Universitat Pompeu Fabra Barcelona

Dynamical strategies for resource sharing in bacteria

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Solvay Workshop
"Dynamics of biological systems"

Université Libre de Bruxelles
May 2, 2018

Universitat Pompeu Fabra Barcelona

Dynamical strategies for resource sharing in bacteria

Rosa Martínez-Corral, Marçal Gabaldà, Marta Dies (UPF)

Jin Park, Michael Elowitz (Caltech)

James Locke (Cambridge)

Jintao Liu, Arthur Prindle, Gürol Süel (UC San Diego)

Munehiro Asally (Warwick)

Solvay Workshop
“Dynamics of biological systems”

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Sidney Brenner

UPF Honorary Doctorate, April 2014

"Mathematics is the art of the perfect,
physics is the art of the optimal,
and biology is the art of the satisfactory."

Evolution as an optimizer

Optimal resource allocation in cellular sensing systems

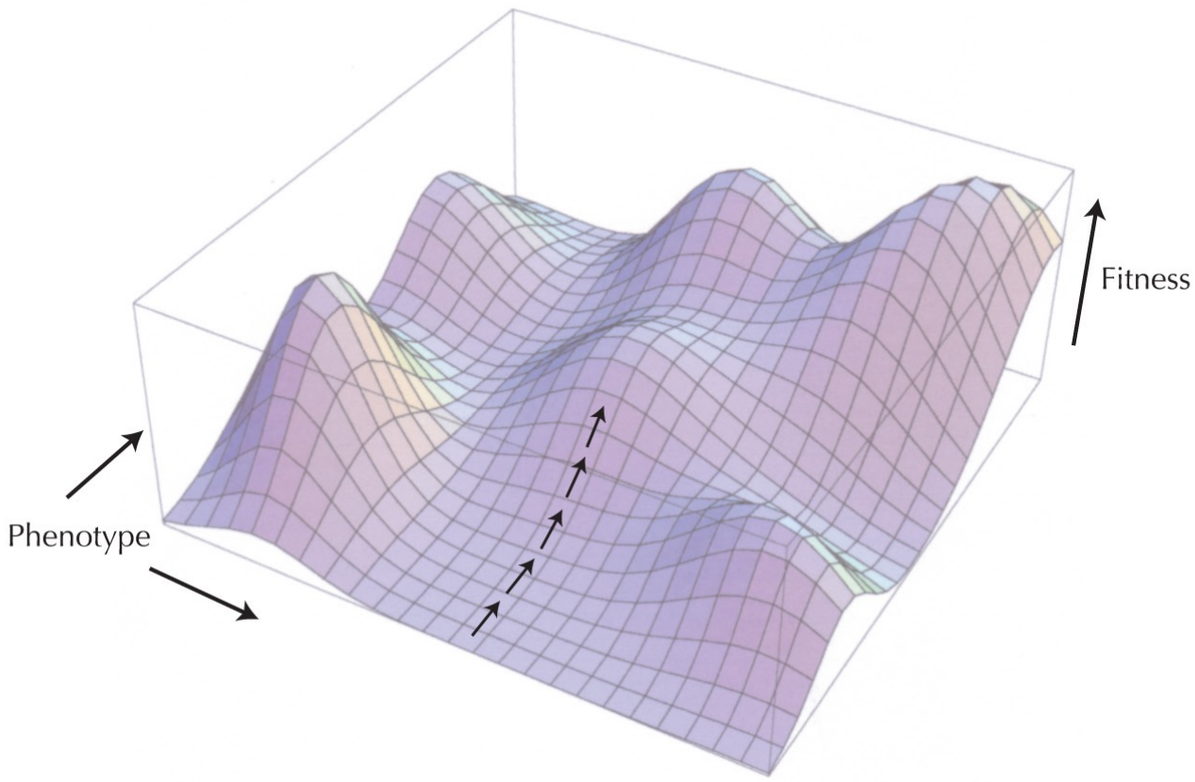
Christopher C. Govern and Pieter Rein ten Wolde[1]

FOM Institute AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

Edited by Yuhai Tu, IBM T. J. Watson Research Center, Yorktown Heights, NY, and accepted by the Editorial Board October 22, 2014 (received for review June 23, 2014)

Living cells deploy many resources to sense their environments, including receptors, downstream signaling molecules, time, and fuel. However, it is not known which resources fundamentally limit the precision of sensing, like weak links in a chain, and which can compensate each other, leading to trade-offs between them. We present a theory for the optimal design of the large class of sensing systems in which a receptor drives a push–pull network. The theory identifies three classes of resources that are required for sensing: receptors and their integration time, readout molecules, and energy (fuel turnover). Each resource class sets a fundamental sensing limit, which means that the sensing precision is bounded by the limiting resource class and cannot be enhanced by increasing another class—the different classes cannot compensate each other. This result yields a previously unidentified design principle, namely that of optimal resource allocation in cellular sensing. It states that, in an optimally designed sensing system, each class of resources is equally limiting so that no resource is wasted. We apply our theory to what is arguably the best-characterized sensing system in biology, the chemotaxis network of *Escherichia coli*. Our analysis reveals that this system obeys the principle of optimal resource allocation, indicating a selective pressure for the efficient design of cellular sensing systems.

cell signaling | thermodynamics | design principles | chemotaxis | information transmission



Evolution, Barton et al, CSHL Press, 2007

Living systems are not wasteful

PNAS

Optimal resource allocation in cellular sensing systems

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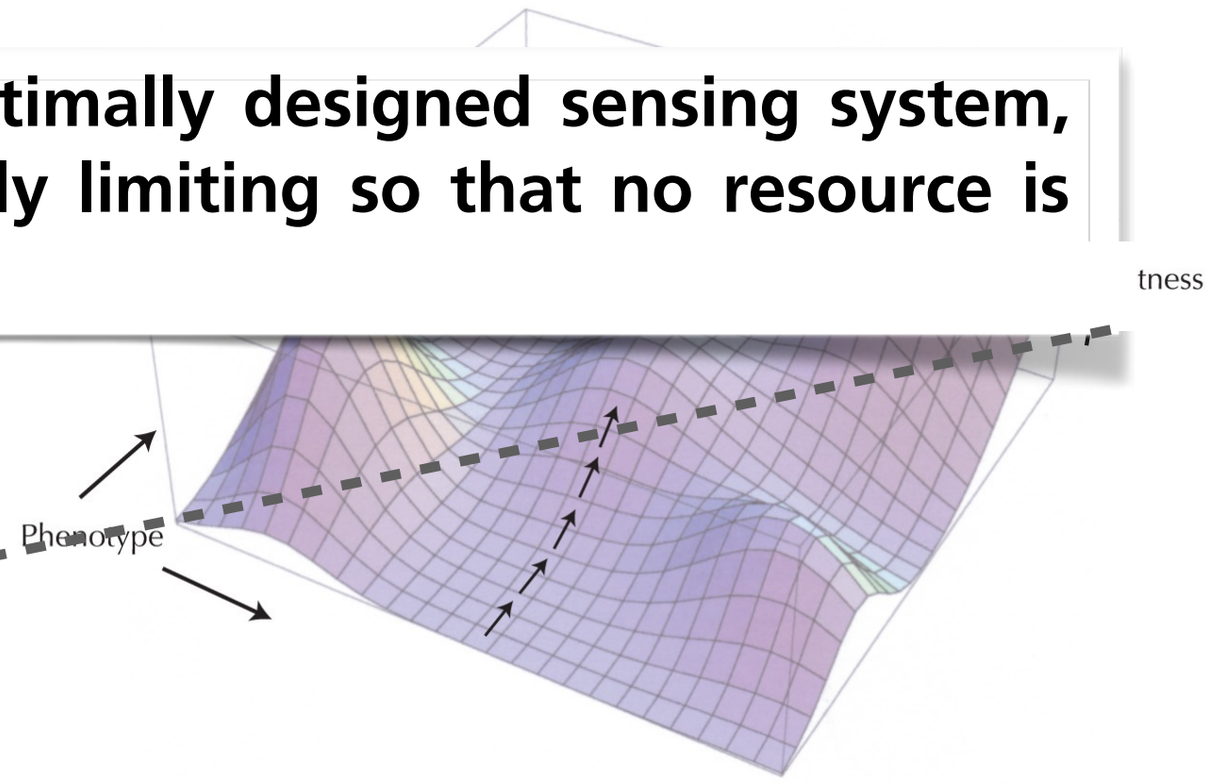
cell signaling | thermodynamics | design principles | chemotaxis | information transmission

