Dynamics of gene regulatory circuits

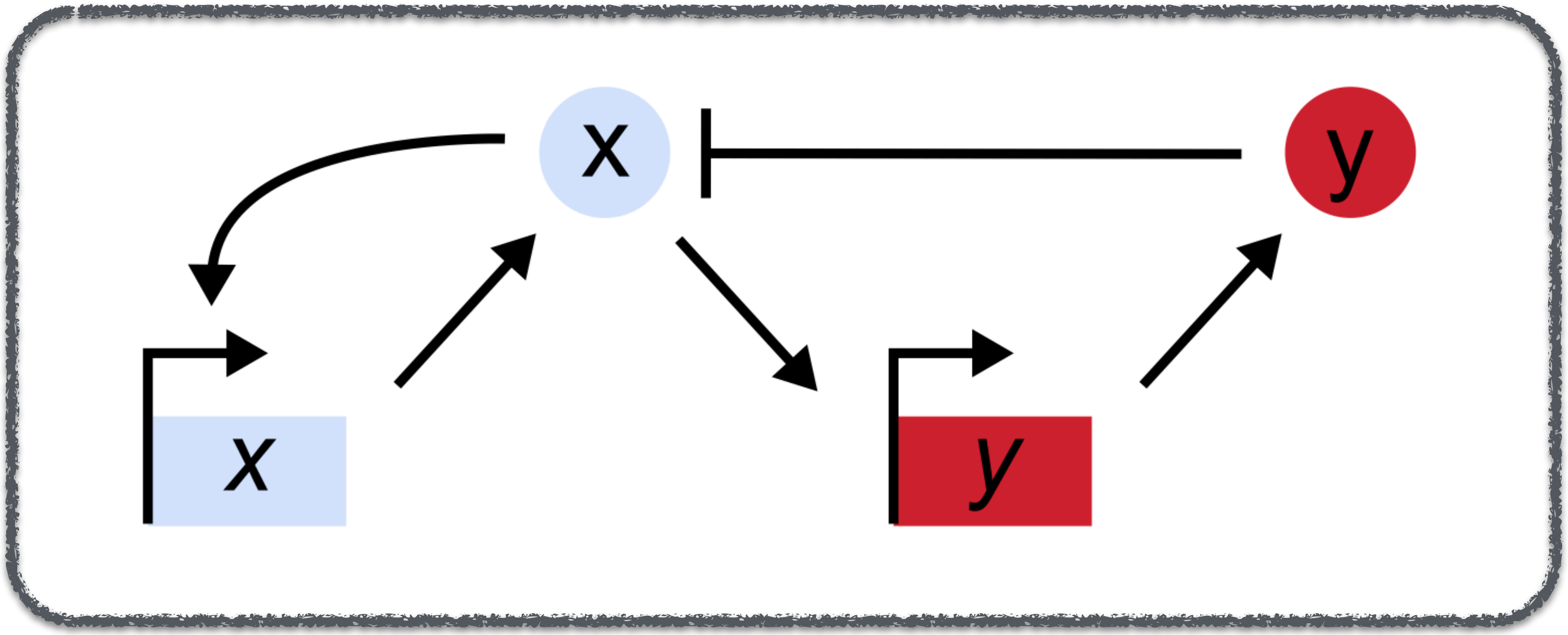
Jordi Garcia Ojalvo
Department of Experimental and Health Sciences
Universitat Pompeu Fabra

E-mail: jordi.g.ojalvo@upf.edu
Web: http://dsb.upf.edu

Advanced Summer School on Applied Dynamics
in Systems and Synthetic Biology

Centre de Recerca Matemàtica
September 6-10, 2021

Combining a positive and a negative feedback

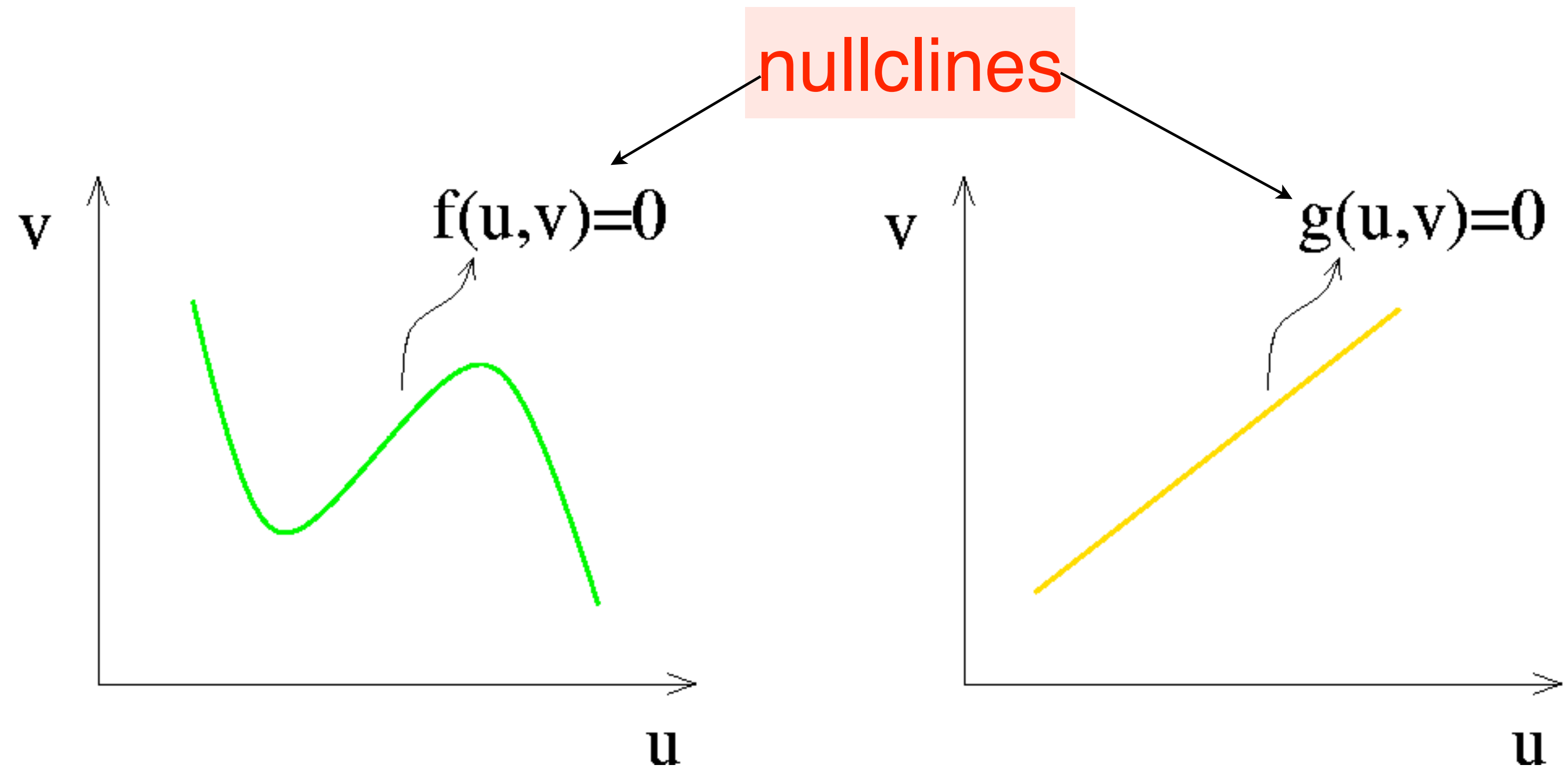


$$\frac{dx}{dt} = a_1 + \frac{b_1 x^n}{{K_1}^n + x^n} - gxy - d_1 x$$

$$\frac{dy}{dt} = a_2 + \frac{b_2 x^m}{{K_2}^m + x^m} - d_2 y$$

Two degrees of freedom: phase plane

$$\tau_u \dot{u} = f(u,v)$$
$$\tau_v \dot{v} = g(u,v)$$



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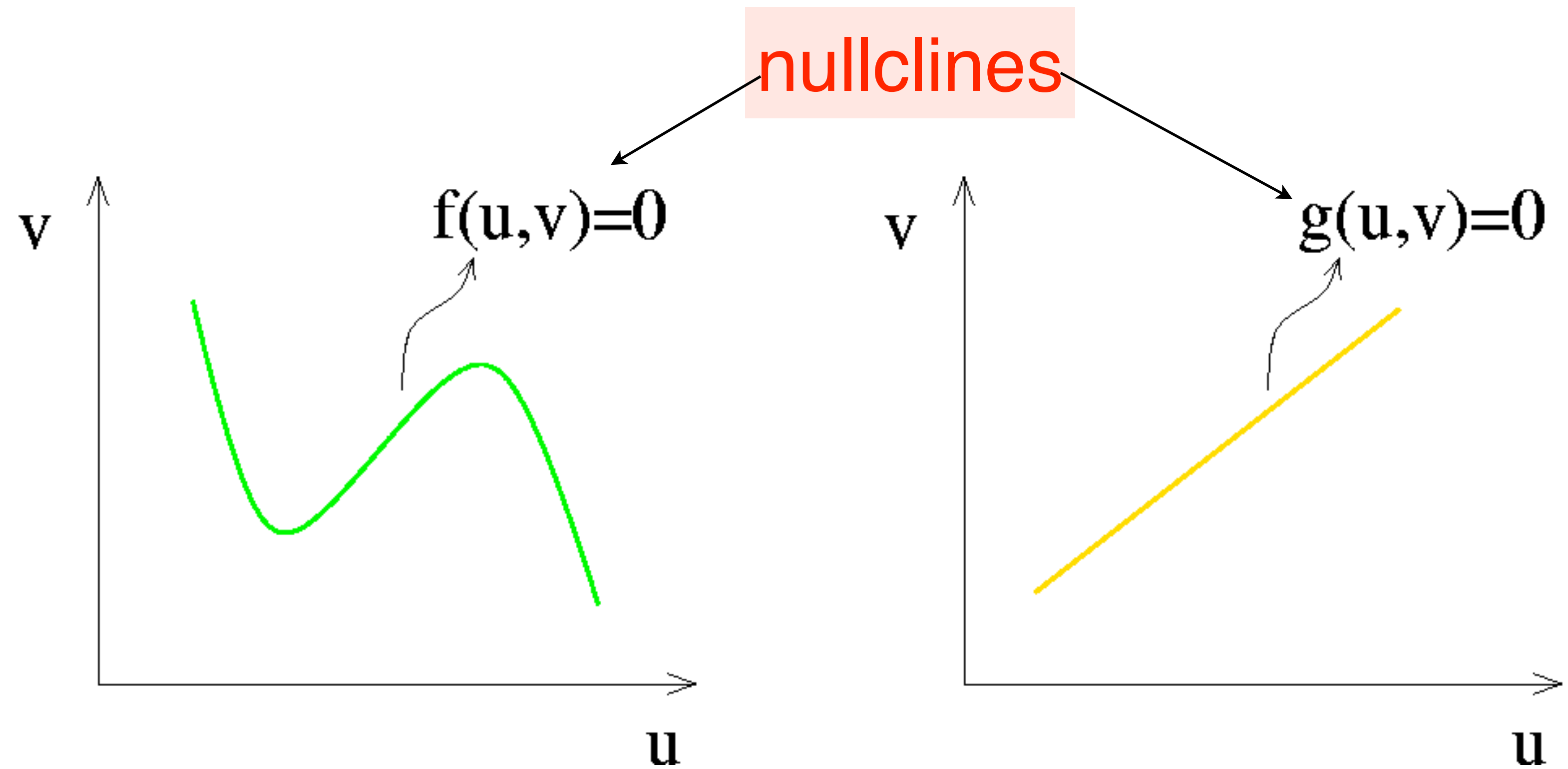

