chemosensors

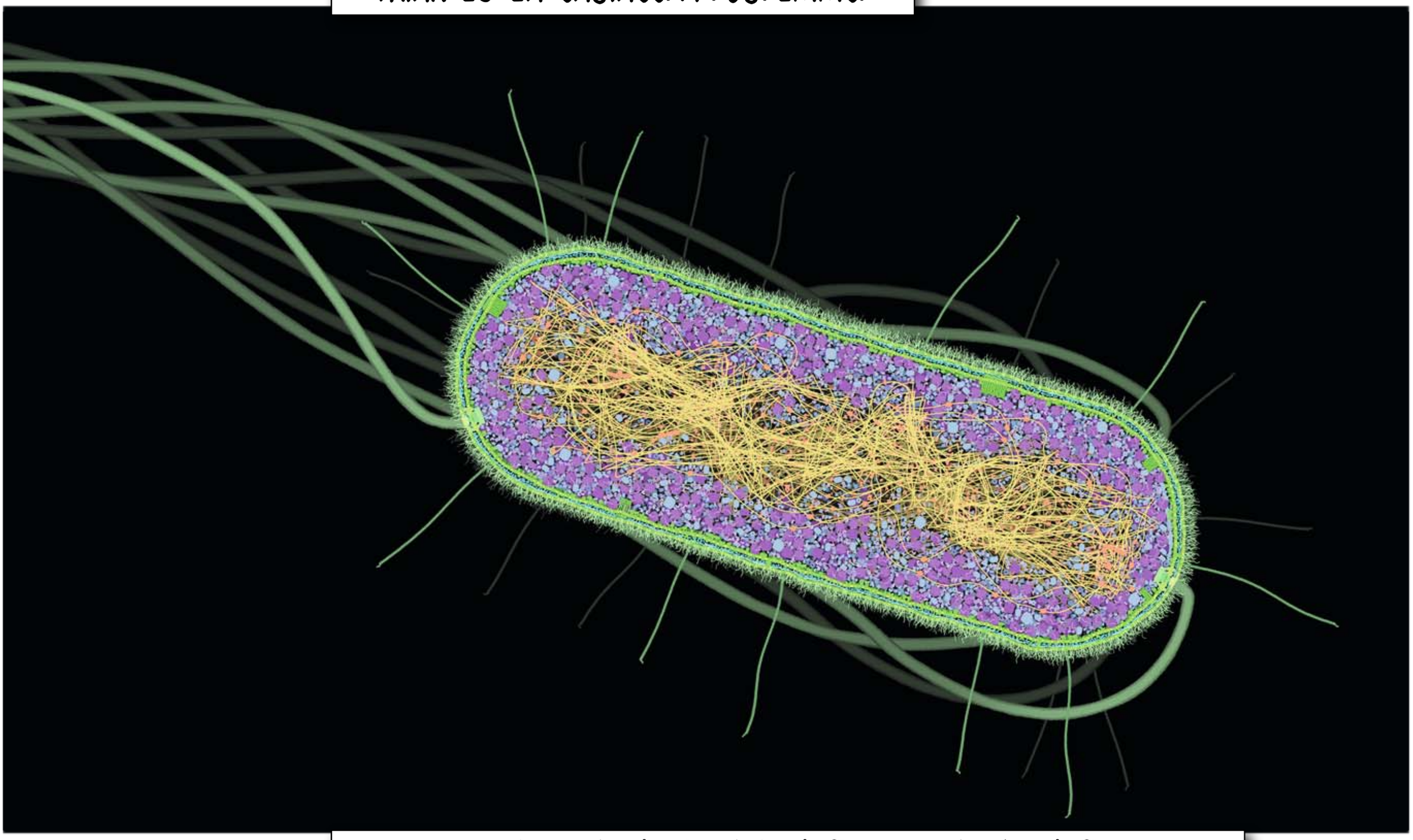
SBM I

vincent Danos

u of Edinburgh, CNRS

pretty neat machine!

think as an engineer/programmer



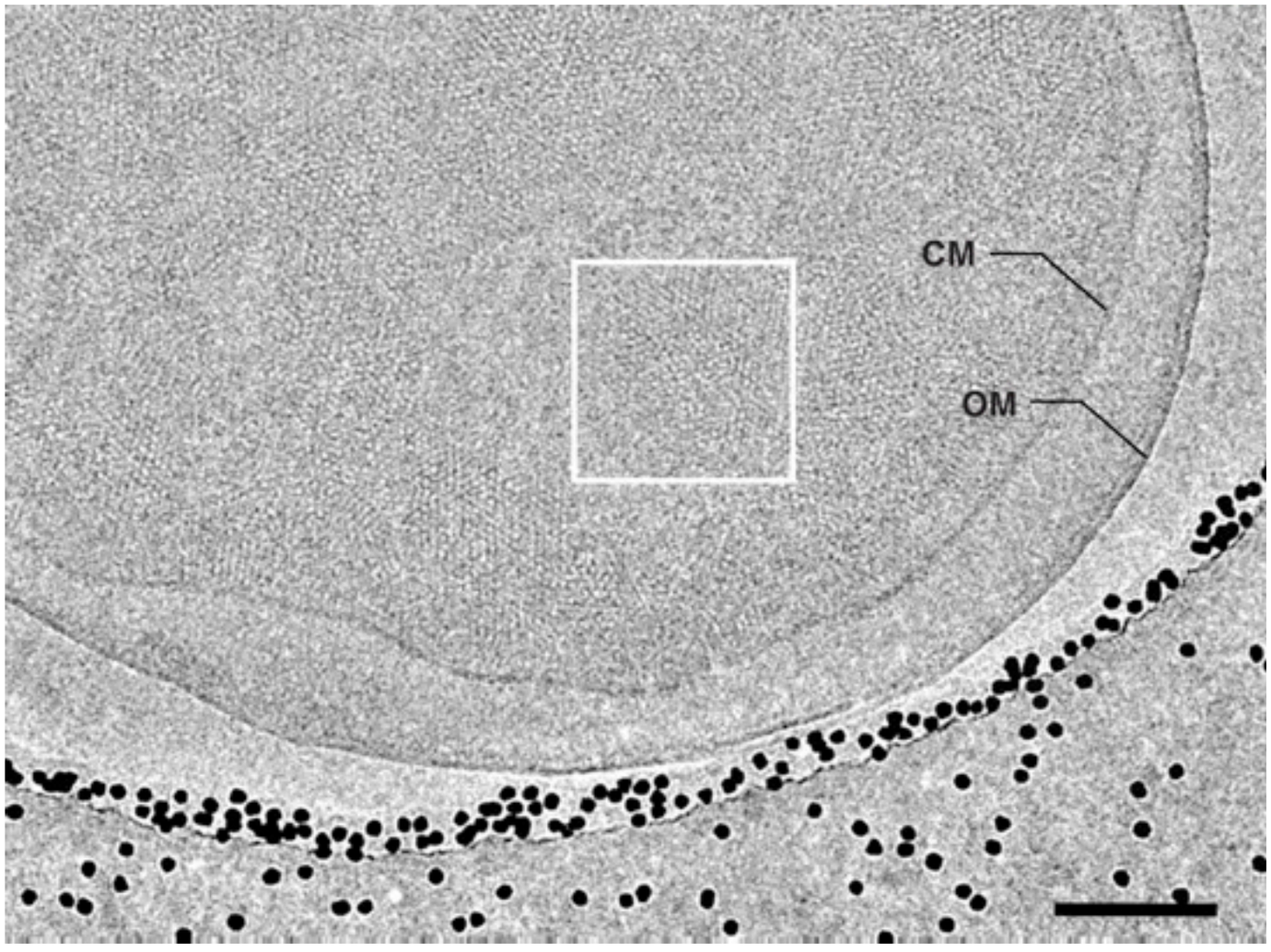
SYNBIO= to look at biology as a technology

1

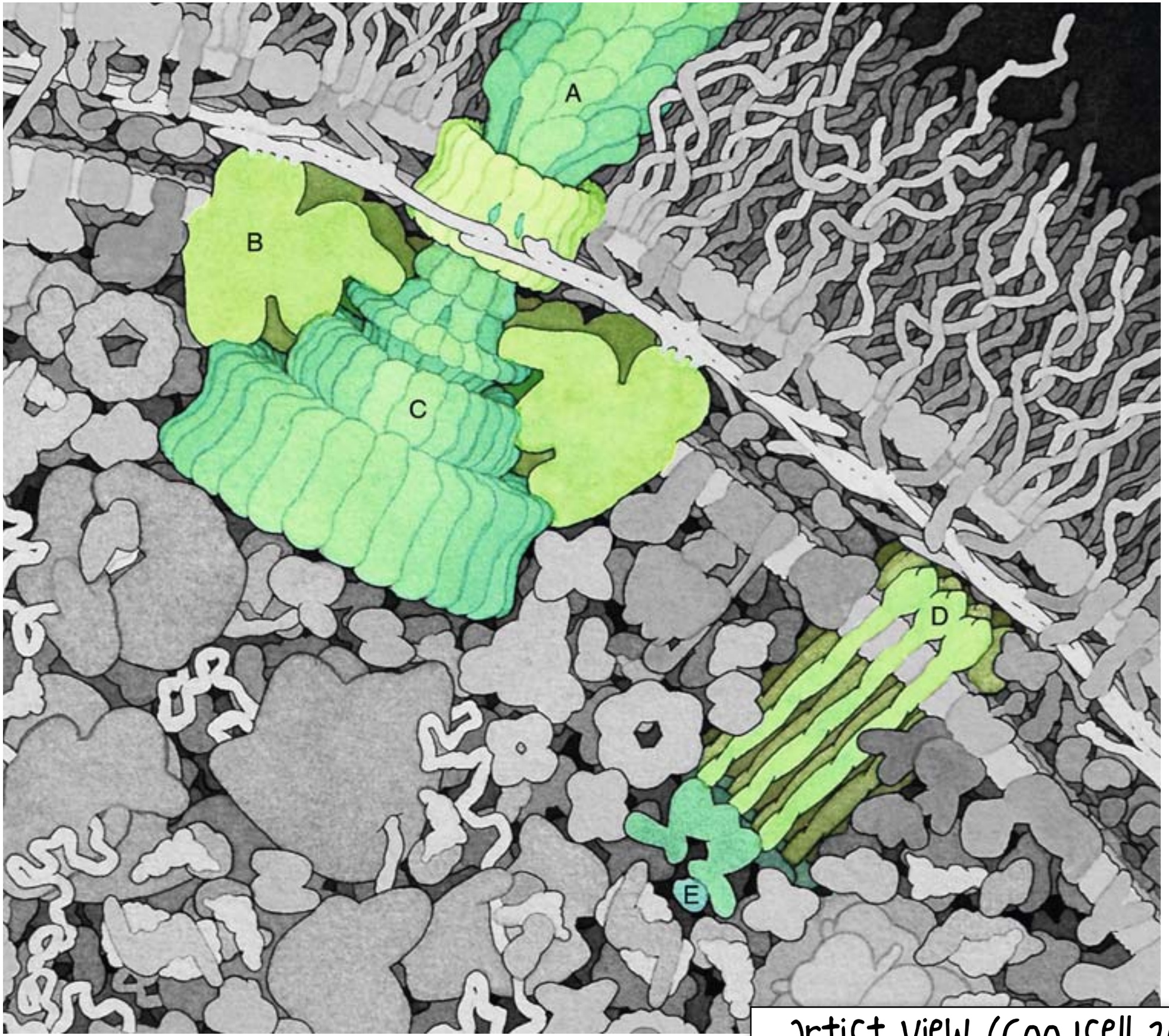
bacterial chemosensors

the concept of adaptation

Cryo-electron microscopy of Tsr chemoreceptor assemblies in E. coli.



