Using information that is only *transiently* available to improve detection of *high doses* in cellular signaling

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FBMC Fisiología y Biología Molecular y Celular

Outline

-Introduction

-Motivation (from a particular model system)

-Question and background

-PART I: developing a general theoretical approach

-Summary I

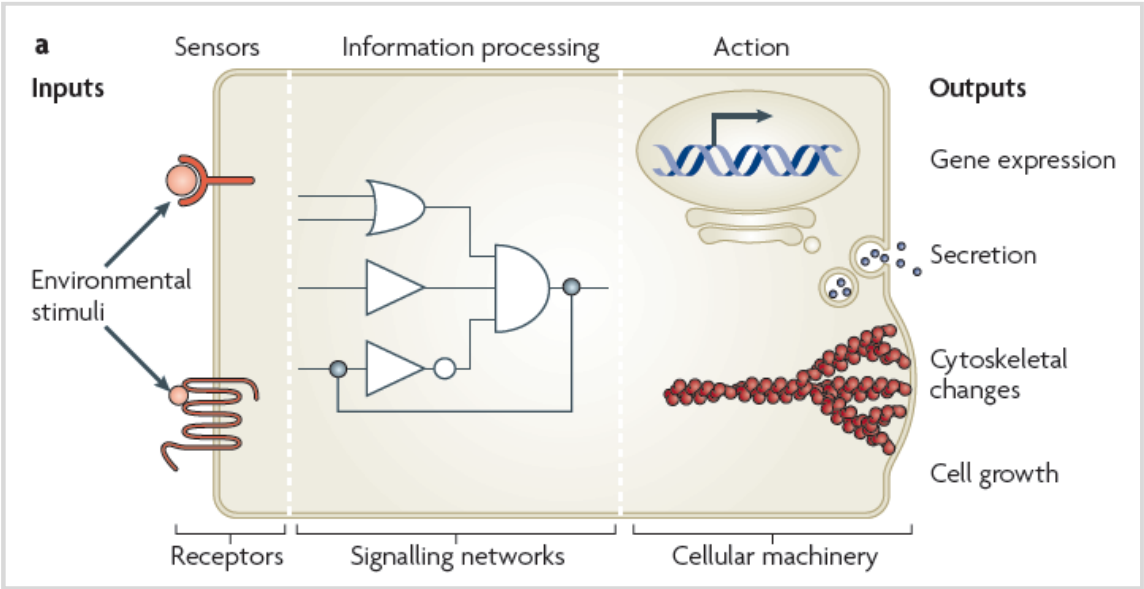
-PART II: applying the theoretical approach to the model system that motivated the question

-Summary II

-Global summary

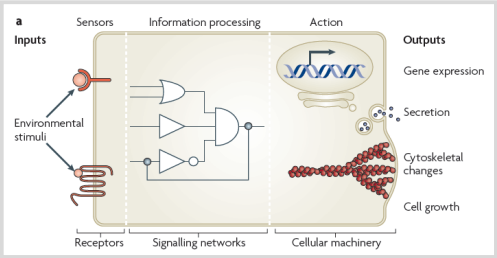
Introduction

1)
sensing
processing
responding

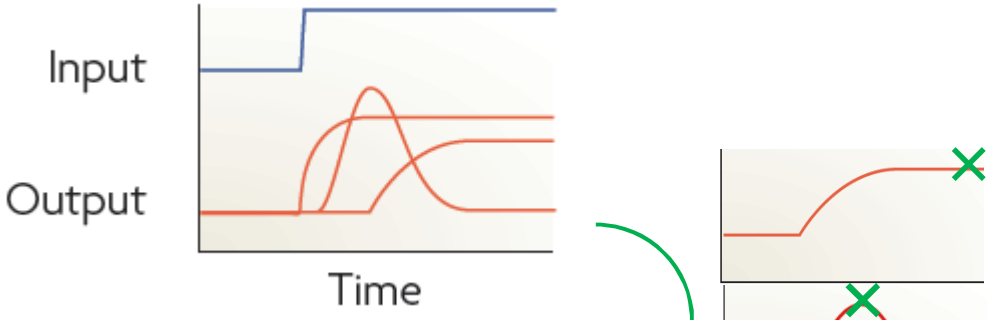


Designing customized cell signalling circuits. WA Lim. Nature Reviews. Molecular Cell Biology. 2010.

2) input-output relationship

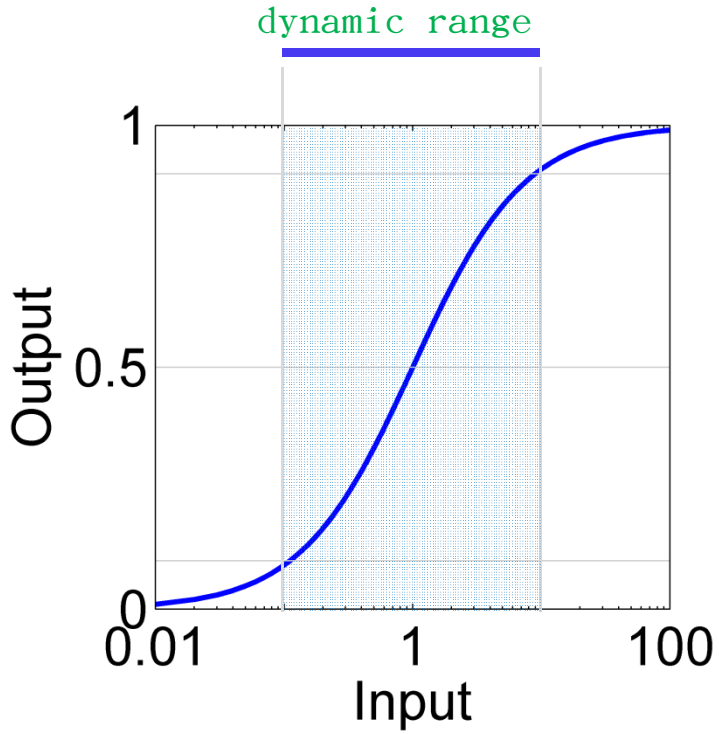


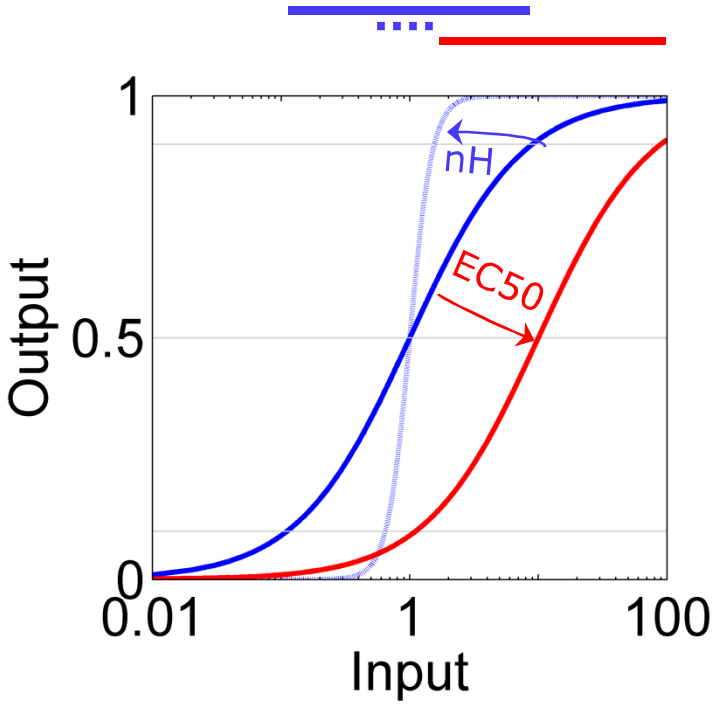
temporal profile



input-output relationship

3) dynamic range





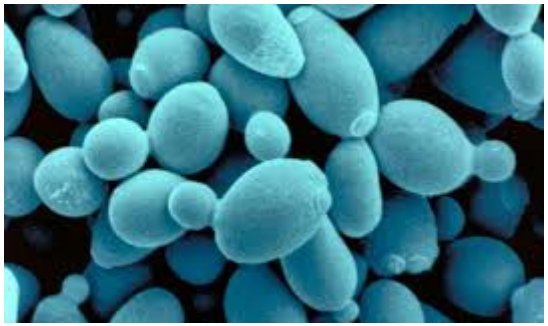
$$O = O_{basal} + (O_{\max} - O_{basal}) \frac{I^{nH}}{EC50^{nH} + I^{nH}}$$

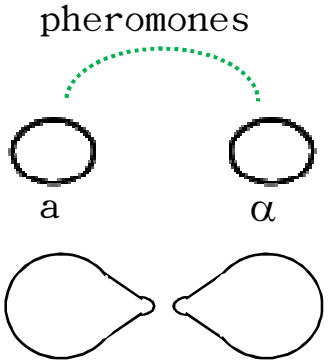
Motivation

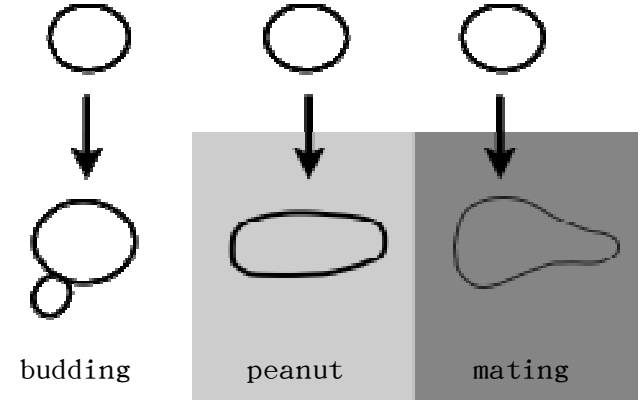
learning from yeast

model organism:

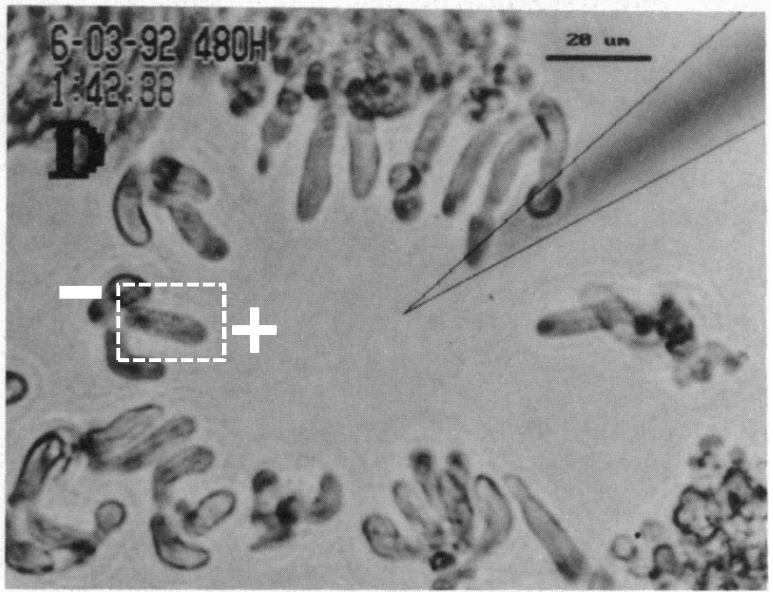
yeast *S cerevisiae*





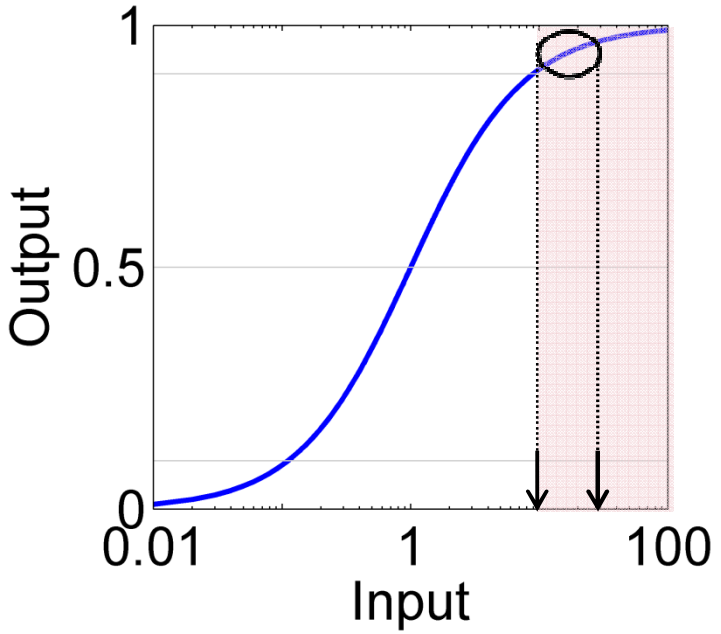


Deducing the position of the "mating partner" from the spatial gradient of pheromone



Polarization of yeast in spatial gradients of alpha mating factor. JE Segall. PNAS. 1993.