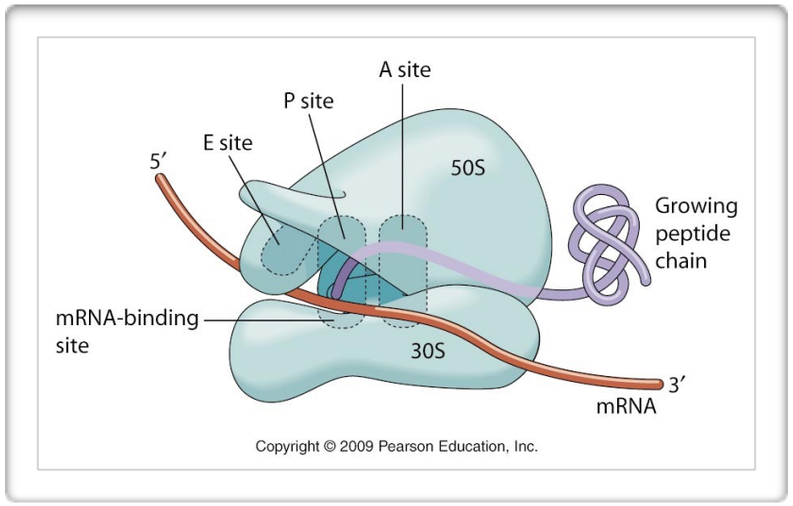
in an optimally designed sensing system, each class of resources is equally limiting so that no resource is wasted

