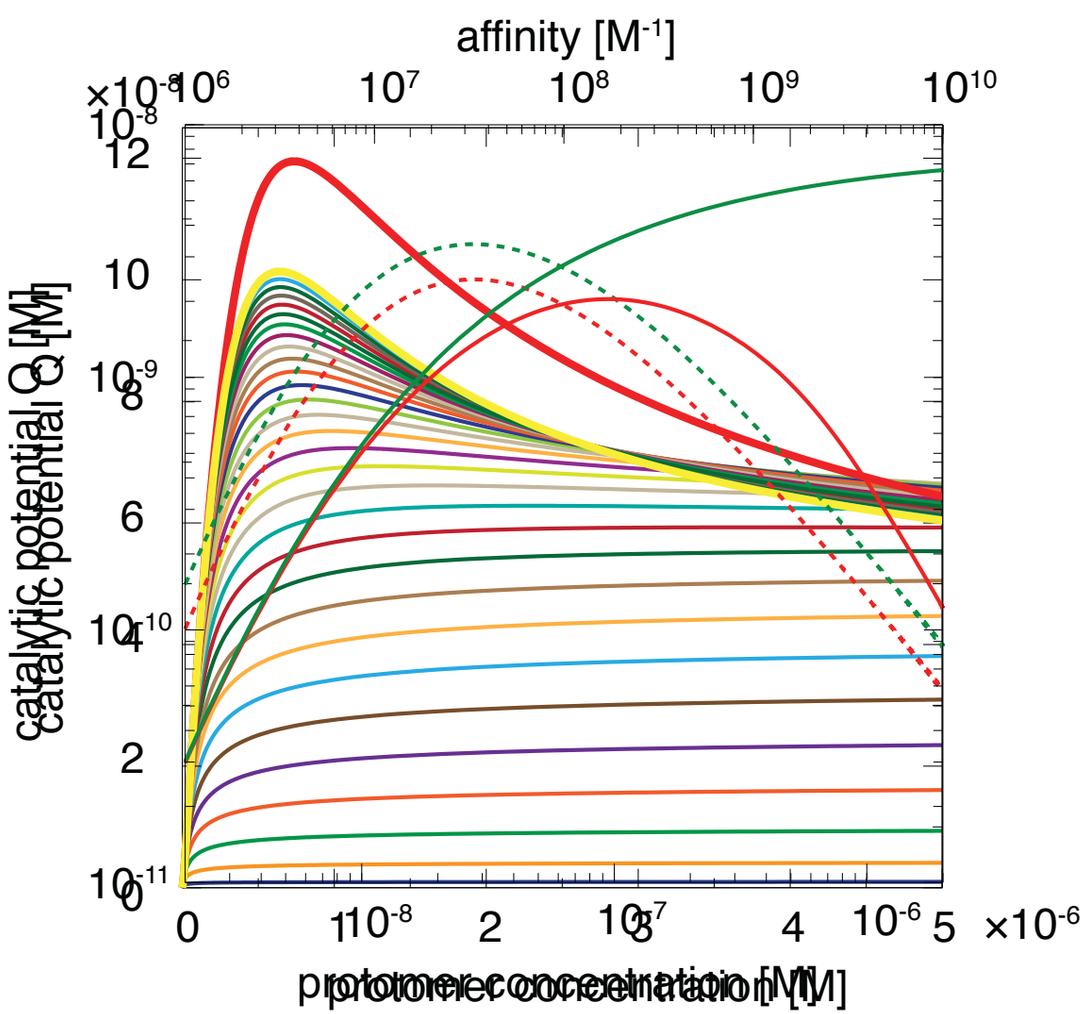
$\alpha = \beta = 10^7\ \text{M}^{-1}, \sigma = 10^8\ \text{M}^{-1}, t_A = 15 \cdot 10^{-9}\ \text{M}, t_B = 0.5 \cdot 10^{-6}\ \text{M}$

Multivalent Scaffolds and Poly-Scaffold

$$t_{S_{(k)}} = \frac{1}{k}\left(\frac{1}{\alpha} + \frac{t_A + t_B}{2}\right)$$

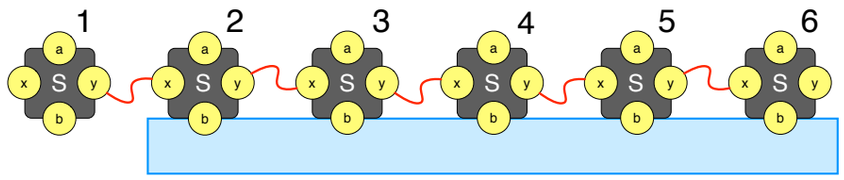


$$= t_S$$

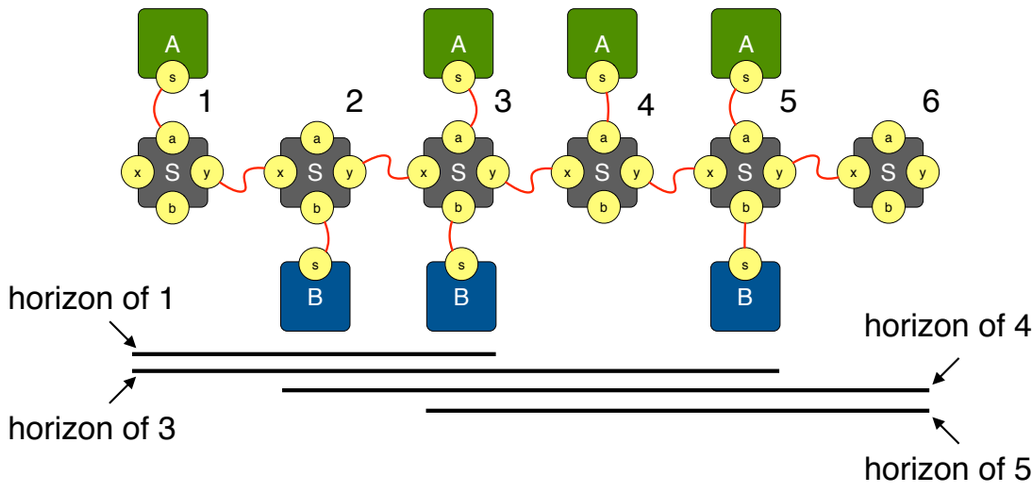


$$\alpha = \beta = 10^7\ \mathrm{M}^{-1}, \sigma = 10^8\ \mathrm{M}^{-1}, t_A = 15 \cdot 10^{-9}\ \mathrm{M}, t_B = 0.5 \cdot 10^{-6}\ \mathrm{M}$$