Khursigara et al. PNAS 2008;105

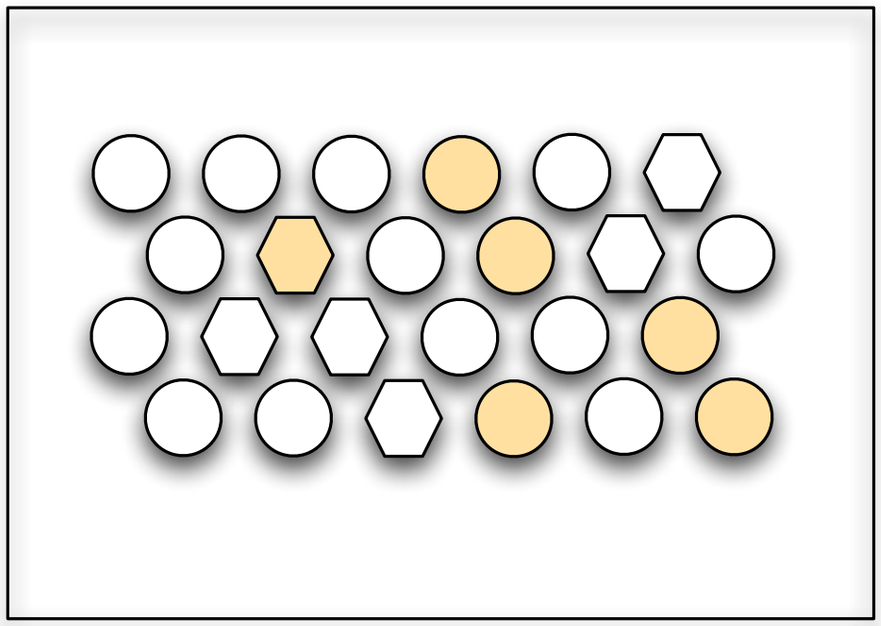


artist view (Goodsell 2010)