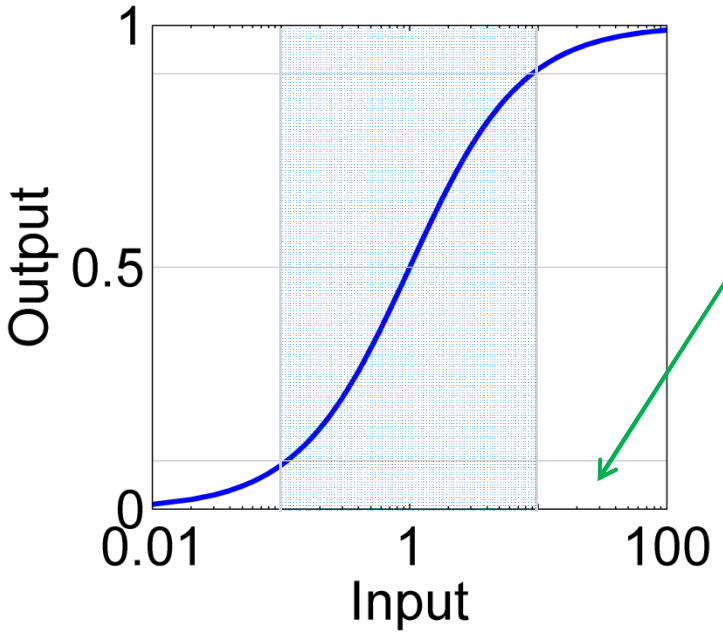
remarkable precision in shallow gradients (1-2% differences front-rear)



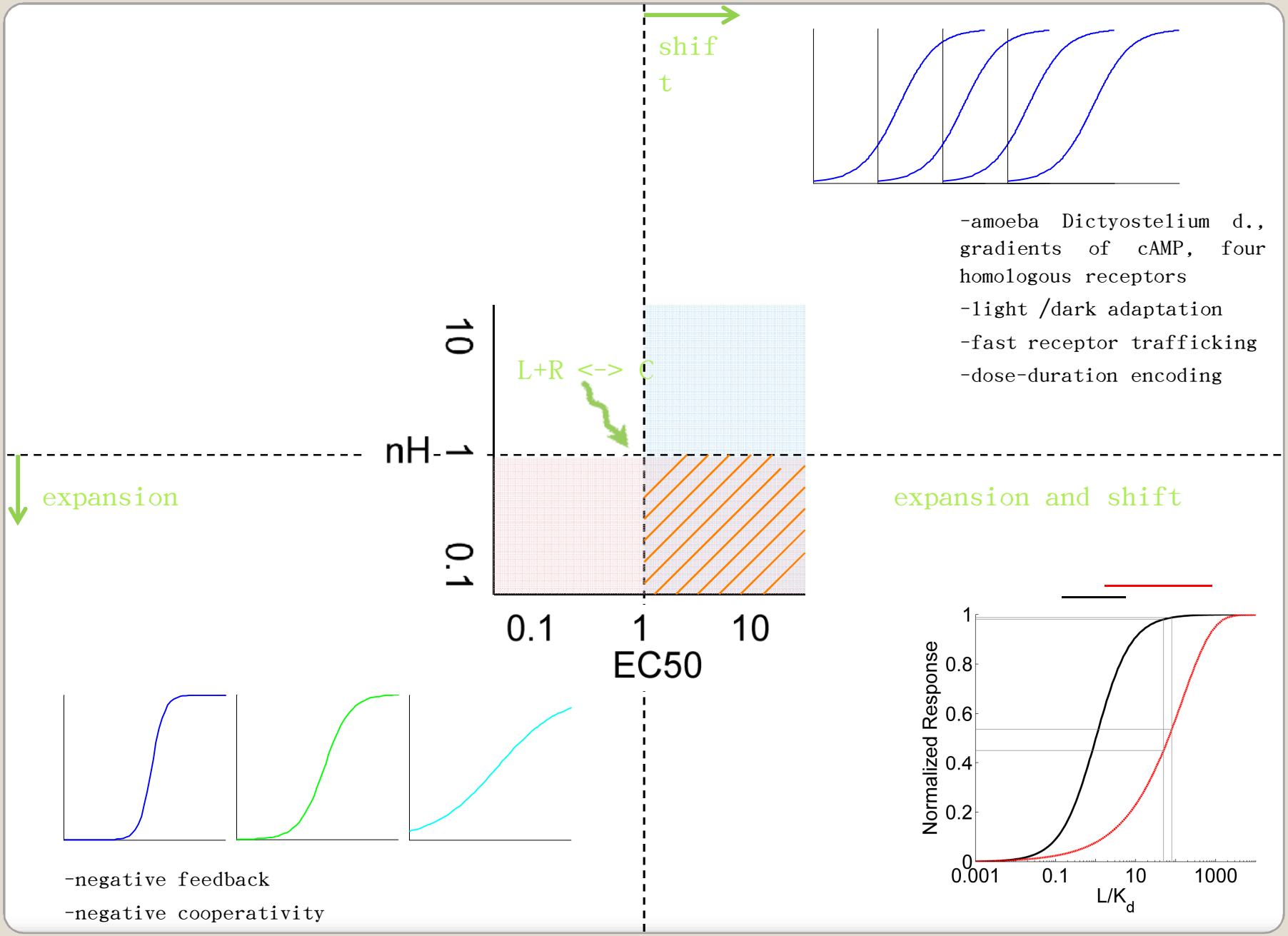
two high concentrations need to be distinguished

The Question

we are addressing and what is already known about it



for a signaling system that needs to operate (also) in the high input region, is there a way to expand/shift its dynamic range?


shif
t
-amoeba Dictyostelium d., gradients of cAMP, four homologous receptors
-light /dark adaptation
-fast receptor trafficking
-dose-duration encoding
10
nH 1
0.1
L+R <-> C
0.1
1
10
EC50
expansion
expansion and shift
-negative feedback
-negative cooperativity
Normalized Response
0
0.2
0.4
0.6
0.8
1
0.001
0.1
10
1000
L/K_d

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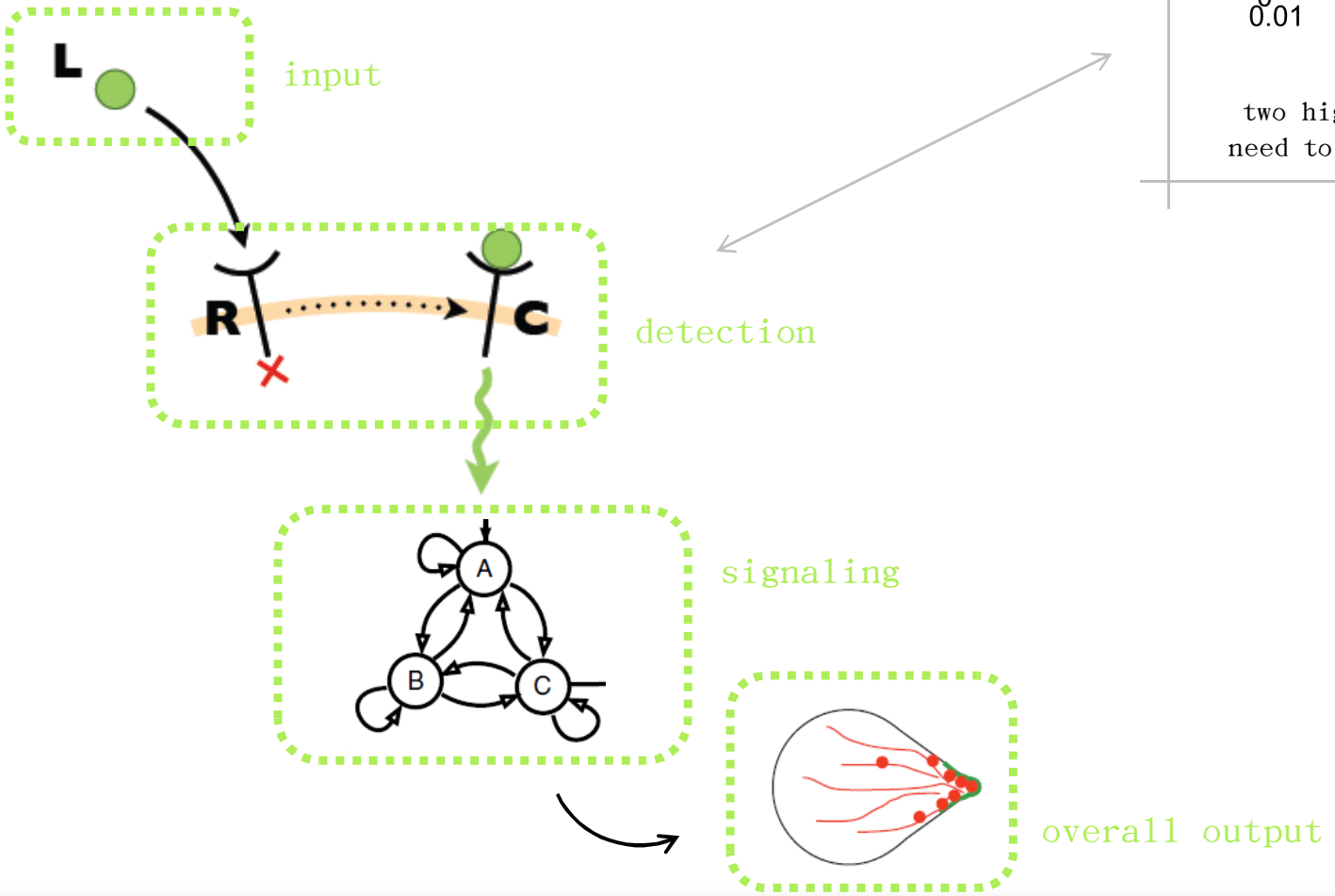
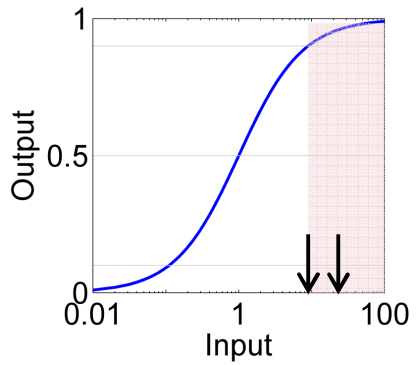
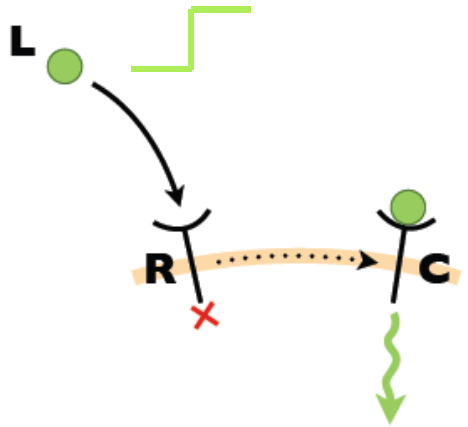
Using information that is only transiently available