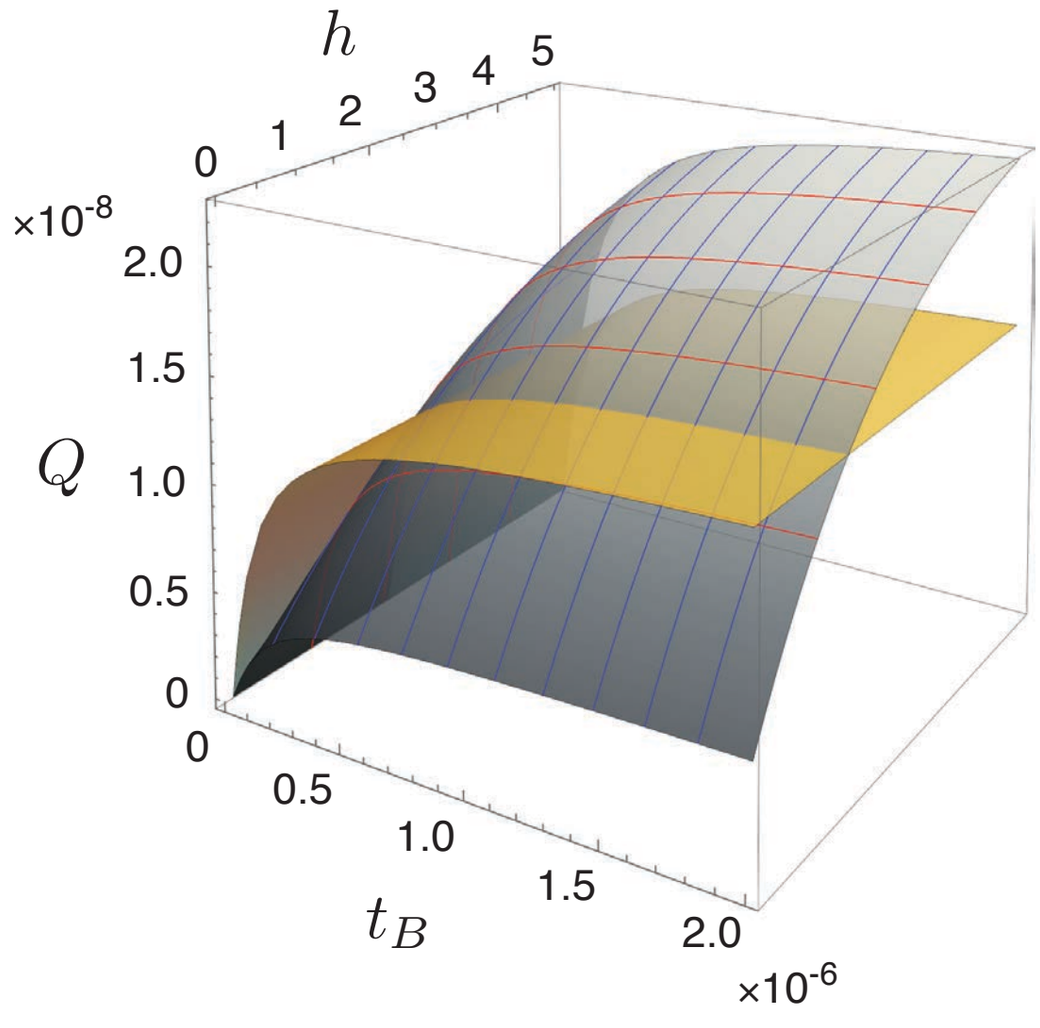
Catalytic Horizon



b-sites within the 2-horizon
of the a-site at position #4



$$Q = p(t_S, t_A, \alpha)\, p(t_S, t_B, \beta)\, \frac{s\left(1 + \sigma s - 2(\sigma s)^{h+1}\right)}{(1 - \sigma s)^3}$$



The Discrete Case

given $t_A \quad t_S \quad t_B$

average "catalytic potential" "catalytic potential" of $S_{l,i,j}$ average number of $S_{l,i,j}$

$$\langle Q \rangle = \sum_{l,i,j} i\, j \, \langle n_{l,i,j} \rangle$$

partition function degeneracy of state n energy of state n

$$Z(\vec{t}) = \sum_{\vec{n}} d(\vec{n}) \varepsilon(\vec{n})$$

# of ways to realize one copy of S_i

resources needed for one copy of S_i

$$\langle n_i \rangle = \varrho_i(\vec{t}) \varepsilon_i \frac{Z(\vec{t} - \vec{\mu}_i)}{Z(\vec{t})}$$

(exponential of) energy of S_i

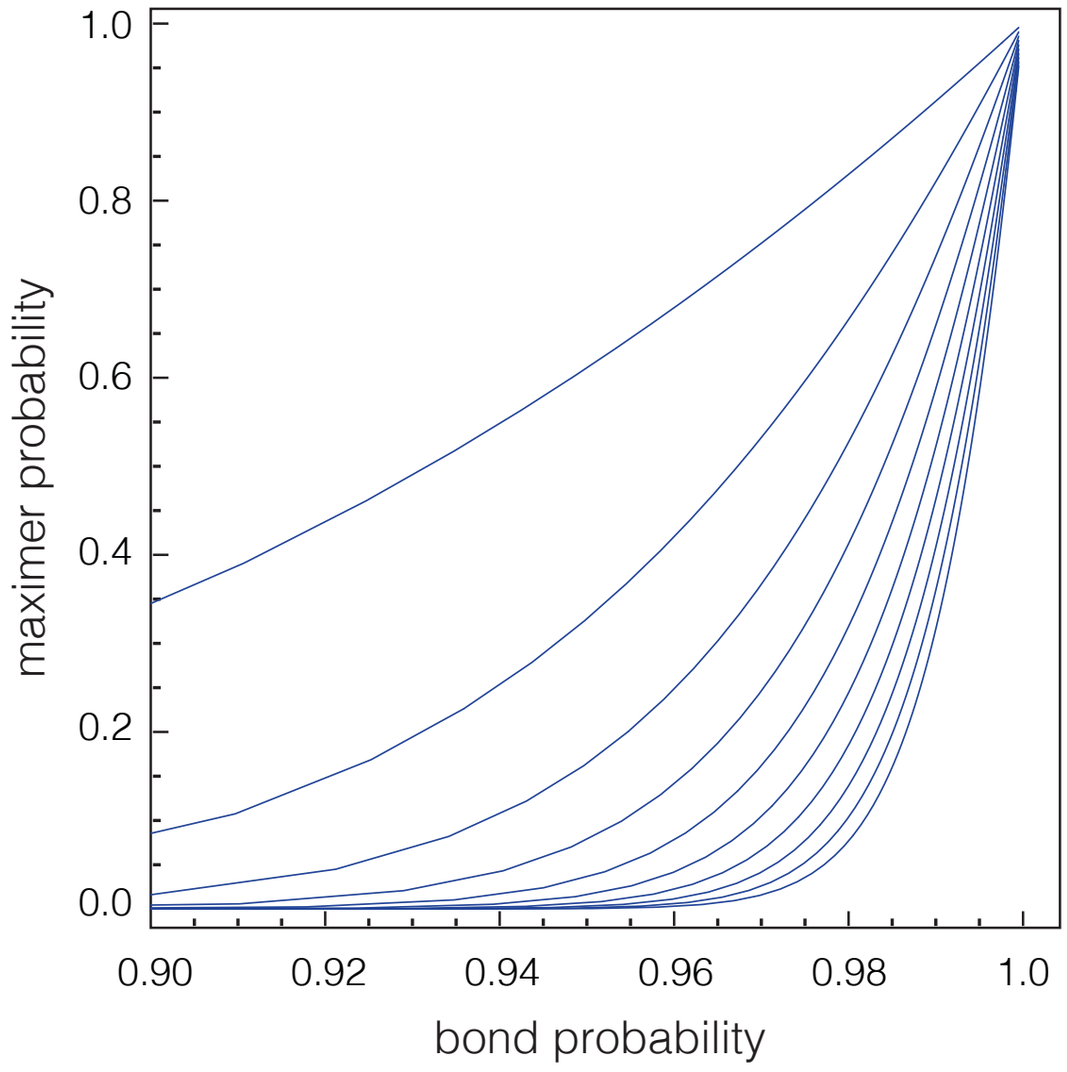
The "Maximer"