high level view & properties

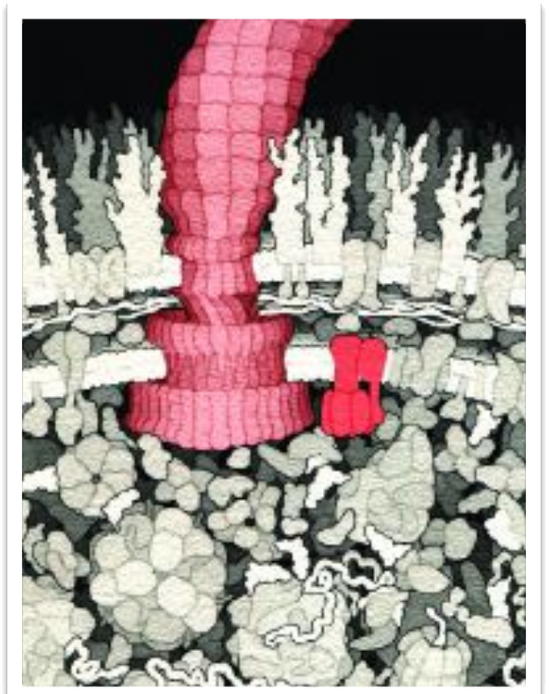
inputs/ligand

receptor array



CheY*

ultra-sensitive engine



- sensitivity
- range
- multitype
- adaptation

difference engine, need to stay in the engine zone

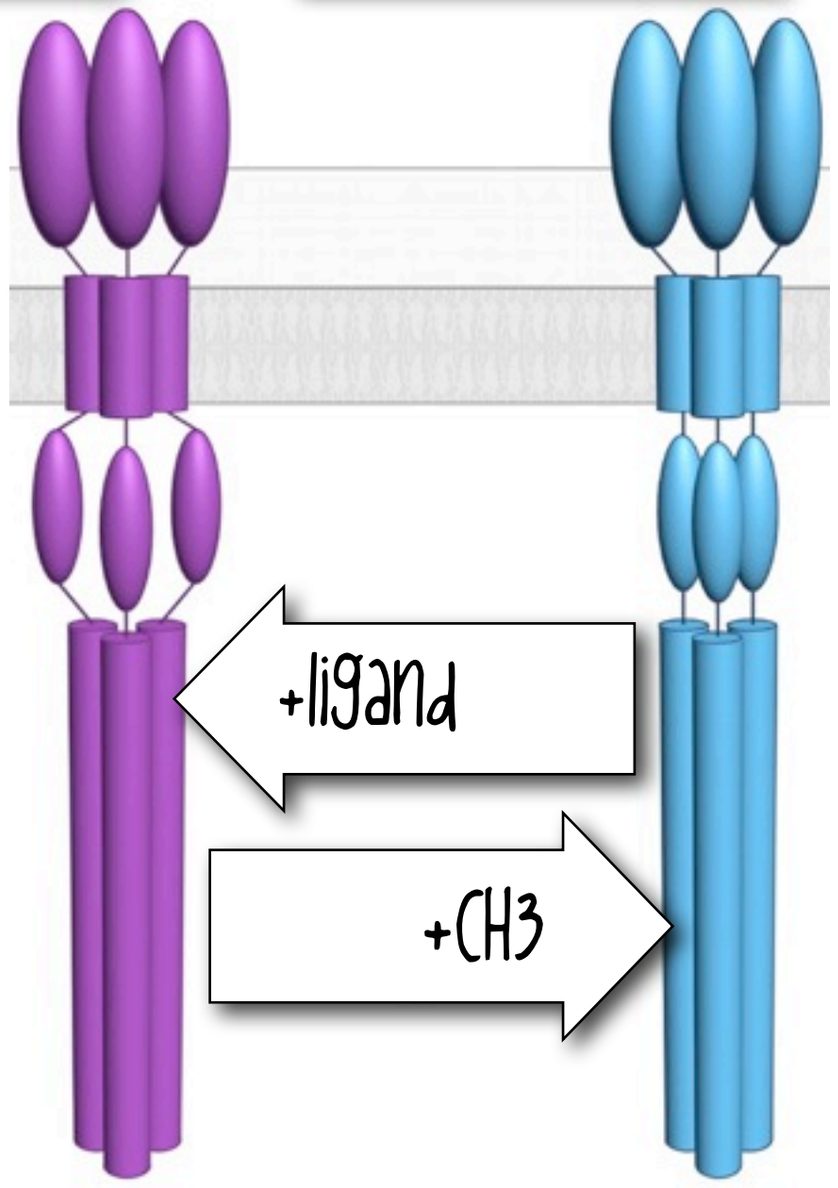
low level view

conformational signaling in chemoreceptor 3x2-mers

favoured by +lig

favoured by +CH3

Kinase off
a=0

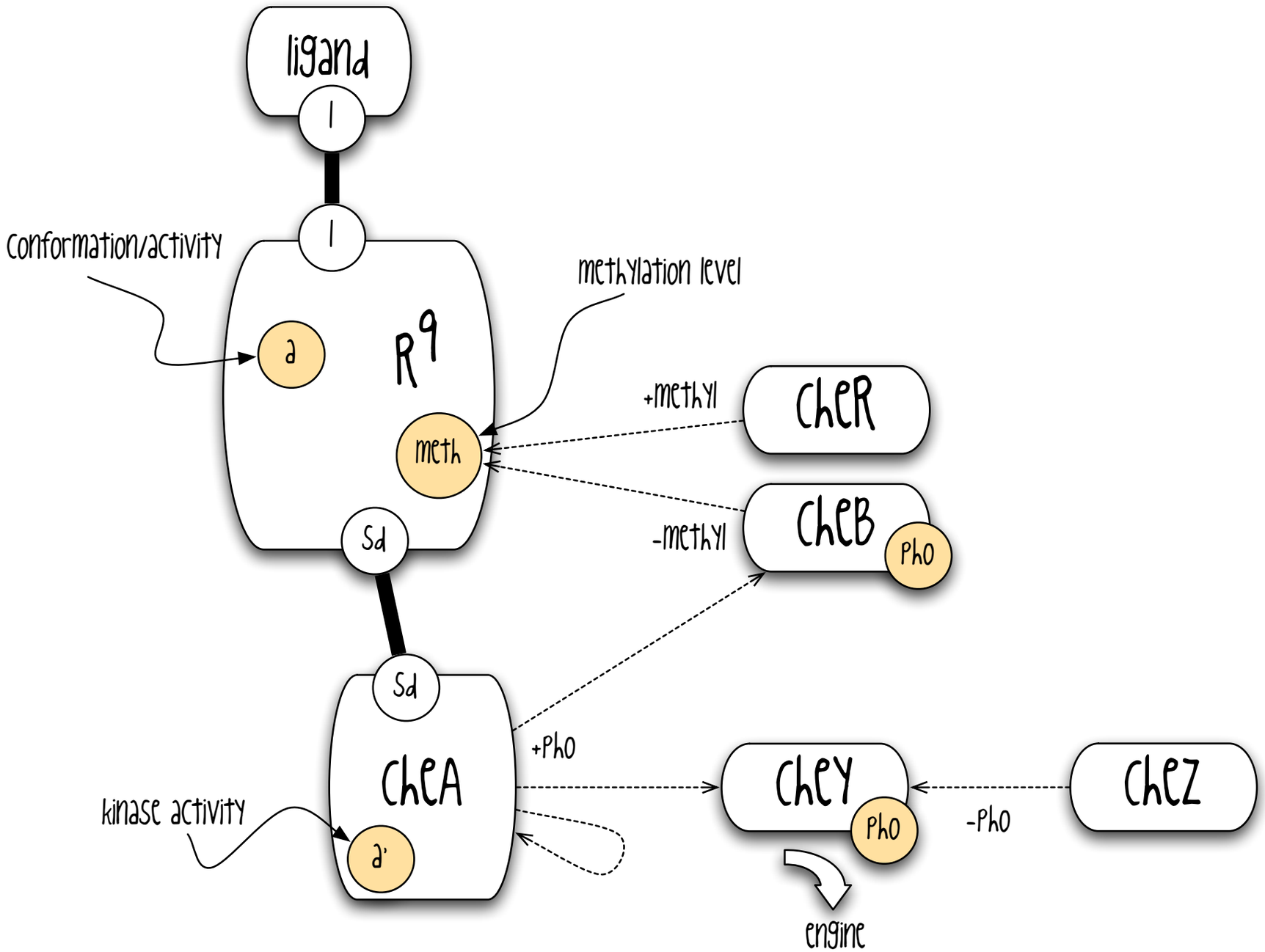


Kinase on
a=1

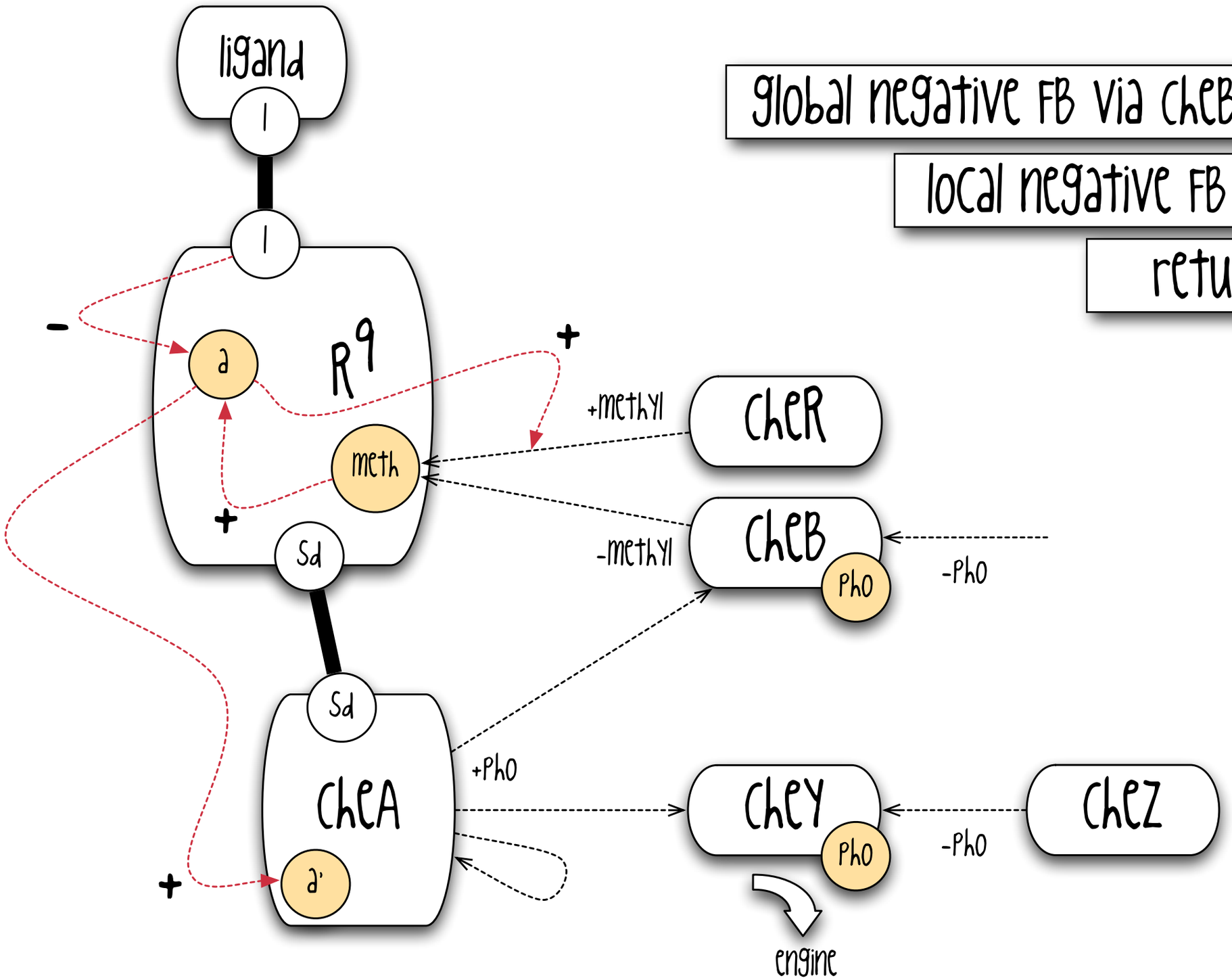
favours +CH3
negative FB

Khursigara et al. PNAS 2008;105

Contact & Catalytic Graph



allosteric graph & the 2 feedbacks



global negative FB via CheB

local negative FB via meth

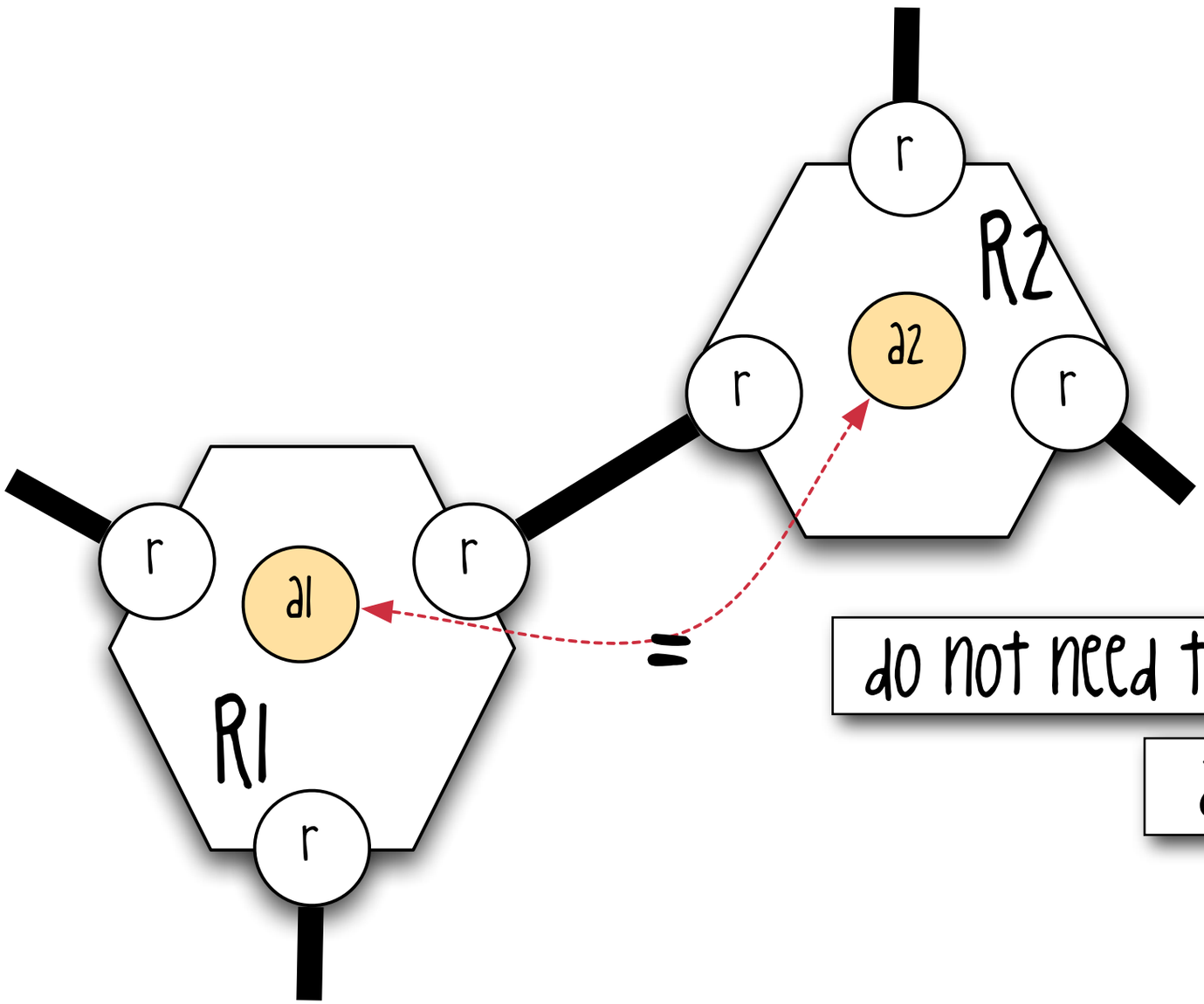
return to <a>

allosteric graph 2

conformational spread (Bray et al.1999)

amplification

hexagonal lattice



do not need to be of the same type!

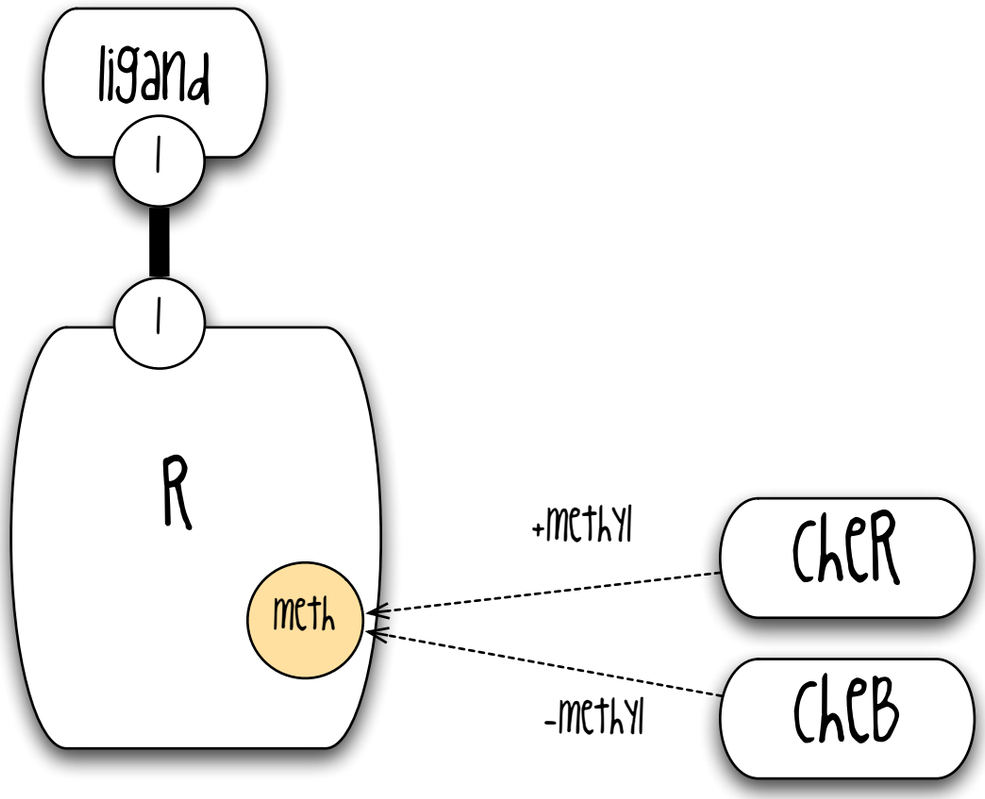
array structure matters ...