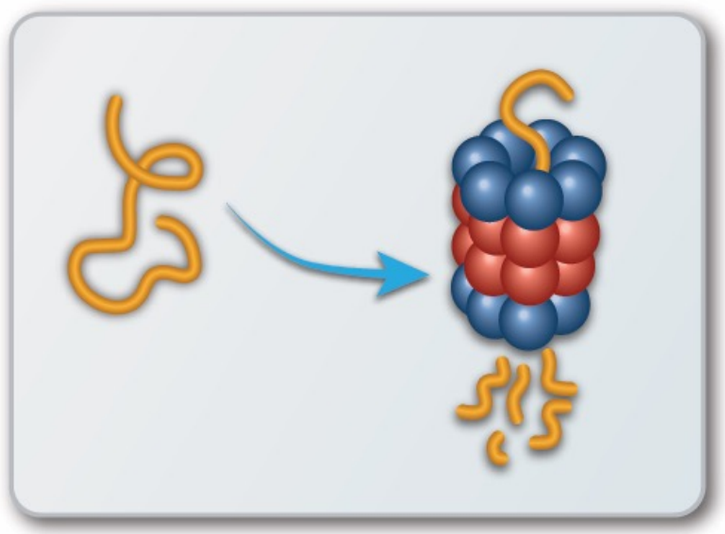


Evolution, Barton et al, CSHL Press, 2007

Limiting resources must be shared

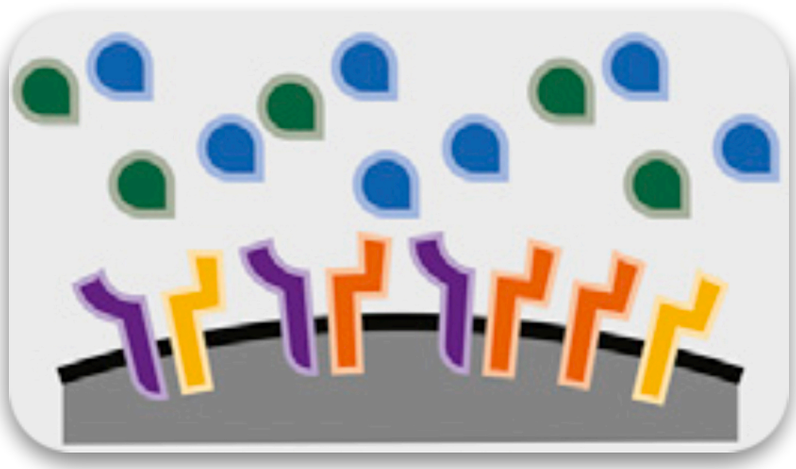
mRNAs share ribosomes



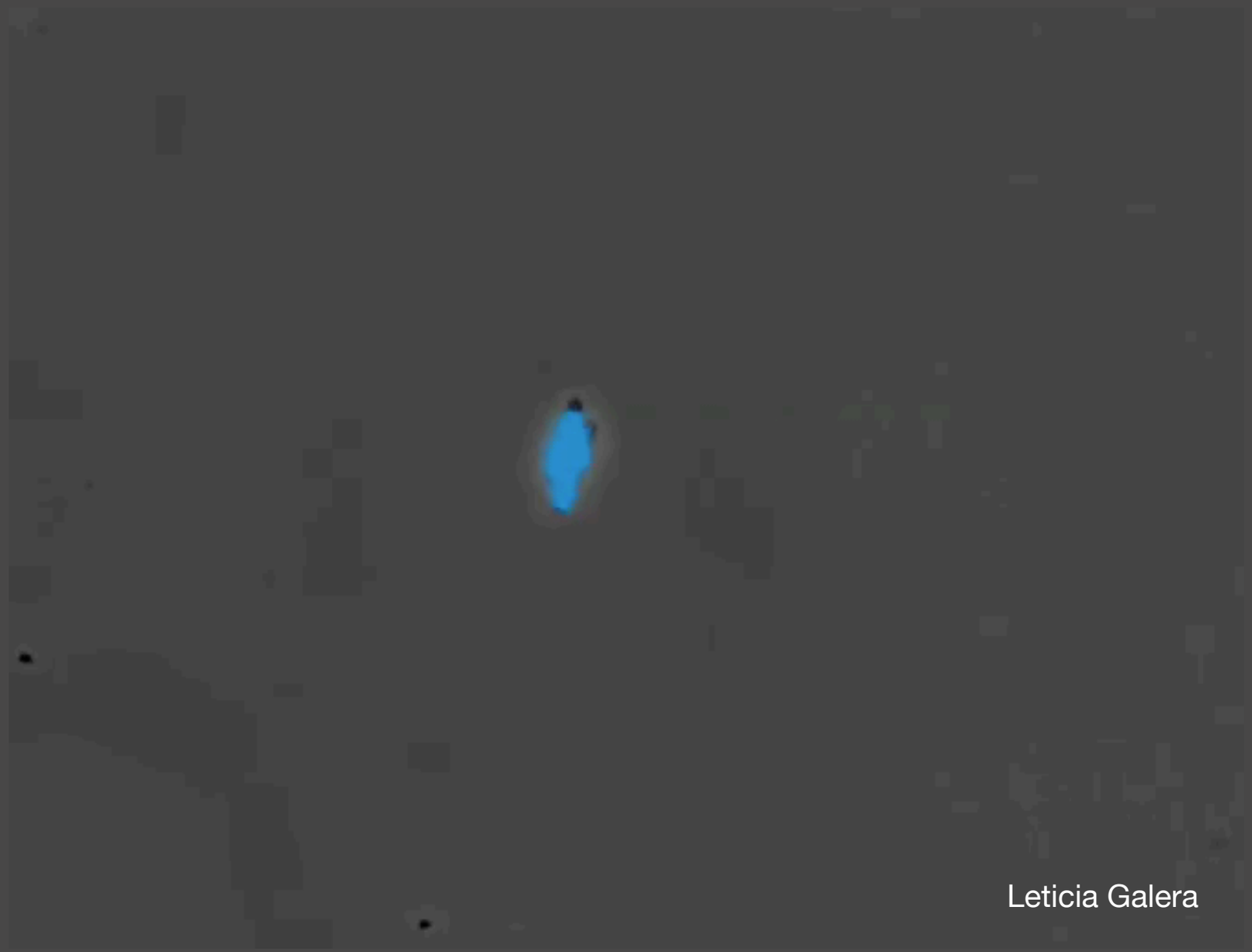


proteins share proteasomes

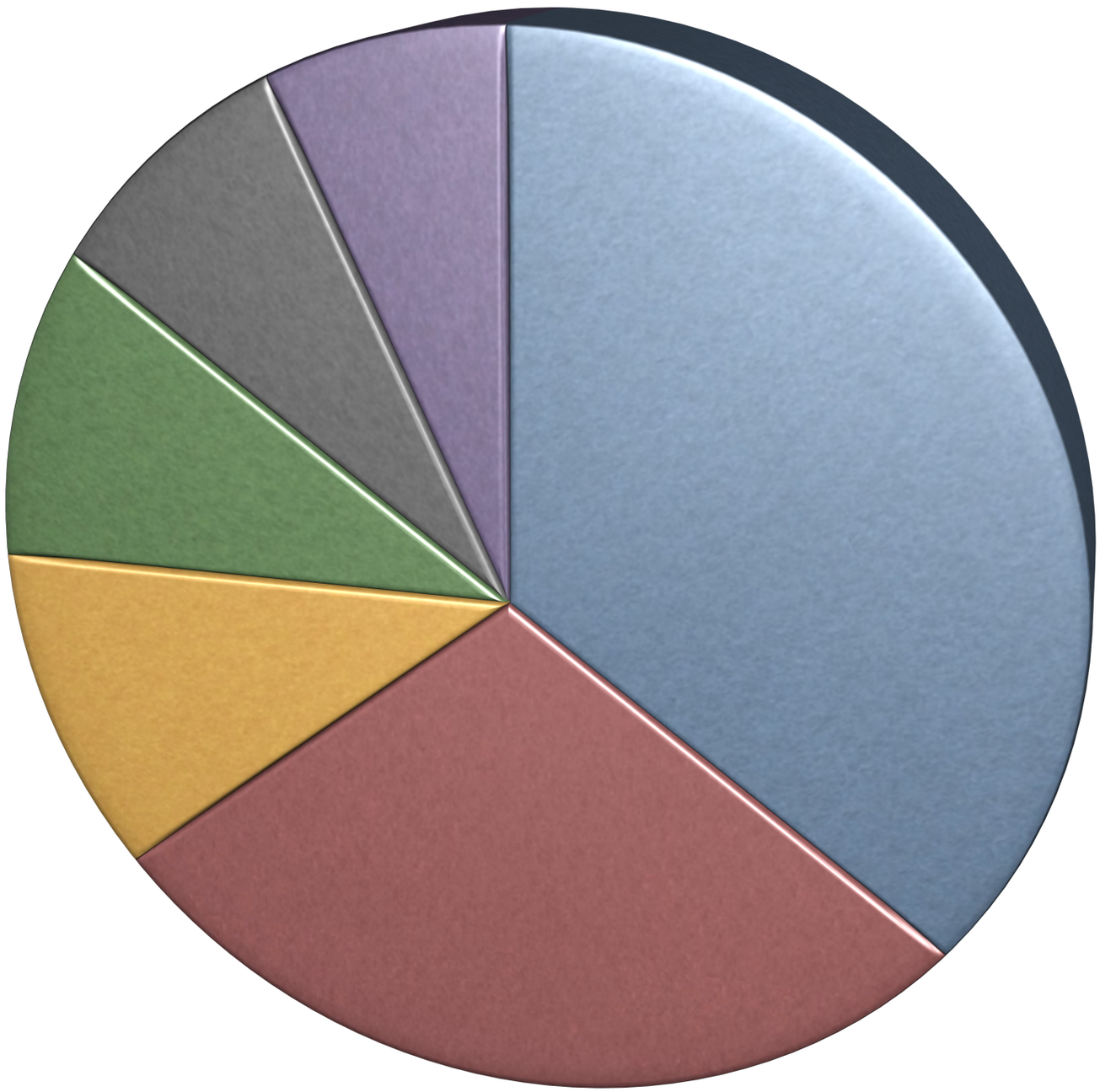
ligands share receptors
receptors share ligands



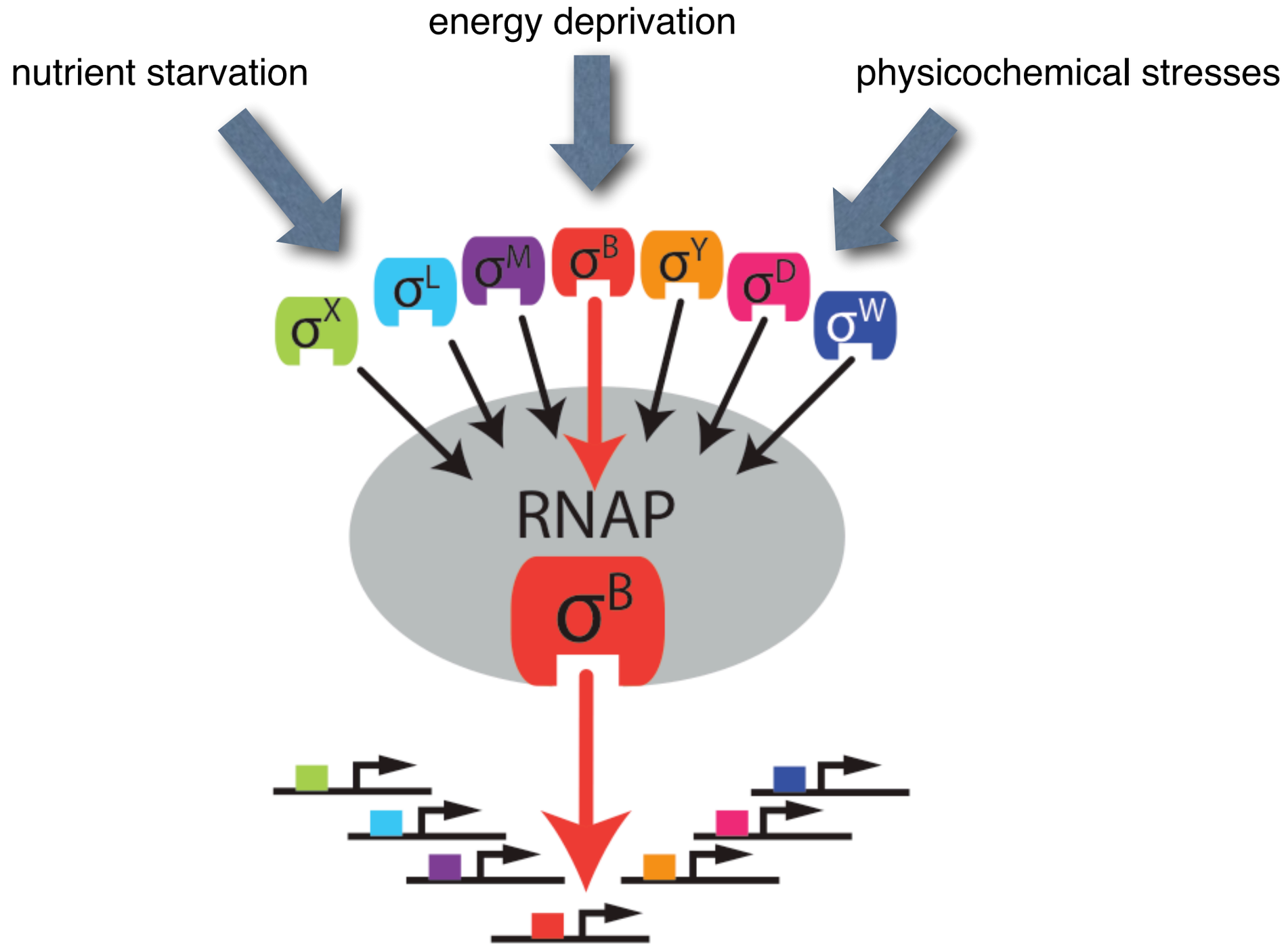
How do cells share limited resources?