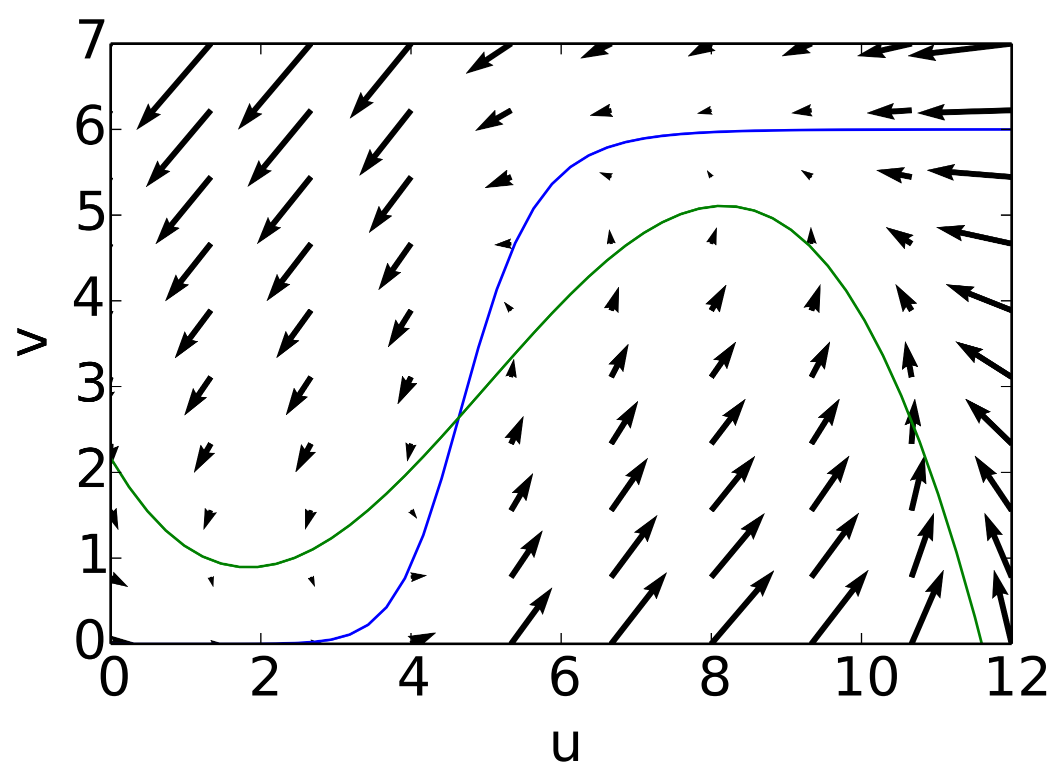

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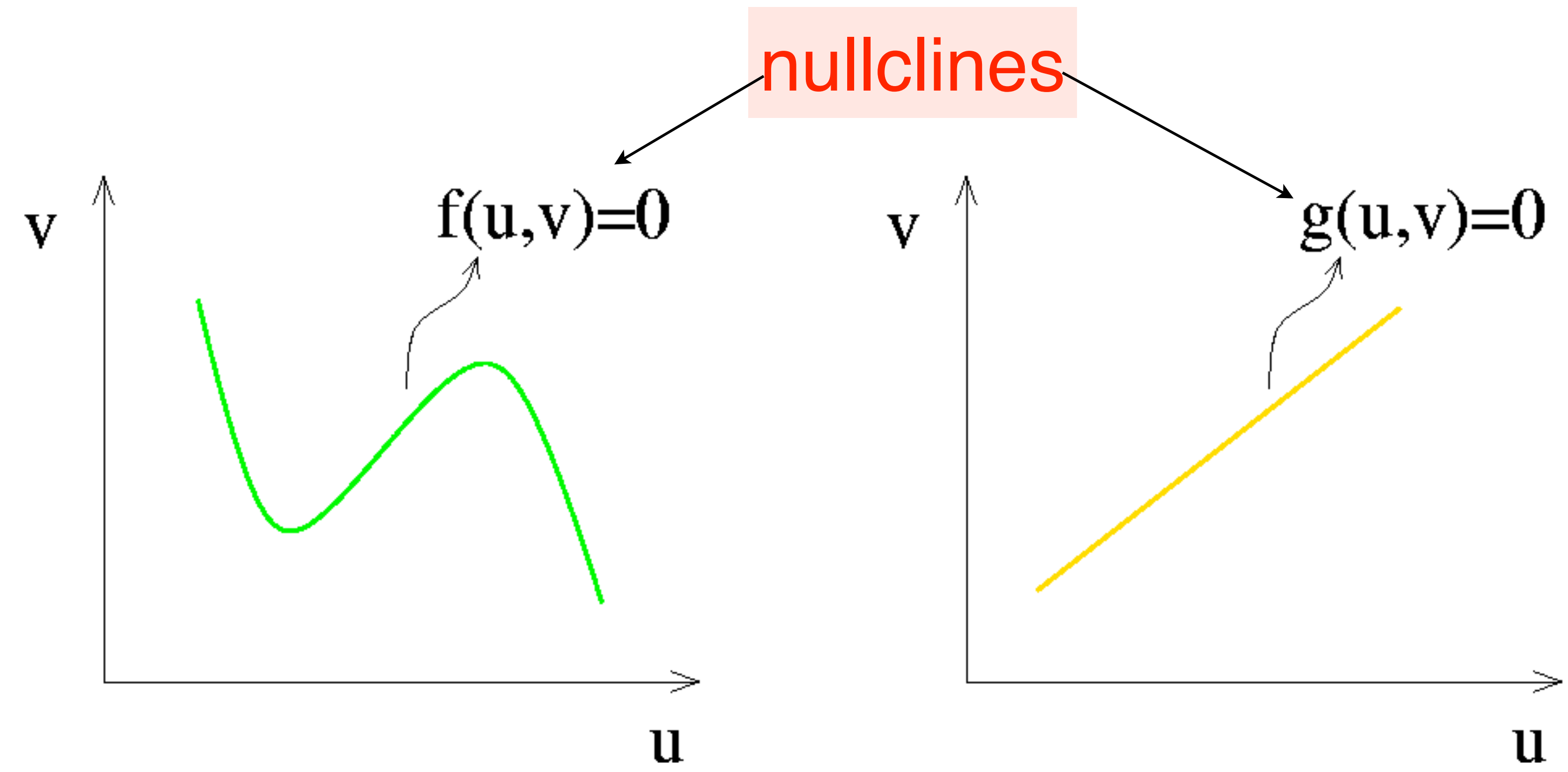
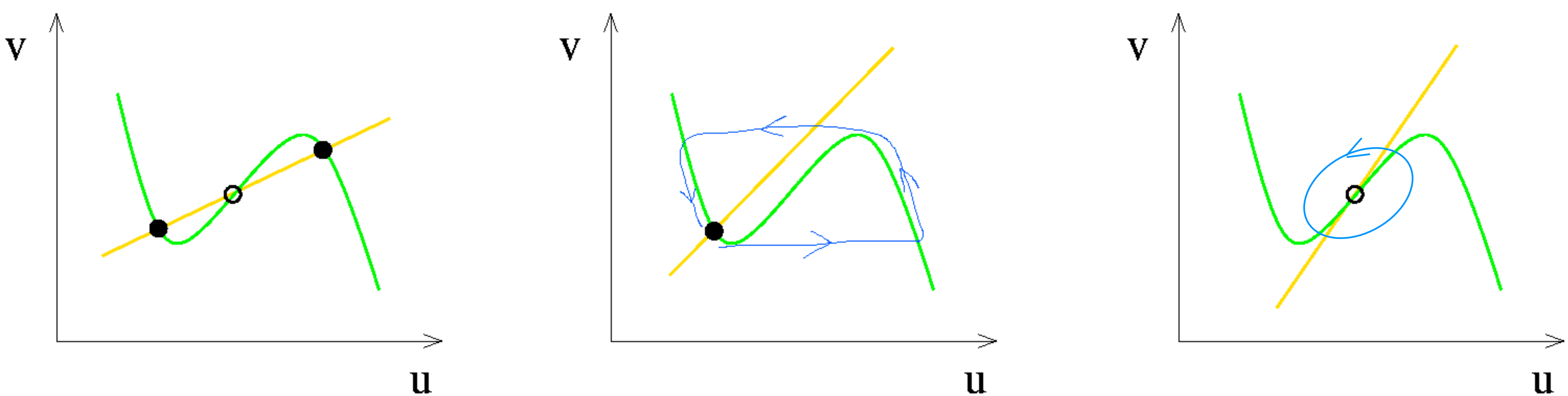
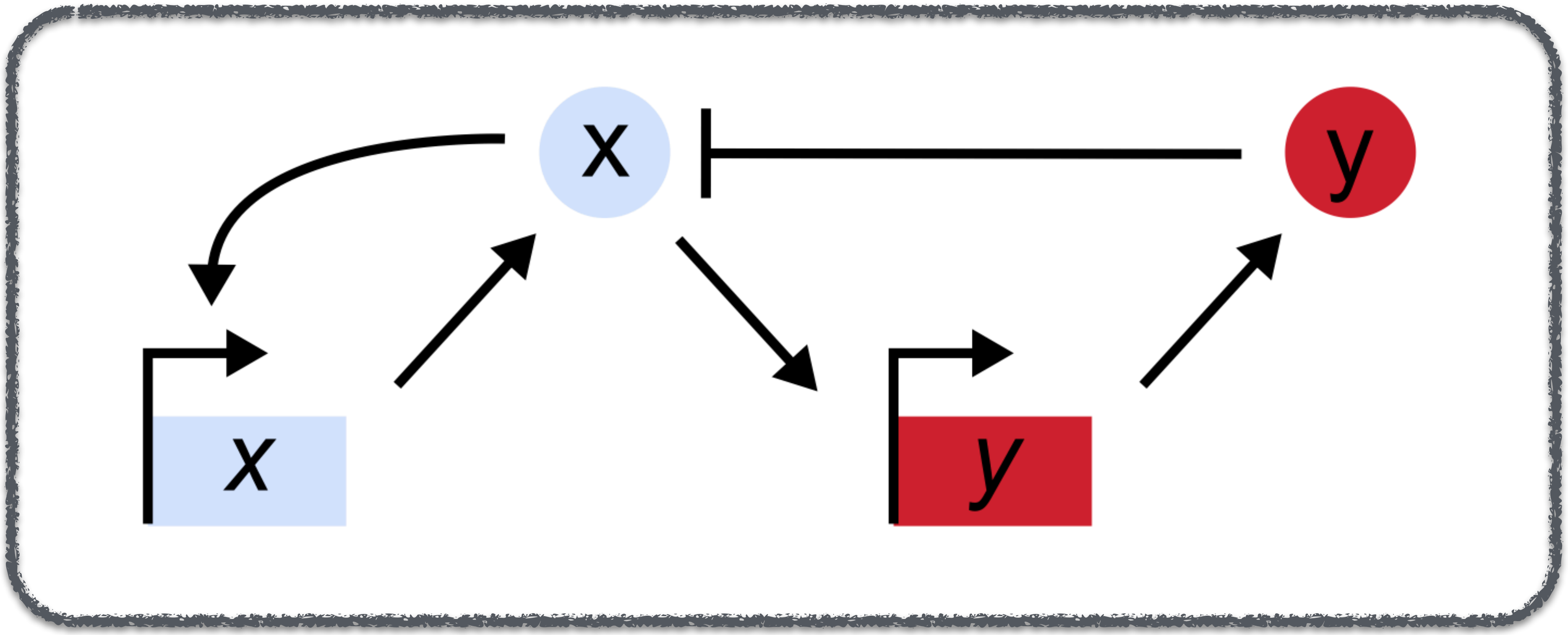




BISTABLE EXCITABLE OSCILLATORY

Combining a positive and a negative feedback



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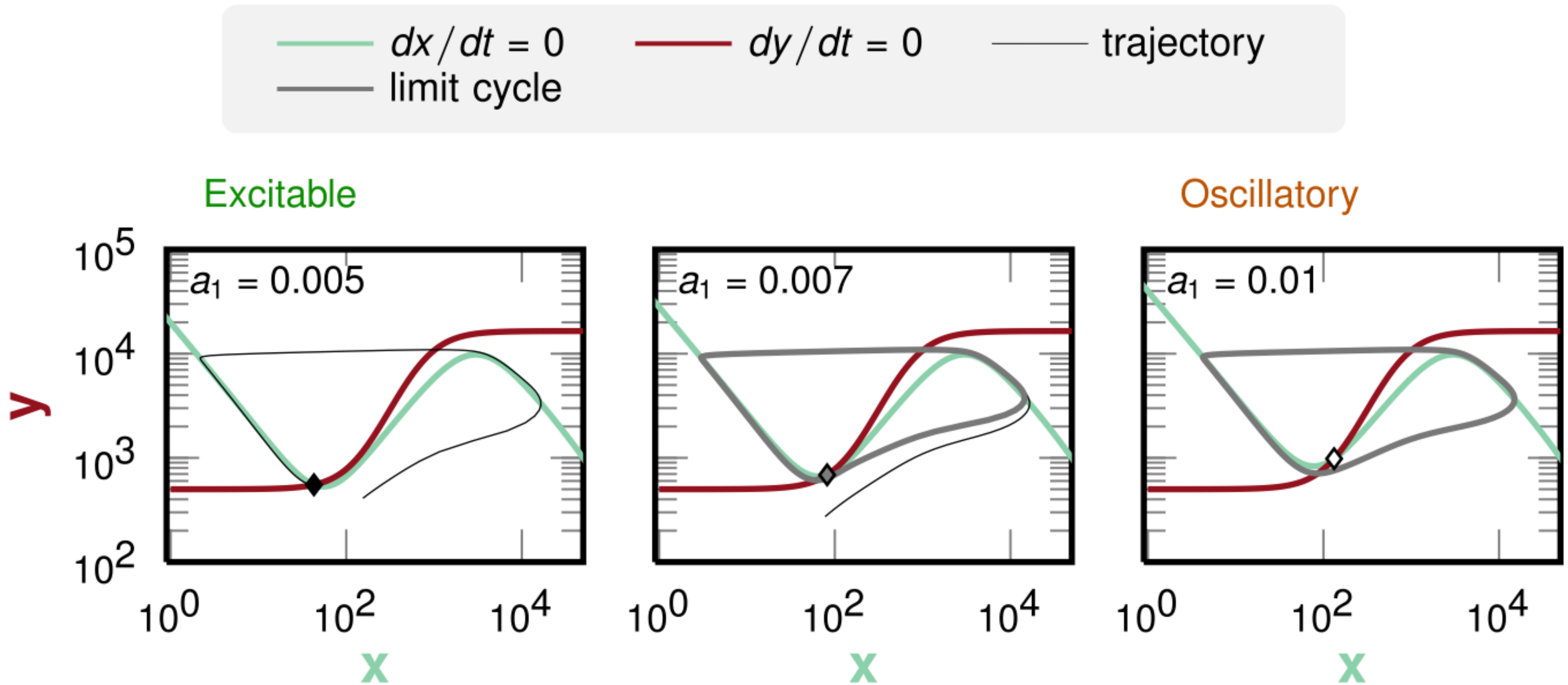
$$\frac{dy}{dt} = a_2 + \frac{b_2 x^m}{{K_2}^m + x^m} - d_2 y$$

From oscillations to pulses



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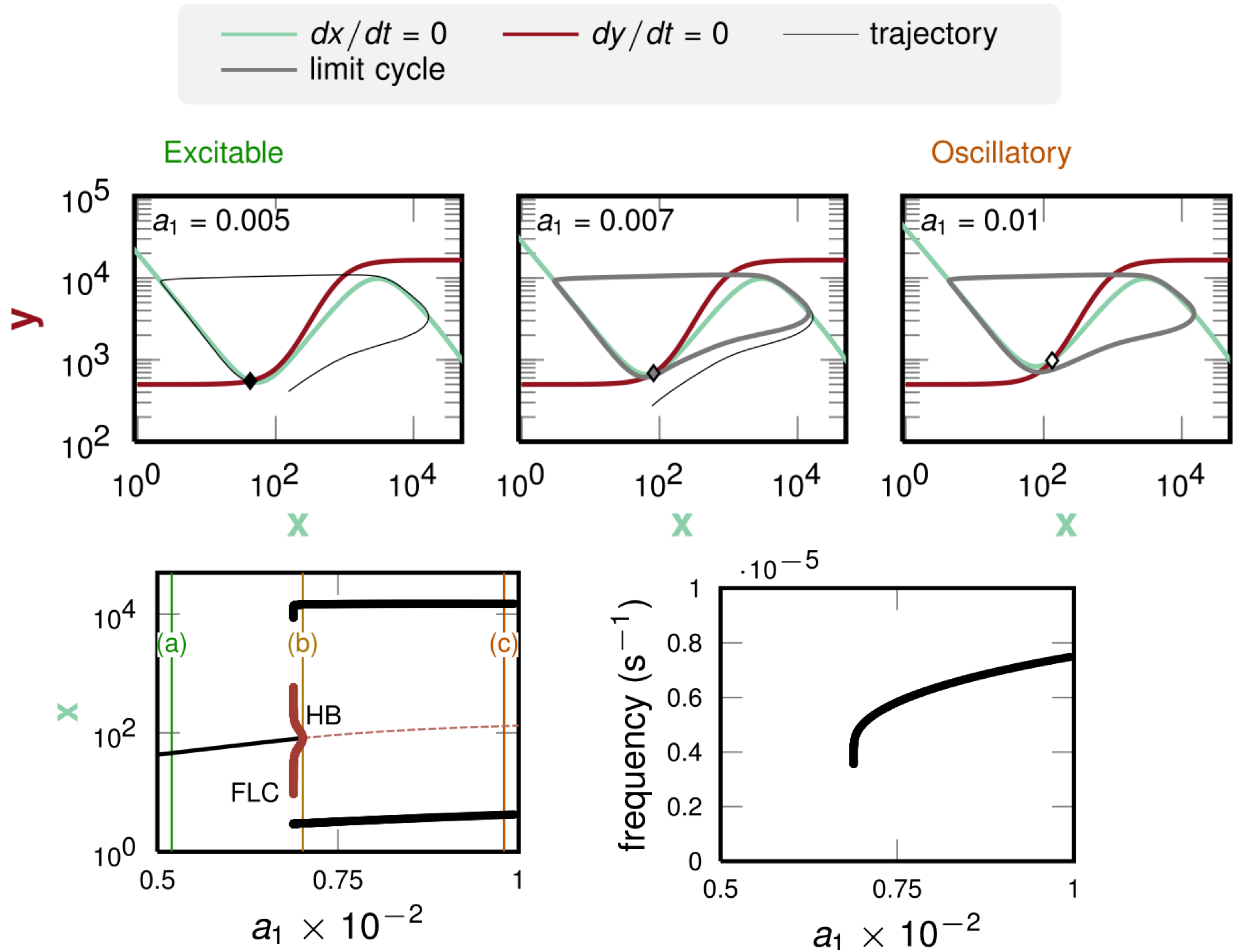
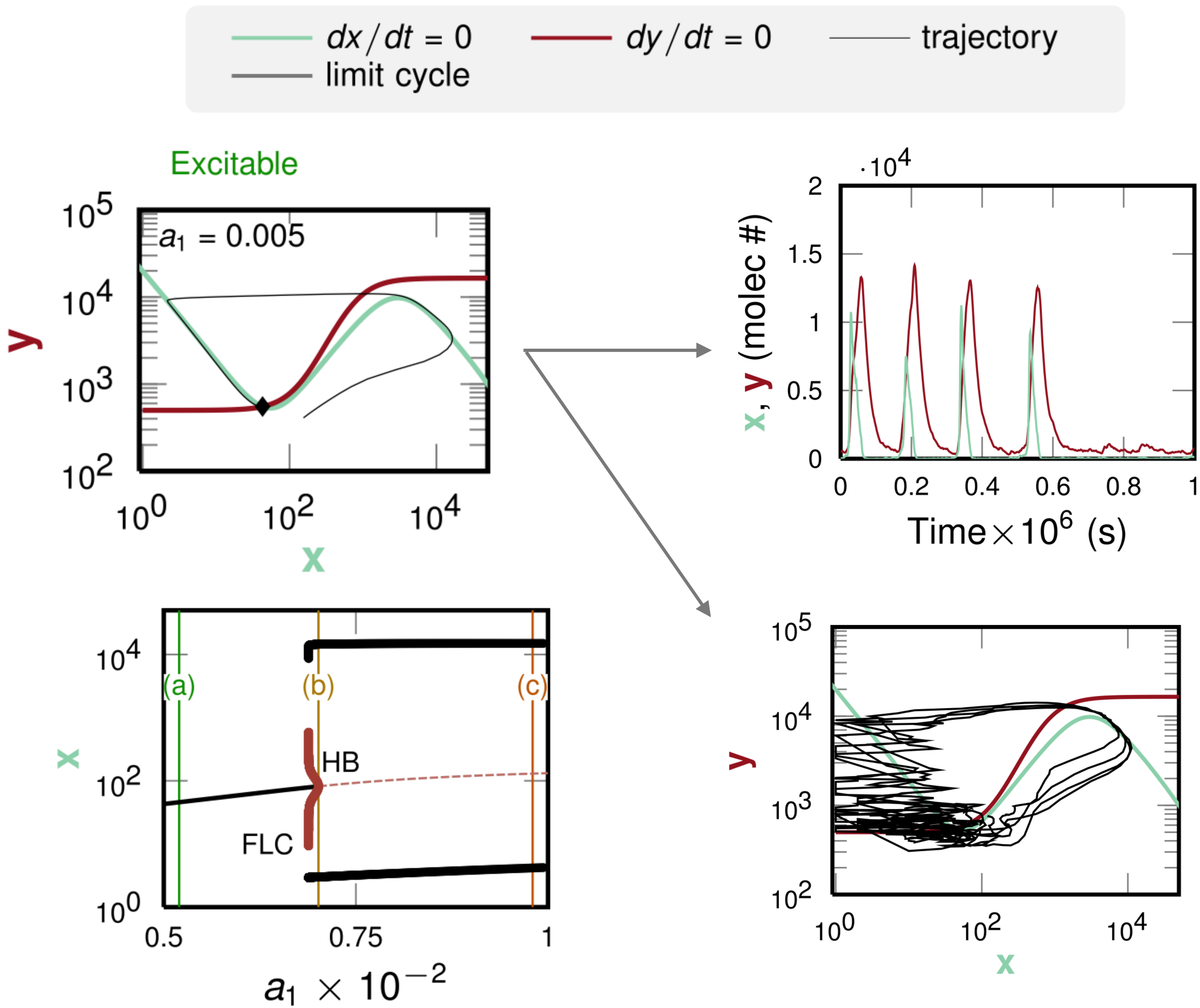
Rue & JGO, Math. Biosci., 2011

Bifurcation analysis



Excitability



subsequent decrease of α back down to 0 does not cause expression to turn off: the cell responds *irreversibly* to a pulse stimulus in α.

3. Consider the following activator-repressor model discussed in class:

$$\frac{dx}{dt} = a_1 + \frac{b_1 x^n}{K_1{}^n + x^n} - gxy - d_1 x$$

$$\frac{dy}{dt} = a_2 + \frac{b_2 x^m}{K_2{}^m + x^m} - d_2 y$$

   Use the tools that you have learned in the different courses of this school to analyze this dynamical system in the plane, as the basal expression rate a_1 of x varies, as shown in the slides. Use these values for the other parameters to perform simulations if necessary: a_2=0.025 nM/s, b_1=15 nM/s, b_2=0.8 nM/s, d_1=d_2=$5\cdot10^{-5}$ s^{-1}, g=$2.5\cdot10^{-7}$ $nM^{-1}s^{-1}$, K_1=3000 nM, K_2=750 nM, and n=m=2.