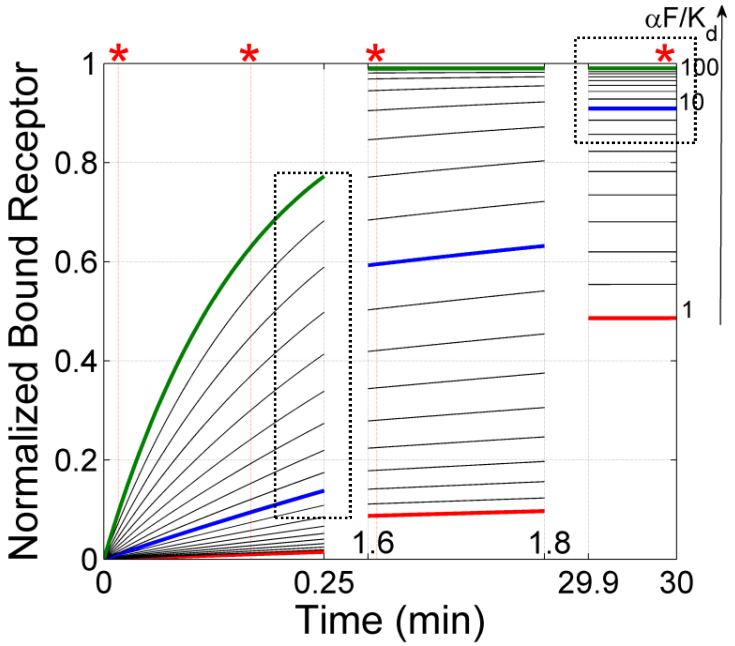


two high concentrations need to be distinguished

(1) Modeling detection



$$L + R \underset{k-}{\overset{k+}{\rightleftharpoons}} C$$



$$dC/dt = k_+ L R - k_- C$$

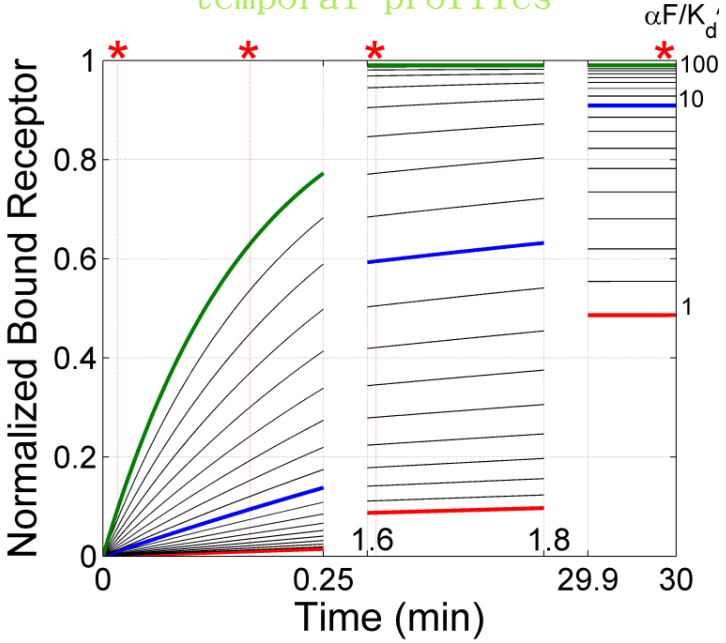
$$C(t,I) = C_{ss} [1-\exp(-t/\tau)]$$

$$C_{ss} = \frac{I}{1 + I}$$

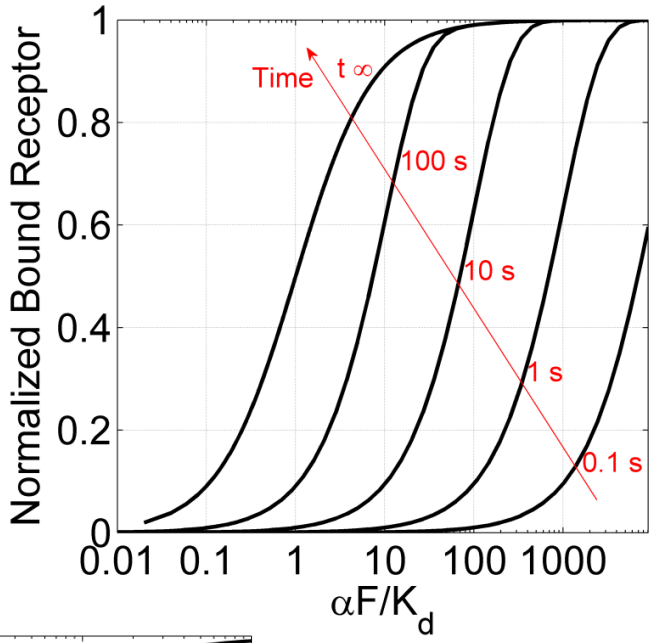
$$\tau = 1/k_- (1+I)$$

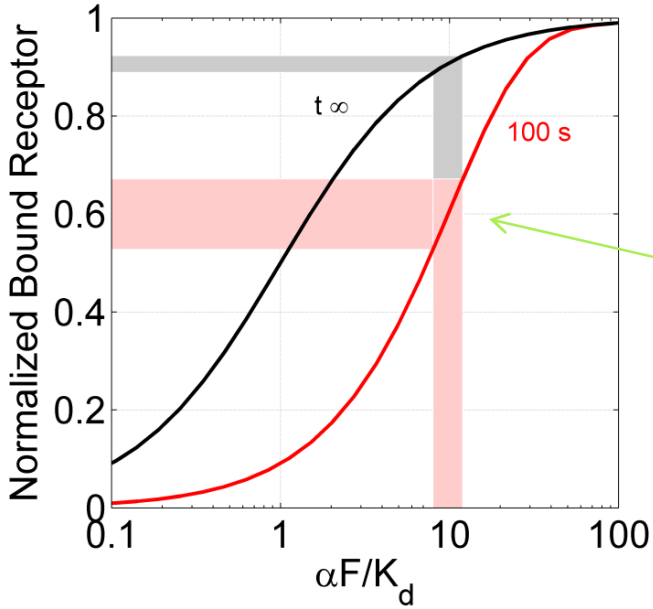
$$I = L/K_d = \alpha F/K_d$$

temporal profiles



input-output curves

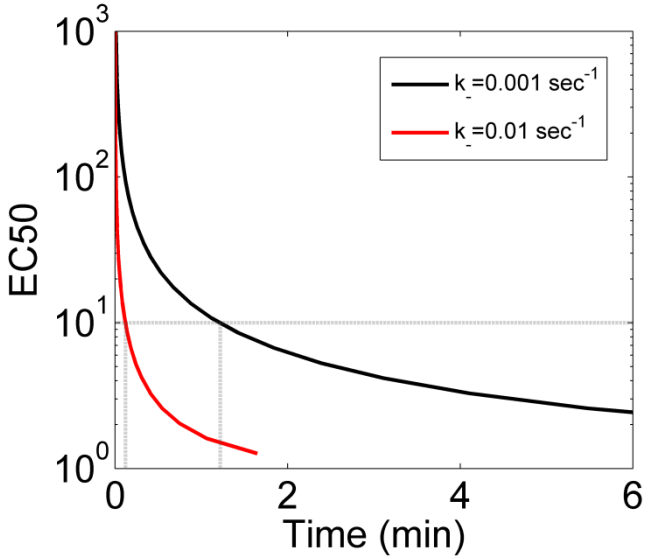




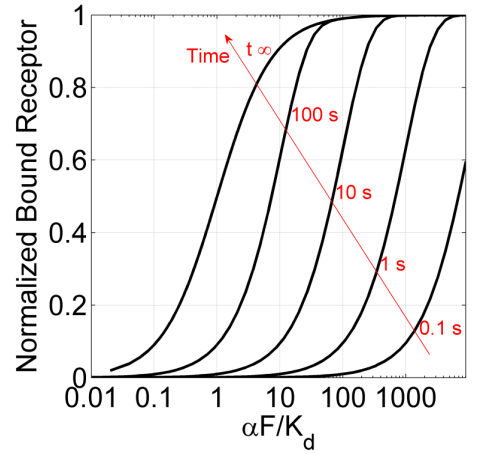
differences in outputs are amplified at early times

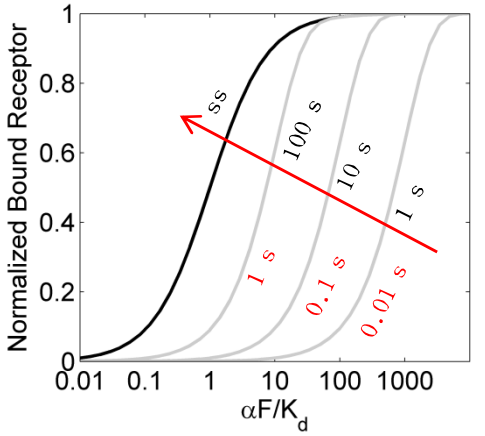
EC50 and nH versus time

$$t = \frac{1}{k_- * (1 + EC_{50})} \log\left(\frac{2 * EC_{50}}{EC_{50} - 1}\right)$$



1. EC50 and nH decreases when time increases
2. for slow binding /unbinding the curve shifts slowly





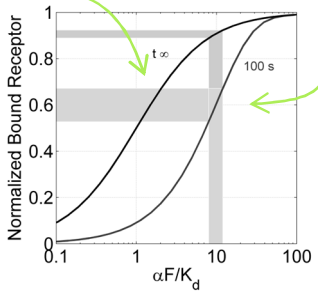
$$\frac{EC_{90}}{EC_{10}} = \frac{-\log(0.1) - t * k_-}{-\log(0.9) - t * k_-} = 81^{1/nH}$$

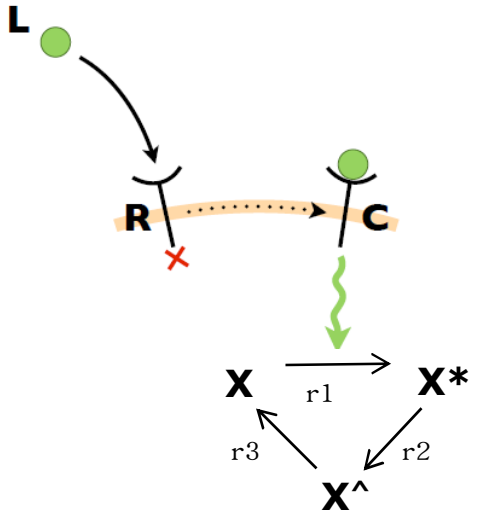
→ n_H=1.42.

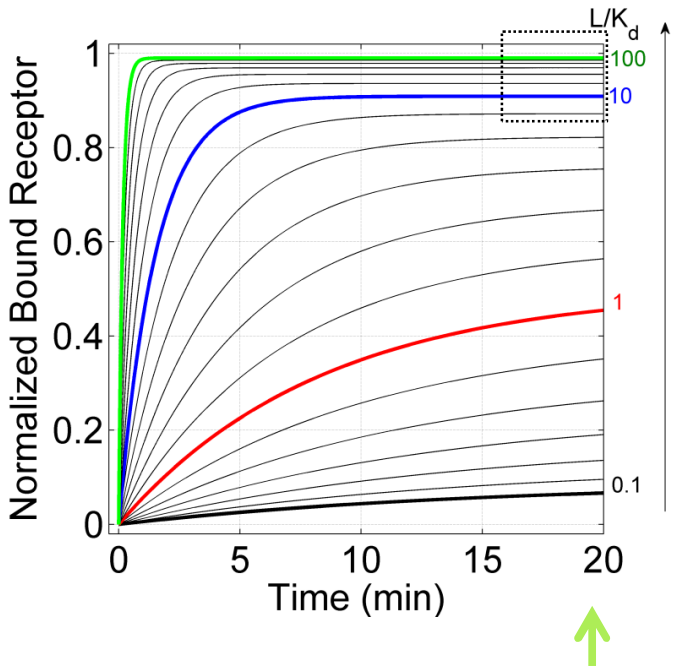
(2) In order to use this information instead of this one,