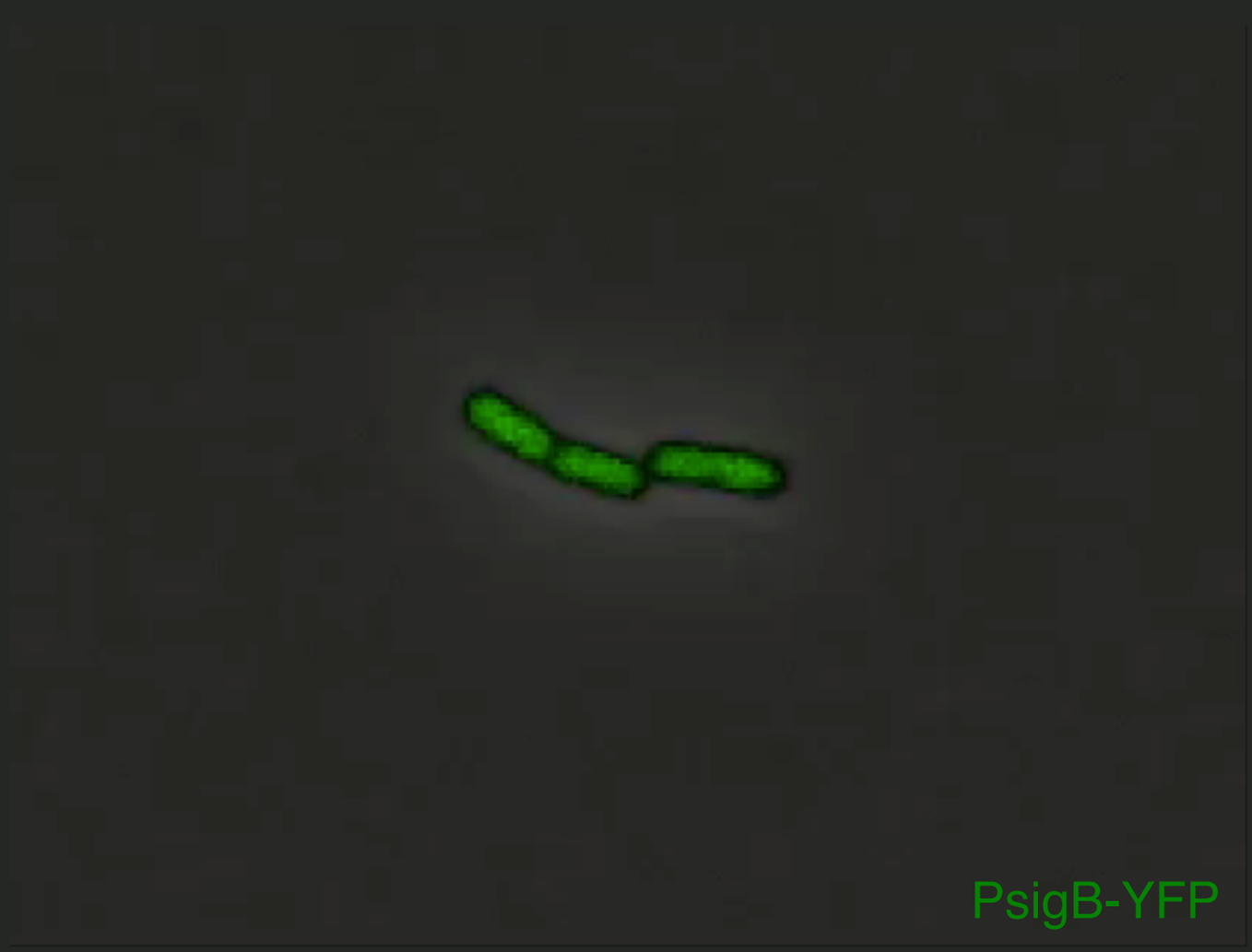
Sharing in concentration



Sharing RNAP by alternative sigma factors in bacteria



σ^B activity pulses in response to energy stress



60 µg/ml mycophenolic acid

[Locke et al, Science, 2011]