4. The following model describes genetic competence in *B. subtilis*:

Dynamics of gene regulatory circuits

1. Gene circuit dynamics
2. Dissecting a genetic circuit
3. Noise in genetic circuits

Stress responses of bacteria

Stresses

Nutrient deprivation

Energy deprivation

Toxins (e.g. antibiotics)

Physical stress (e.g. osmosis)

Chemical stress (e.g. pH)

https://www.sciencefocus.com

Responses

Motility

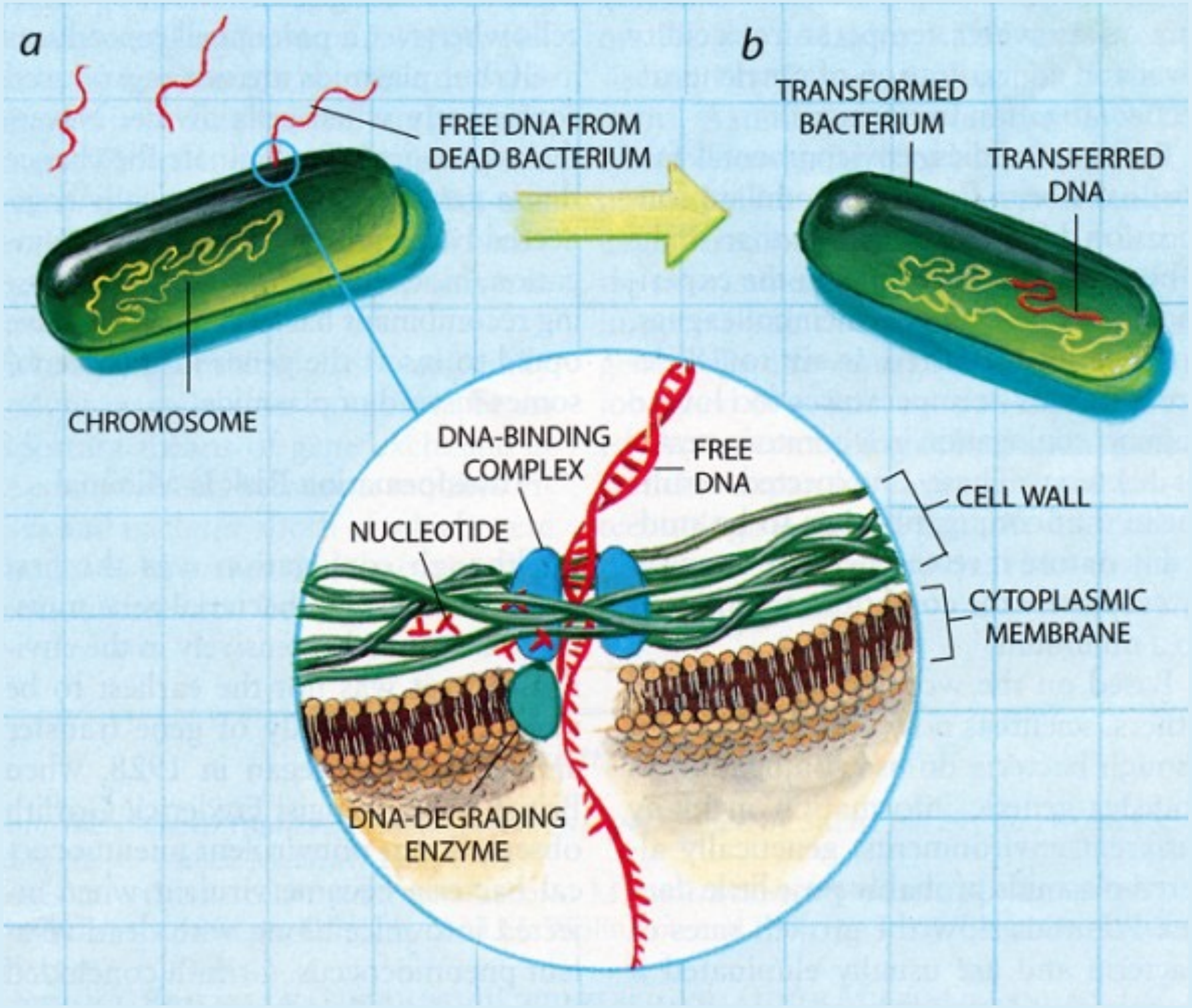
Sporulation

Biofilm formation

Cannibalism

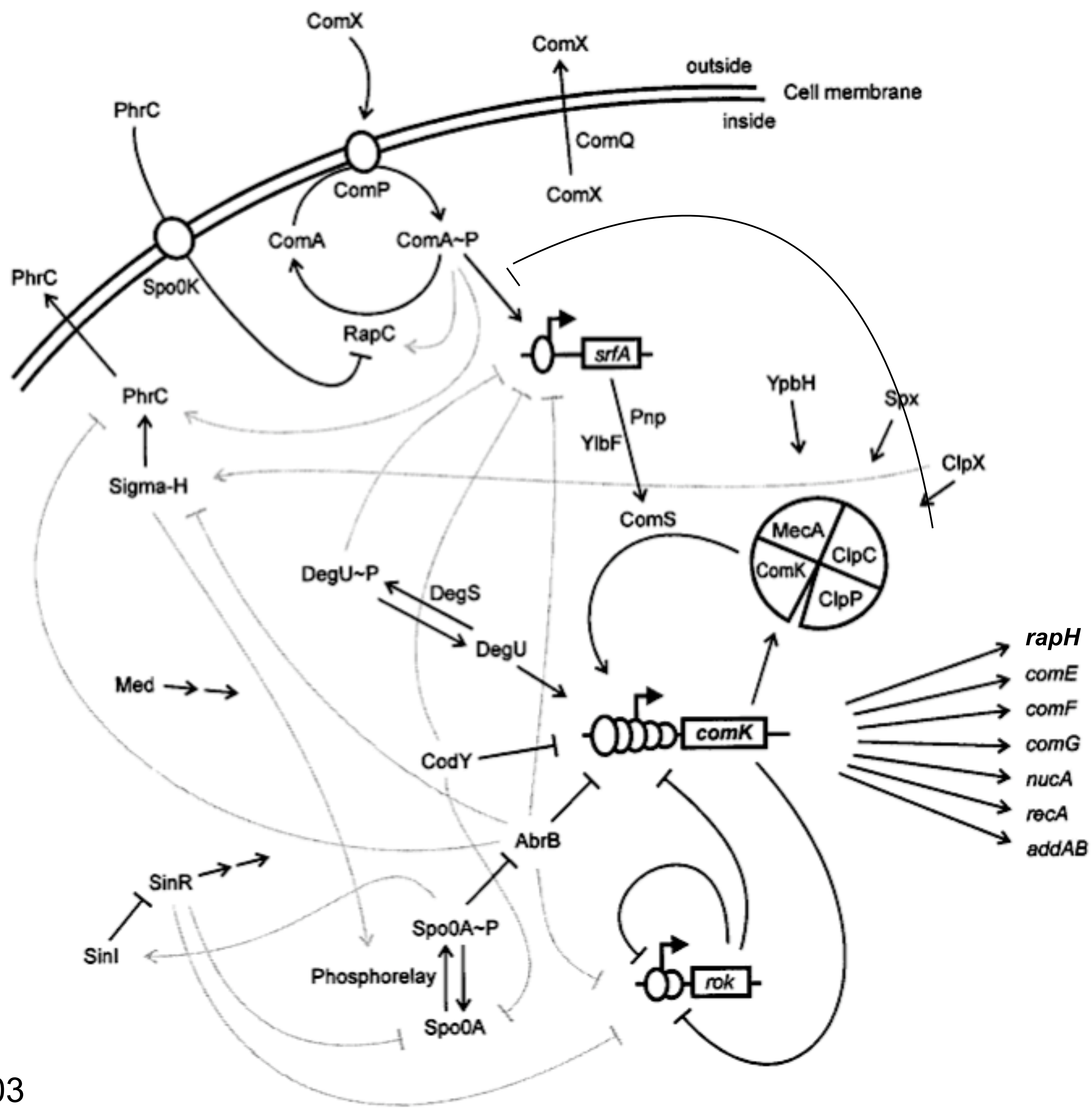
Genetic competence

Genetic competence



https://www.cmbn.no/tonjum/fuge-camst/koomey.html

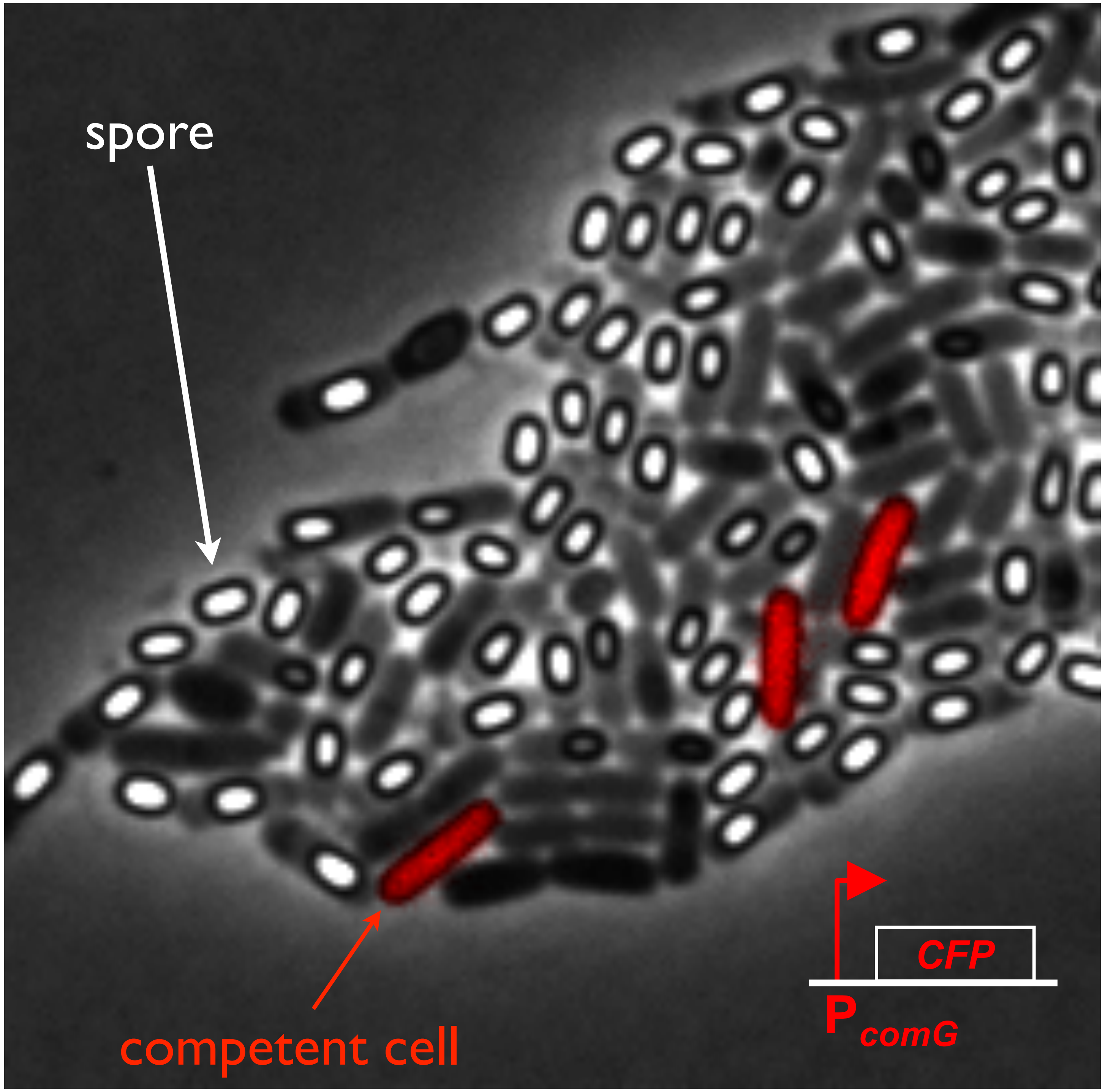
Gene network underlying genetic competence



adapted from
Hamoen et al,
Microbiology 2003

Stress response of bacteria

B. subtilis under low nutrient conditions



Stress response of bacteria

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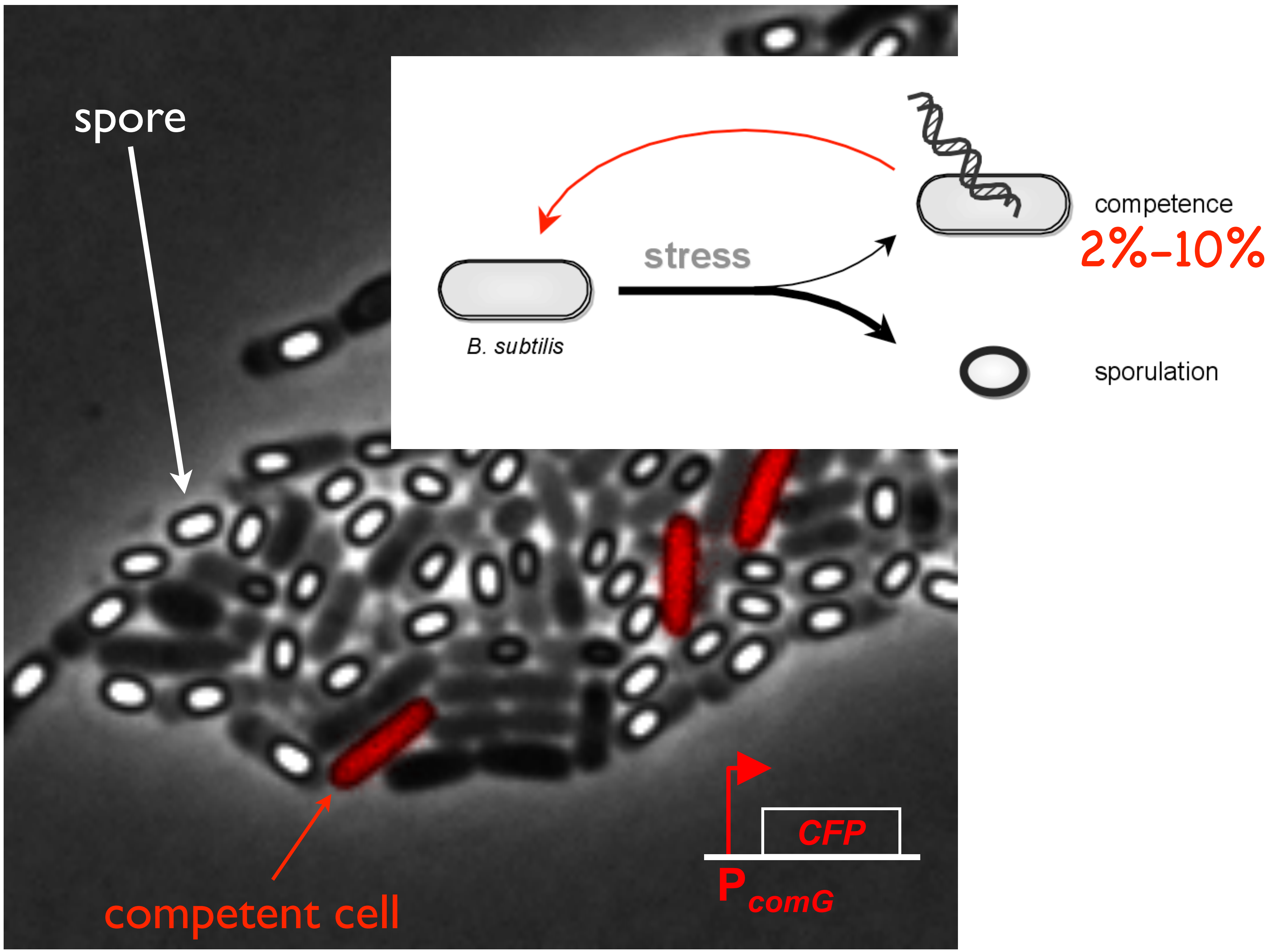
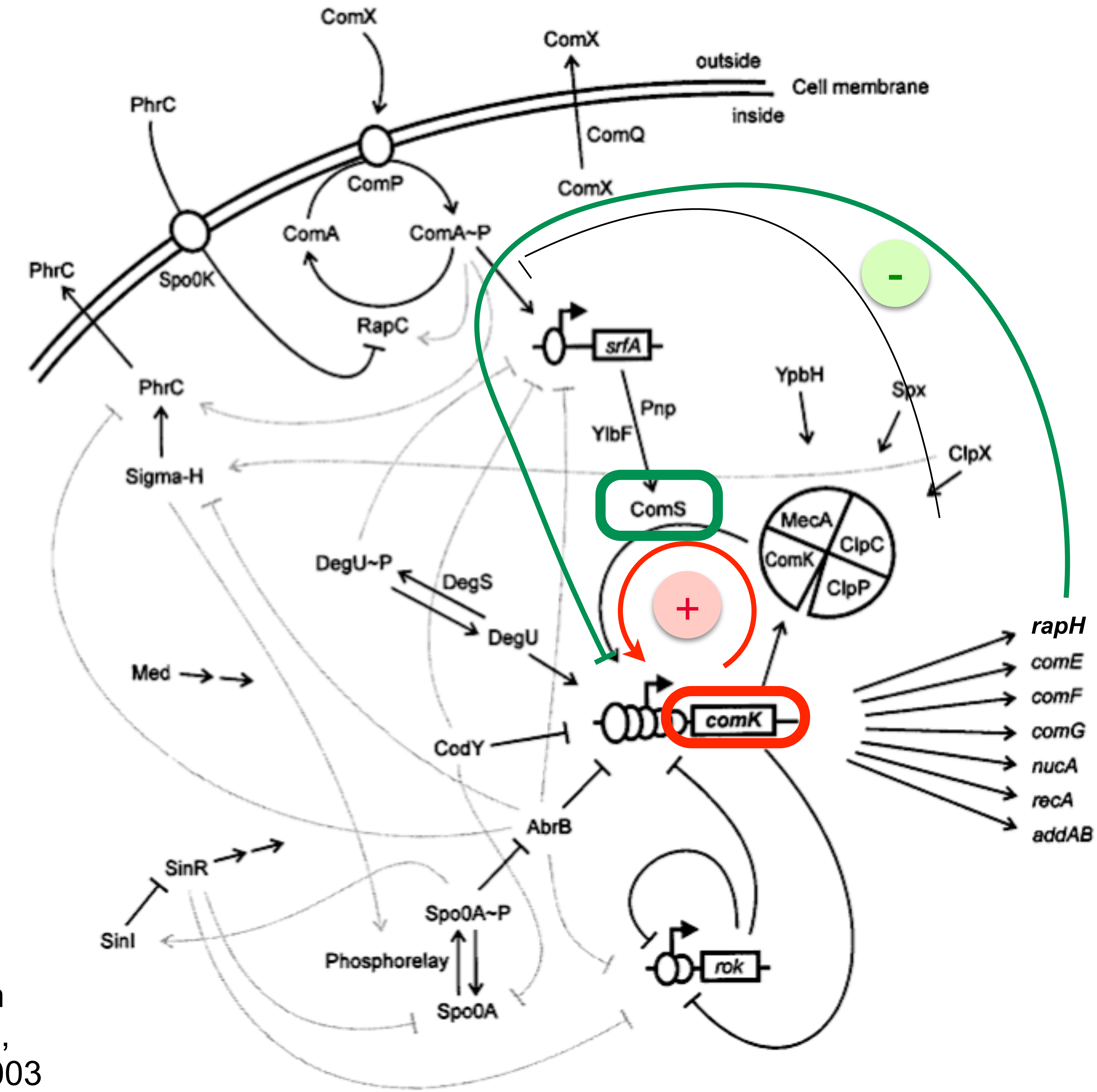