bond probability:

$$p = \frac{t_S - W}{t_S} = 1 - \frac{1}{t_S}\frac{s}{1-\sigma s}$$

$$\downarrow$$

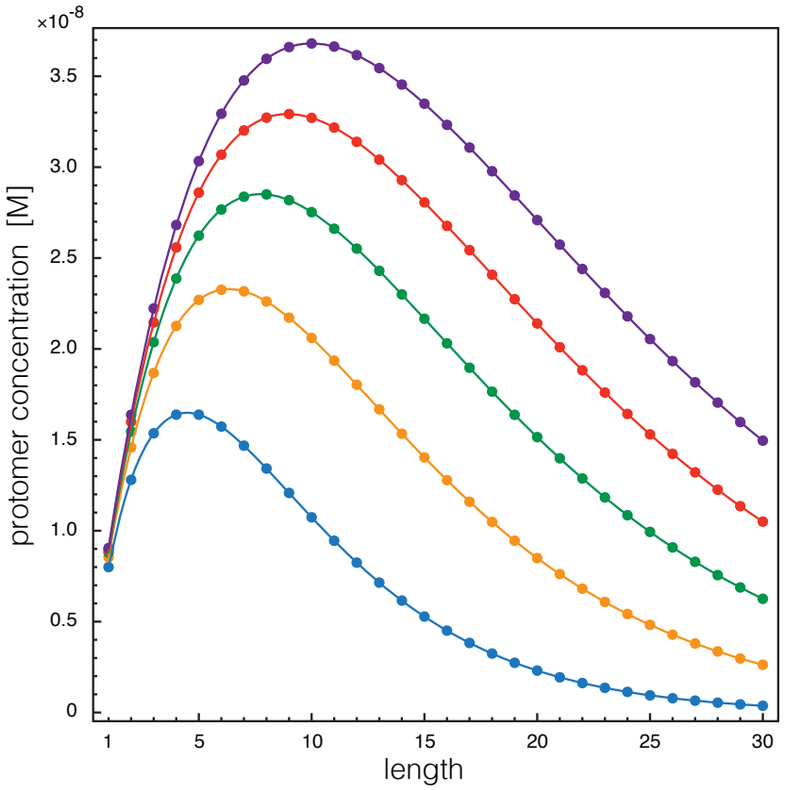
$$p = 1 - \frac{2}{1+\sqrt{1+4\sigma t_S}}$$