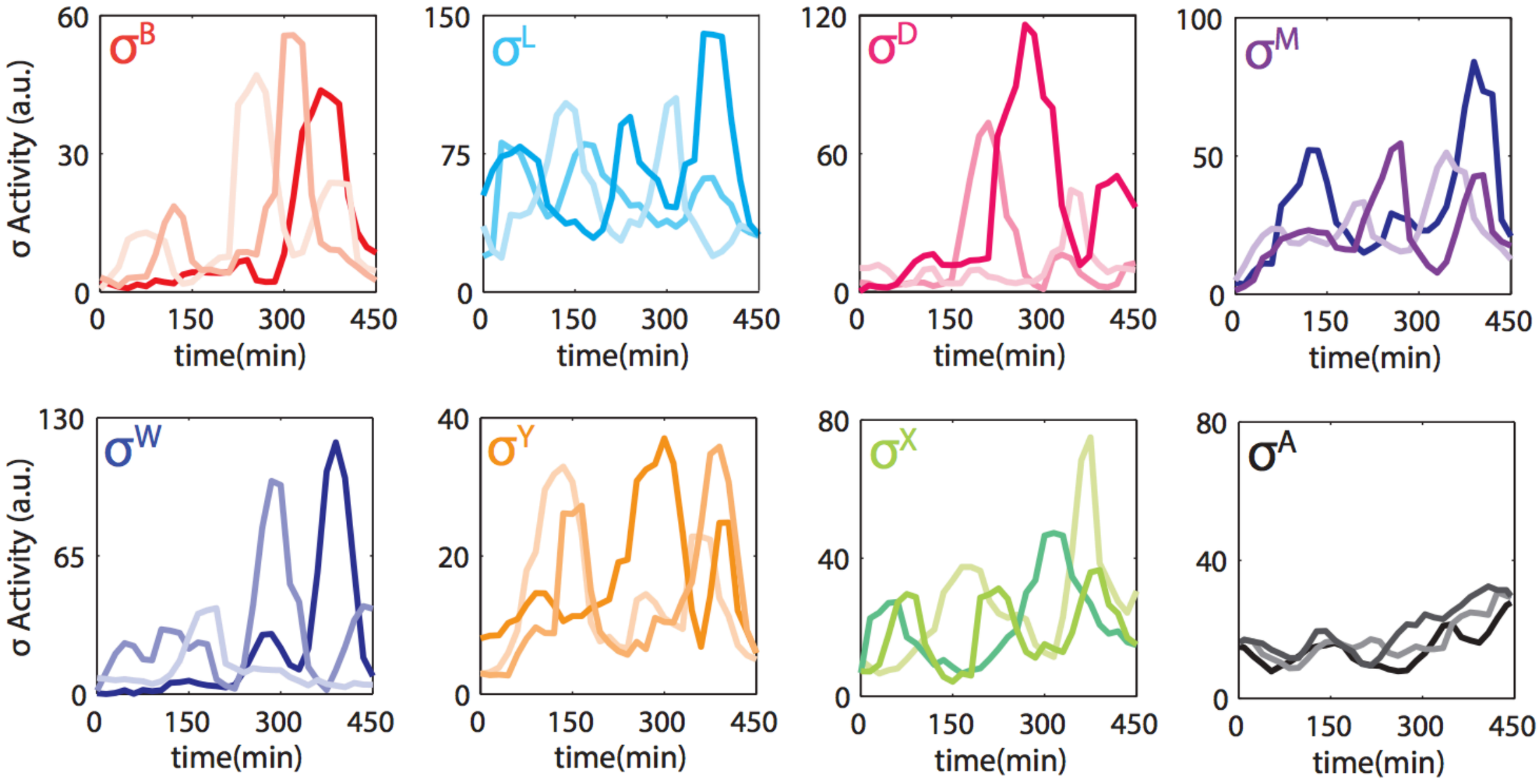
Other alternative sigma factors pulse

σ^B σ^D σ^L σ^M

σ^W σ^X σ^Y σ^A

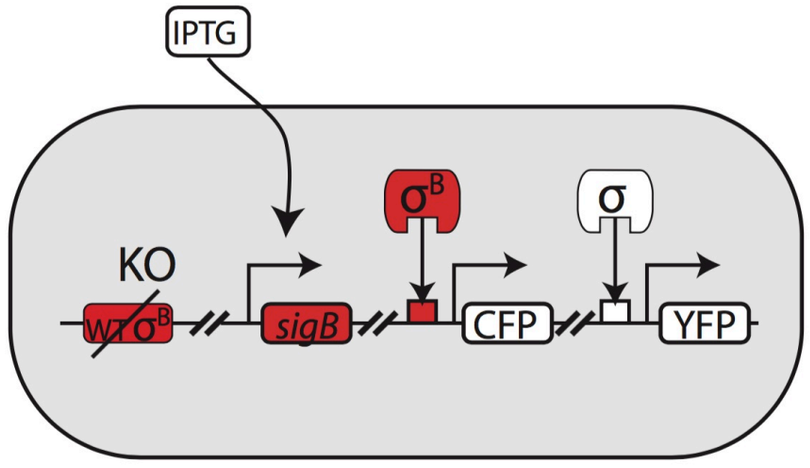
Jin Park

Other alternative sigma factors pulse



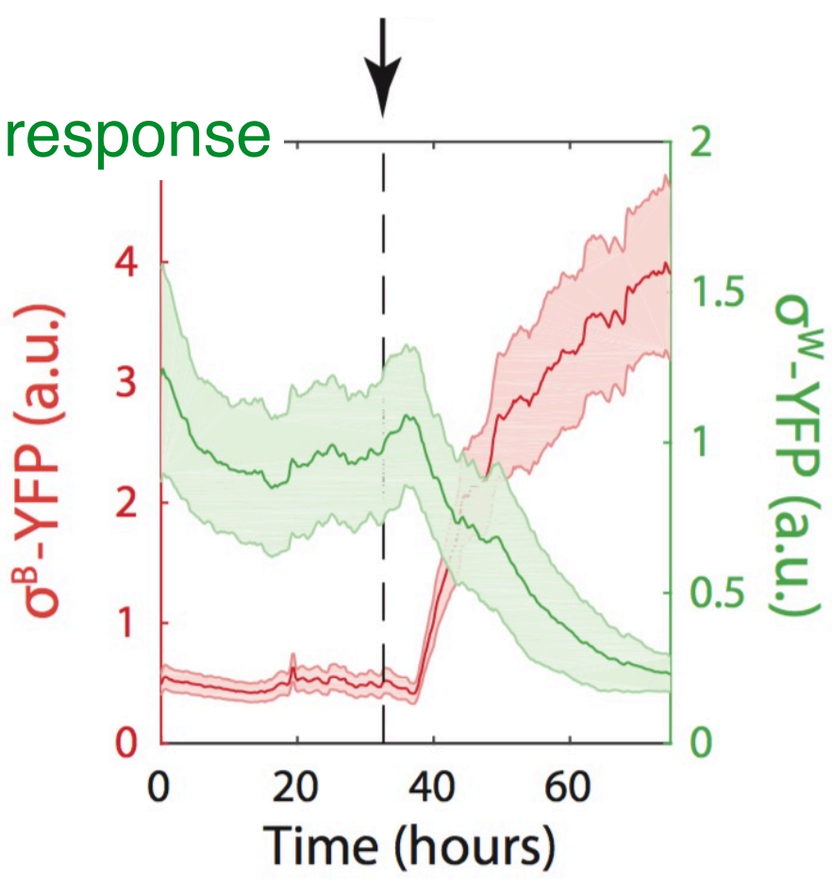
40 µg/ml mycophenolic acid in minimal medium