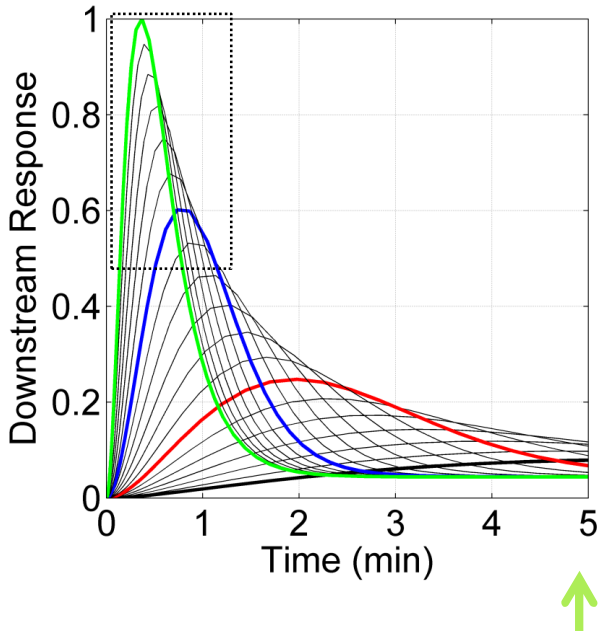
we select a

fast and transient downstream step

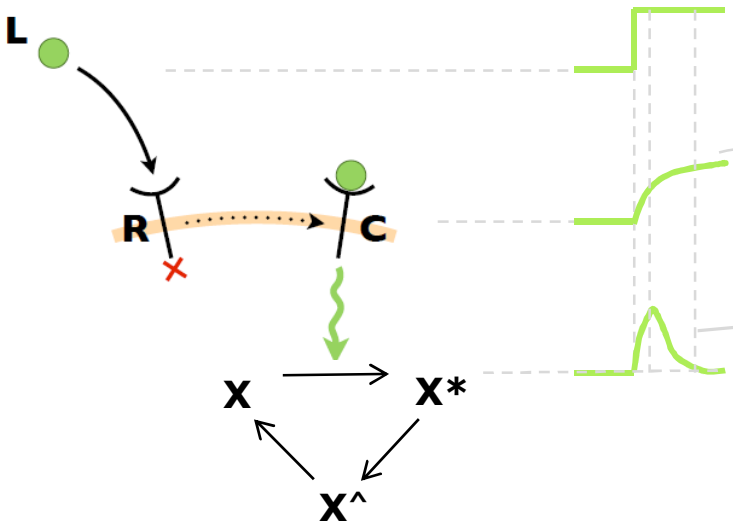


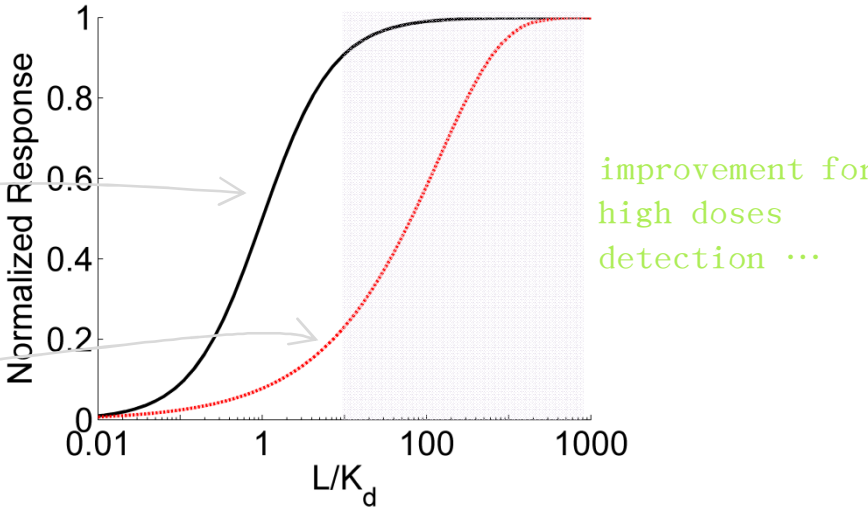




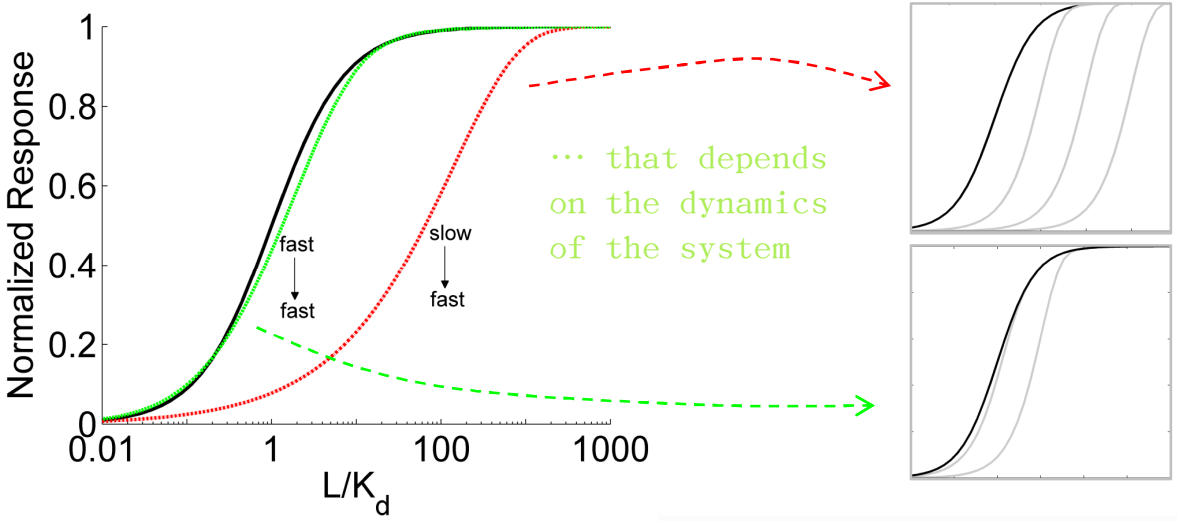


(3) PRESS: pre-equilibrium sensing and signaling





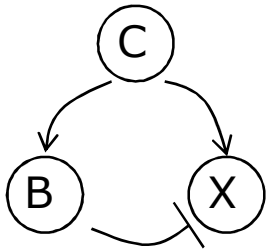
improvement for high doses detection …

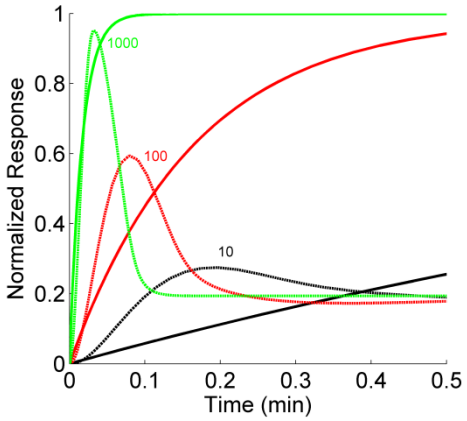


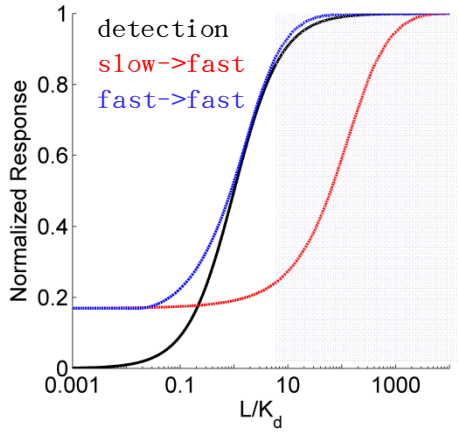
… that depends on the dynamics of the system

Simple models with transient signaling perform PRESS

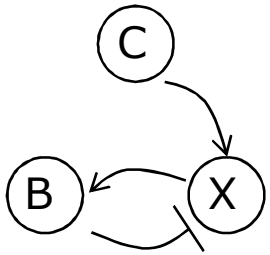
X controlled by incoherent feed-forward loop (IFFL)

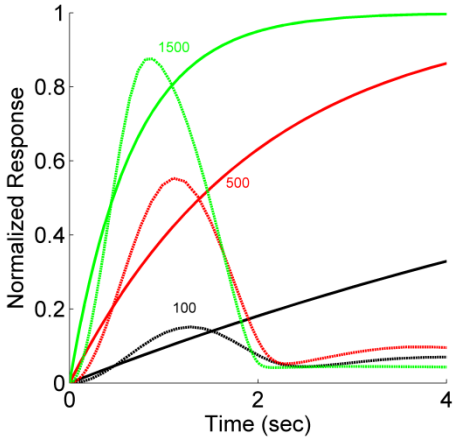


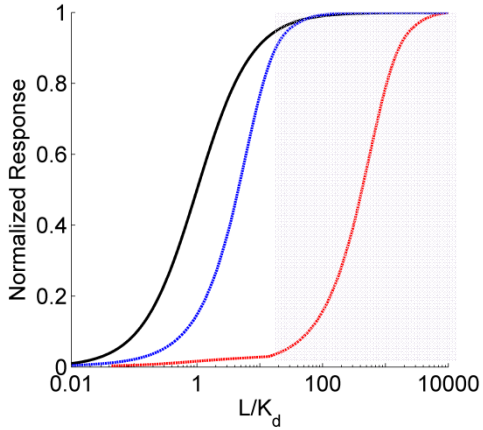




X controlled by negative feedback loop (NFBL)

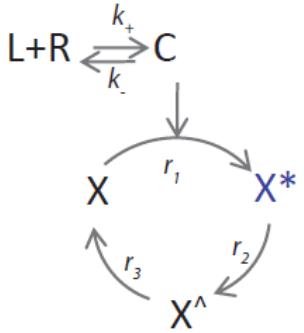


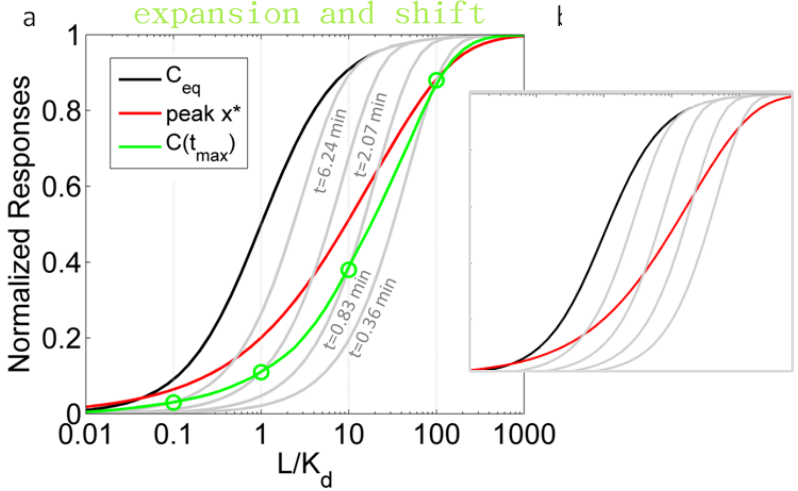


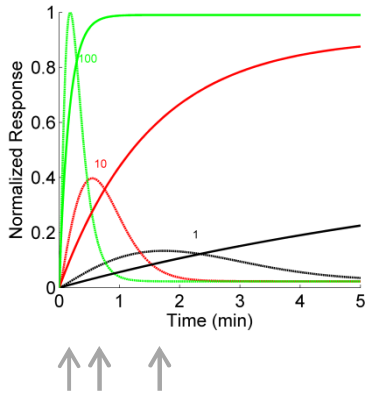


The shift in the dynamic range could come also with an expansion depending on the characteristics of the transient step

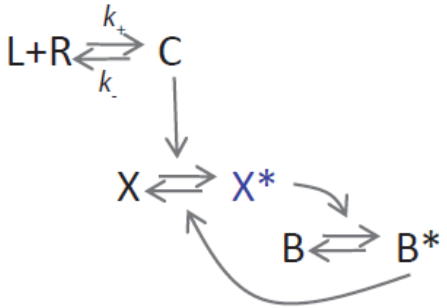
X with a refractory state

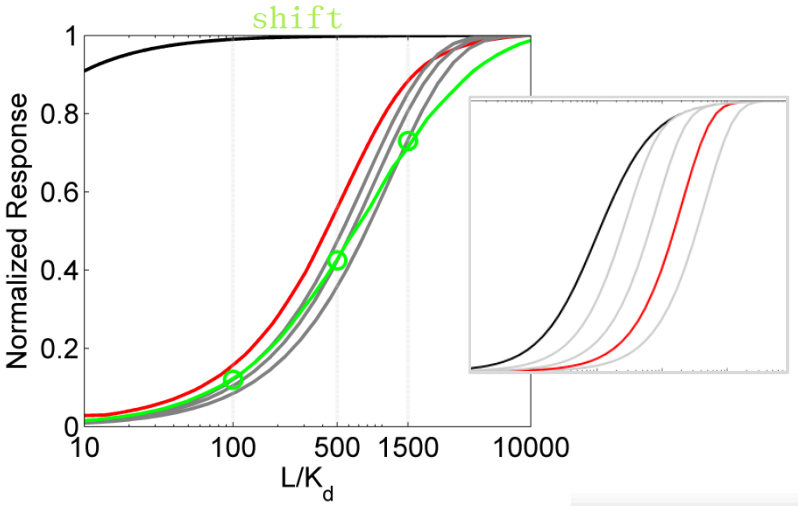


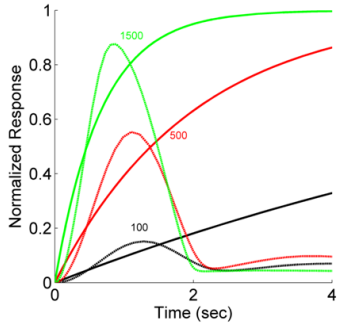




X controlled by negative feedback loop (NFBL)

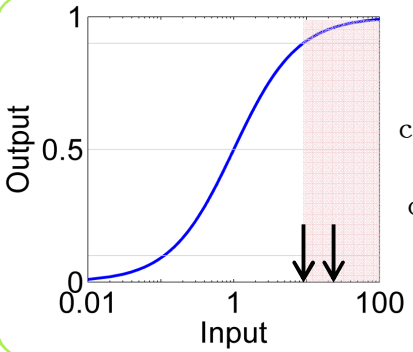




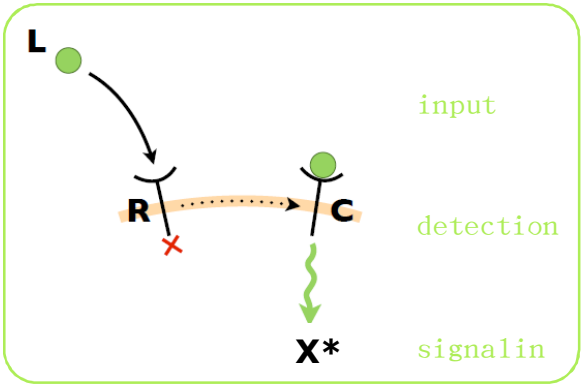


Summary I

the problem



two high concentrations need to be distinguished



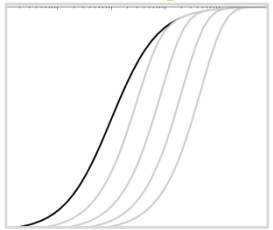
input

detection

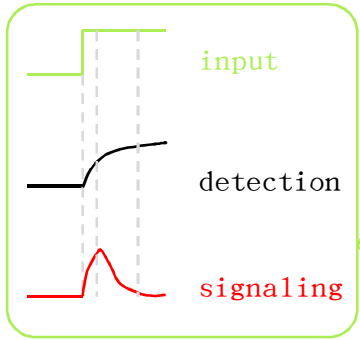
signalin

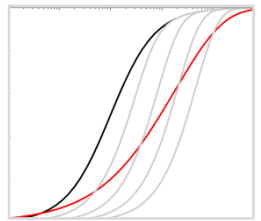
g

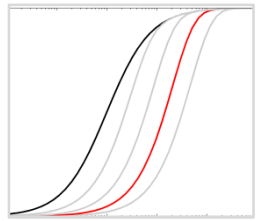
time-dependent dose-response



PRESS







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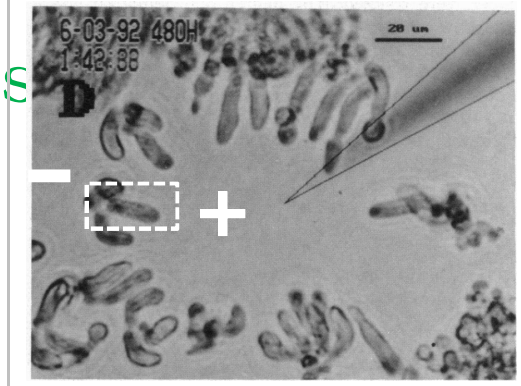
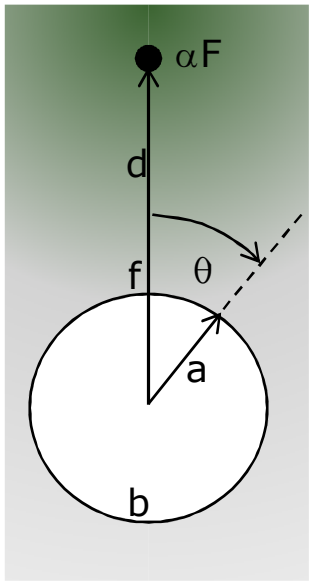
PRESS can operate during yeas polarization in a chemical gradient