cfp
PcomG
yfp
PcomS

Molecular network underlying genetic competence

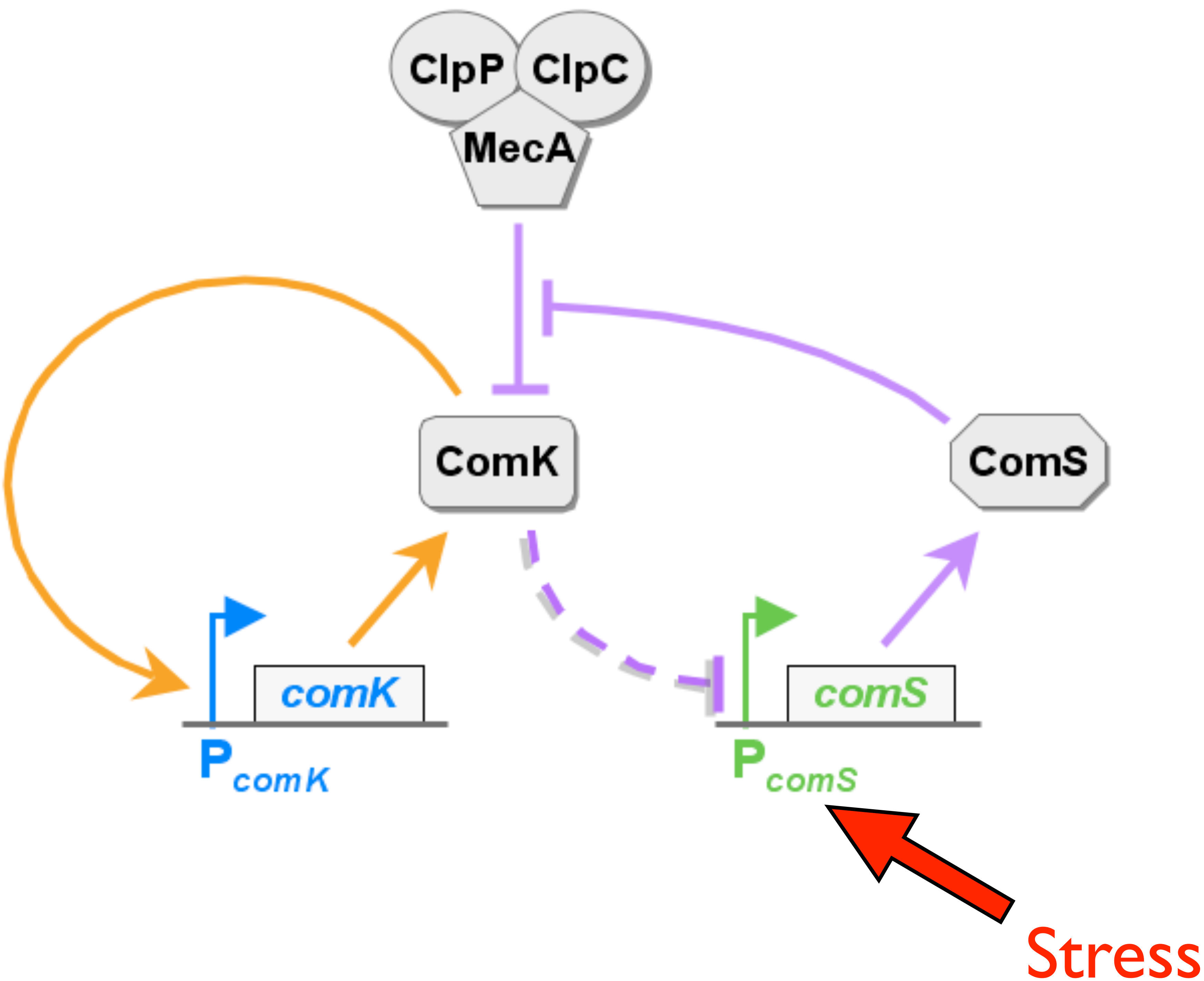


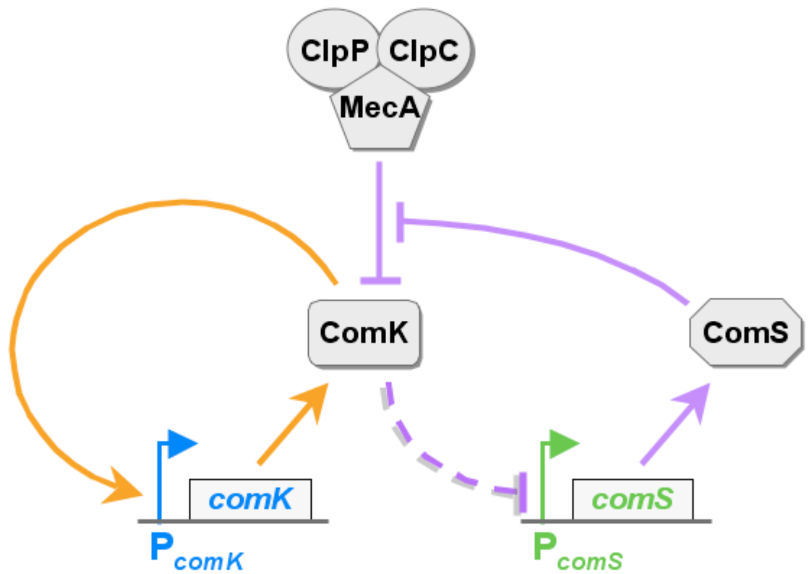
stress sensor

master regulator

adapted from Hamoen et al, Microbiology 2003

A genetic circuit for genetic competence





Competitive degradation:

$$\mathrm{MecA} + \mathrm{ComK} \underset{}{\overset{\gamma_{\pm a}}{\rightleftharpoons}} \mathrm{MecA\text{-}ComK} \overset{\gamma_1}{\rightarrow} \mathrm{MecA}$$
$$\mathrm{MecA} + \mathrm{ComS} \underset{}{\overset{\gamma_{\pm b}}{\rightleftharpoons}} \mathrm{MecA\text{-}ComS} \overset{\gamma_2}{\rightarrow} \mathrm{MecA}$$

$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \gamma_a M_f K + \gamma_{-a} M_K - \delta_k K$$
$$\frac{dS}{dt} = \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \gamma_b M_f S + \gamma_{-b} M_S - \delta_s S$$
$$\frac{dM_K}{dt} = -(\gamma_{-a} + \gamma_1) M_K + \gamma_a M_f K$$
$$\frac{dM_S}{dt} = -(\gamma_{-b} + \gamma_2) M_S + \gamma_b M_f S$$

$$M_f + M_K + M_S = M_{\text{total}} = \text{constant}$$

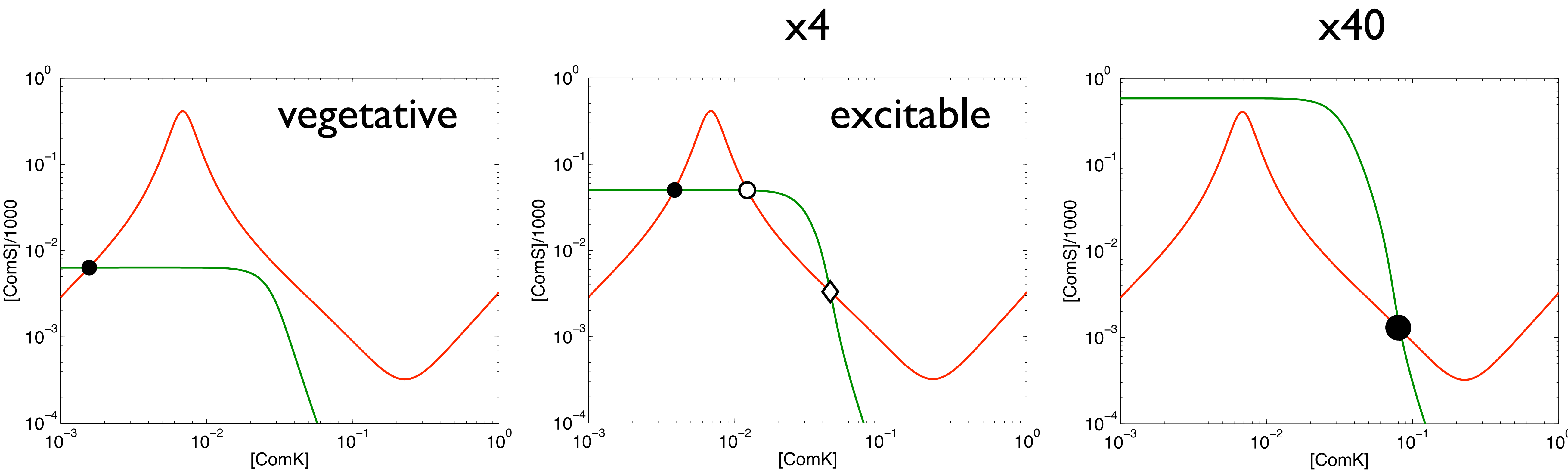
- Adiabatic elimination of M_k and M_s:

$$
\begin{aligned}
\frac{dK}{dt} &= \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K \\
\frac{dS}{dt} &= \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \frac{\gamma_s S}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_s S
\end{aligned}
$$

stress

- Nulcline plots for increasing stress (β_s):

$\beta_s \longrightarrow$



$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K$$

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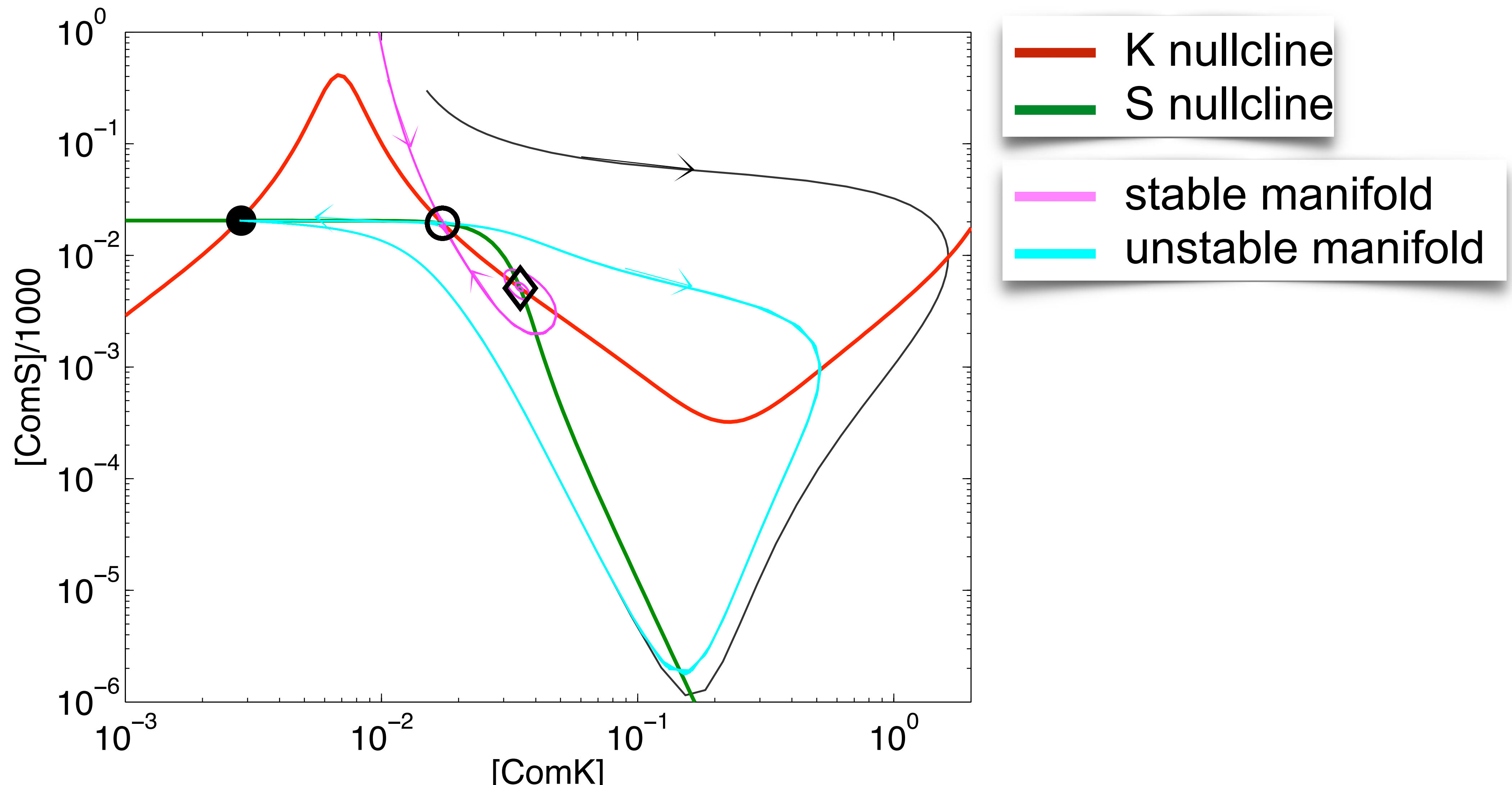
- ● stable fixed point
- ○ saddle
- ◇ unstable node/focus

Excitable dynamics of competence



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$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K$$