Sigma factors compete for available RNA polymerase



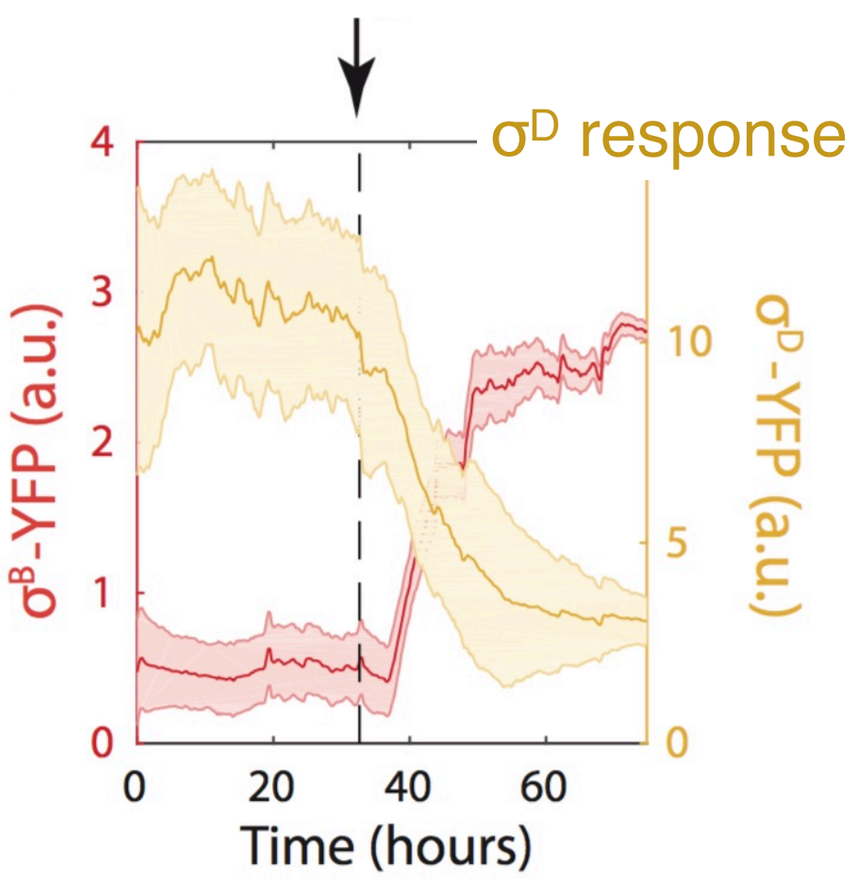
σB induction

σW response

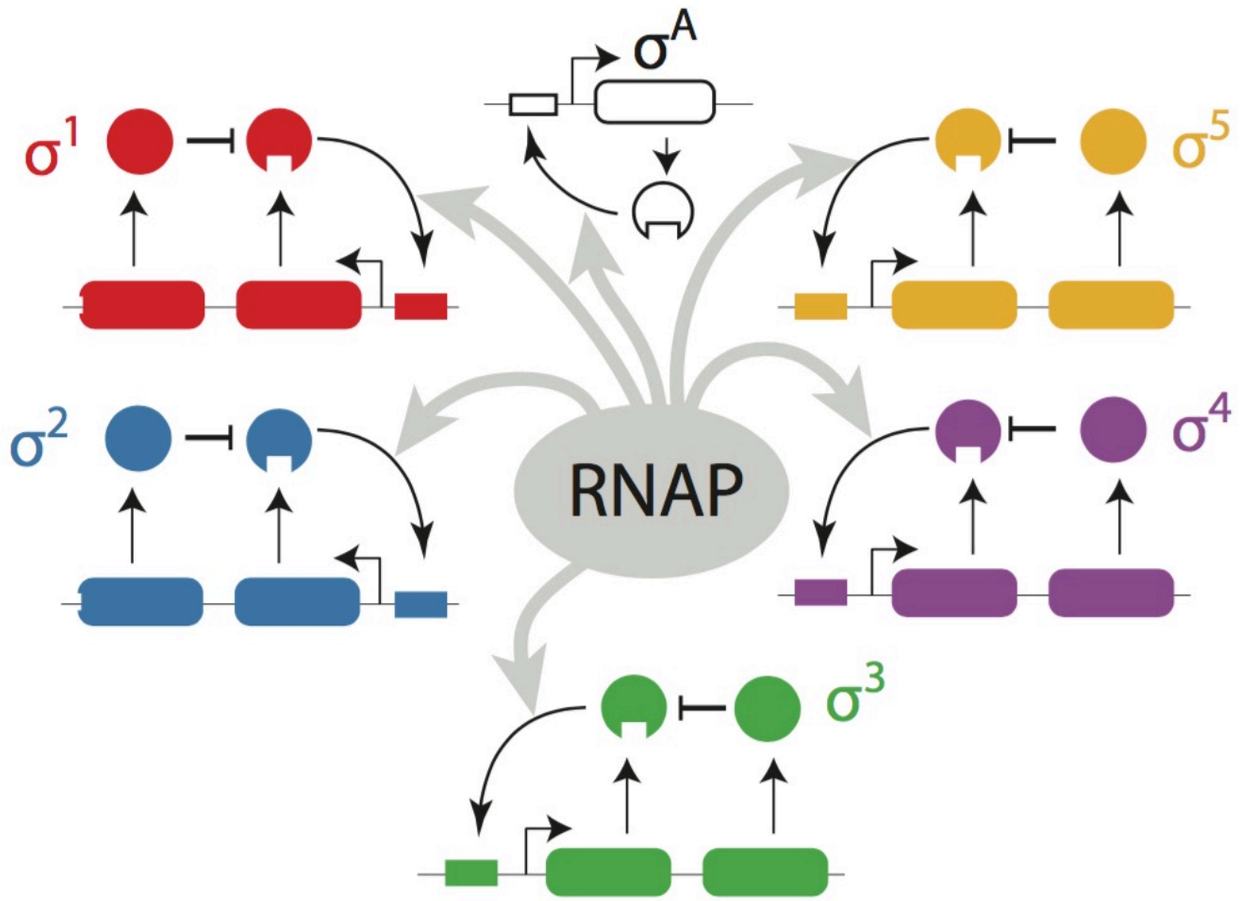


σB induction

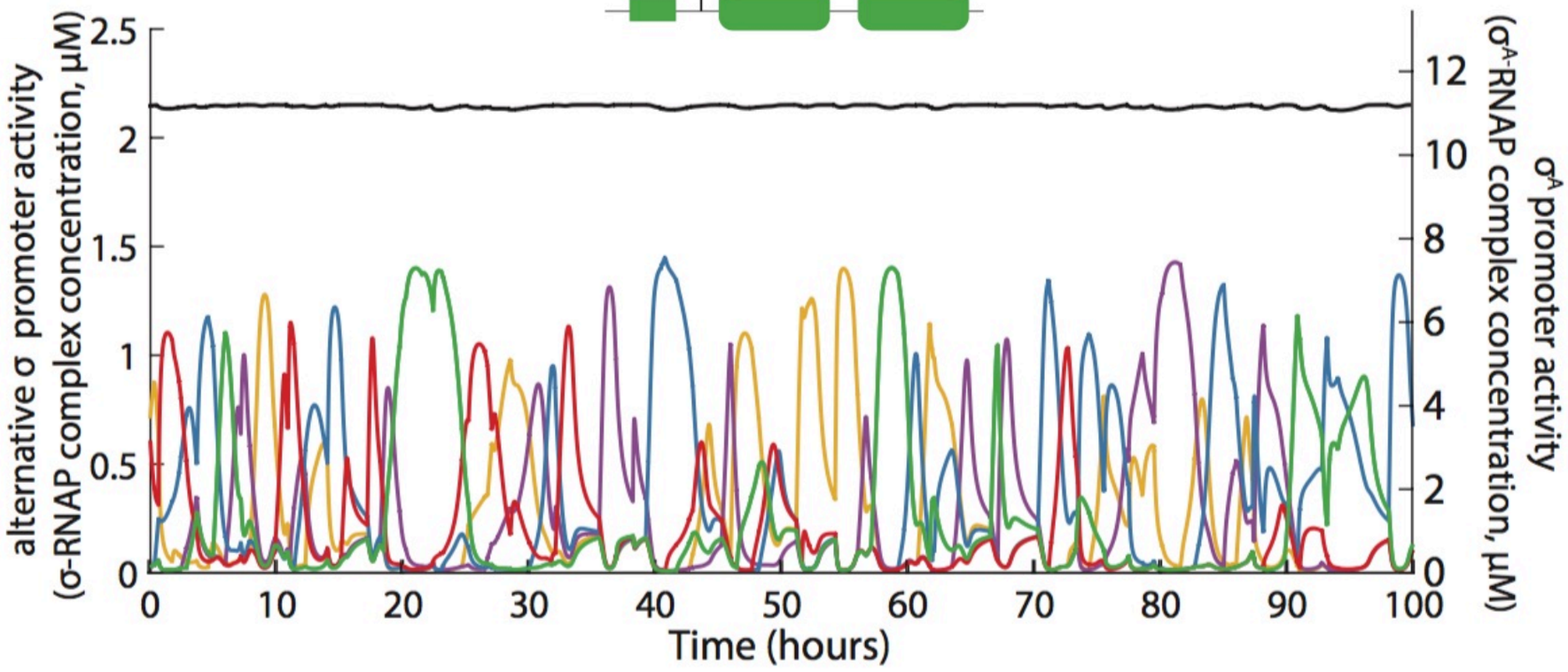
σD response



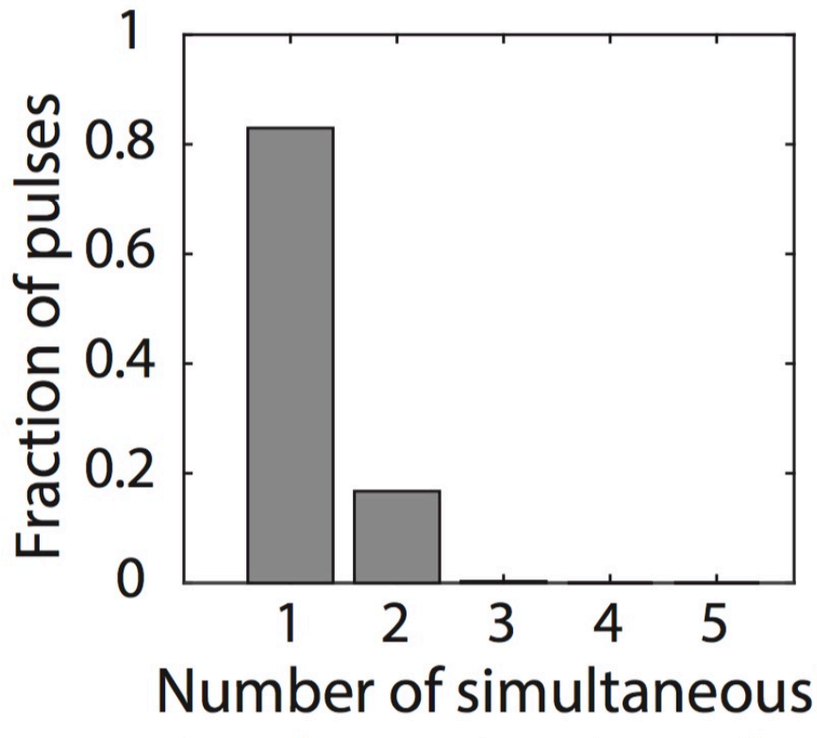
Mathematical model of multiple sigma factors sharing RNAp