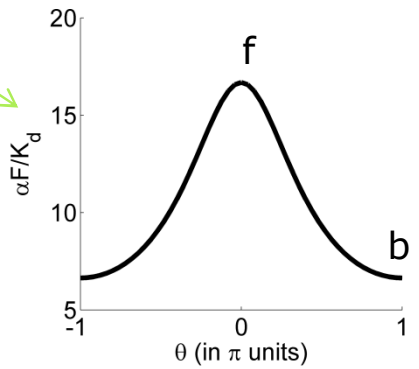


(1) Mathematical description: yeast in a gradient



yeast cell -> impermeable sphere

stimulus -> steady-state gradient $\alpha F(\theta)$



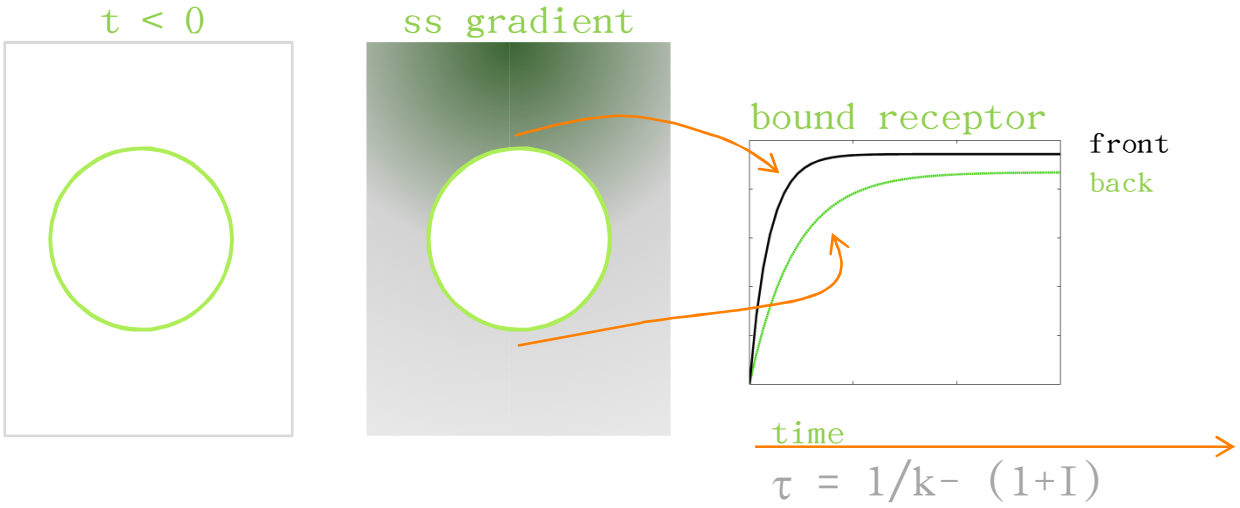
$$\alpha F(\theta) + R \underset{k-}{\overset{k+}{\rightleftharpoons}} C$$

$$C(t,\theta) = Css\,[1-\exp(-t/\tau)]$$

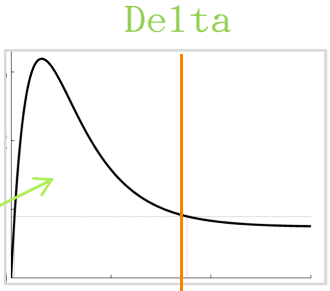
$$\frac{I}{1+I} \qquad I = \alpha F(\theta)/K_d \qquad 1/k- \;(1+I)$$

$p_1=(q/4\pi Dd)/K_d \quad p_2=a/d \quad p_3=k-$

(2) Mathematical description: scoring the front-back differences



$\tau = 1/k- (1+I)$



information that is only

transiently available

Delta(t) = C(t, front) — C(t, back)

(3) Mathematical description: characterizing *Delta*

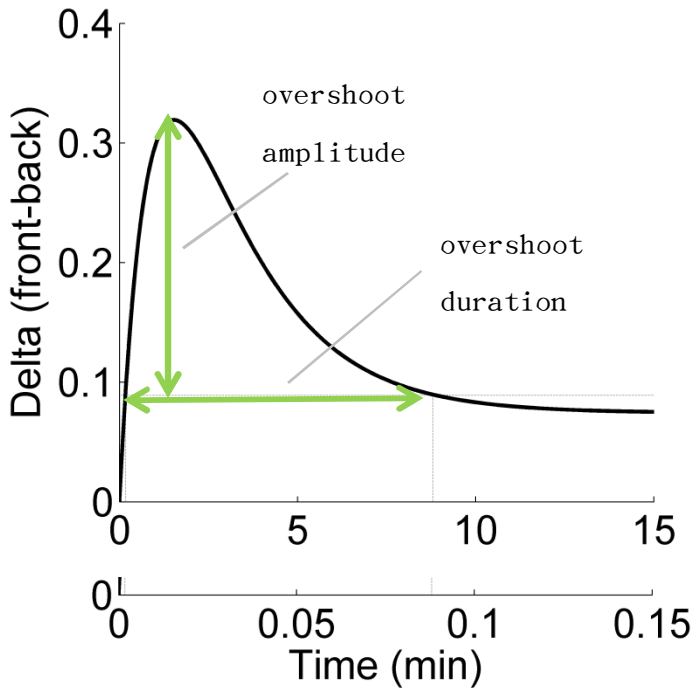
$$Delta_{(t)} = \underbrace{\frac{\widetilde{\alpha F}_f - \widetilde{\alpha F}_b}{(1+\widetilde{\alpha F}_f)(1+\widetilde{\alpha F}_b)}}_{\text{Delta eq}} + \frac{\widetilde{\alpha F}_b}{1+\widetilde{\alpha F}_b}\exp\{-t[k_-(1+\widetilde{\alpha F}_b)]\} - \frac{\widetilde{\alpha F}_f}{1+\widetilde{\alpha F}_f}\exp\{-t[k_-(1+\widetilde{\alpha F}_f)]\}$$

exponential gradient

$$\widetilde{\alpha F}_f = \widetilde{\alpha F}_b * const_2 \text{(with } const_2>1\text{)}$$

linear gradient

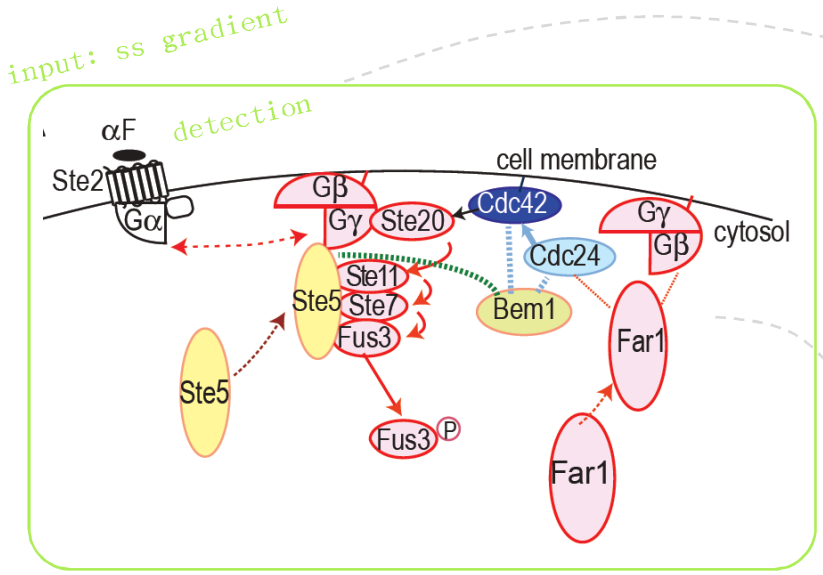
$$\widetilde{\alpha F}_f = \widetilde{\alpha F}_b + const_1$$



k- = 0.001 1/sec

k- = 0.1 1/sec

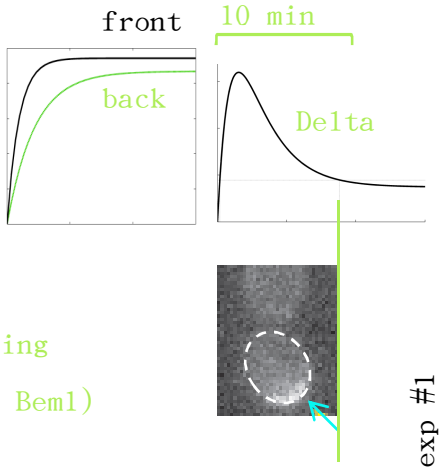
(4) Yeast can polarize fast, within the temporal window compatible with PRESS



pheromone response system

signaling

(Ste5, Bem1)



exp #1

20% of the cells have Ste5 polarized in the first 10 min

exp #2

Bem1	No internal cue
Average Repositioning Time (min)	10.8 ± 8.1

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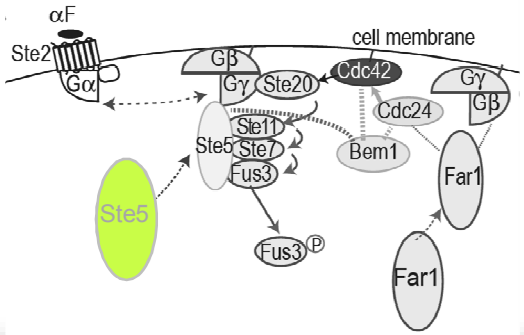
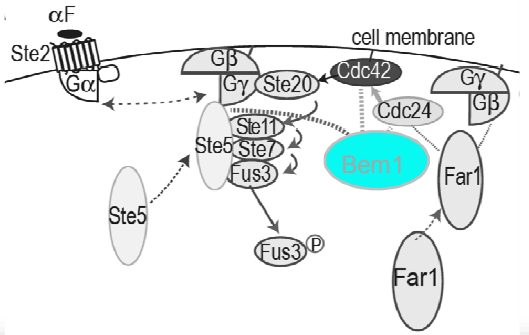
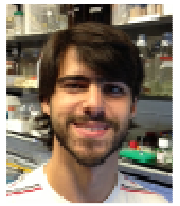


exp #1

exp #2





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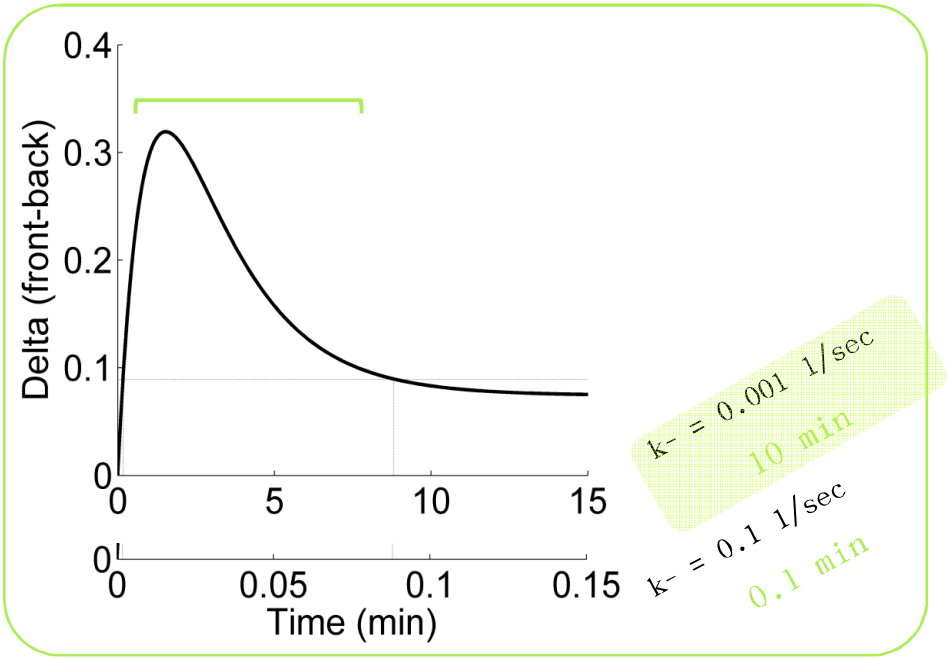
(5) If we accelerate binding