2

Perfect adaptation - conceptually

W. Fontana 2008 lecture notes

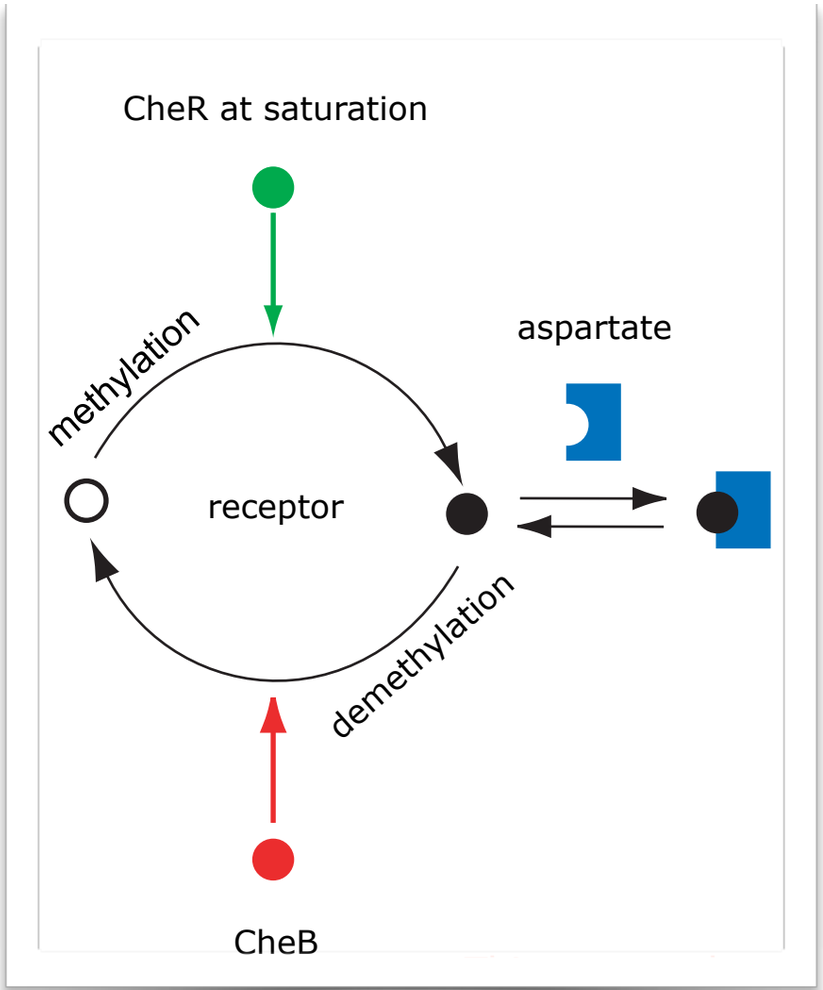
pause for a minimalistic model

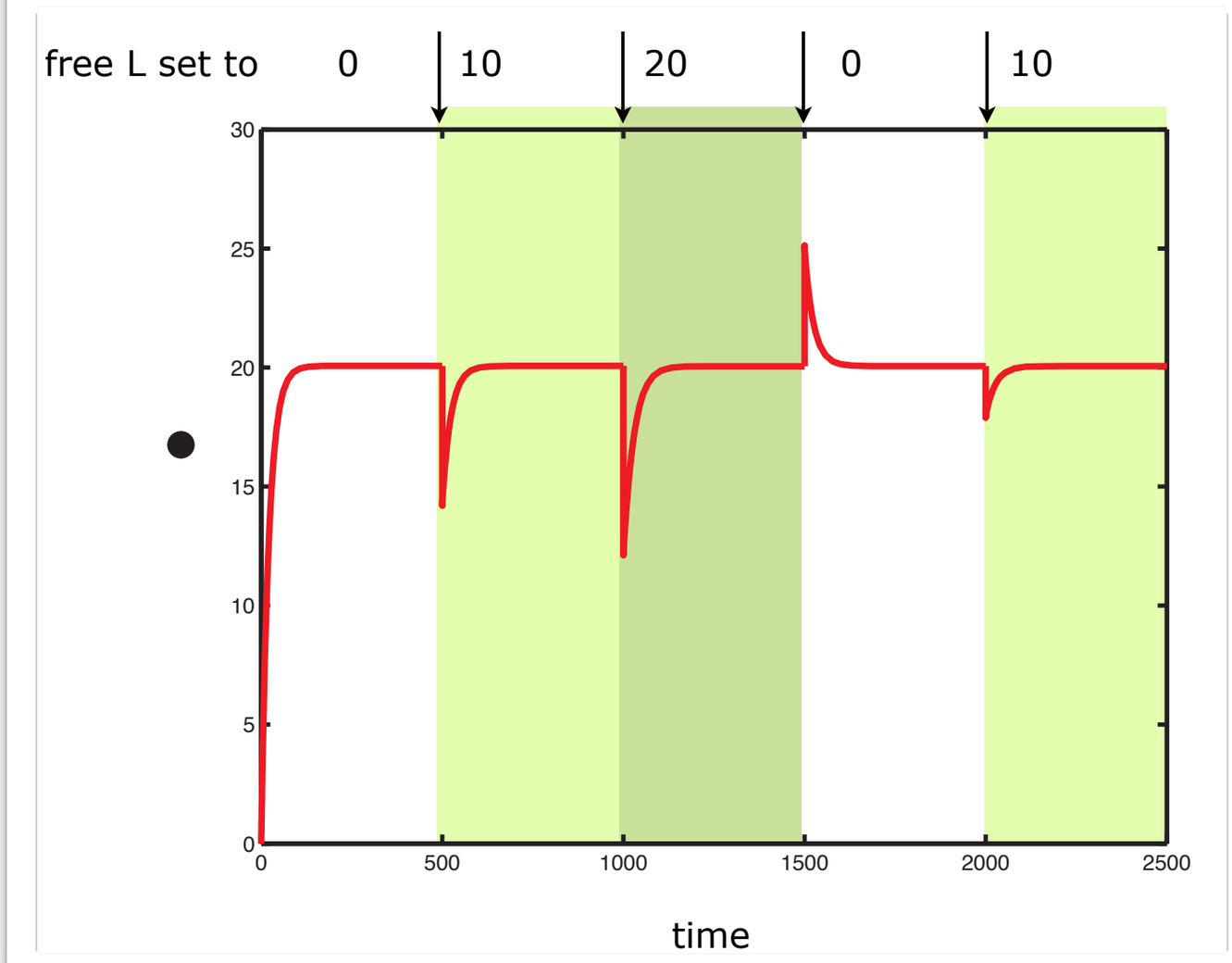


perfect adaptation - conceptually

qualitative kinetics

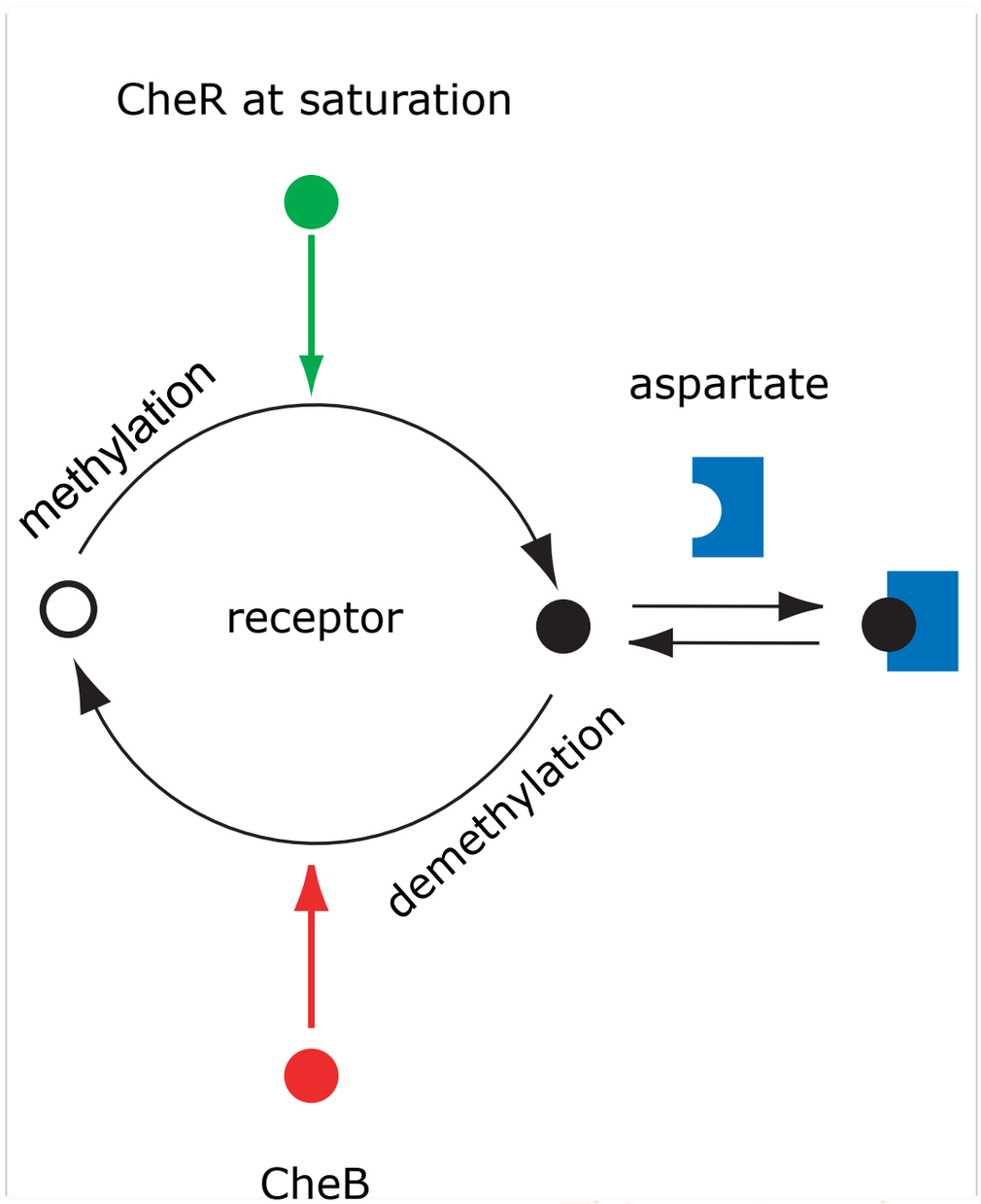
CheR saturated - 0th order kinetics
flux independent of input