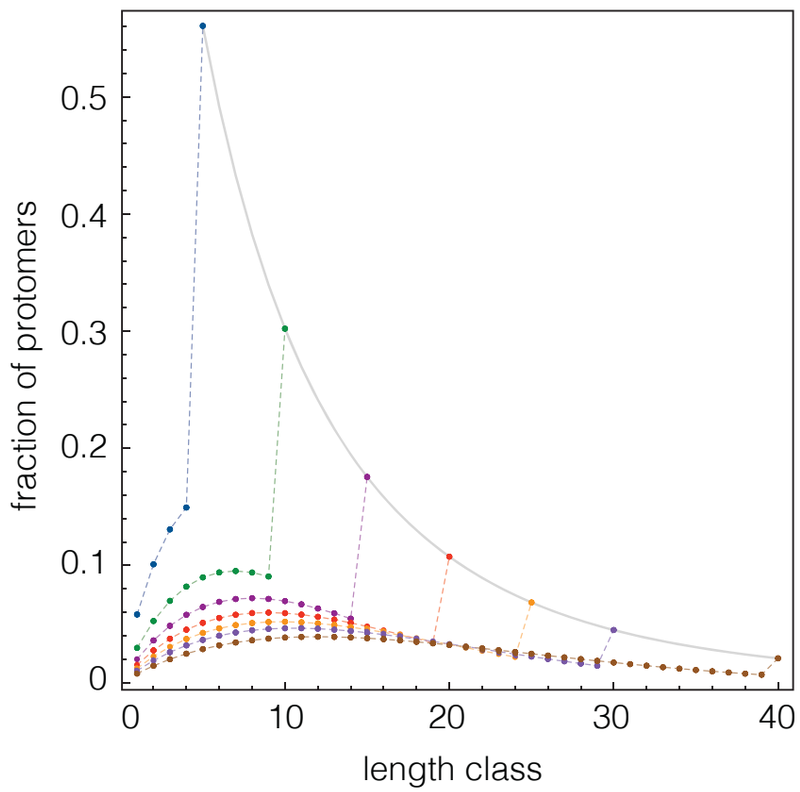
"continuum" vs "discrete" Case

mass distribution as a function of t_S

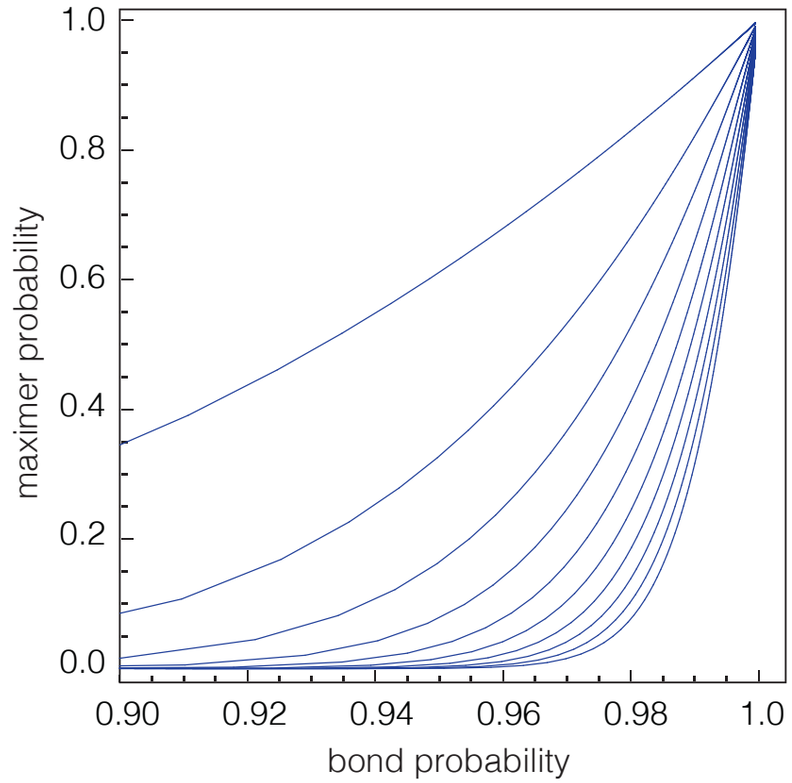
"continuum" version (concentrations)



"discrete" version(particle *numbers*)

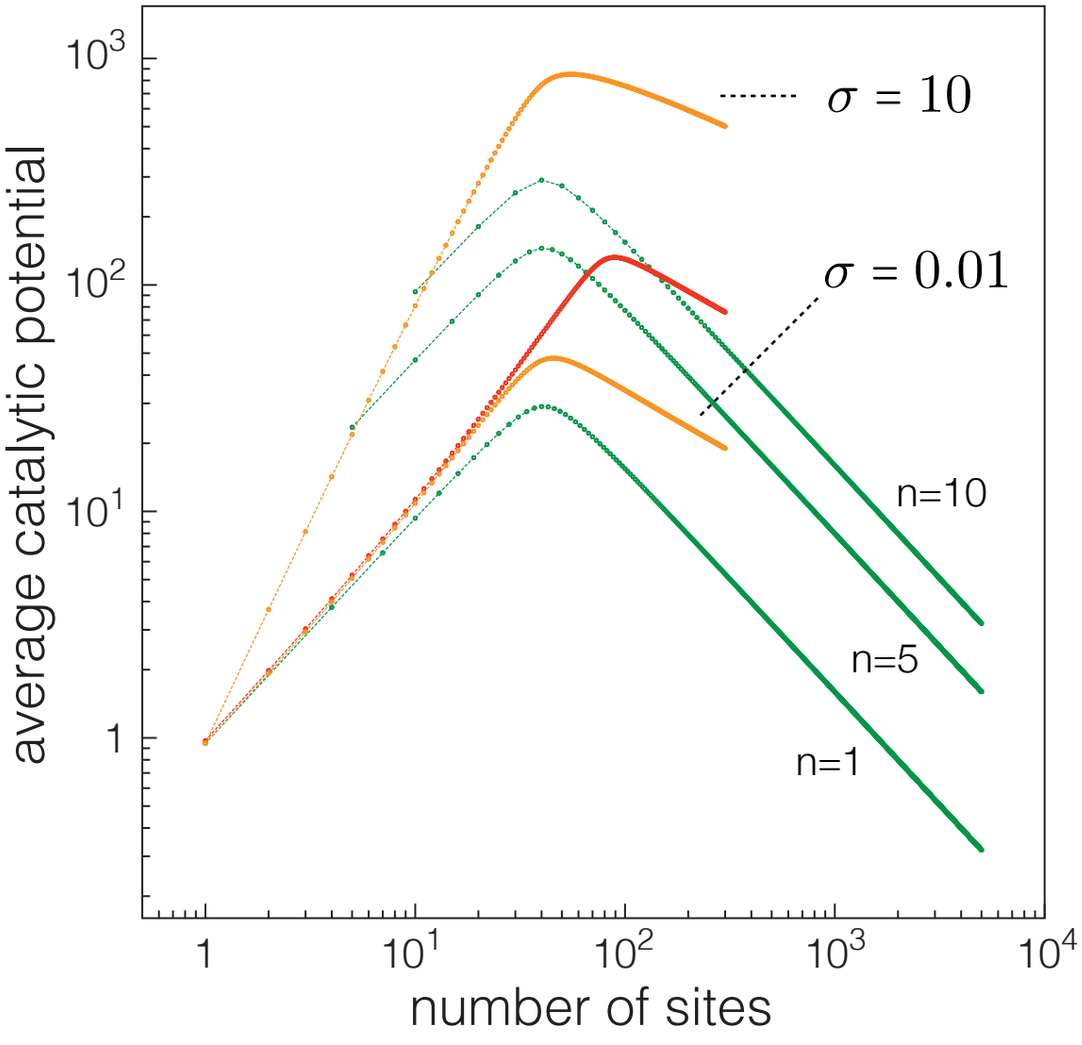


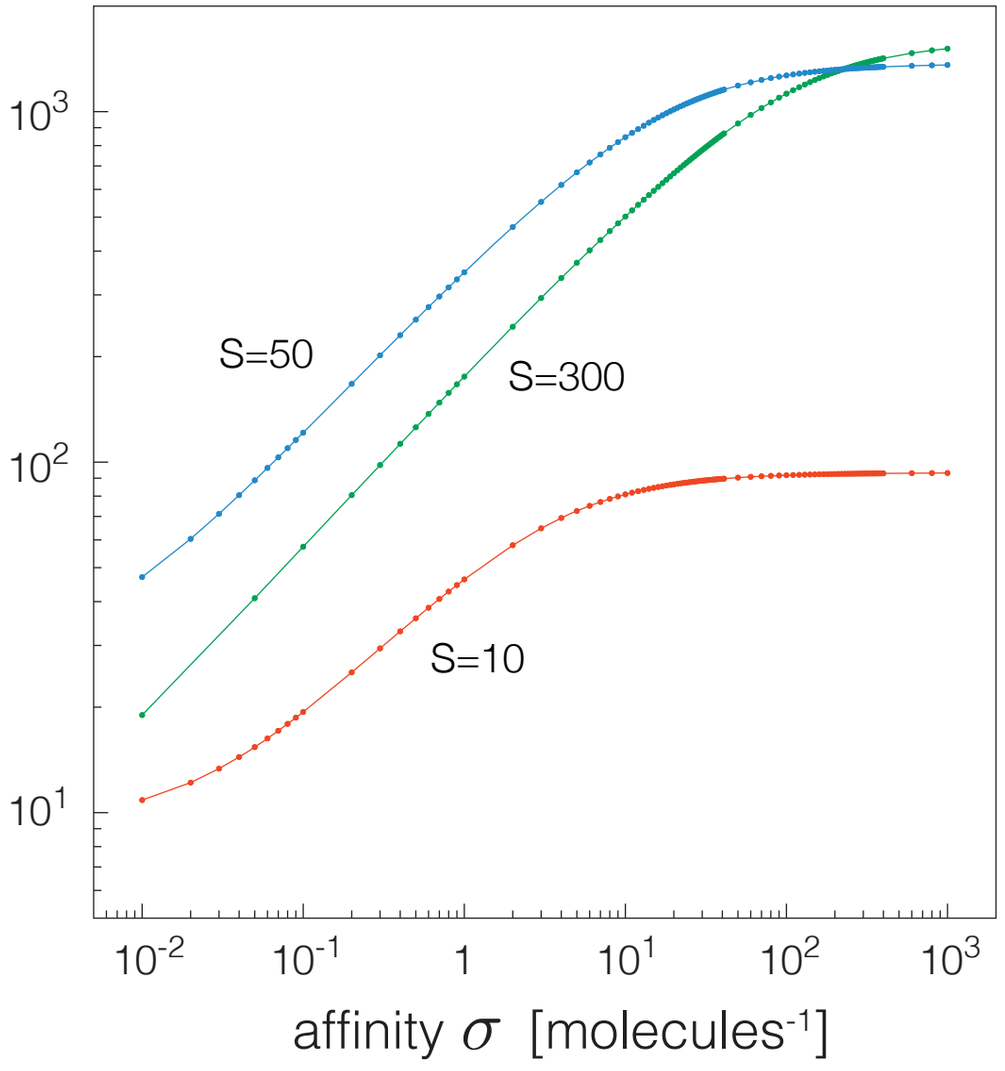
"discrete"