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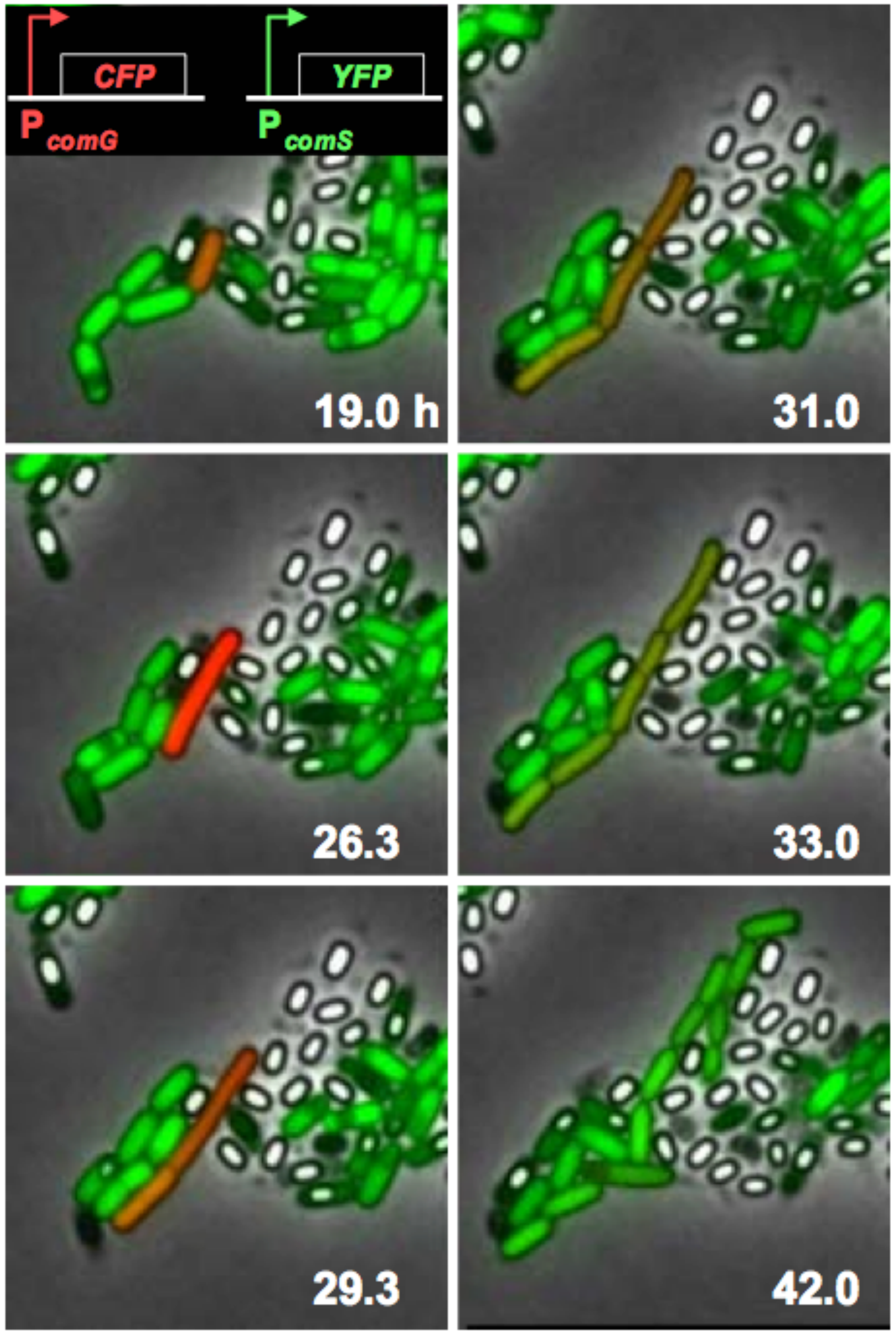
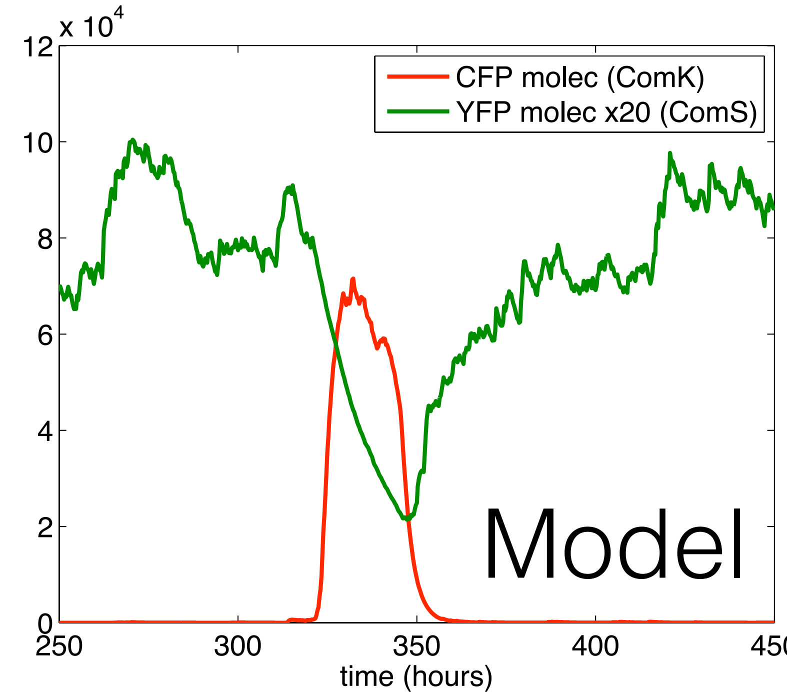
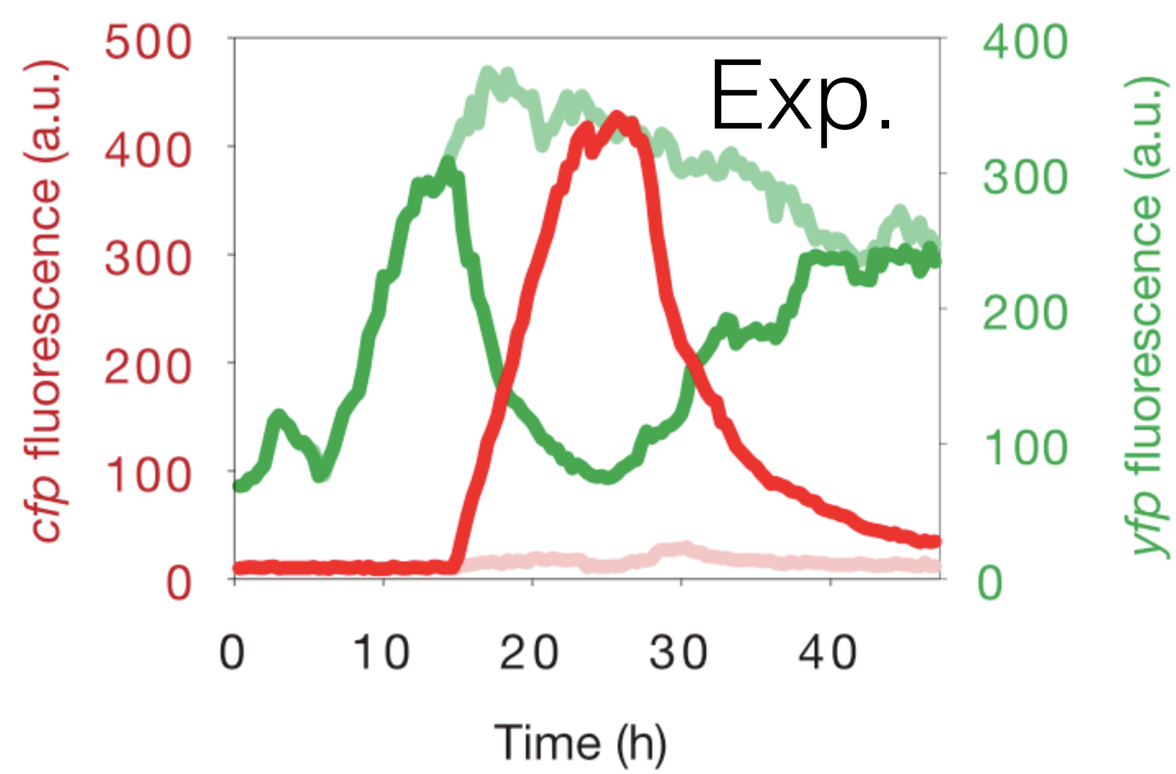
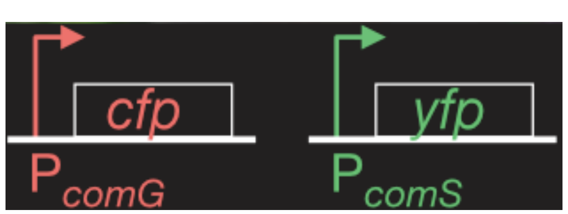
Testing the model: ComK-ComS anticorrelation

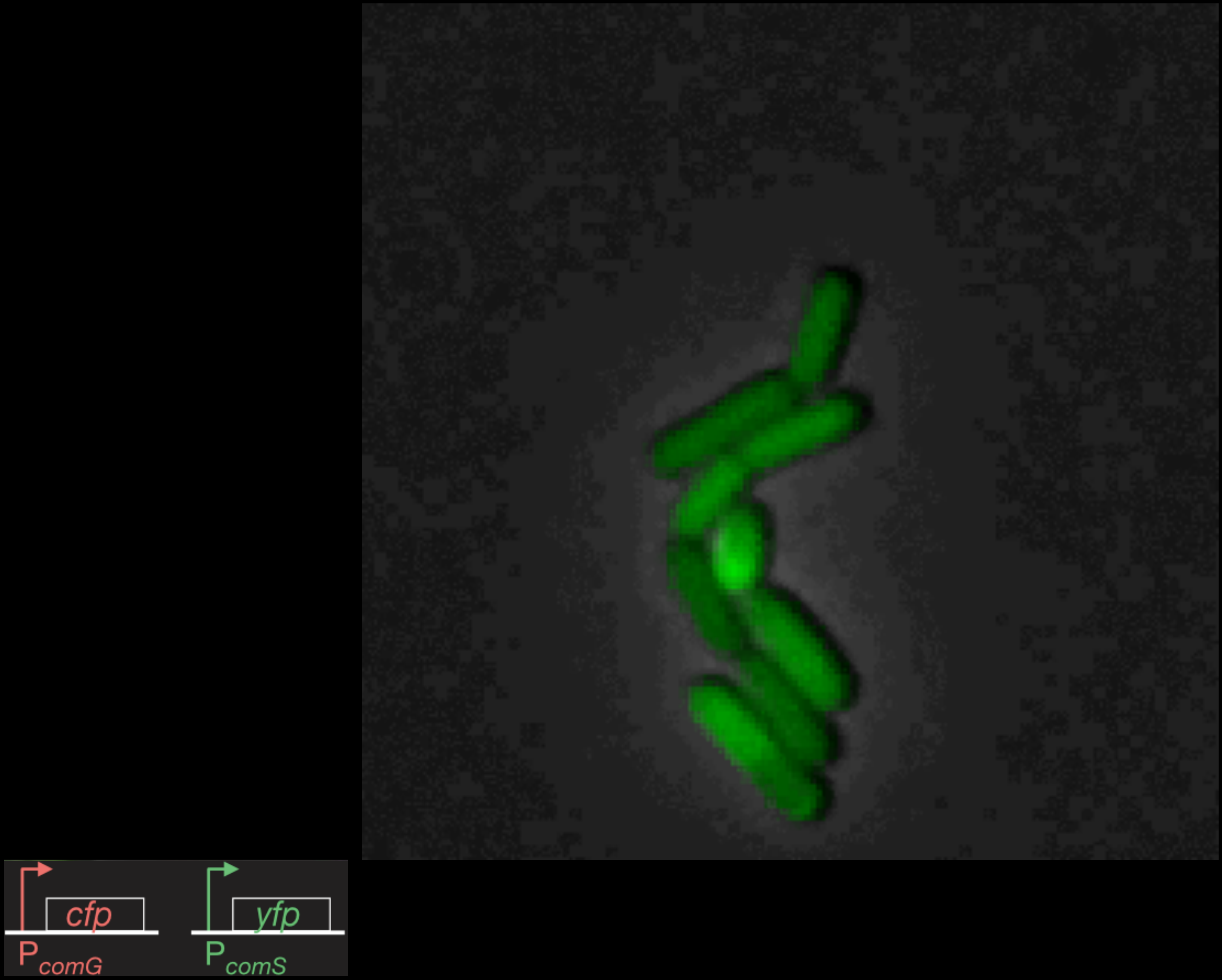








Süel, JGO, Lieberman & Elowitz, Nature (2006)


cfp
yfp
P comG
P comS

Bifurcation analysis of the competence system

$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K$$

$$\frac{dS}{dt} = \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \frac{\gamma_s S}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_s S$$

Two experimentally controllable parameters (by means of an IPTG-inducible promoter):

α_k: basal production of ComK protein

α_s: basal production of ComS protein

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Department of Experimental and Health Sciences
Universitat Pompeu Fabra
Barcelona Biomedical Research Park (PRBB)
Dr. Aiguader 88, 08003 Barcelona

ADVANCED SUMMER SCHOOL ON APPLIED DYNAMICS IN SYSTEMS AND SYNTHETIC BIOLOGY

EXERCISES - GENE REGULATORY CIRCUITS

4. The following model describes genetic competence in *B. subtilis*:

$$\begin{aligned} \frac{dK}{dt} &= \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K \\ \frac{dS}{dt} &= \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \frac{\gamma_s S}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_s S \end{aligned}$$

Again, use the tools that you have learned in the different courses of this school to analyze this dynamical system in the plane, as the parameters α_k, α_s and β_s vary (one at a time or in pairs). Reproduce and study the response of the system in the different dynamical regimes studied in class. Consider the following baseline parameter values:

Parameter	Value	Parameter	Value	Parameter	Value
α_k	0.00875 molec/s	γ_k , γ_s	0.001 s^{-1}	k_k	5000 molec
α_s	0.0004 molec/s	δ_k , δ_s	10^{-4} s^{-1}	k_s	833 molec
β_k	7.5 molec/s	Γ_k	25000 molec	n	2
β_s	0.06 molec/s	Γ_s	20 molec	p	5

Bifurcation analysis of the competence system

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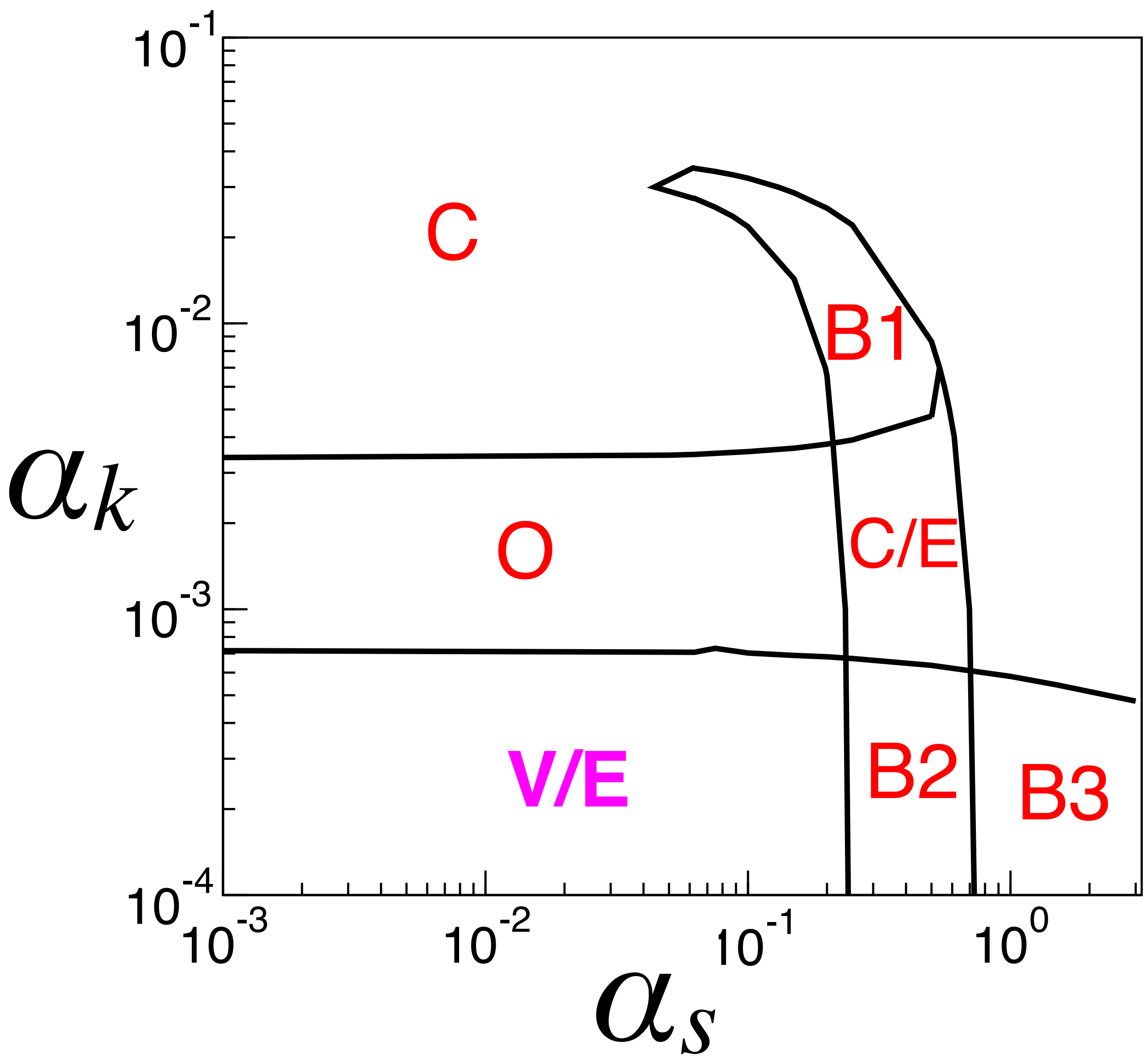
Bifurcation analysis of the competence system