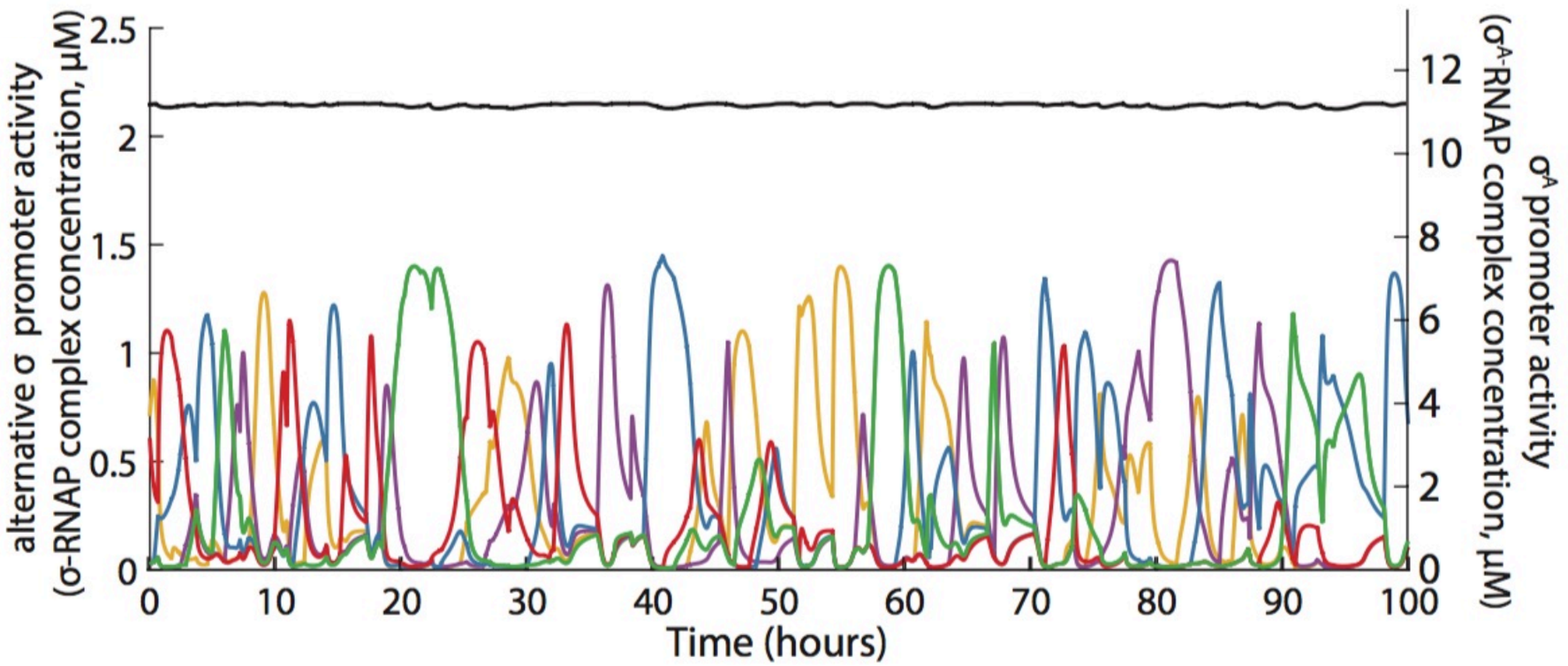


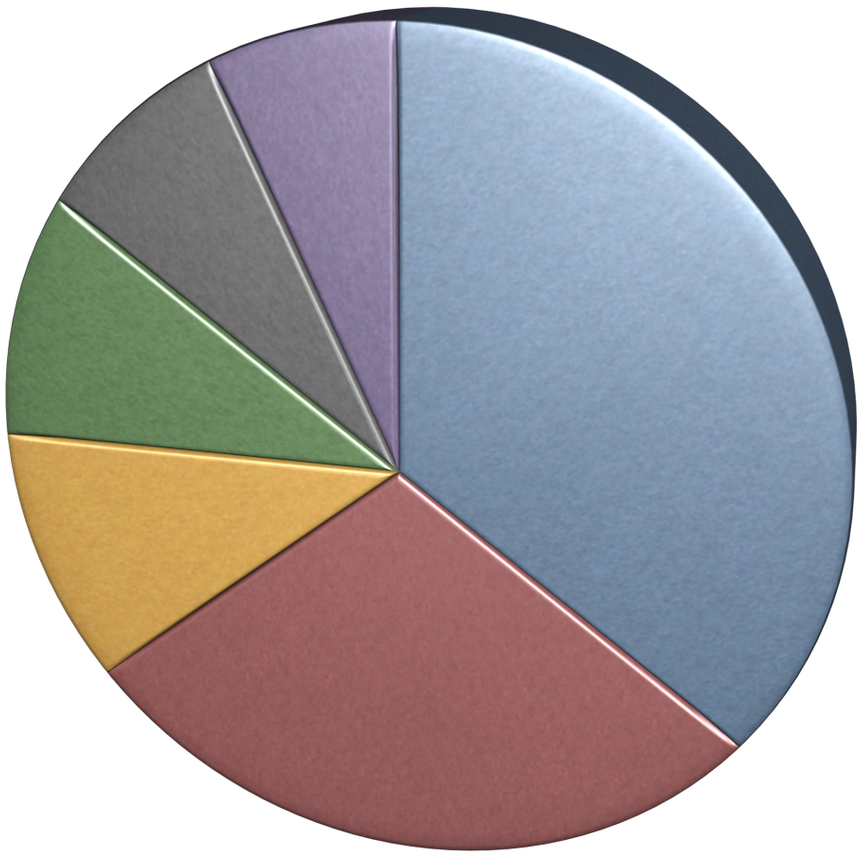
Marta Dies



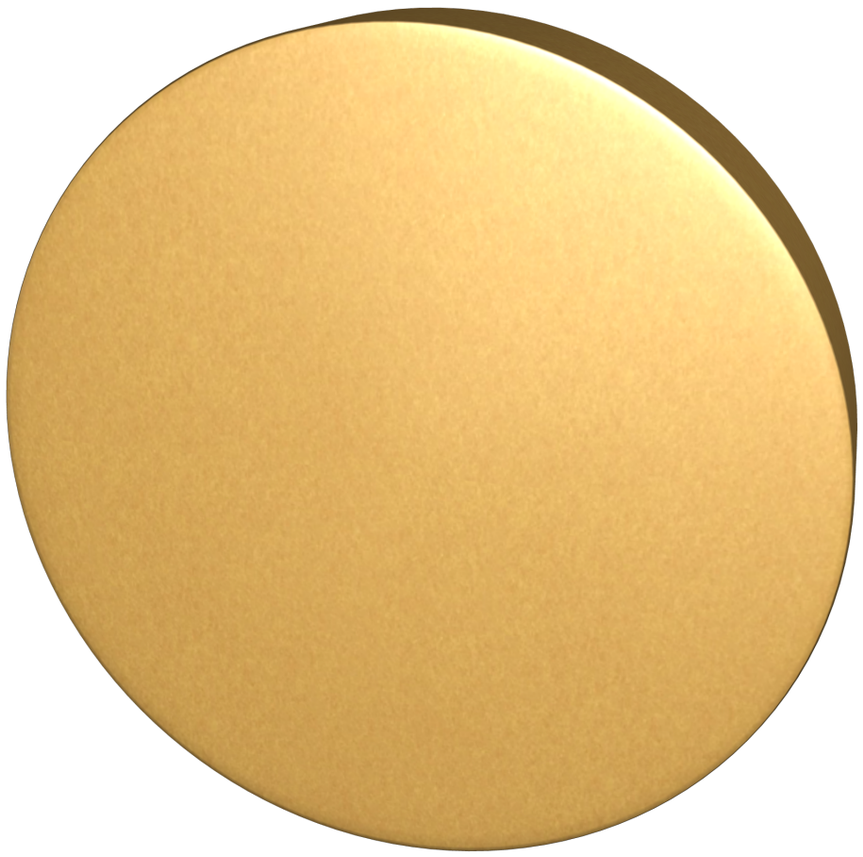
Only one sigma factor is active most of the time