$$p = 1 - 2/(1 + \sqrt{1 + 4\sigma t_S})$$

Equilibrium in the Discrete Case





Conclusions

- linear polymerizing scaffolds have critical points
  achievable in a flow setting, but not in an equilibrium scenario

- poly-scaffolds are highly regulatable
  via affinity and protomer concentration

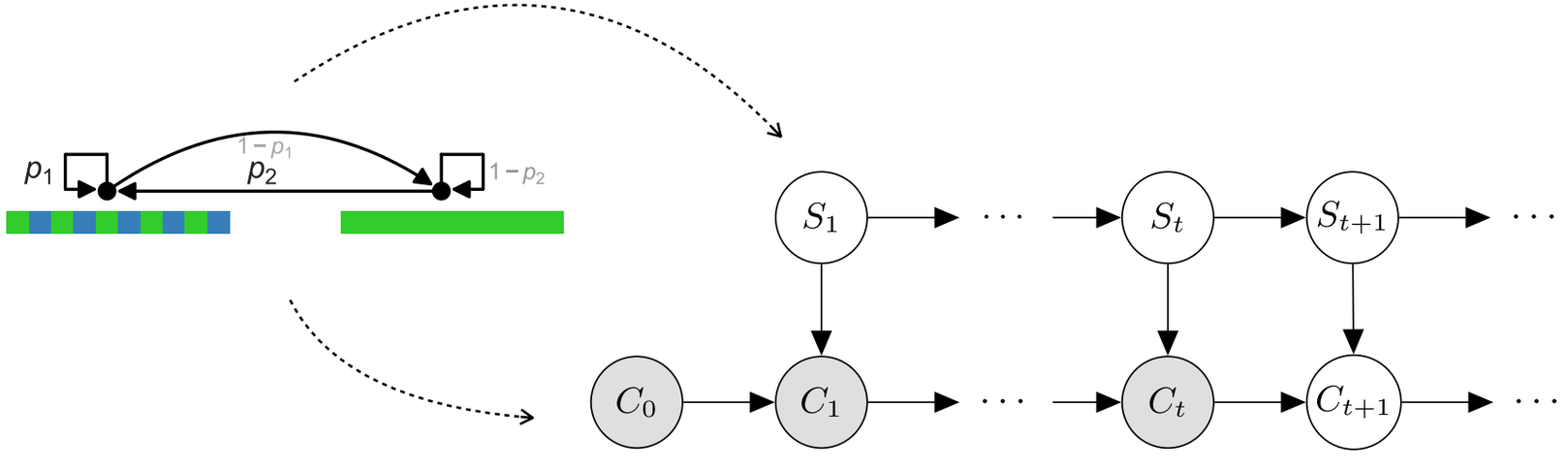
- poly-scaffolds are qualitatively different from multivalent scaffolds
  steeper on the upslope, softer on the downslope

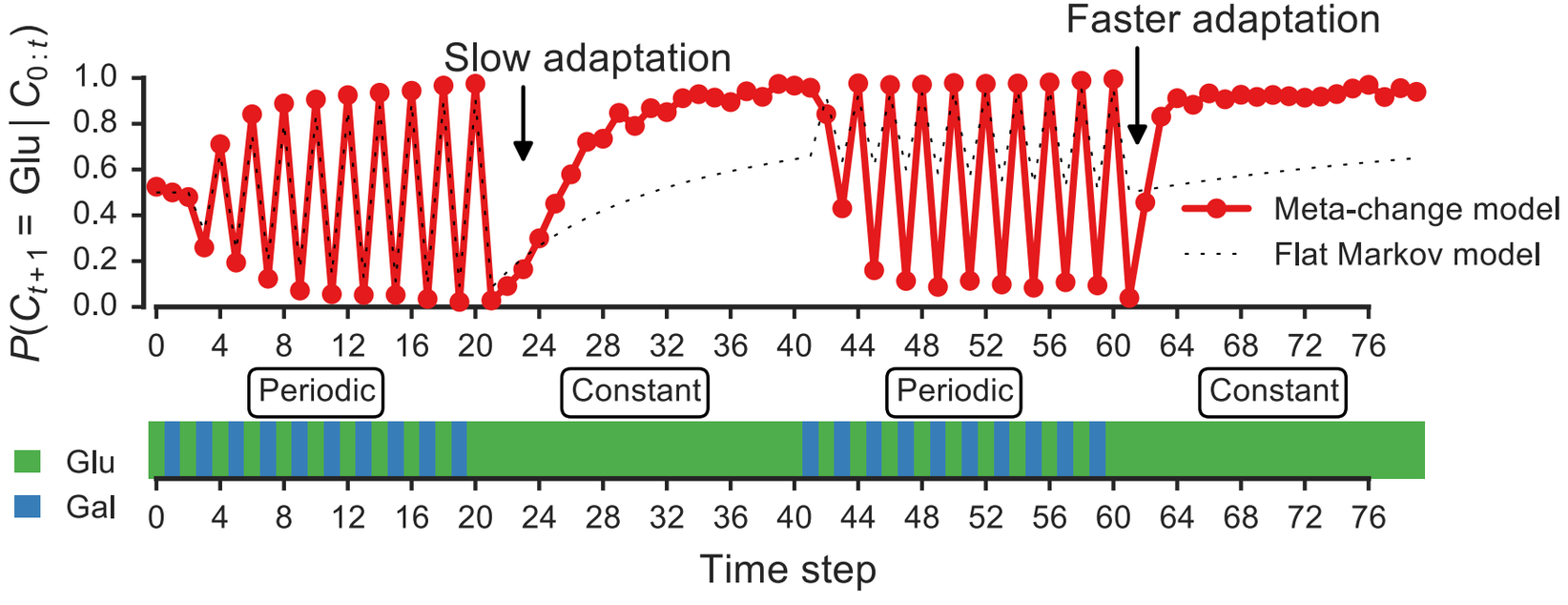
- insights into the prozone effect for general scaffold architectures