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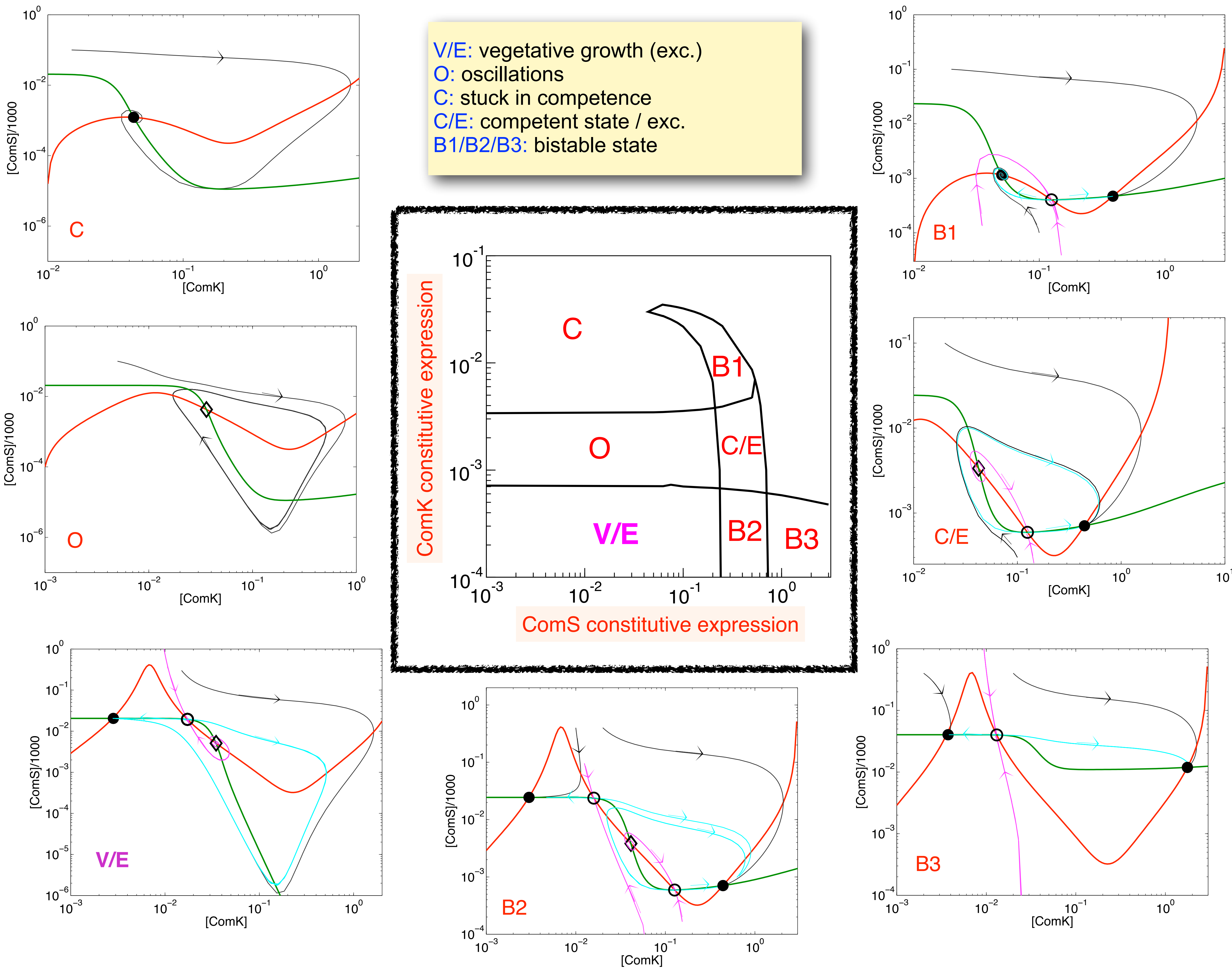
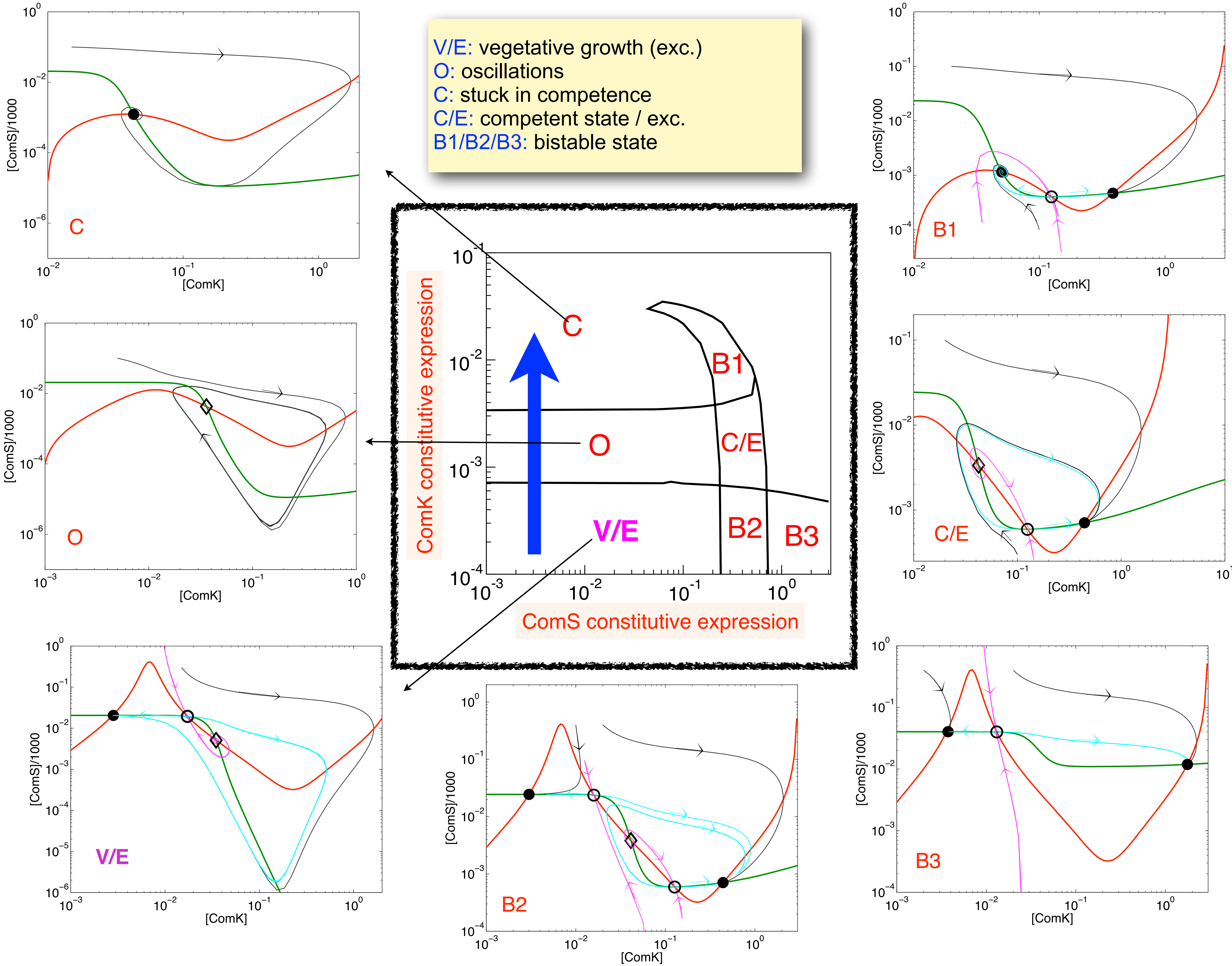


V/E: vegetative growth (exc.)
O: oscillations
C: stuck in competence
C/E: competent state / exc.
B1/B2/B3: bistable state
ComK constitutive expression
ComS constitutive expression
C
B1
O
C/E
V/E
B2
B3
[ComS]/1000
[ComK]



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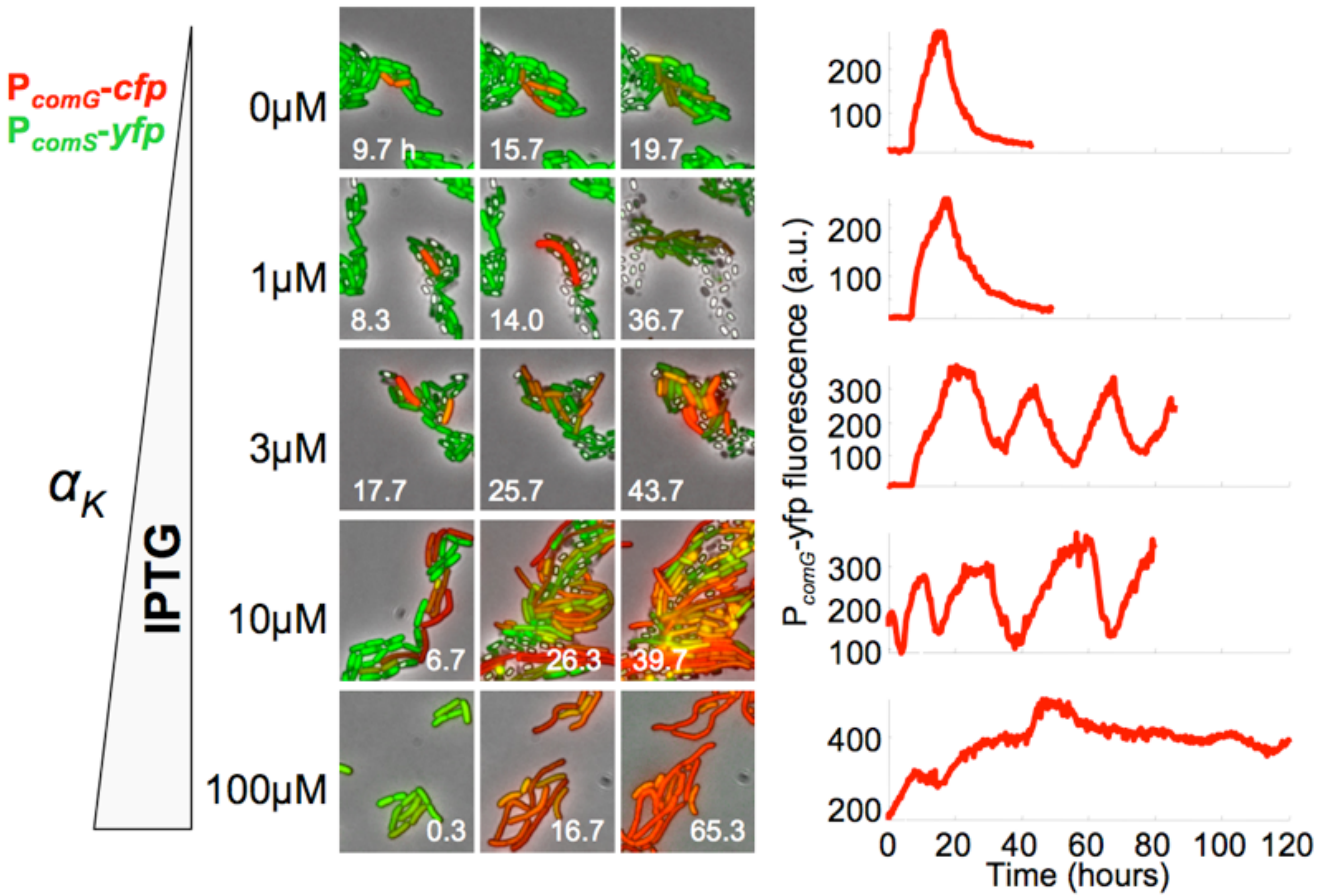
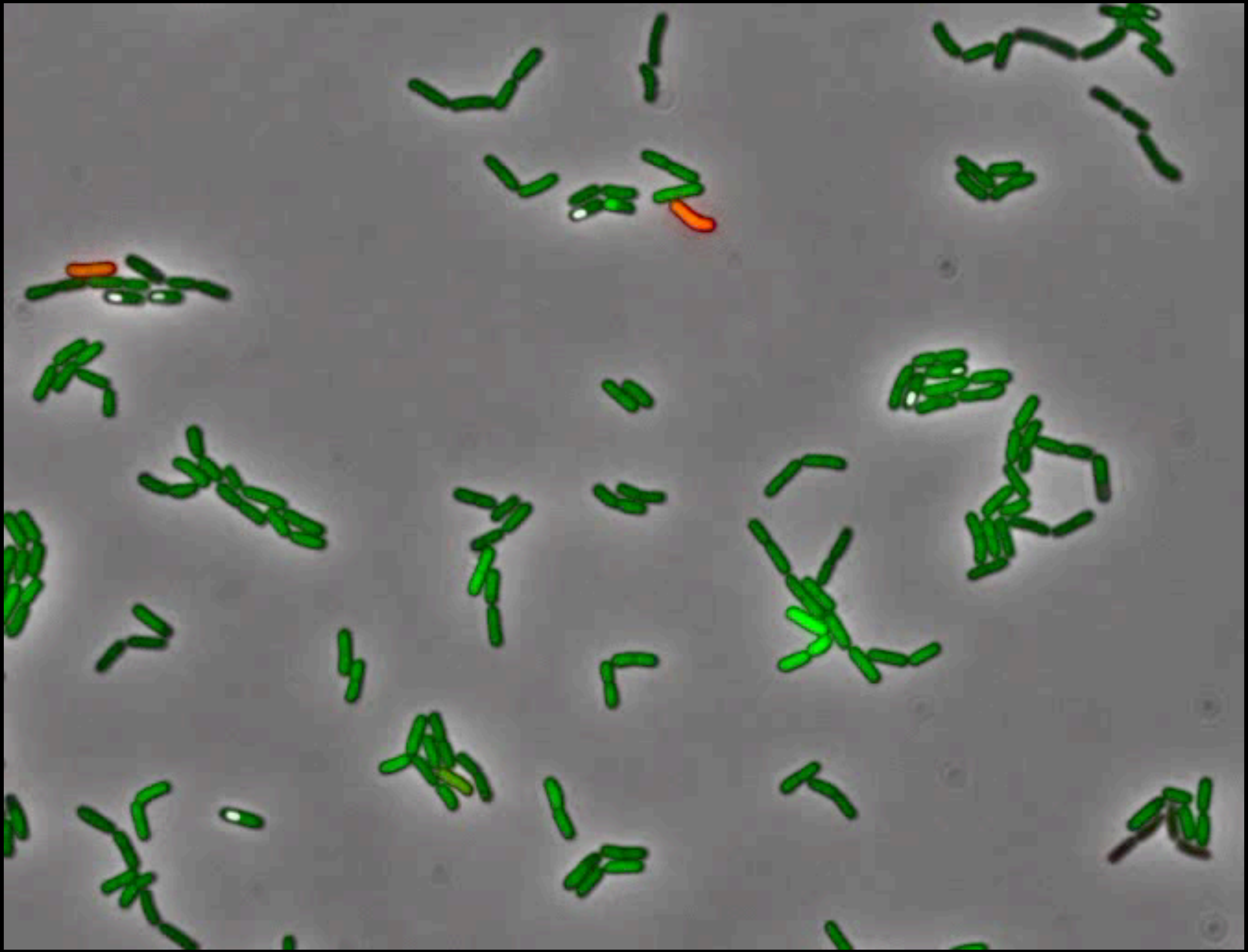
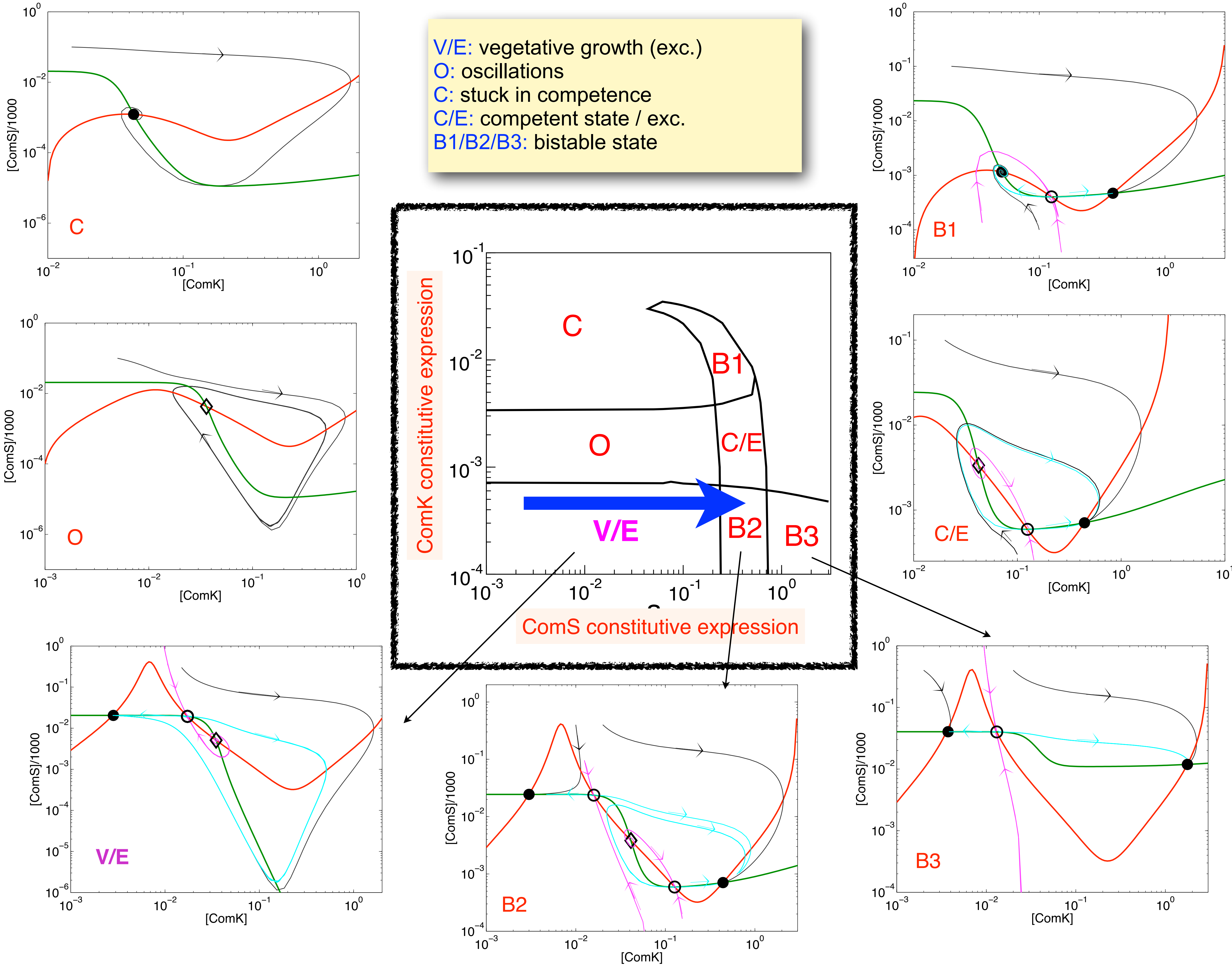
V/E
B1
C/E
B2
B3
[ComS]/1000
[ComK]

- Adding an additional copy of the *comK* gene under the control of an IPTG-inducible promoter