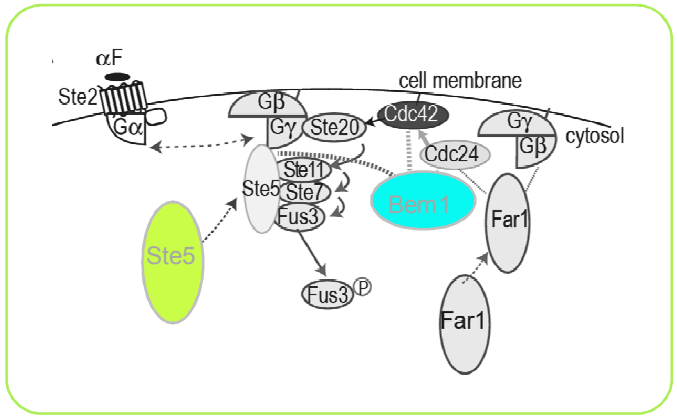
the temporal window with increased (gradient) information is reduced

and then is harder to detect the gradient

theoretical analysis



experimental evidence

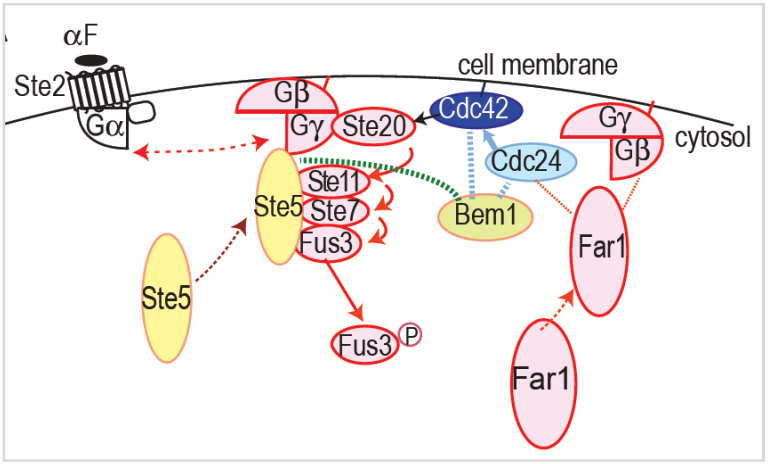


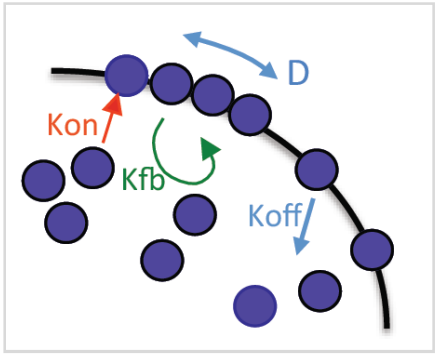
nature Vol 454 | 14 August 2008 | doi:10.1038/nature07119

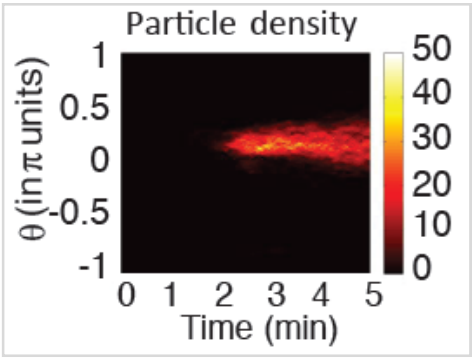
LETTERS

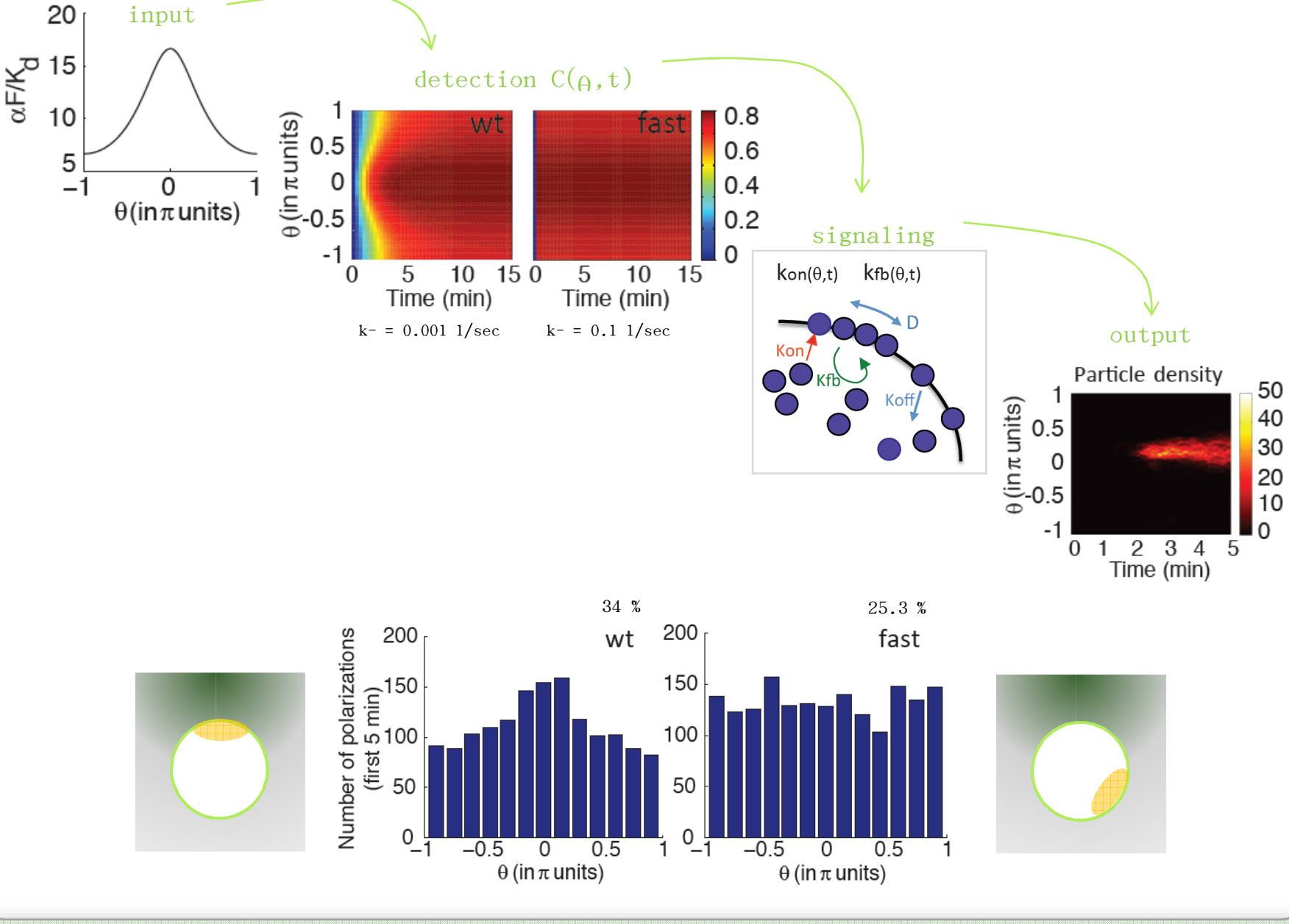
On the spontaneous emergence of cell polarity

Steven J. Altschuler[1], Sigurd B. Angenent[2], Yanqin Wang[1] & Lani F. Wu[1]

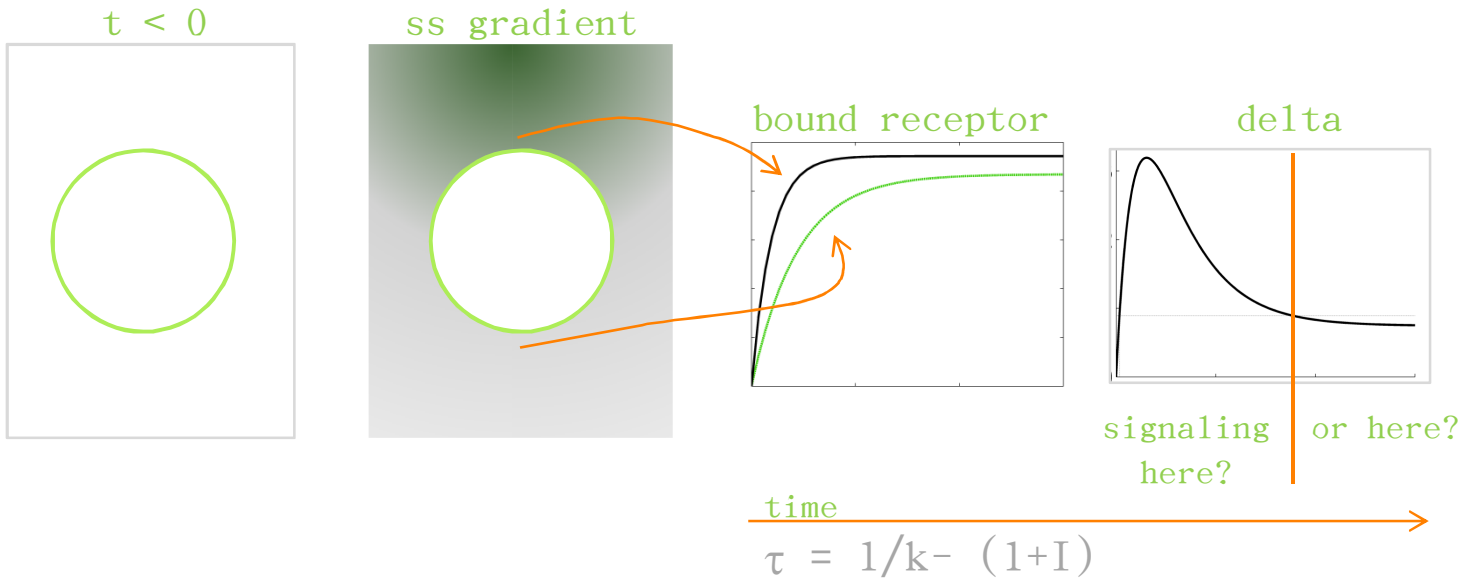




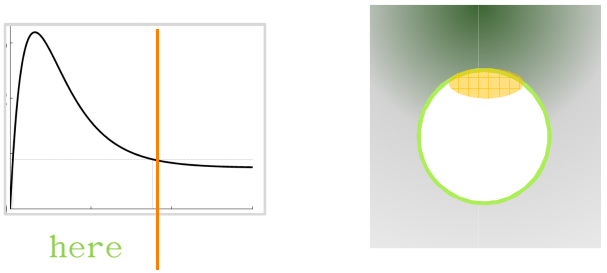



input
detection C(θ,t)
signaling
output
αF/Kd
θ (in π units)
wt
fast
Time (min)
k- = 0.001 1/sec
k- = 0.1 1/sec
kon(θ,t)
kfb(θ,t)
D
Kon
Kfb
Koff
Particle density
34 %
25.3 %
Number of polarizations (first 5 min)

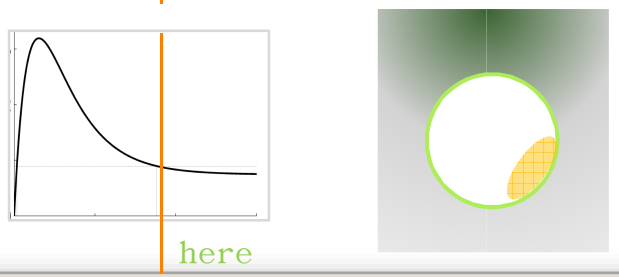
Summary II



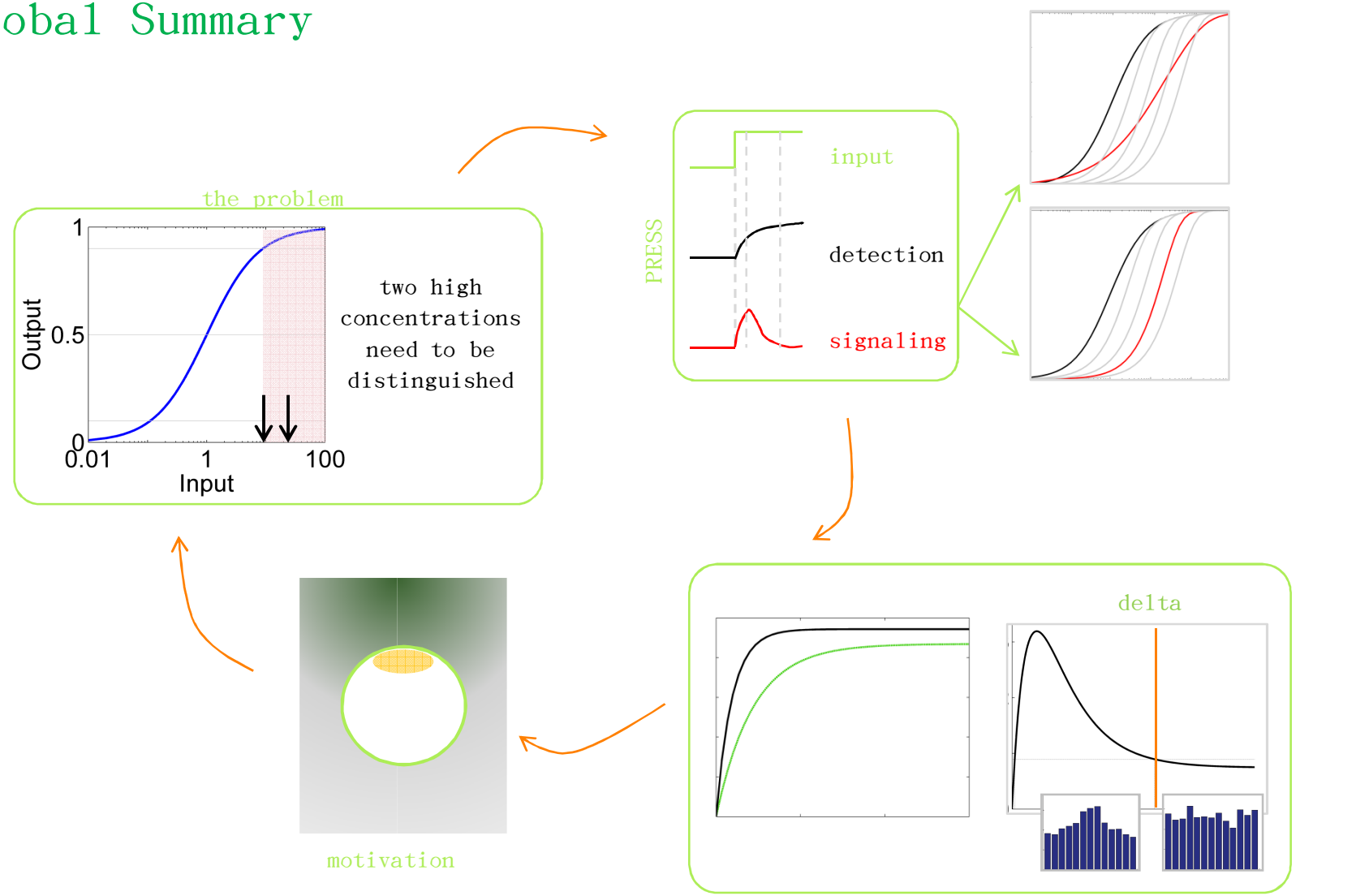
slow binding (low k-)



fast binding (high k-)