Learning

- supervised (e.g. classification)
- unsupervised (e.g. clustering)
- reinforcement (e.g. game playing)

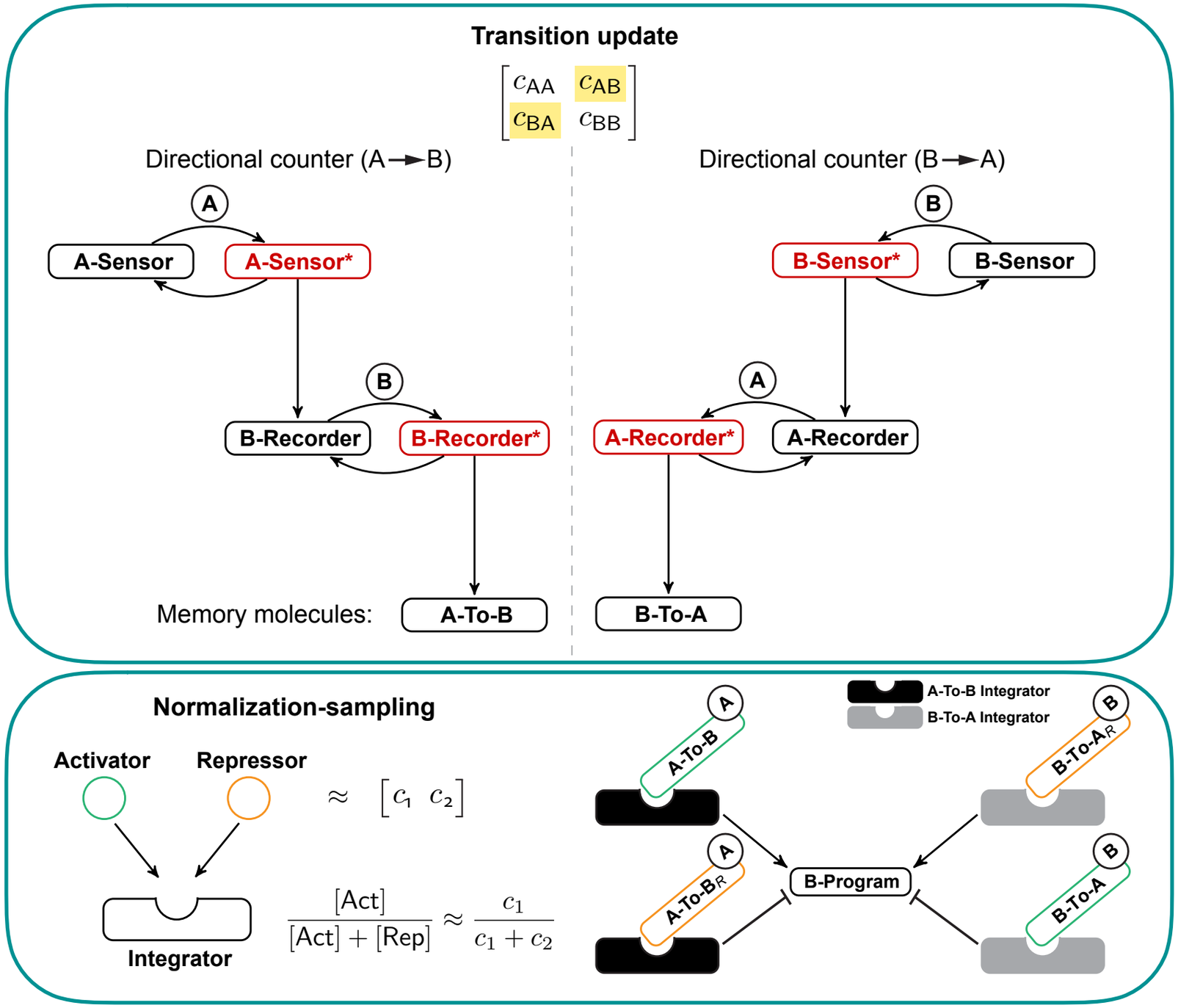
Learning in Changing Environments





Katz and Springer (2016), Probabilistic adaptation in changing microbial environments. *PeerJ* 4:e2716; DOI 10.7717/peerj.2716

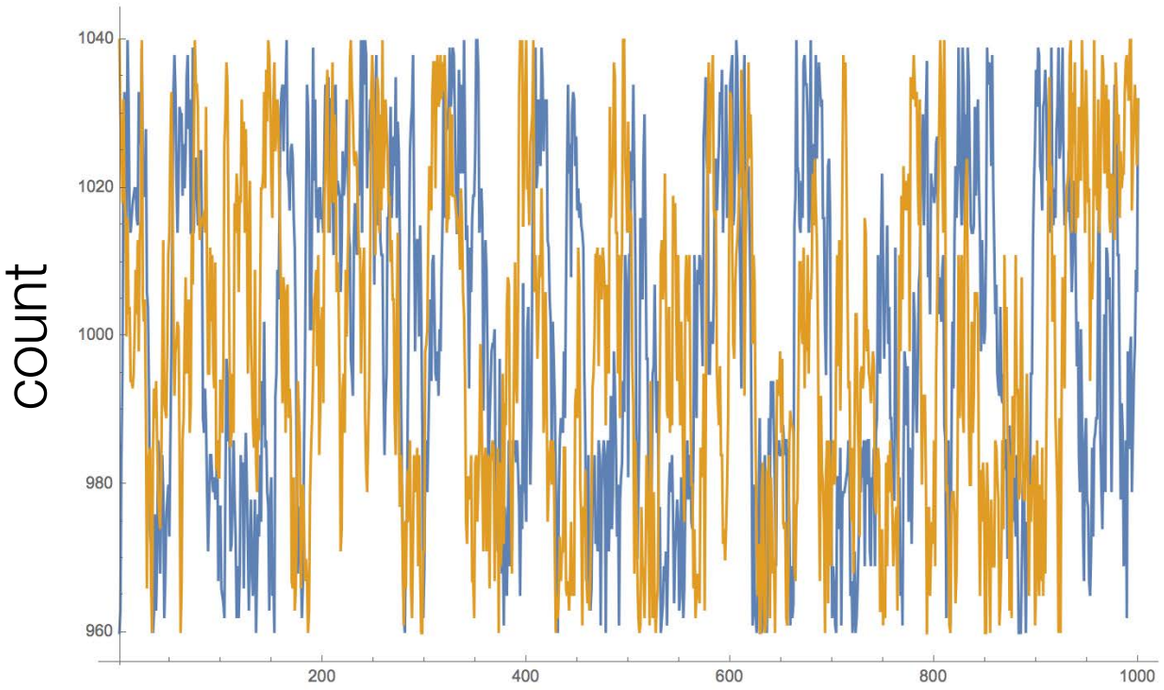
Learning in Changing Environments



?