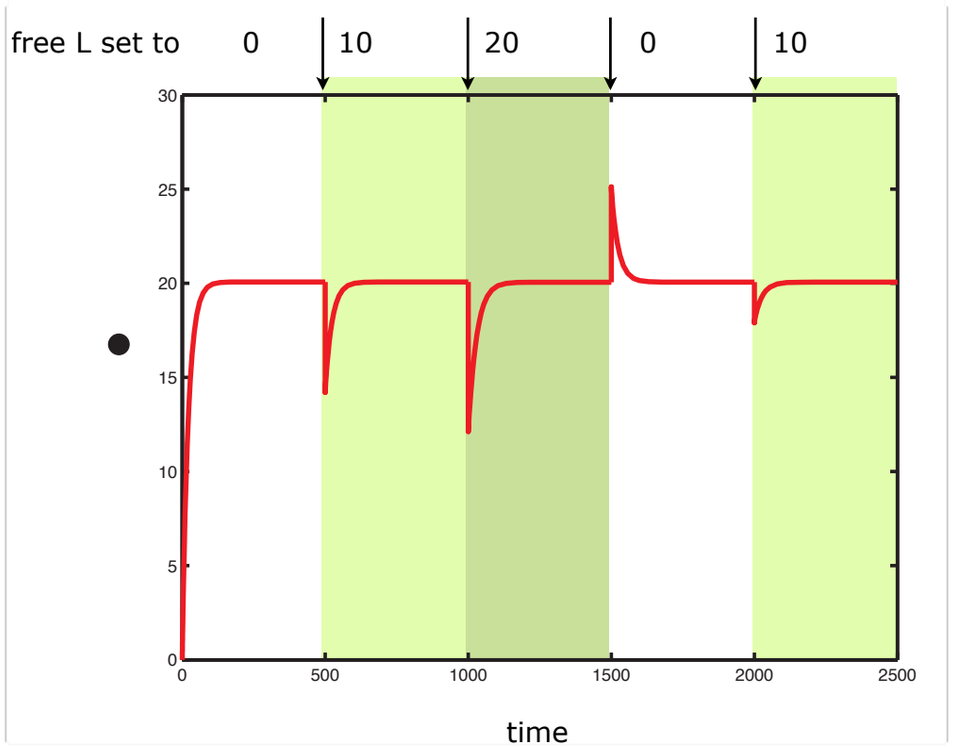




CheB saturated - 1st order kinetics
flux dependent on input

a difference calculator

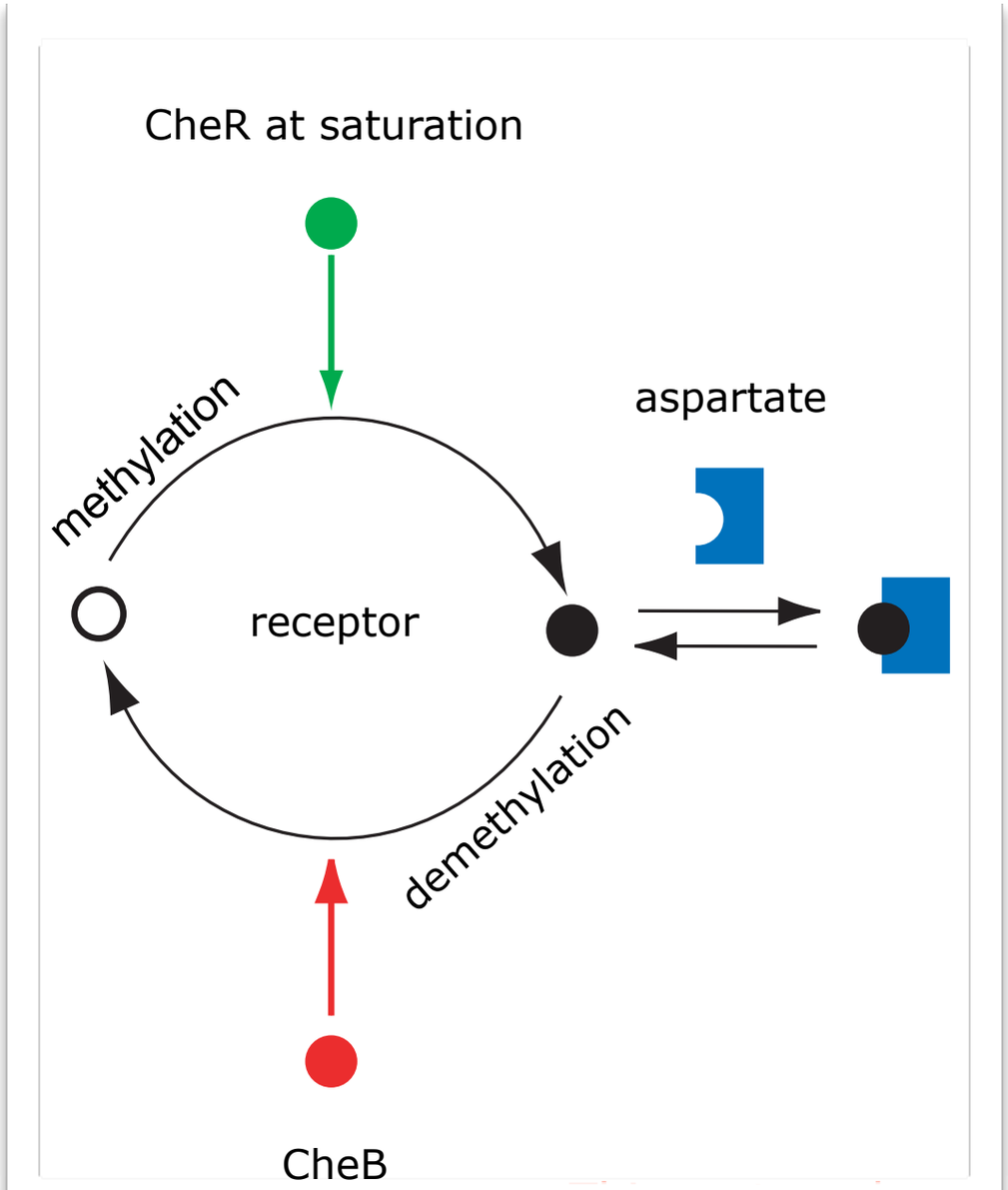


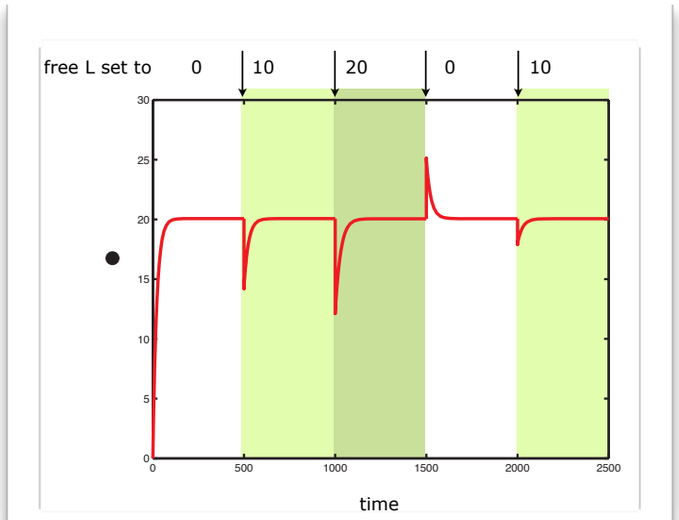


- new injected ligands capture black receptors

- number of inputs to 1st order red reaction decreases, hence red velocity decreases

- green reaction is 0th order so velocity stays the same, so green replenishes the stock of free black receptors (digging in the reserve of white receptors)
- until their number reaches its pre-injection level (now fewer white receptors around - still enough to saturate green)





second injection of 10 ligands at time 2000 gets a smaller response - WhY?

WhY does the level of black return to the initial value?

at some point green will fail to saturate (WhY?) and then the principle slowly breaks down

a Kappa model of this simple system

http://kappalanguage.org

```
%agent: Ea(x)
%agent: Eb(x)
%agent: S(x~0~1)
%agent: L(x)
```

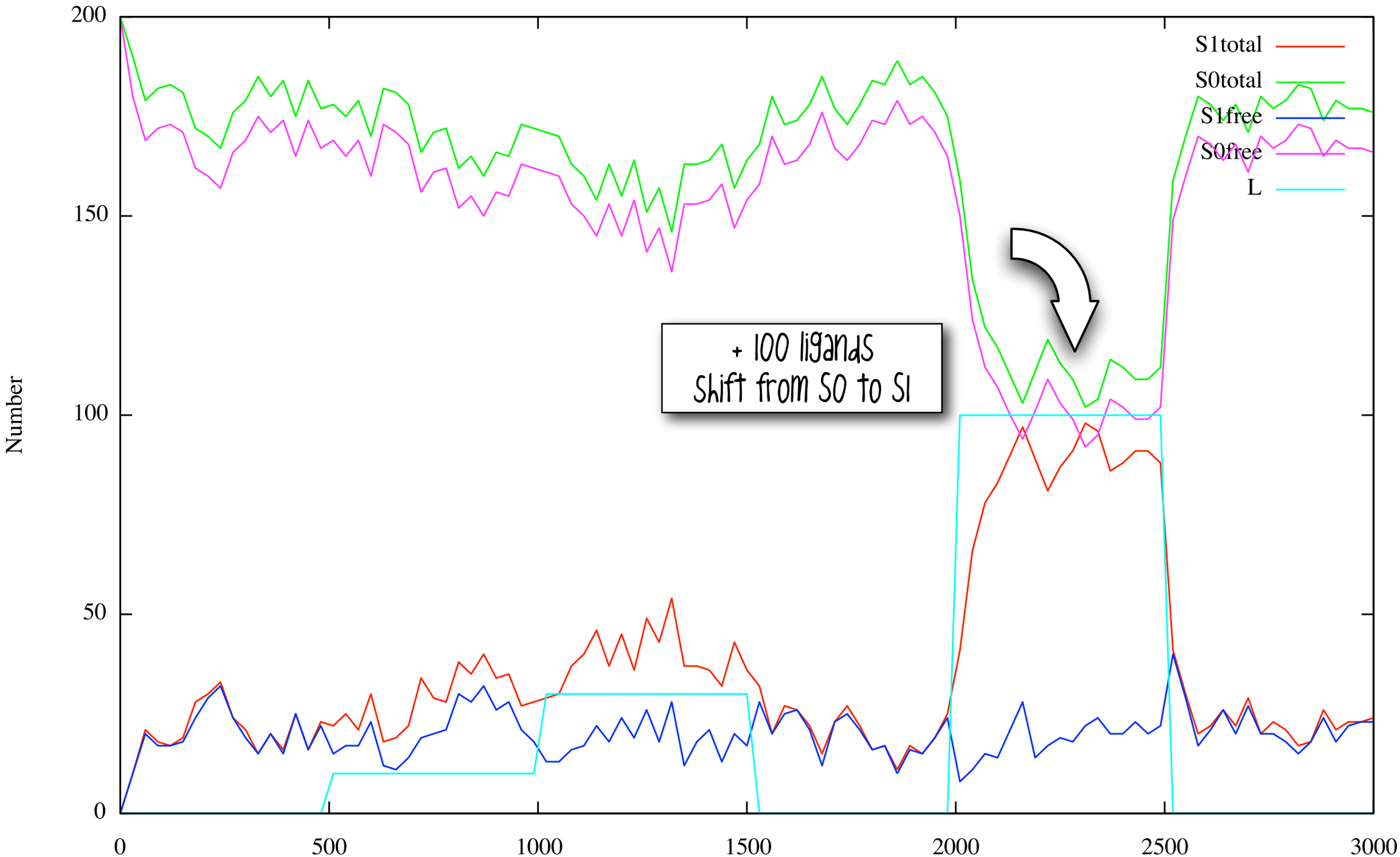
```
%var: 'kl'      10
%var: 'kl-'     100

%var: 'k1a'      1
%var: 'k1a-'     1
%var: 'k2a'      0.1

%var: 'k1b'      0.001
%var: 'k1b-'     1
%var: 'k2b'      1

%var: 'n_Ea'     10
%var: 'n_Eb'     100
%var: 'n_S'      200
%var: 'n_L'      0
```

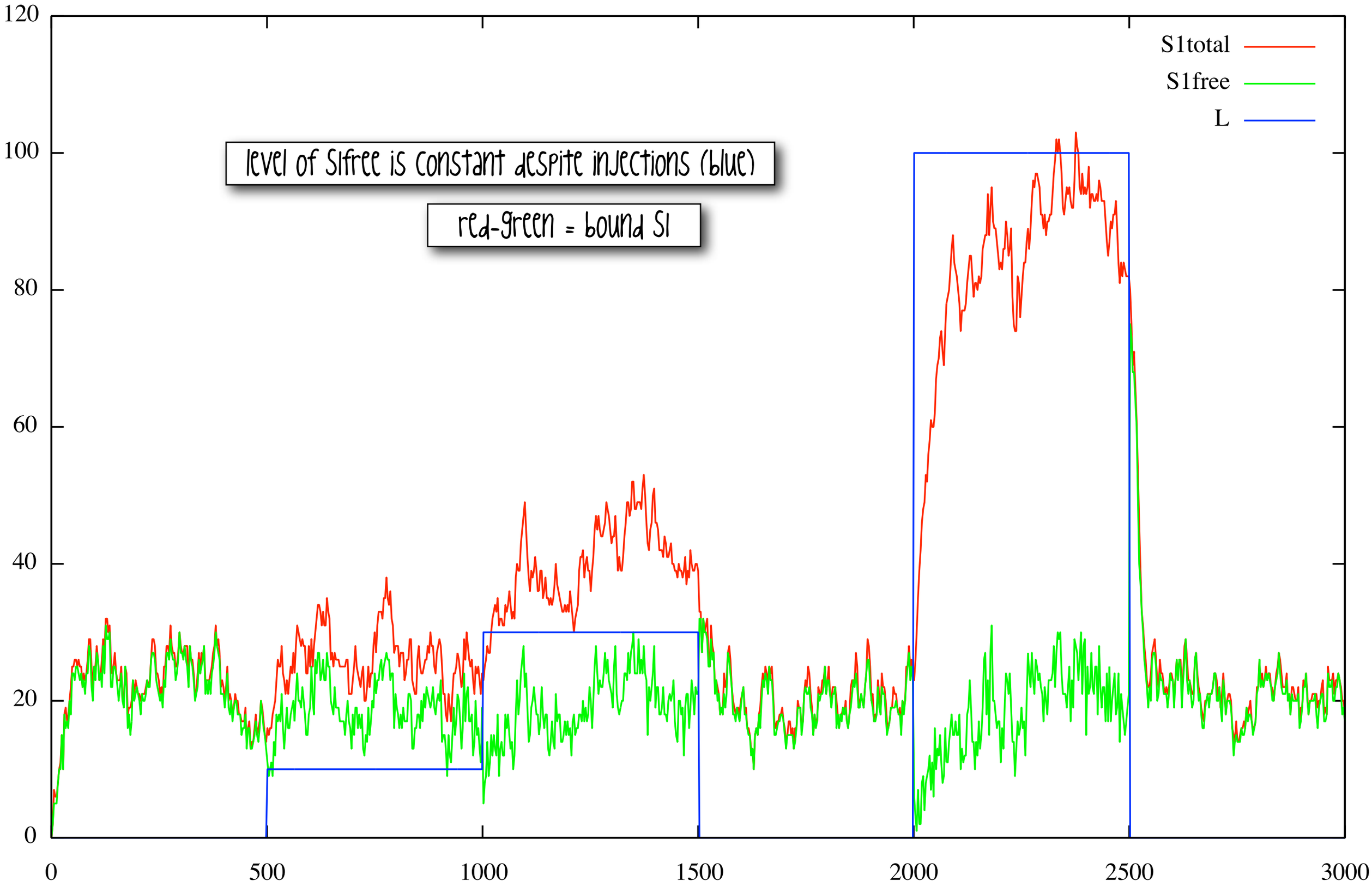
```
%init: 'n_Ea' (Ea())
%init: 'n_Eb' (Eb())
%init: 'n_S'  (S(x~0))
%init: 'n_L'  (L(x))
```

```
'bind LS1' L(x),S(x~1) -> L(x!1),S(x~1!1) @ 'kl'
'unbind LS1' L(x!1),S(x~1!1) -> L(x),S(x~1) @ 'kl-'

'bind EaS0' Ea(x),S(x~0) -> Ea(x!1),S(x~0!1) @ 'k1a'
'unbind EaS0' Ea(x!1),S(x~0!1) -> Ea(x),S(x~0) @ 'k1a-'
'flip01' Ea(x!1),S(x~0!1) -> Ea(x),S(x~1) @ 'k2a'

'bind EbS1' Eb(x),S(x~1) -> Eb(x!1),S(x~1!1) @ 'k1b'
'unbind EbS1' Eb(x!1),S(x~1!1) -> Eb(x),S(x~1) @ 'k1b-'
'flip10' Eb(x!1),S(x~1!1) -> Eb(x),S(x~0) @ 'k2b'
```

```
%mod: [T] > 500 do $ADD 10 (L(x))
%mod: [T] > 1000 do $ADD 20 (L(x))
%mod: [T] > 1500 do $DEL [inf] (L(x?))
%mod: [T] > 2000 do $ADD 100 (L(x))
%mod: [T] > 2500 do $DEL [inf] (L(x?))

%obs: 'S1total' S(x~1?)
%obs: 'S0total' S(x~0?)
%obs: 'S1free'  S(x~1)
%obs: 'S0free'  S(x~0)
%obs: 'L' L(x?)
```