Suel, JGO, Kulkarni, Dworkin, Elowitz, Science, 2007





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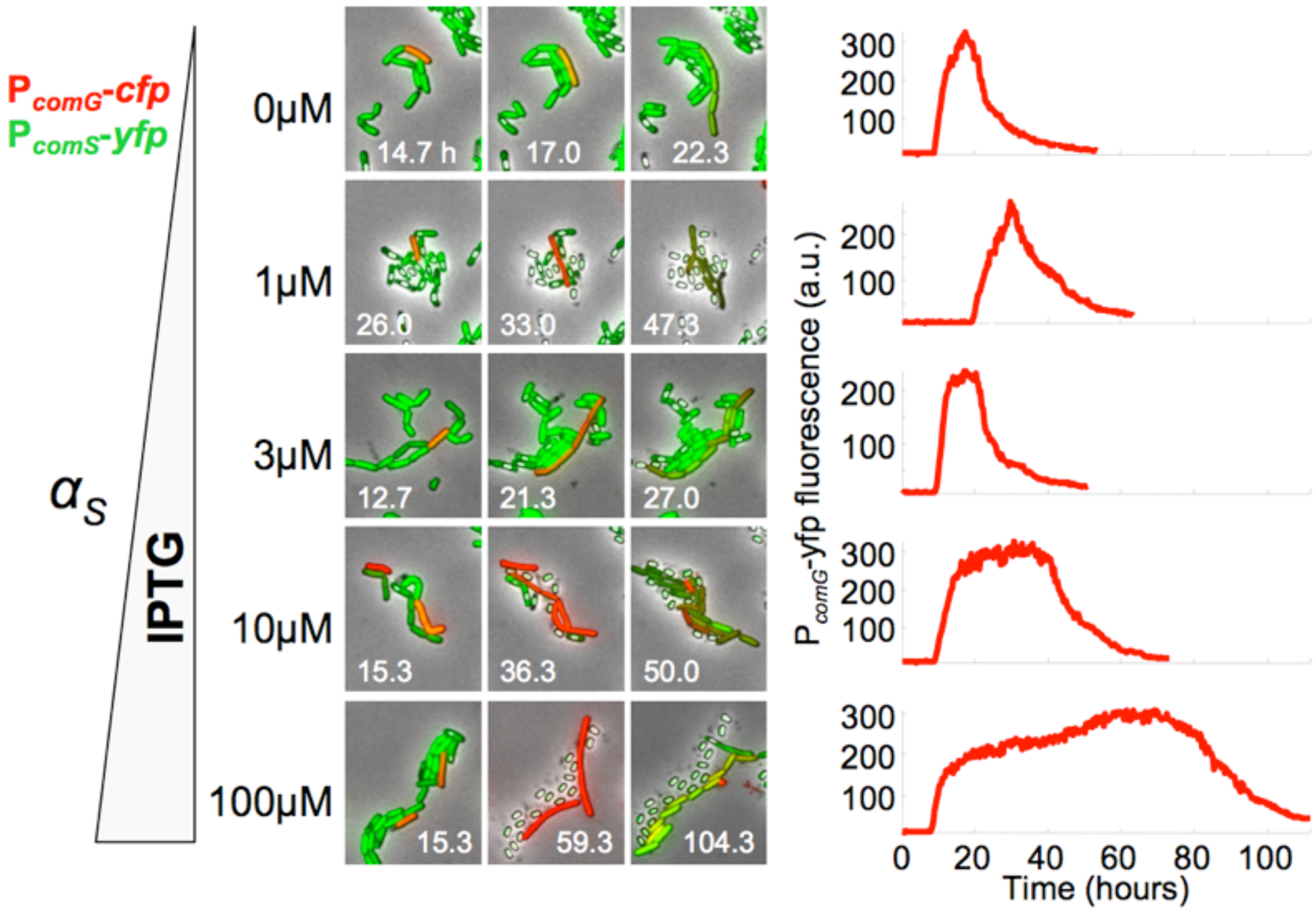
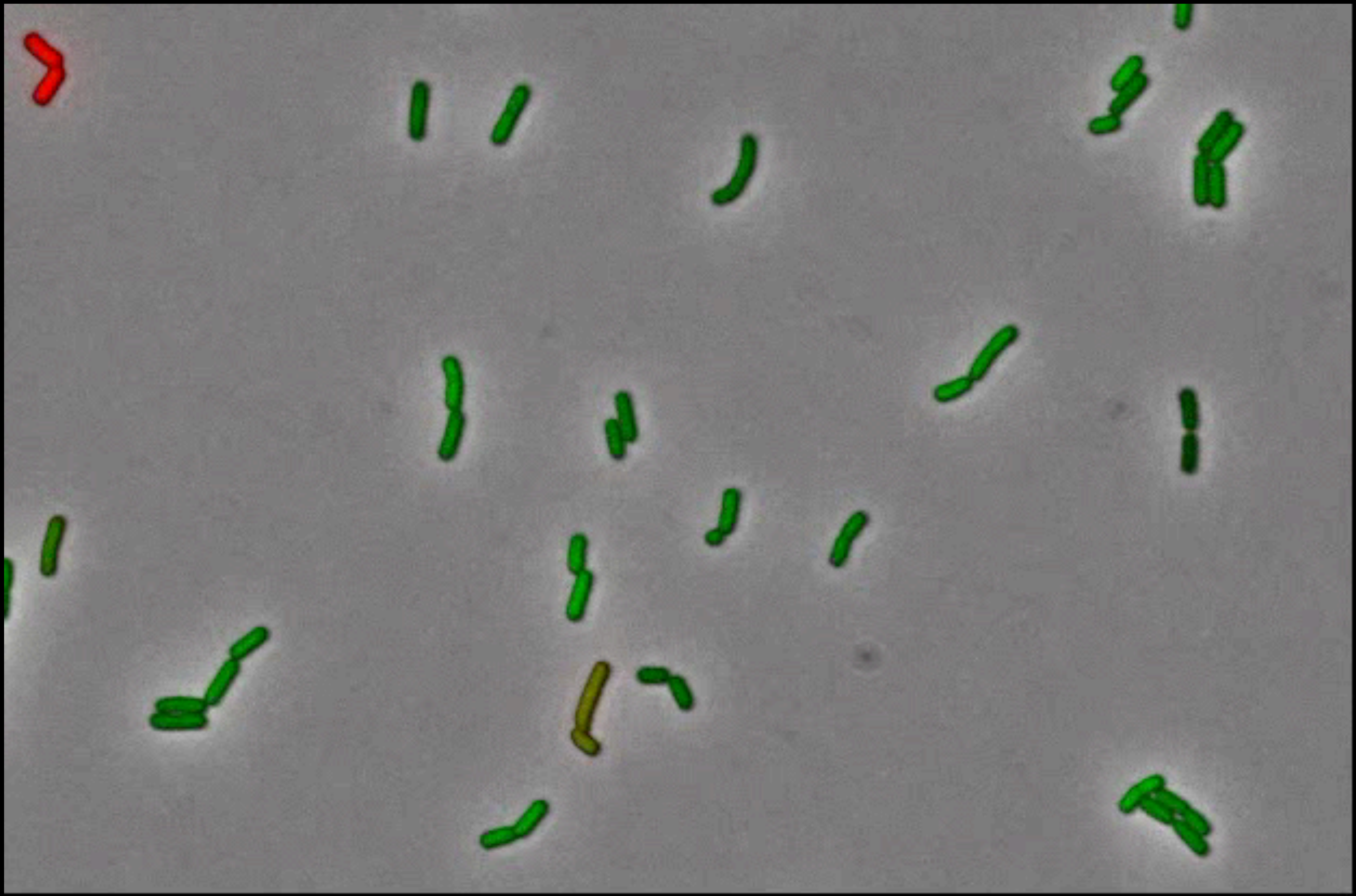
ComK constitutive expression
ComS constitutive expression
C
B1
O
C/E
V/E
B2
B3
[ComS]/1000
[ComK]

- Adding an additional copy of the *comS* gene under the control of an IPTG-inducible promoter

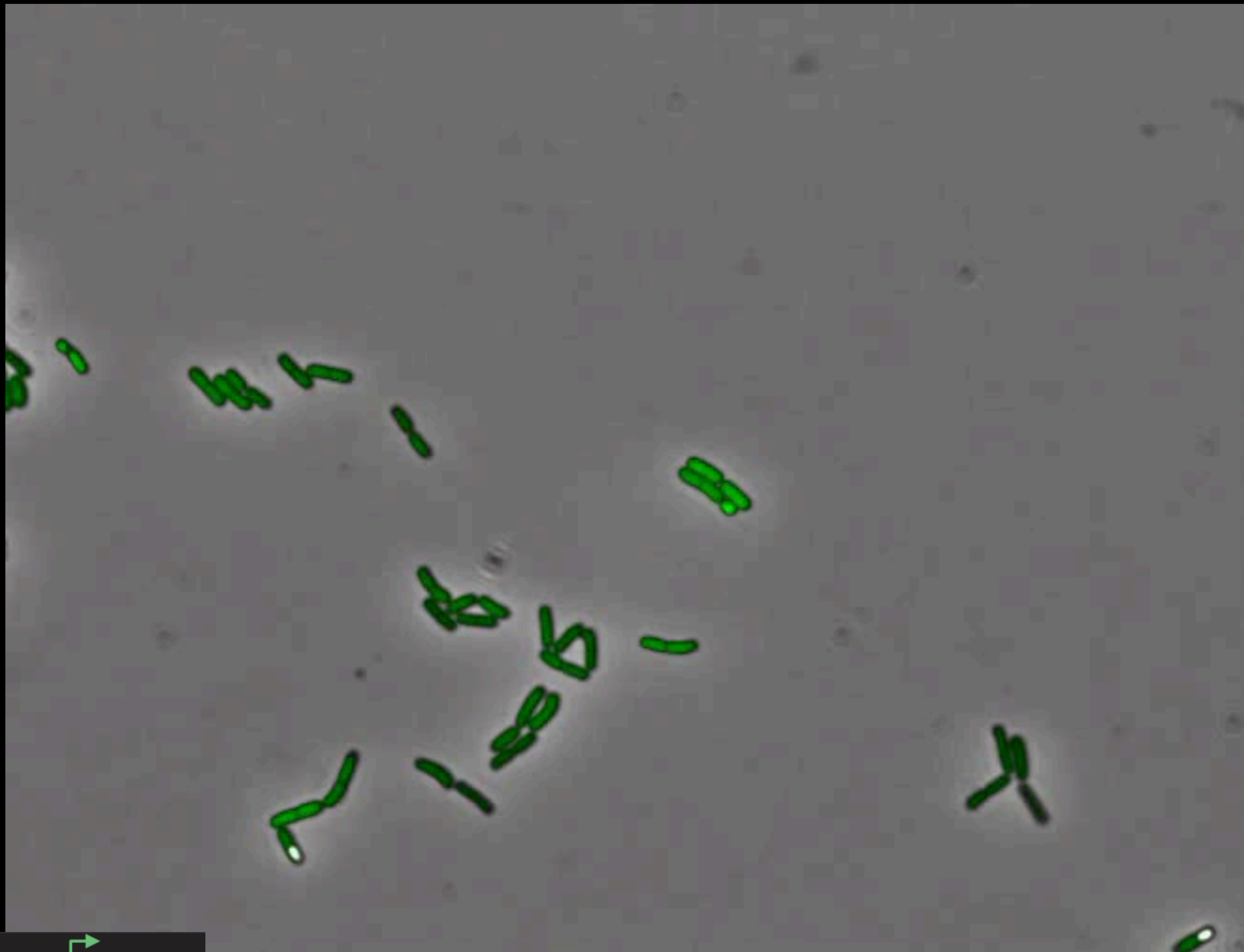


Suel, JGO, Kulkarni, Dworkin, Elowitz, Science, 2007



Dynamics of gene regulatory circuits

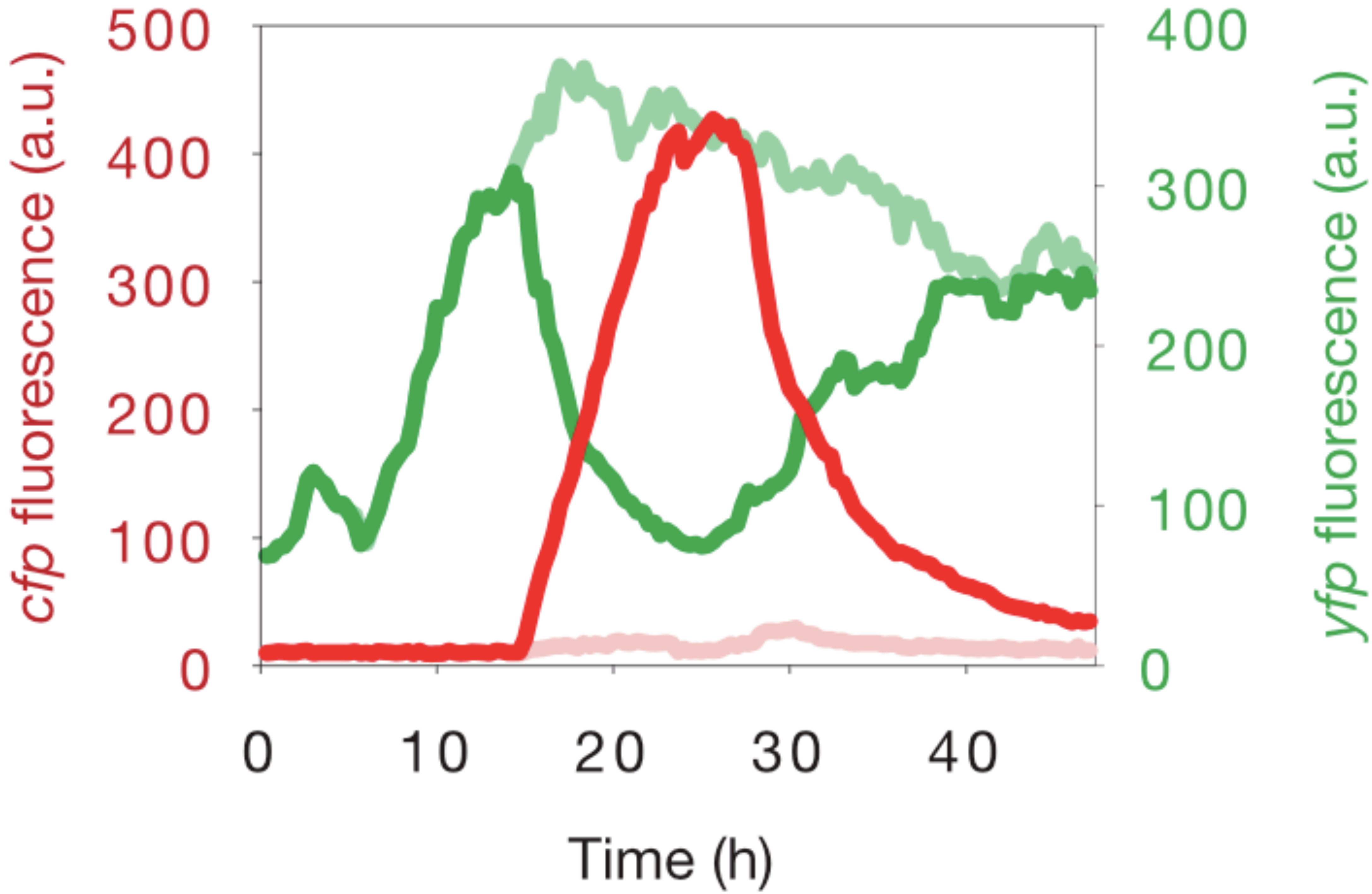
1. Gene circuit dynamics
2. Dissecting a genetic circuit
3. Noise in genetic circuits