Katz, Springer, Fontana. Embodying probabilistic inference in biochemical circuits. Work in progress.

Representation of Distributions in Chemical Networks



X

Y

$$\pi(s|s_0) = \frac{1}{M_{s_0}} \prod_{i=1}^{M} \frac{e^{-s_i G_i}}{s_i!}$$

The stationary distributions of detailed balanced systems consist exclusively of restrictions of products of Poisson distributions.

Y

X

Every distribution with finite support can be expressed as the marginal of the limit distribution of some detailed balanced system.

D. Cappelletti, A. Ortiz-Muoz, D. Anderson, E. Winfree. Stochastic Chemical Reaction Networks for Robustly Approximating Arbitrary Probability Distributions. *Theoretical Computer Science* 801 (2020) 6495

Representation of Distributions in Chemical Networks

Define chemical species $P_{i,j}$

such that

$\#P_{i,j} = 1$ if and only if $\#X = i$ and $\#Y = j$

using

$P_{i,j} \rightleftharpoons P_{i+1,j} + X$

$P_{i,j} \rightleftharpoons P_{i,j+1} + Y$

with

$G_X = 0$

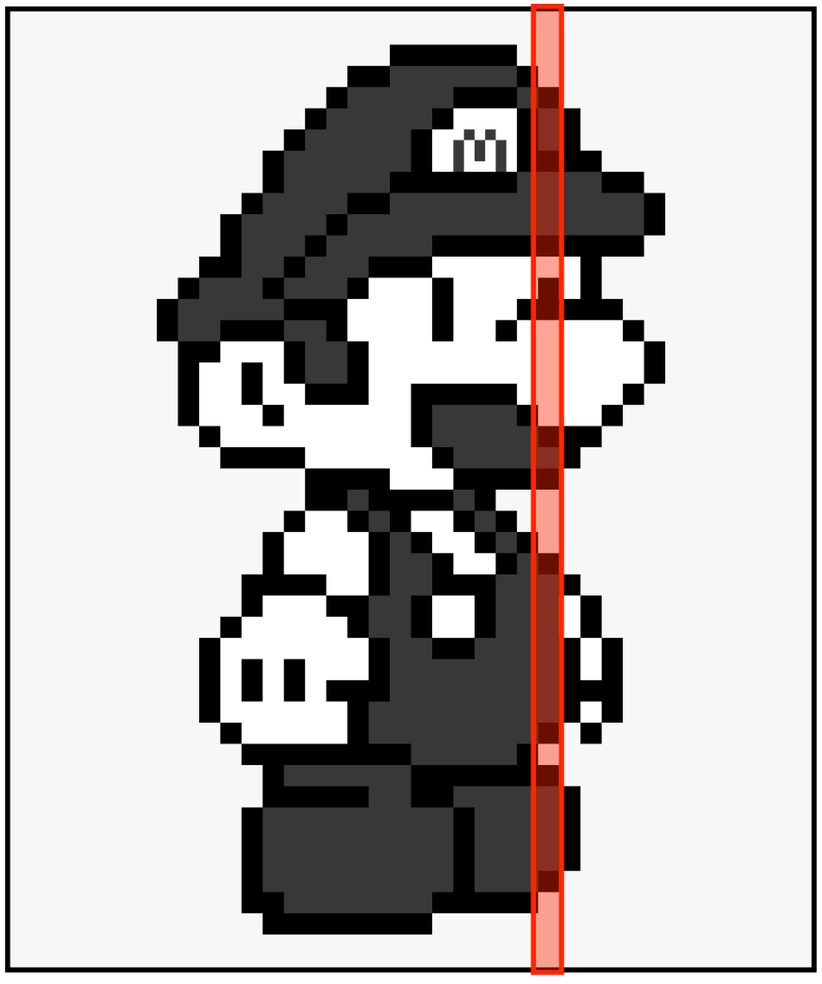
$G_Y = 0$

(free energies of formation)

$G_{i,j} = -\ln(i!\, j!\, p_{ij})$

and appropriate initial condition $(\#P_{i,j}, \#X, \#Y)$

(fix X to condition)