Kappa - Stochastic version





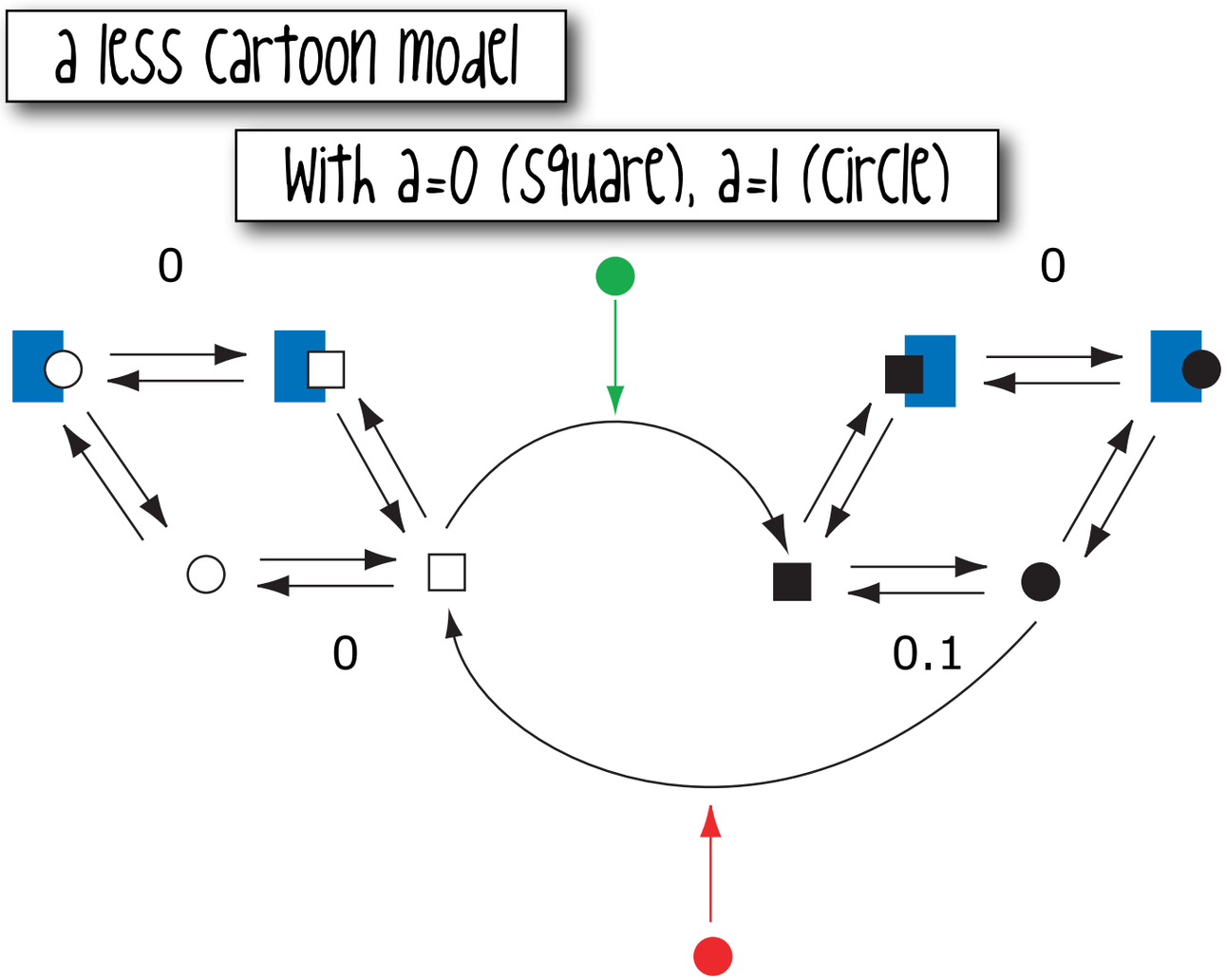
Monday, 3 October 2011

a cartoon model

integration of the full set of kinetic equations (not the MM approximation).

parameters: $k_l = 10^3, k_{-l} = 10^4, k_1^{(a)} = 1, k_{-1}^{(a)} = 1, k_2^{(a)} = 0.1, k_1^{(b)} = 0.001,$
$k_{-1}^{(b)} = 1, k_2^{(b)} = 1, E_a = 10, E_b = 100, S = 200$

a less cartoon model

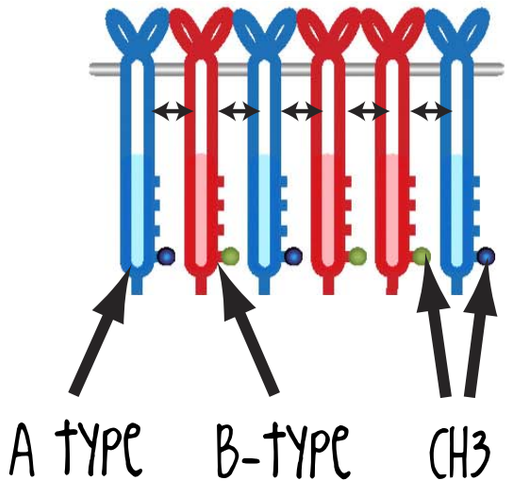


3

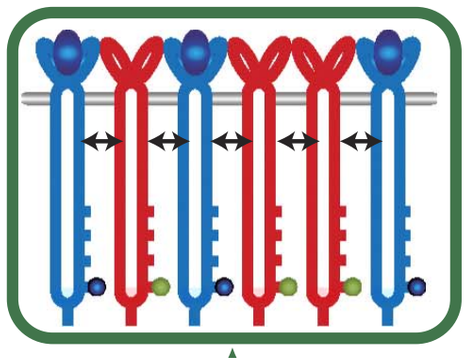
bacterial chemosensors

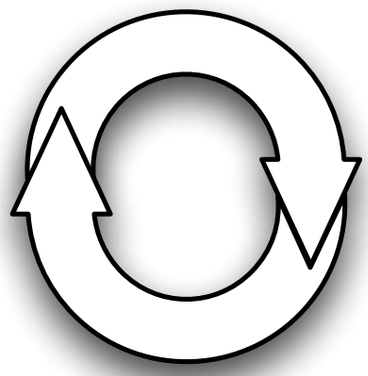
a mixed party of receptors

mixed receptor array

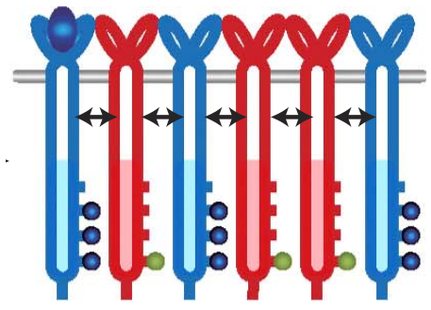


+A-lig: a goes down
propagation by coupling

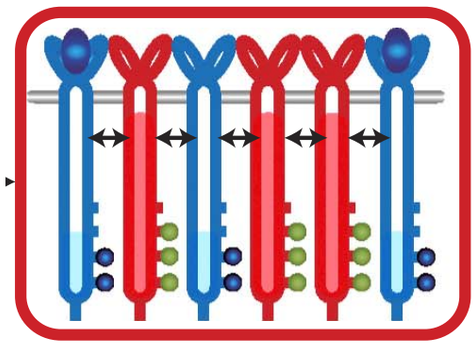




a goes back to normal (adaptation)
CH_3 has gone higher for AS



negative FB: a goes up again
(faster for B-type)



Lan et al. MSB 2011, 7:475

CH_3 levels encode the chemical landscape

Time scales

We can distinguish three different time scales (in increasing order):
- l, a the ligand binding and conformation (including conformation spread on the lattice) sub-state space
- m, B, R, A, Y and the engine control
- R^q lattice composition and structure (including transcriptional control, excluding hypothetical fast local rearrangements by conformation spread) -not considered here.

This leads to a natural split of the model into a quasi-equilibrium part, described via an energy assignment, for the ast time-scale, and an other one for the dynamics of methylation.

Model I, energy part - fast time scale, quasi-equilibrium

The energy $E(q, l, a, m)$ of a receptor of type q in state (l, a, m) is defined as the sum of the following 3 types of terms:
- RR-coupling with $C_{qq'} < 0$ a symmetric function (this term depends on the R-neighbours of R, it is responsible for the conformational spread):

$$E(R^q(a) : R^{q'}(a')) = aC_{qq'}(a' - 1/2) \tag{1}$$

- LR-coupling with K_q^a the dissociation constant of the $L_q : R^q(a)$ complex:

$$E(L_q : R^q(a)) = \log K_q^a - \log[L_q] \tag{2}$$

- ma-coupling with $m_{q,0}$ the set point for methylation of an active R^q, $\alpha_q < 0$:

$$E(R^q(m, a)) = a\alpha_q(m - m_{q,0}) \tag{3}$$

The above fixes the probability $p(q, l, a, m)$ that a given q-receptor is in state (l, a, m) as a function of $[L_q]$, its level of methylation, and the conformation of its neighbours.