Global Summary



Acknowledgements

IFIBYNE CONICET U B A

FBMC Fisiología y Biología Molecular y Celular


Dr. Alejandro Colman-Lerner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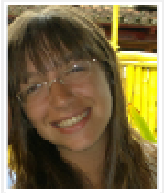
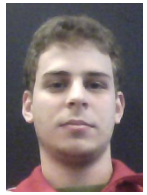
Lic. Gustavo Vasen


Lic. Juan Pablo Di Bella


Lic. Laila Kazimierski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Andreas Constantinou


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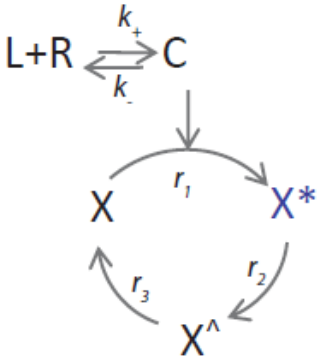
departamento de física
Juan José Giambiagi

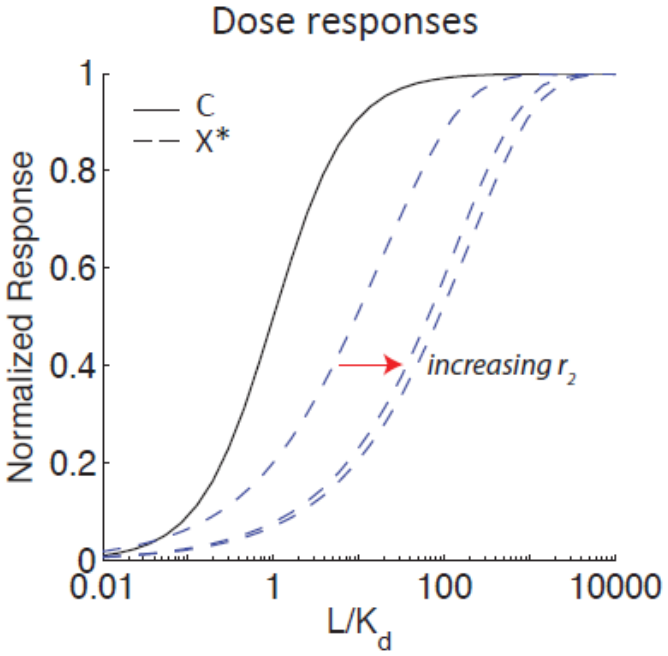

Dr. Ariel Chernomoretz

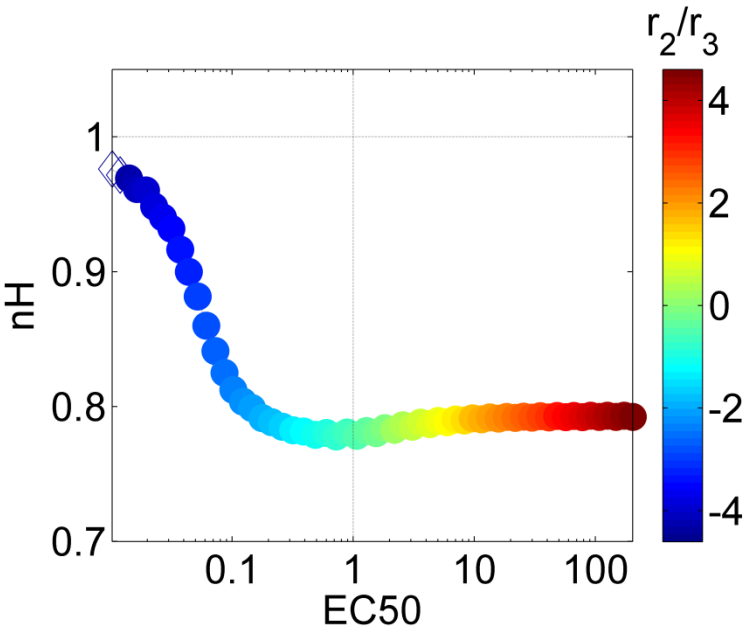
Facultad de Ciencias Exactas y Naturales
UBA EXACTAS

Thank you!



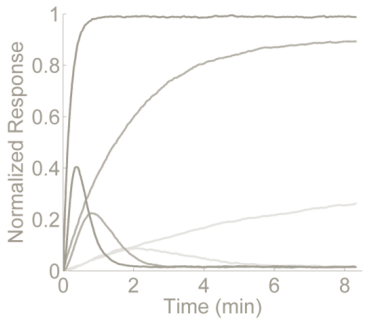
X with
refractory state

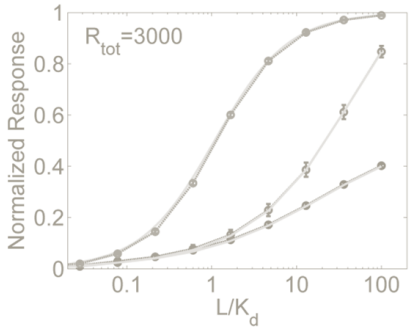


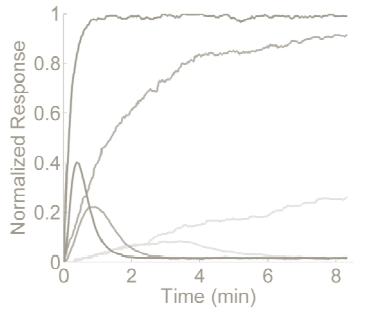


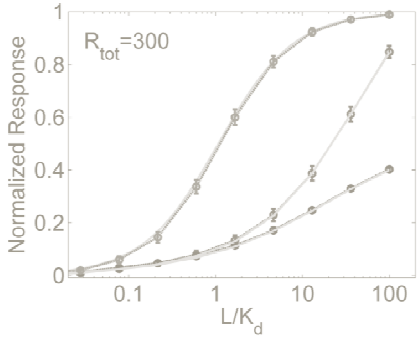
The effect of noise during PRESS

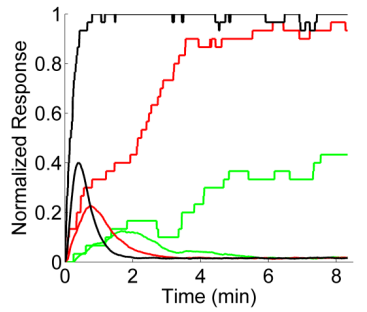
increasing noise

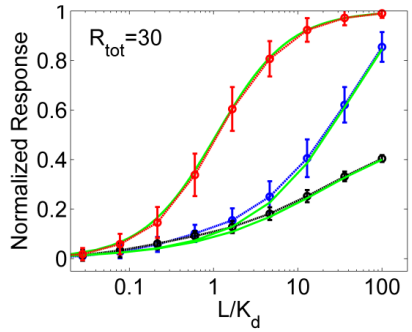


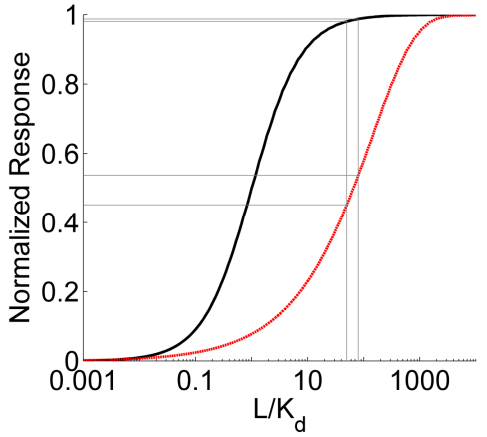




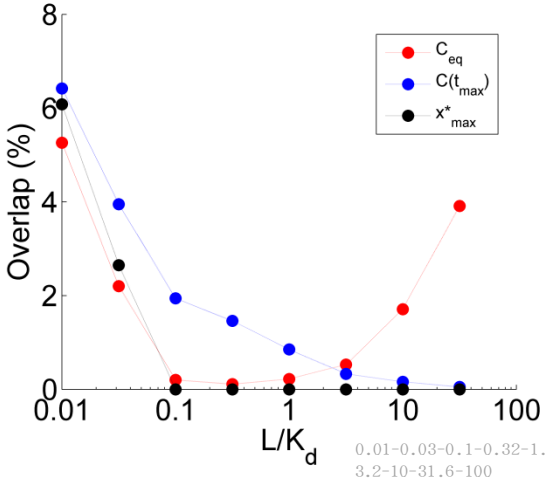






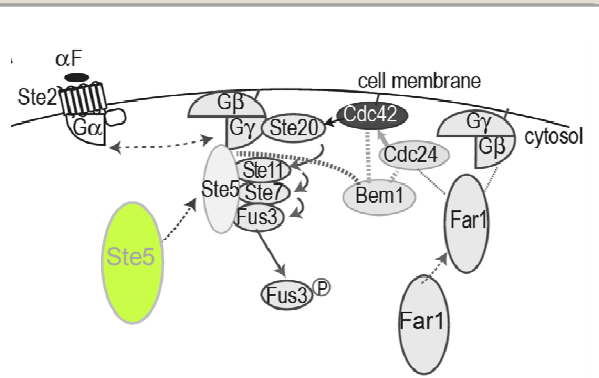


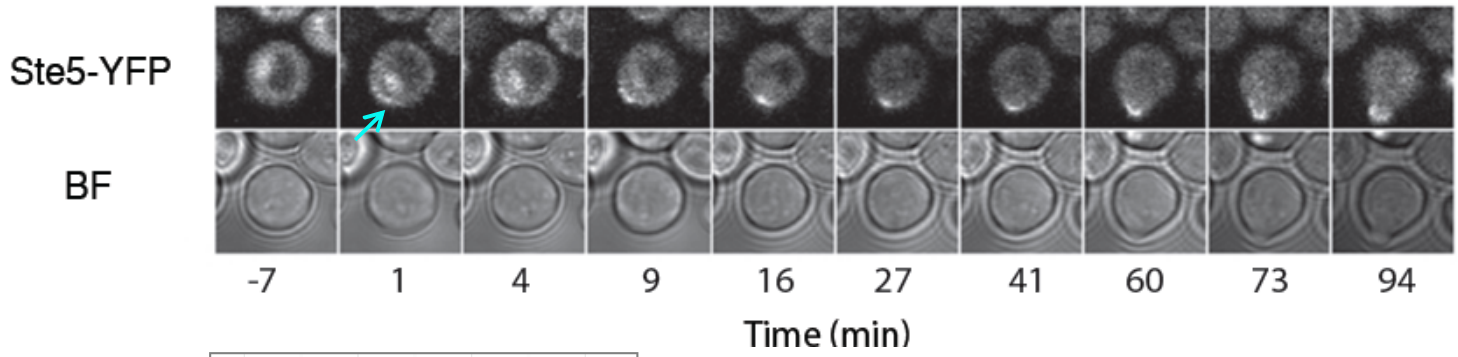
is noise amplified in PRESS mode?