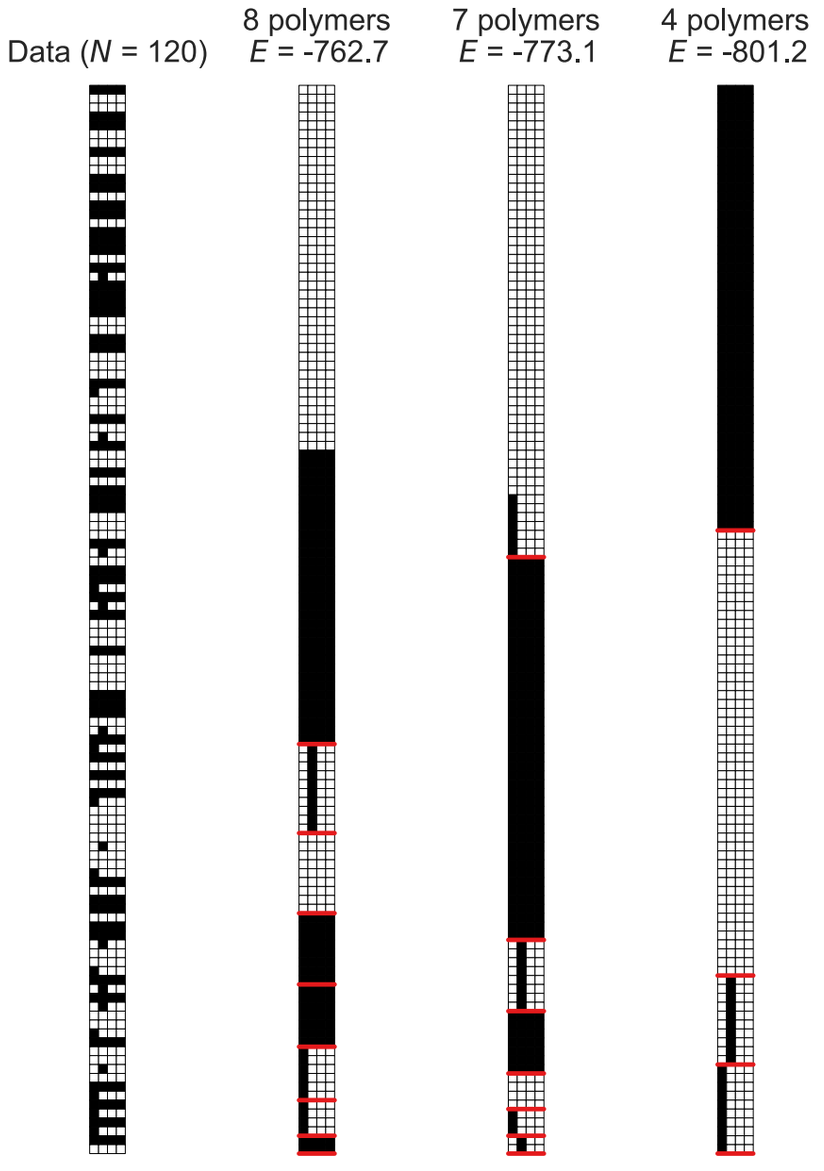


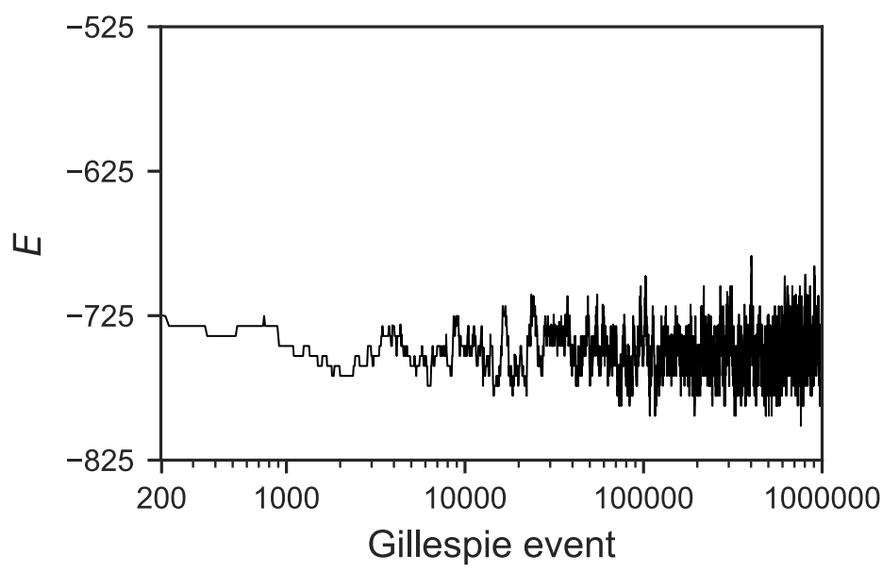
Y

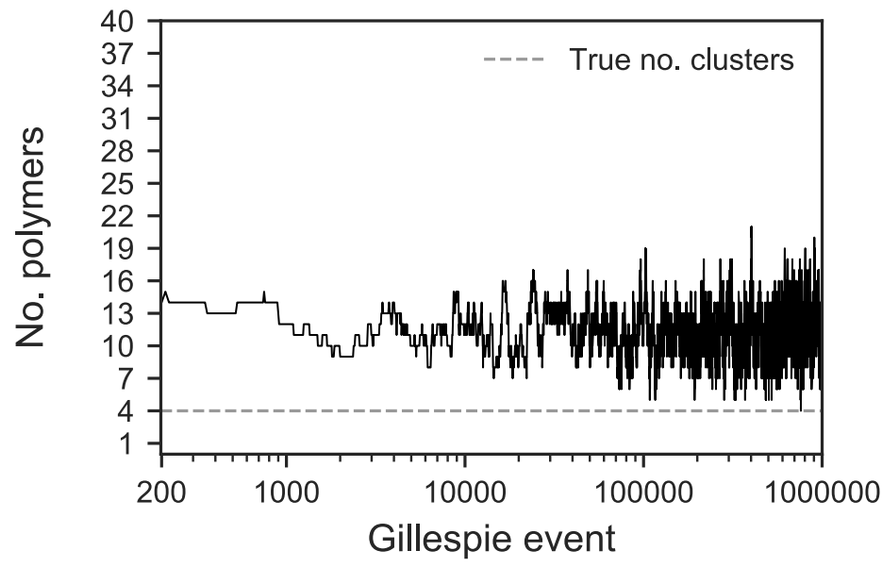
X

D. Cappelletti, A. Ortiz-Munoz, D. Anderson, E. Winfree. Stochastic Chemical Reaction Networks for Robustly Approximating Arbitrary Probability Distributions. *Theoretical Computer Science* 801 (2020) 6495

Clustering By Polymerization



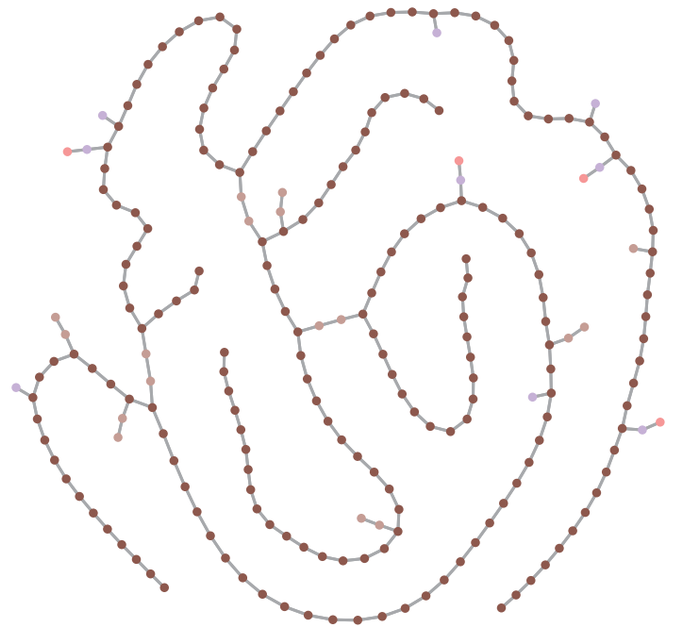




$$K_{ij} = e^{-(d(i,j)+\varepsilon)/\beta}$$

Katz, Fontana. Probabilistic data clustering with polymer equilibria. Work in progress

Transient "Molecular Synapses" Between Pathways?



controllable facilitation of crosstalk

The Main Themes of the Course

Encoding of phenotype by a genotype and environment (e.g. neutrality)

Exploitation vs exploration (e.g. error thresholds)

Mechanistic modeling of cellular information processing

models based on unstructured agents (ODE, master equations)

models based on structured agents (graph-rewriting)

a “language of circuits” vs a “language of interactions”

Causality via non-determinism and via probability

hard vs soft causality

enablement vs counterfactuals

How to deploy these ideas to study mechanisms of learning?

Thank YOU !

Frédéric Doyen

Raynald Belay

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