Lan et al. MSB 2011, 7:475

Model 2 - differential part/methylation levels

In the second part of the model, we need to describe how the CheB, CheR dynamics kicks in.

$$d/dt\, p(q,m) \quad = \quad (1-a)\cdot k_R^q(p(q,m-1)-p(q,m)) + a\cdot k_B^q(p(q,m+1)-p(q,m))$$

where:
- $p(q,m)$ is the probability that an R^q is in methylation state m,
- k_R^q, k_B^q are the rates at which an R^q is methylated/demethylated by the associated enzymes CheR , CheB,
- a is either the activity state of the said R^q, or the average activity $\langle a_q \rangle$ of the R^q population (mean field), or the global average $\langle a \rangle$ over the population of all receptors (regardless of their type).

Lan et al. MSB 2011, 7:475

average activity of an R♡9 in methyl-state m

$$\langle a_{q,m} \rangle = \frac{e^{-\sum_{nn} H_c(q,1,a',q') - H_m(R^q(m,0))} + e^{-\sum_{nn} H_c(q,1,a',q') - H_l(q,1) - H_m(R^q(m,0))}}{e^{-H_m(R^q(m,0))} + e^{-H_l(q,0)} + e^{-\sum_{nn} H_c(q,1,a',q') - H_m(R^q(m,0))} + e^{-\sum_{nn} H_c(q,1,a',q') - H_l(q,1) - H_m(R^q(m,0))}}$$

total average activity of an R♡9

$$\langle a_q \rangle = \sum_m p(q,m) \langle a_{q,m} \rangle$$

mean field approx:
replace Hc(nn) with Hc(<a9>)

need to specify a number of nn

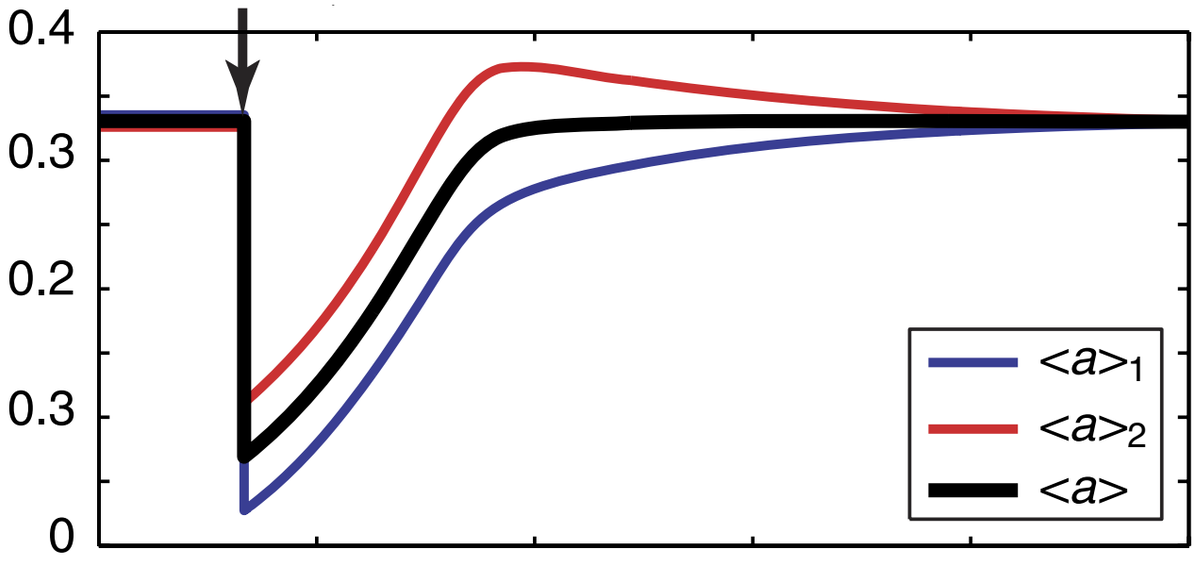
1. P'(9,M) = P(9,M) + dt * d/dt P(9,M)

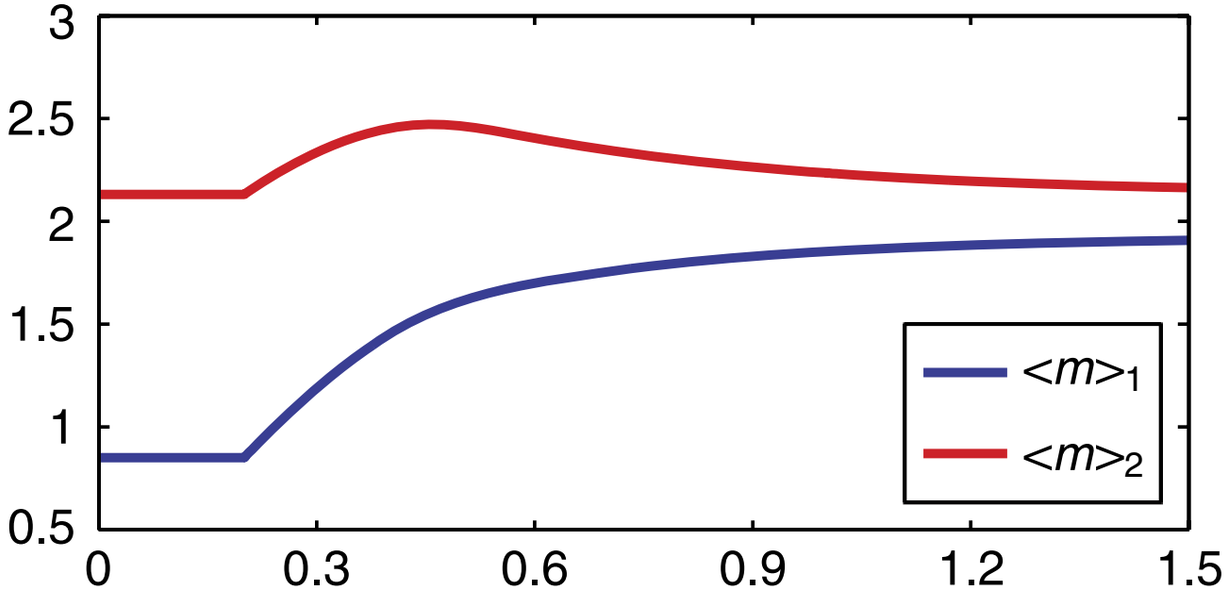
2. Solve fixpoint in R^12
<a9,M> = F(<a9>,[L])
<a9> = Sum_M P'(9,M) * <a9,M>

about the mean field approx:

one can also do a Monte-Carlo simulation - more later

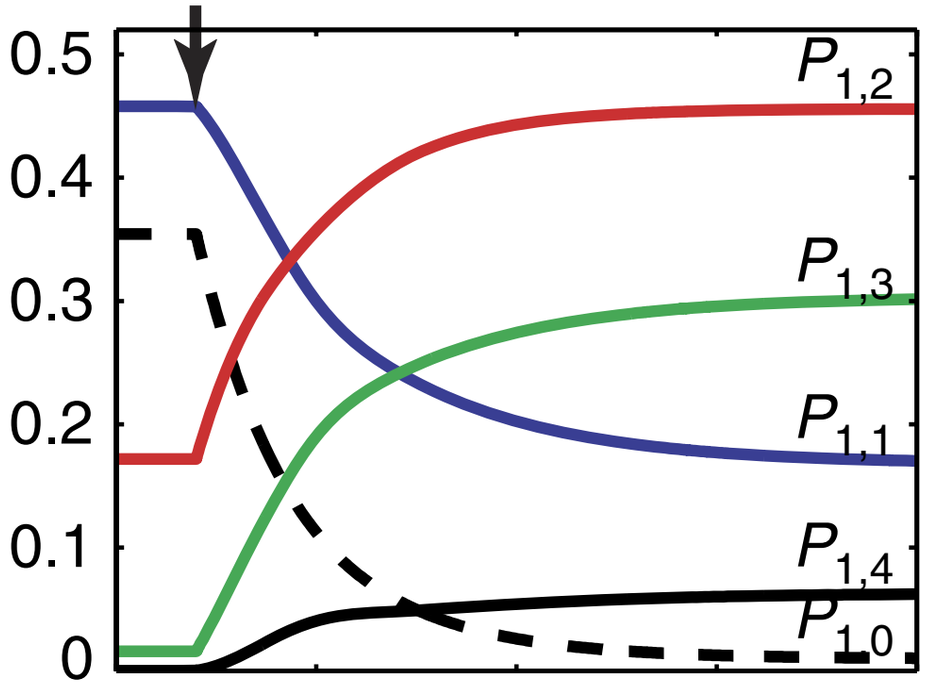
blue=A=1=ligand target
red=B=2=other receptors

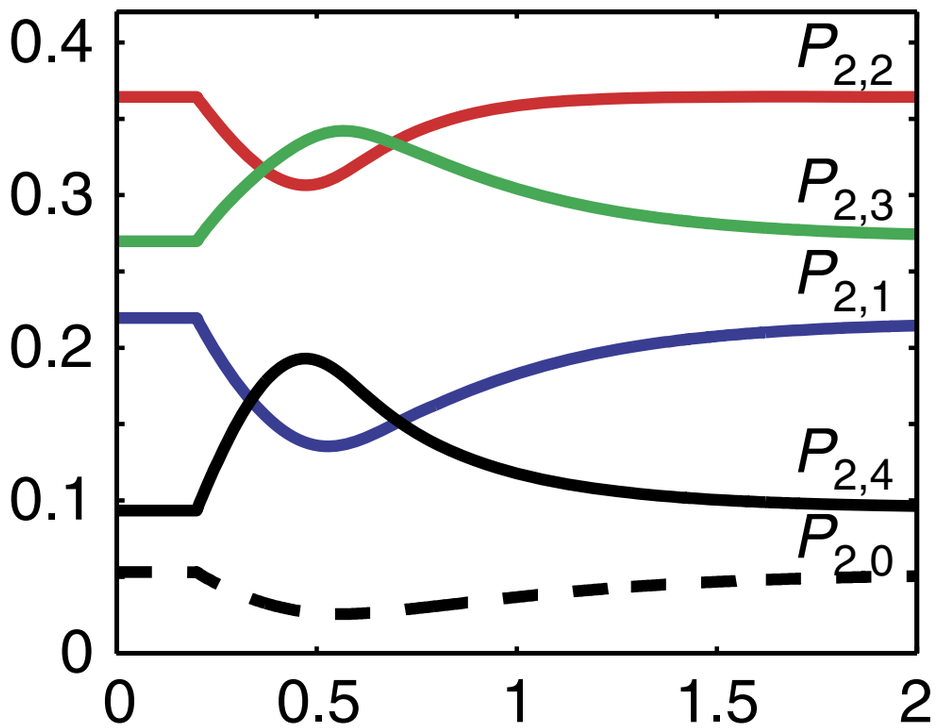




a= activity
<m> = average methylation

methylation distribution (t)