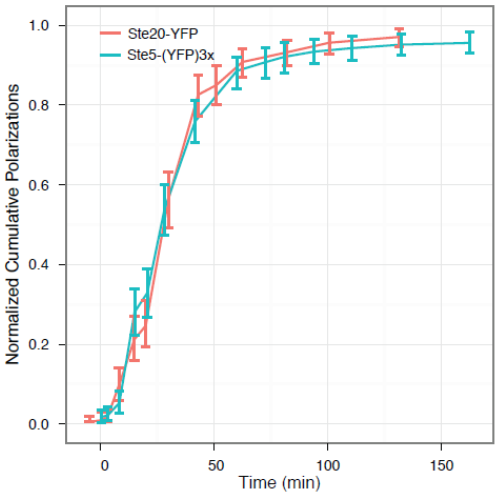


the improvement gained by PRESS is not lost by the effect of noise

Experiment #1.
Polarization of Ste5, isotropic stimulation







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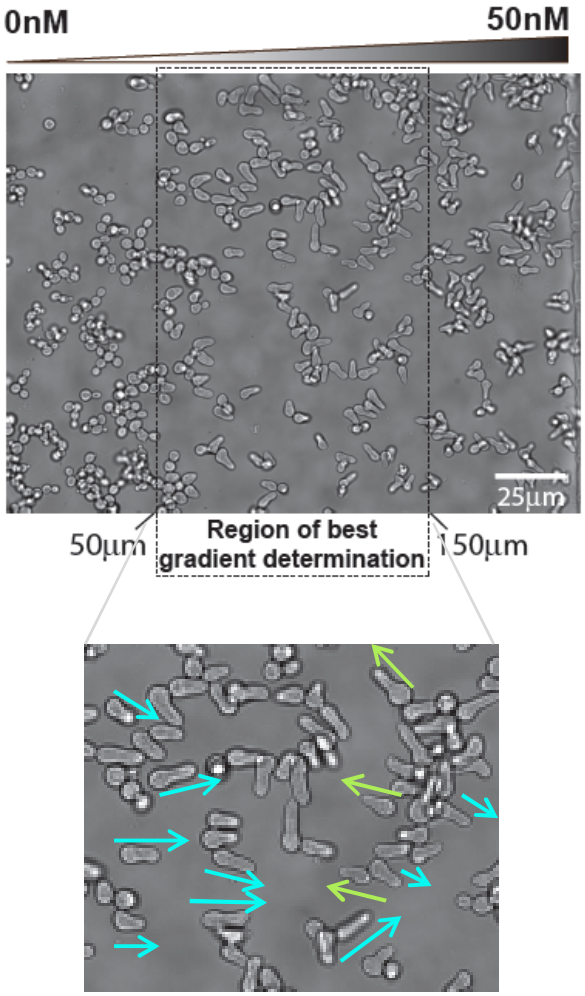
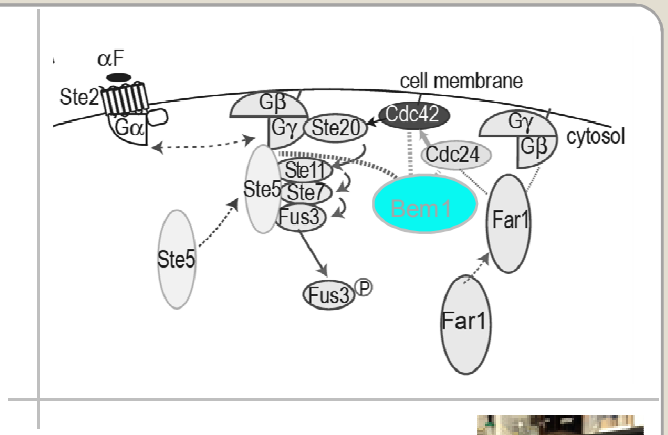
Experiment #2.
Relocalization of Beml, linear gradient





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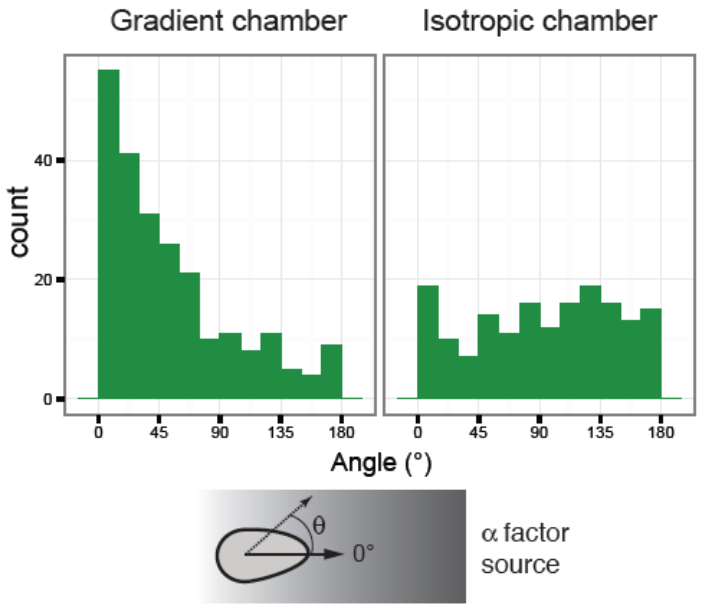
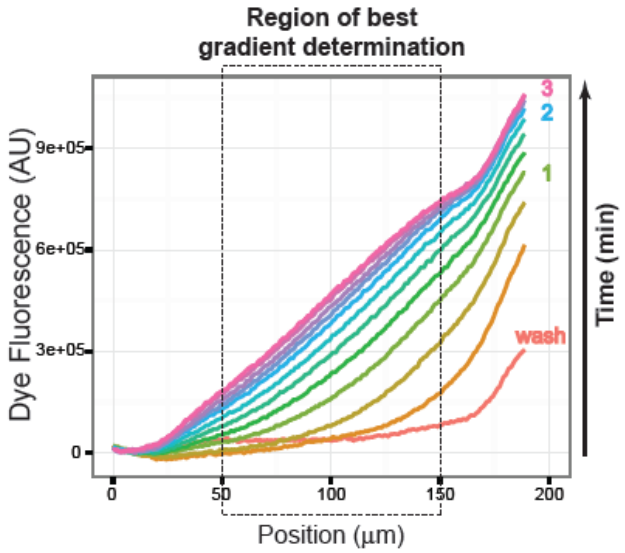
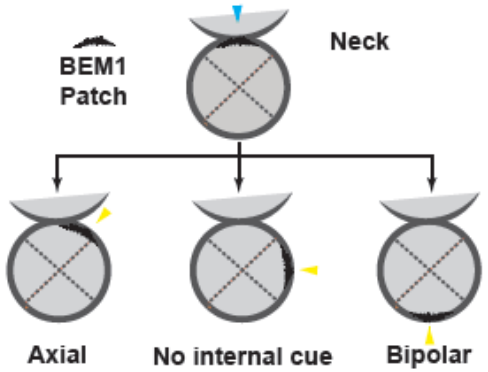


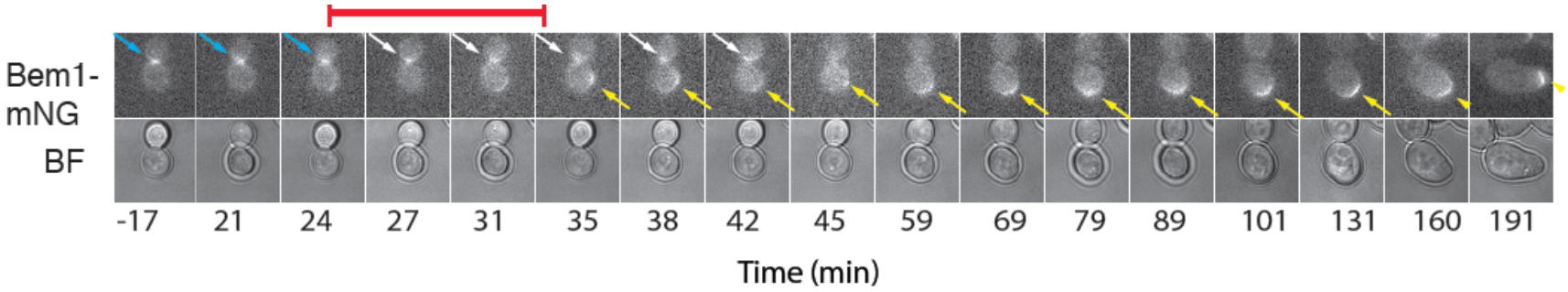
the gradient is linear and it reaches steady-state in ~ 3 min

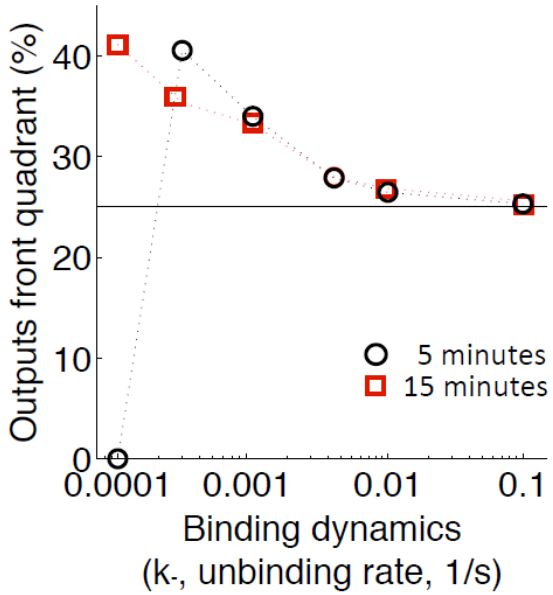


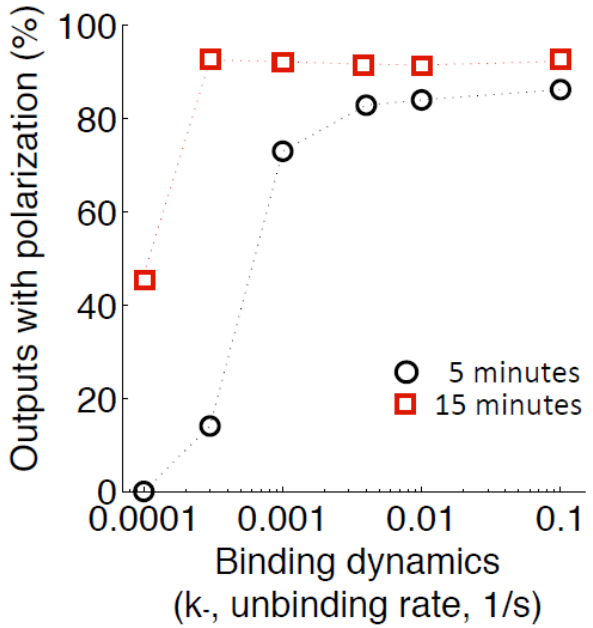
measurement of patch repositioning time

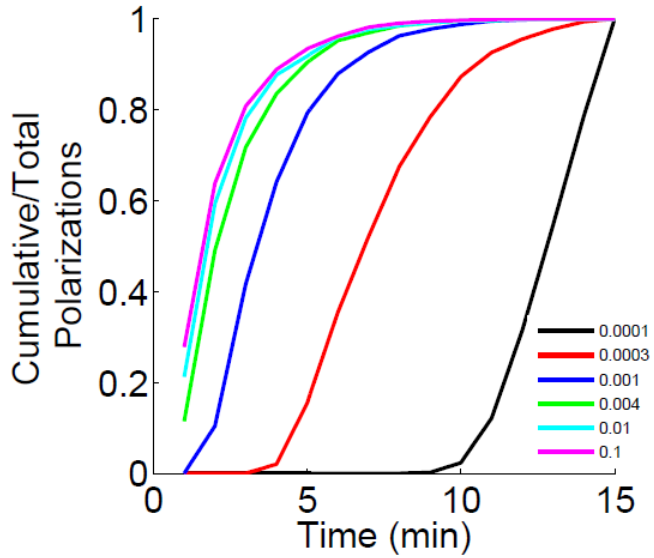


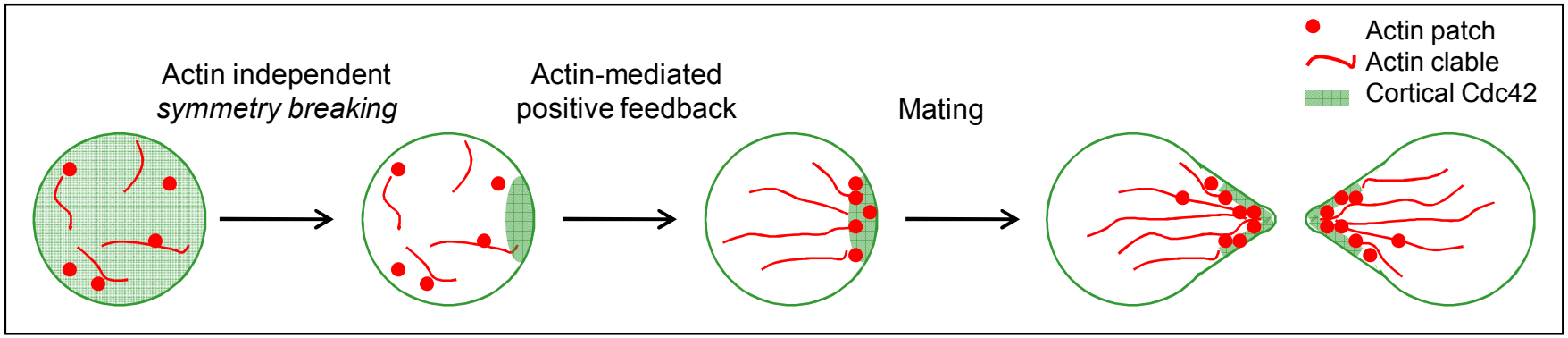
	Axial	No internal cue	Bipolar
Average Repositioning Time (min)	3.6 ± 0.1	10.8 ± 8.1	10.6 ± 8.7




Outputs front quadrant (%)
40
30
20
10
0
0.0001
0.001
0.01
0.1
Binding dynamics
(k-, unbinding rate, 1/s)
5 minutes
15 minutes


Outputs with polarization (%)
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
Binding dynamics
(k-, unbinding rate, 1/s)
5 minutes
15 minutes


Cumulative/Total
Polarizations
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Time (min)
0.0001
0.0003
0.001
0.004
0.01
0.1


Actin independent
symmetry breaking
Actin-mediated
positive feedback
Mating
Actin patch
Actin clable
Cortical Cdc42