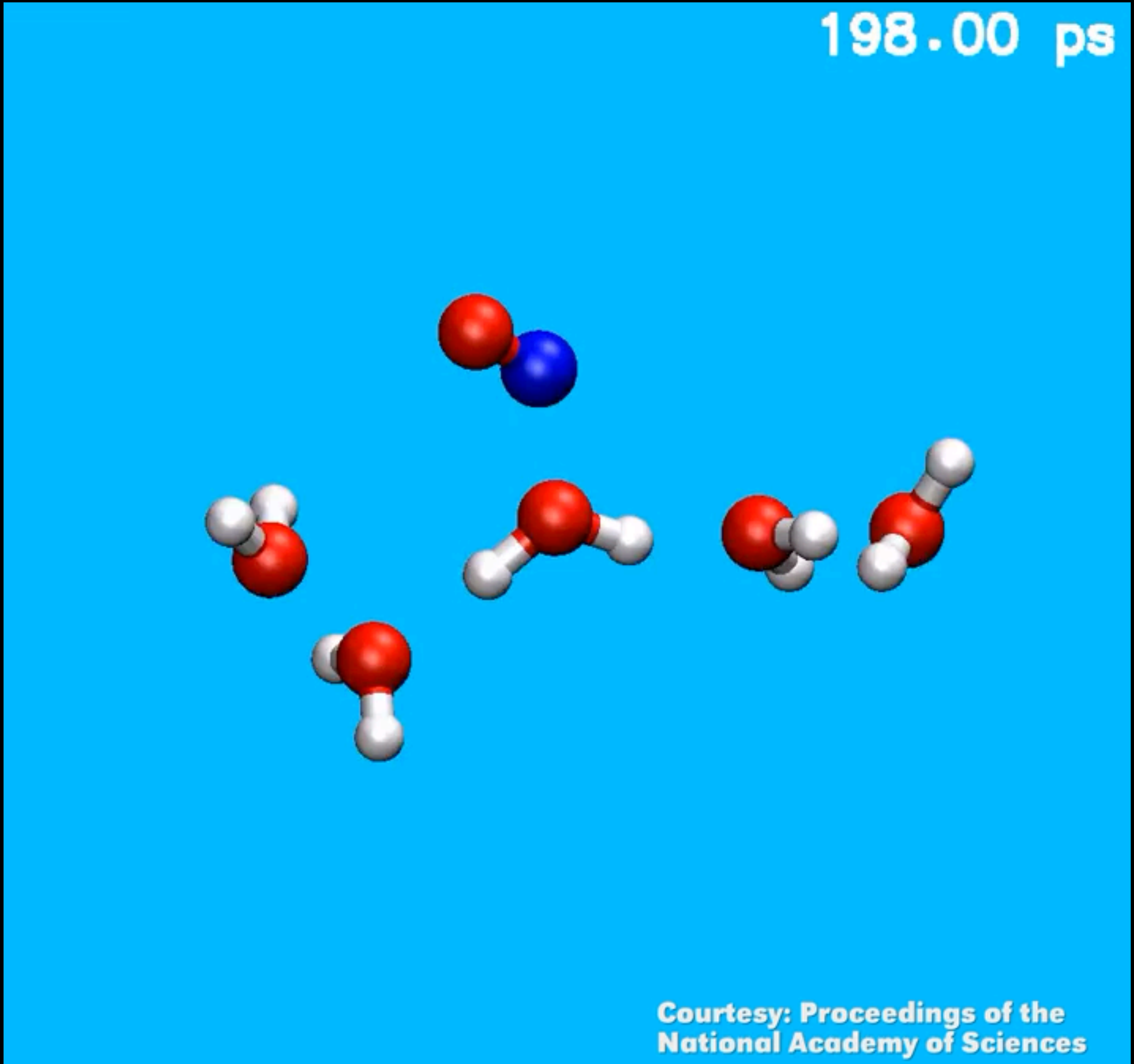



cfp
P comG
yfp
P comS

An example of stochastic decision making

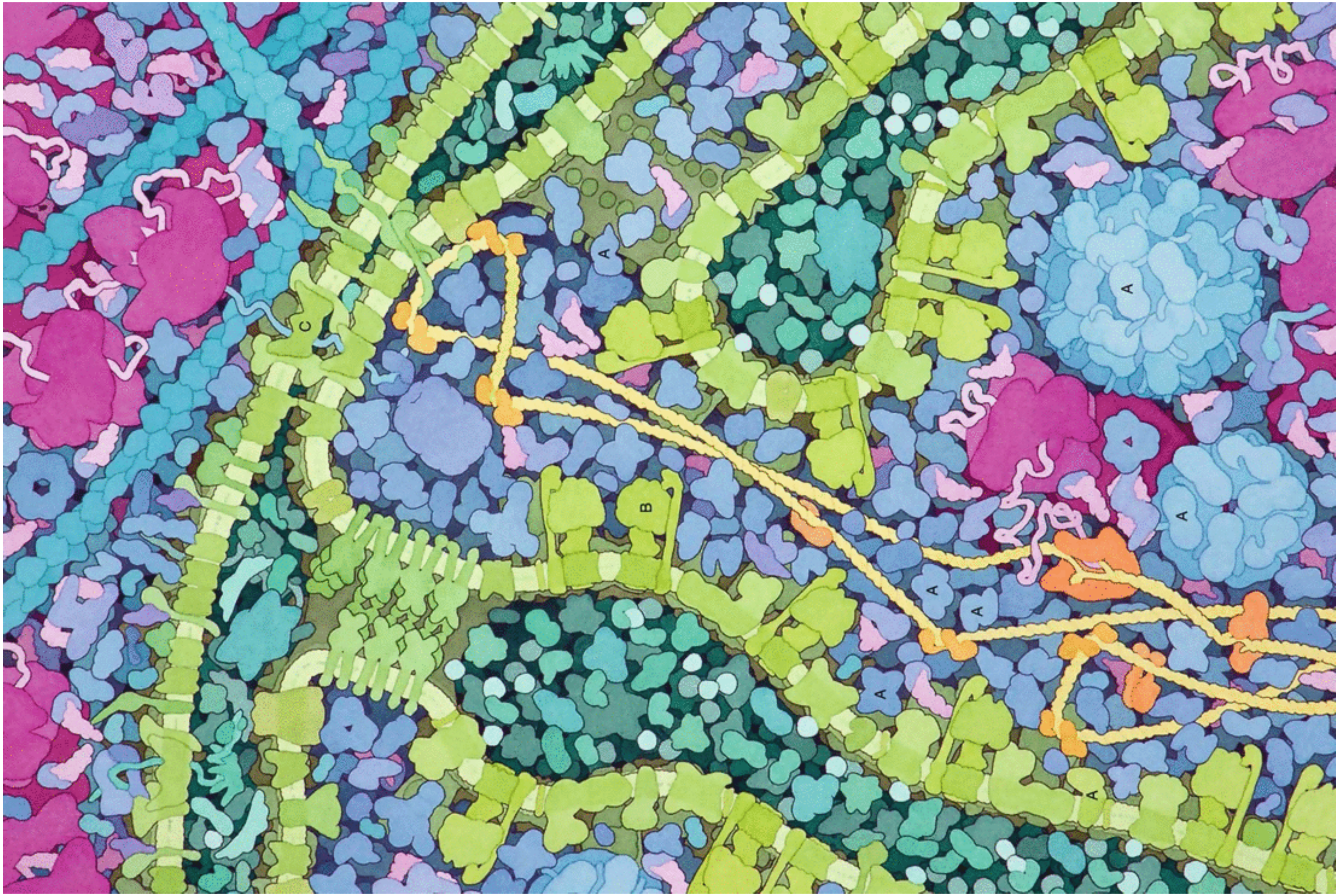
- Dynamics of two sister cells:





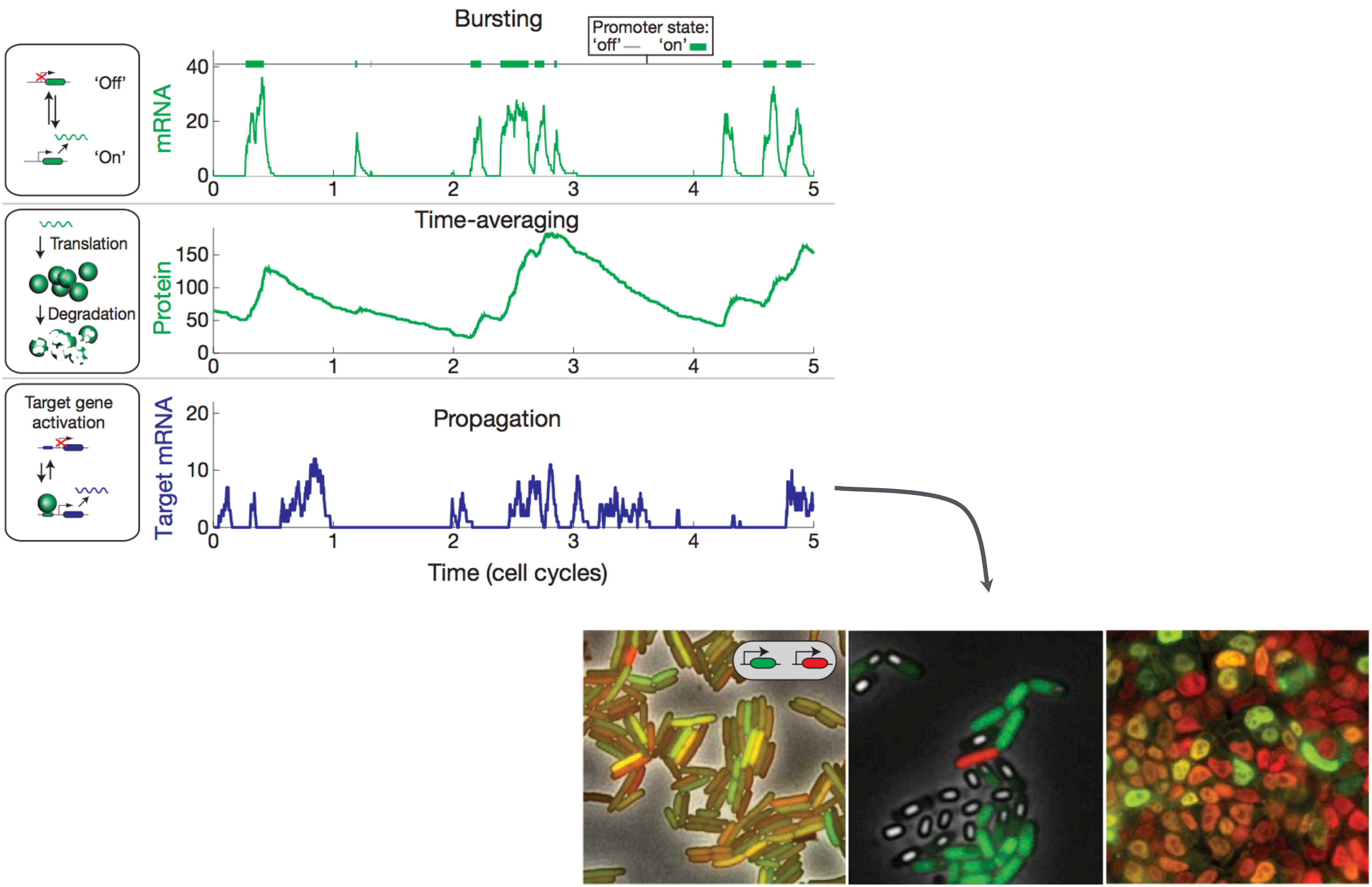
https://www.youtube.com/watch?v=FhJ-1AOHRy0

The crowded interior of cells



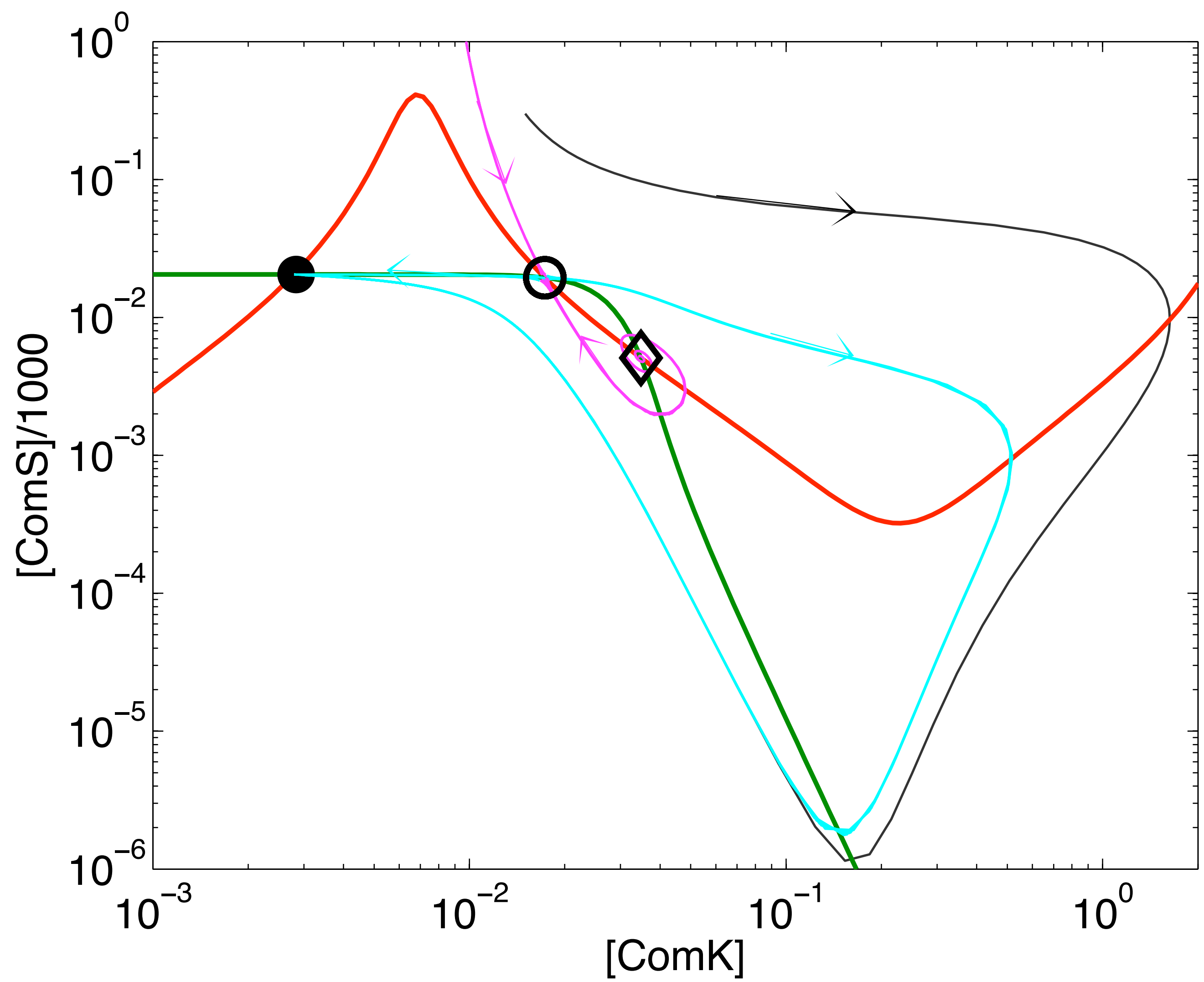
The Machinery of Life, D.S. Goodsell

Noise propagates down gene circuit cascades



Eldar and Elowitz, Nature **467**, 167, 2010

The competence circuit is an excitable system

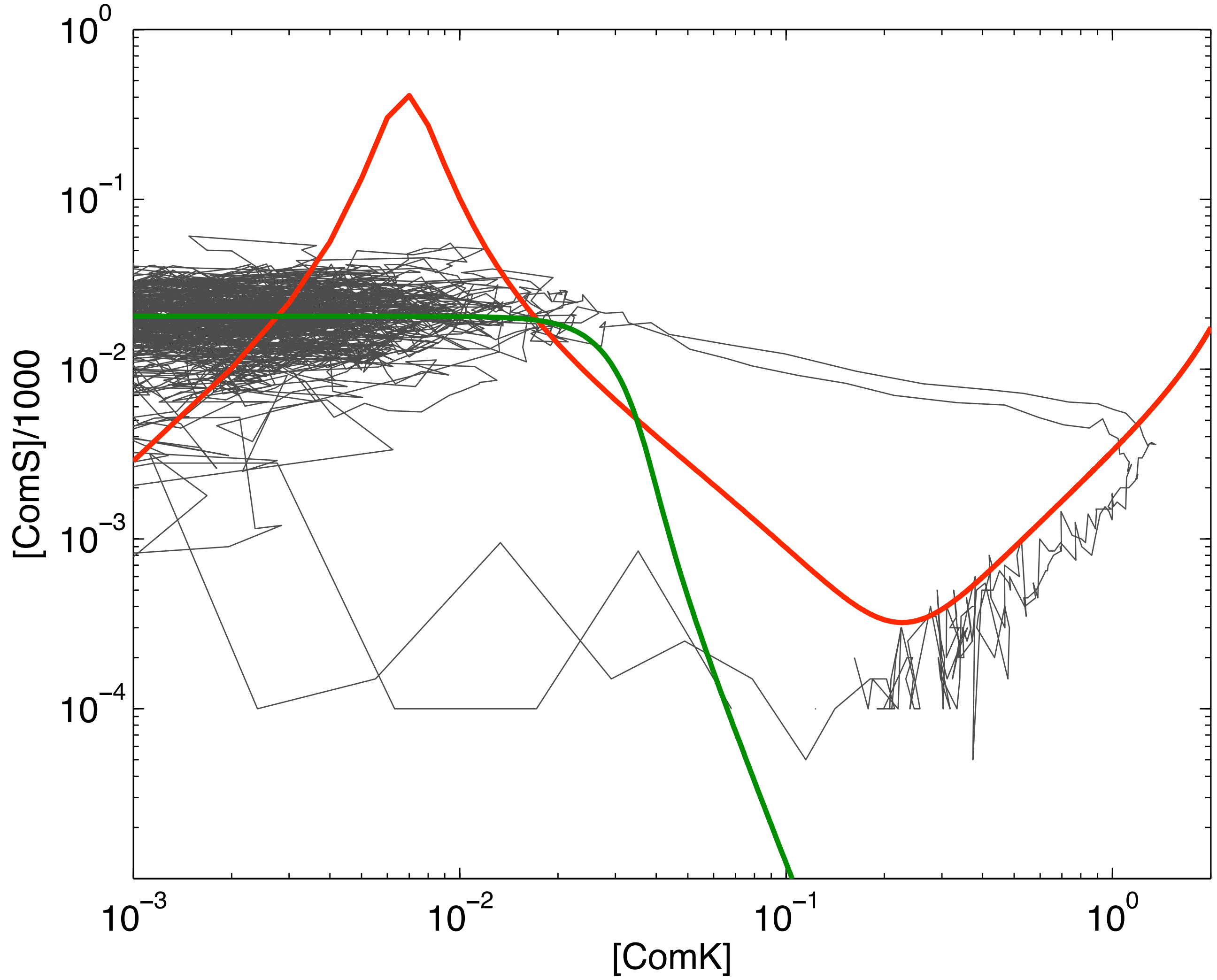


- ● stable fixed point
- ○ saddle
- ◇ unstable node/focus

$$\frac{dK}{dt} = \alpha_k + \frac{\beta_k K^n}{k_k^n + K^n} - \frac{\gamma_k K}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_k K$$

$$\frac{dS}{dt} = \alpha_s + \frac{\beta_s}{1 + (K/k_s)^p} - \frac{\gamma_s S}{1 + \frac{K}{\Gamma_k} + \frac{S}{\Gamma_s}} - \delta_s S$$

The competence circuit is an excitable system



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Dynamics of gene regulatory circuits

- ✓ 1. Gene circuit dynamics
- ✓ 2. Dissecting a genetic circuit
- ✓ 3. Noise in genetic circuits

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Thank you!

Jordi Garcia Ojalvo
Department of Experimental and Health Sciences
Universitat Pompeu Fabra

E-mail: jordi.g.ojalvo@upf.edu
Web: http://dsb.upf.edu