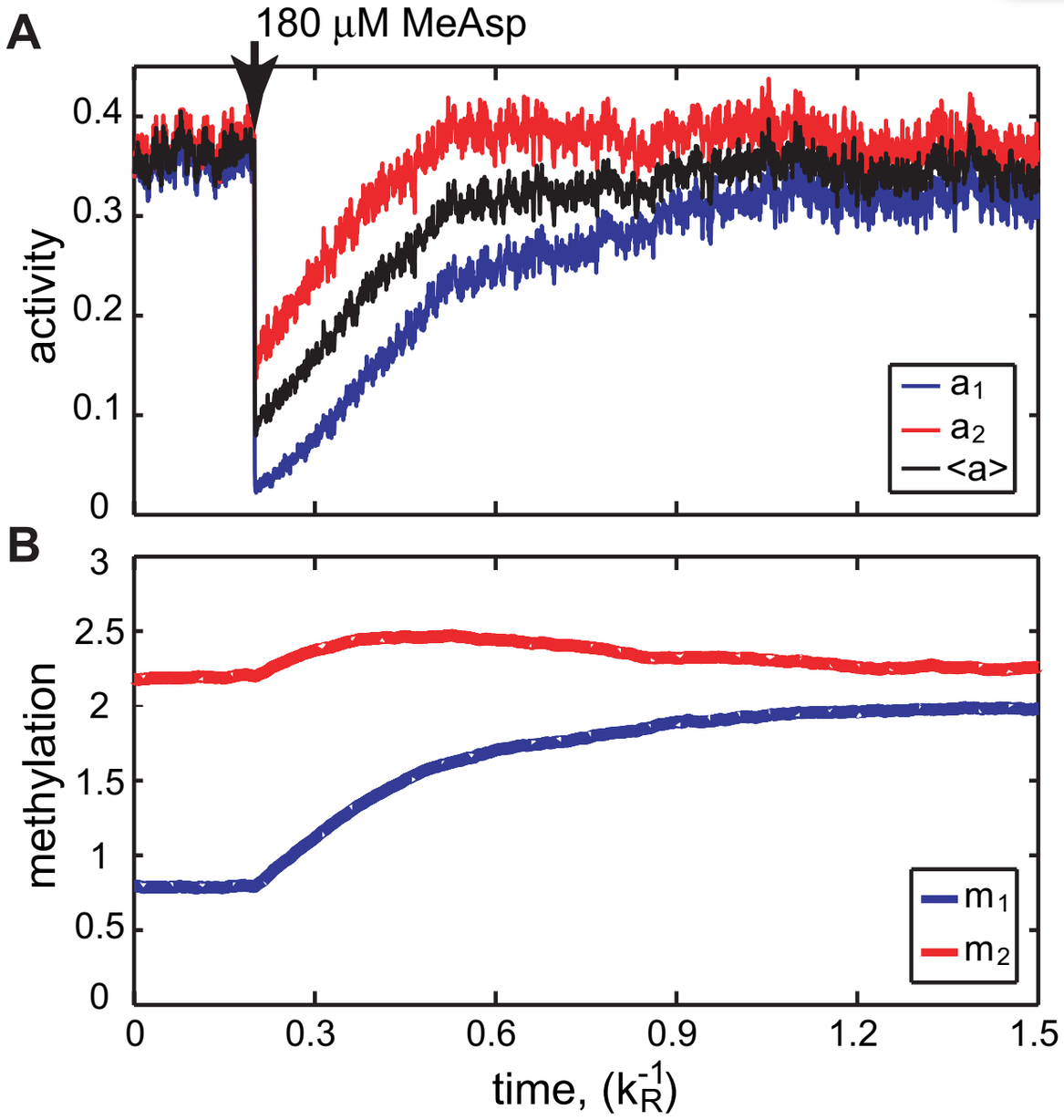


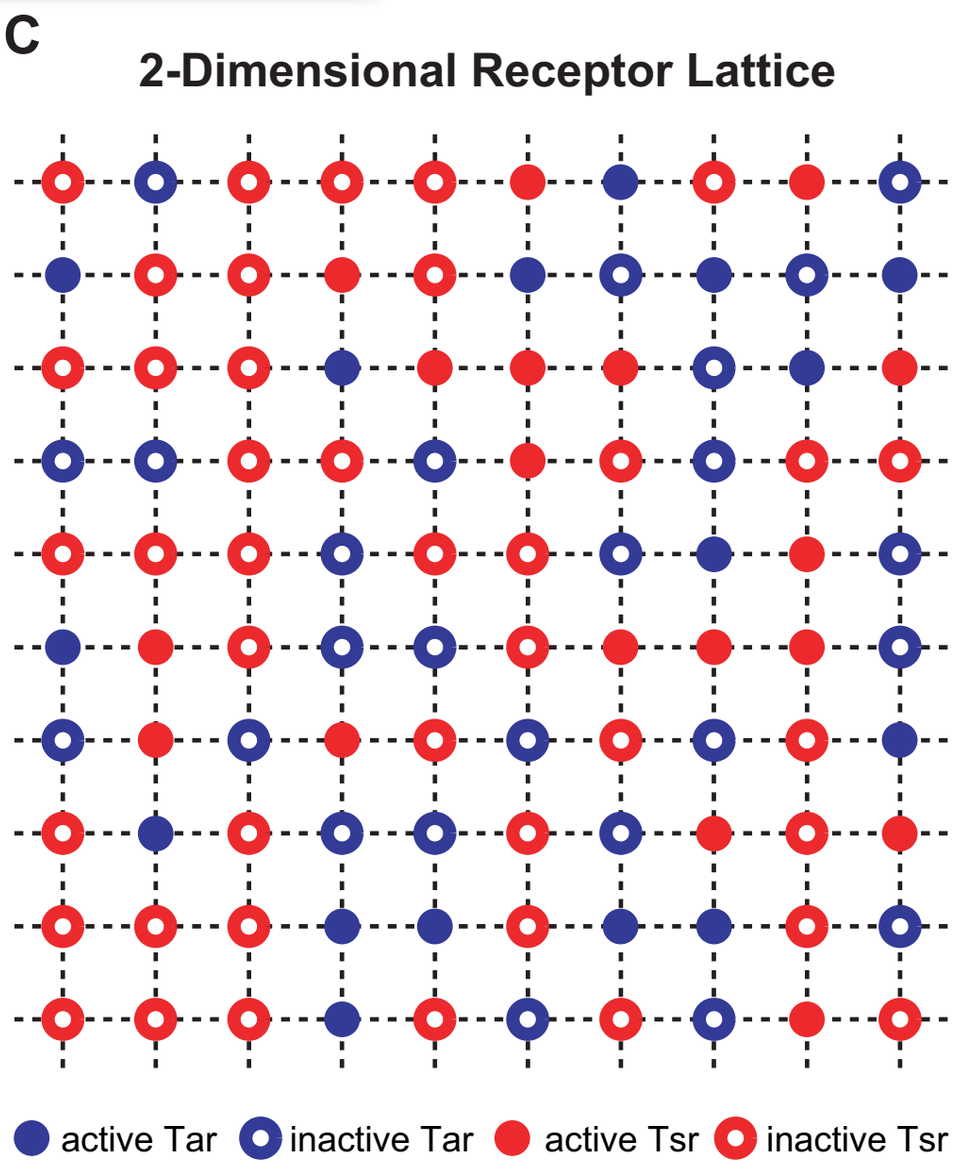


Monte-Carlo simulation

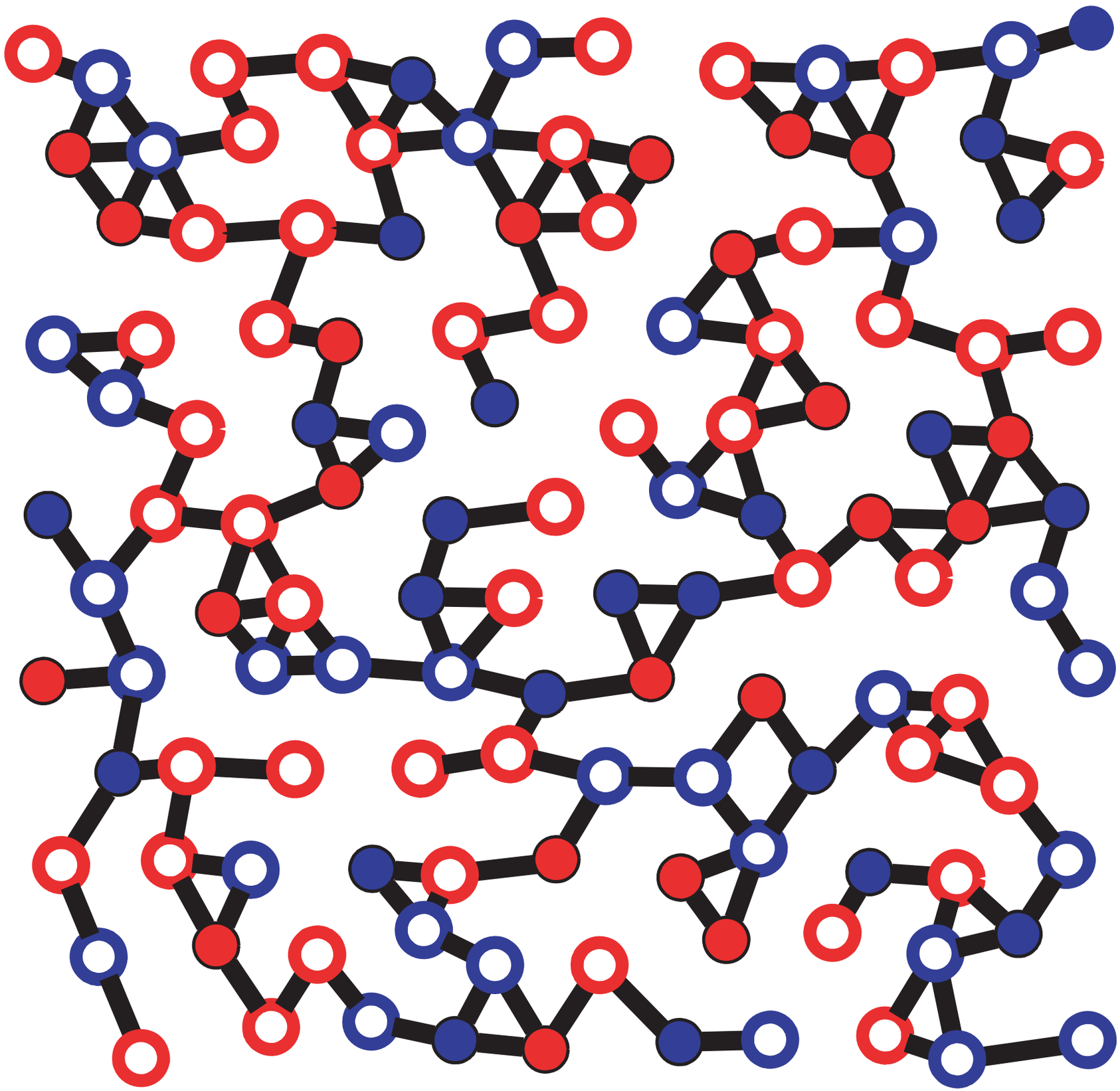
on a 30x30 square lattice

With Tsr:Tar=2:1





Coupling/signal amplification dependent on lattice

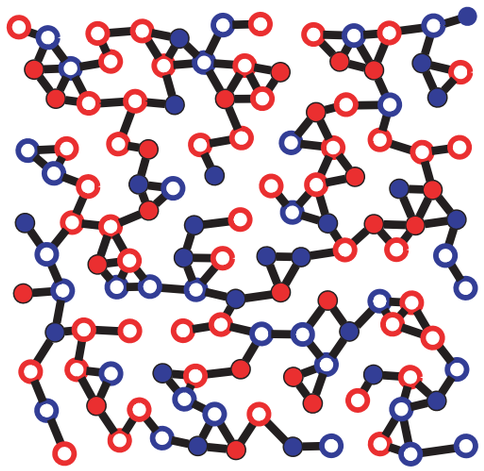


pretty neat machine!

(double) negative FB's

Ising conformational coupling

signal-specific memory & adaptation



but ... amplification depends on the receptor network

... need to model the network itself

more subtle questions: mixed type repartition has an influence on function? on structure?

how would you modify this machine and to do what?

think of the molecular components new and old

the modeling aspects

the security problems as well

that is what the IGEM computation asks ...
(and then of course you get to try to build the system for real!)

ED team for IGEM'11 won again best model prize at the regionals!