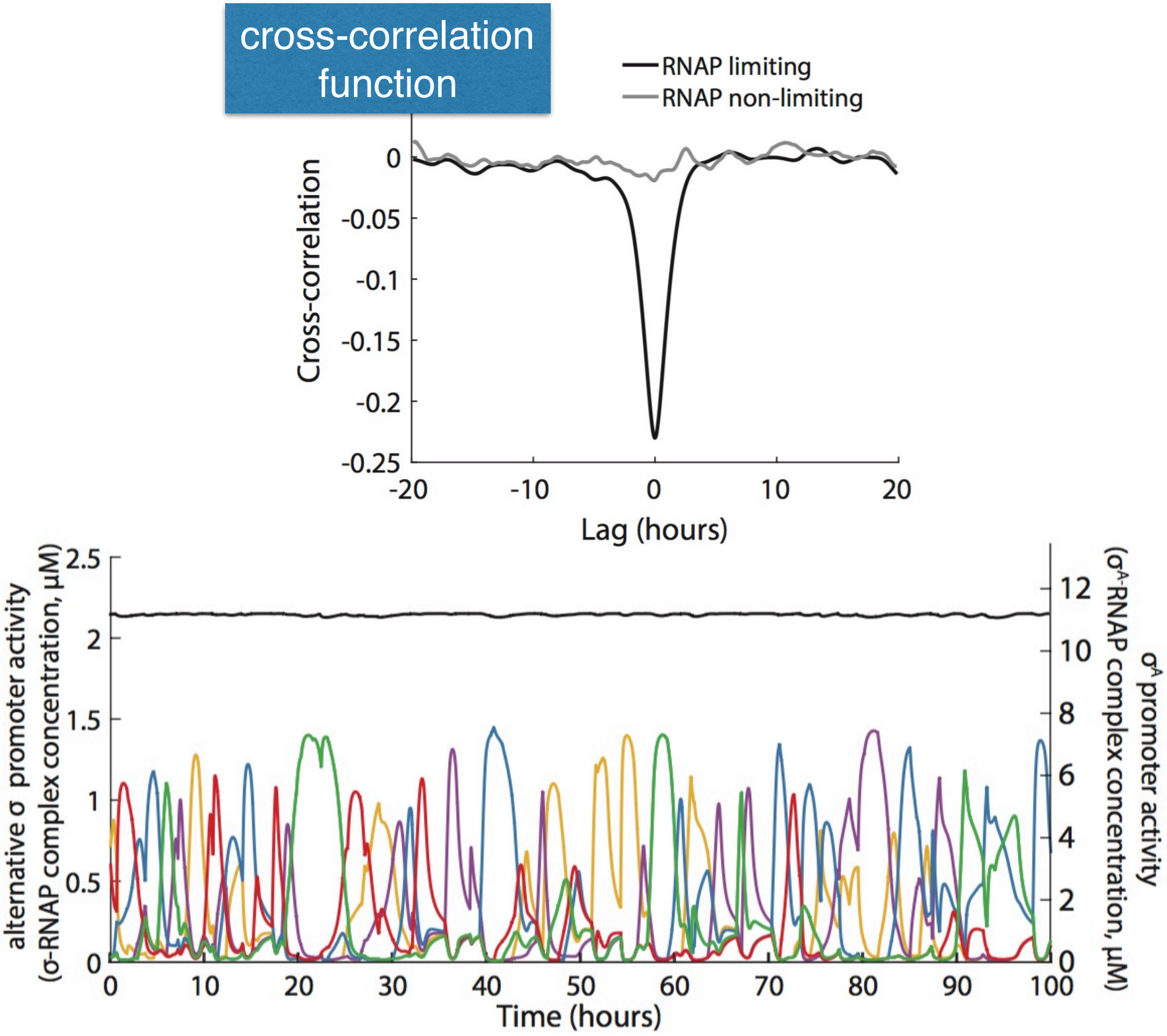


concentration-share

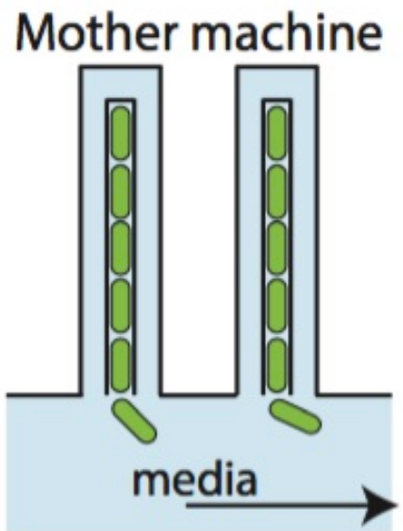


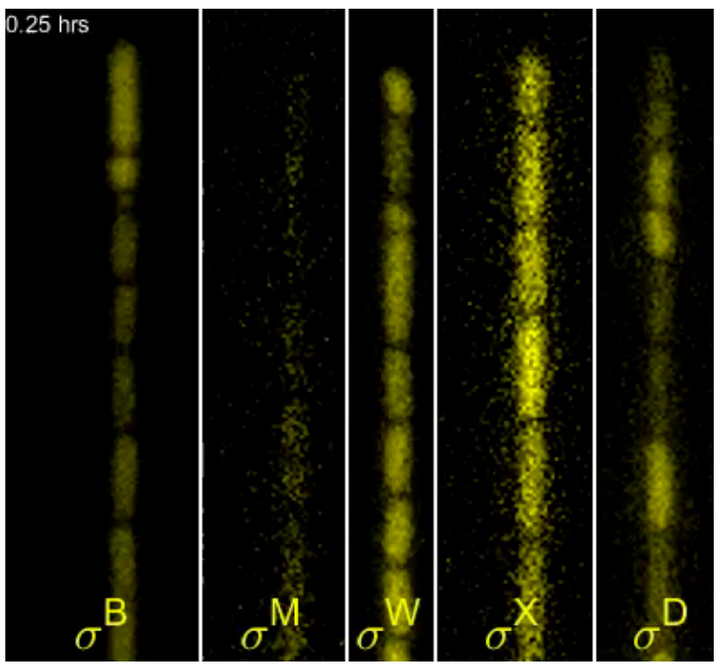
time-share

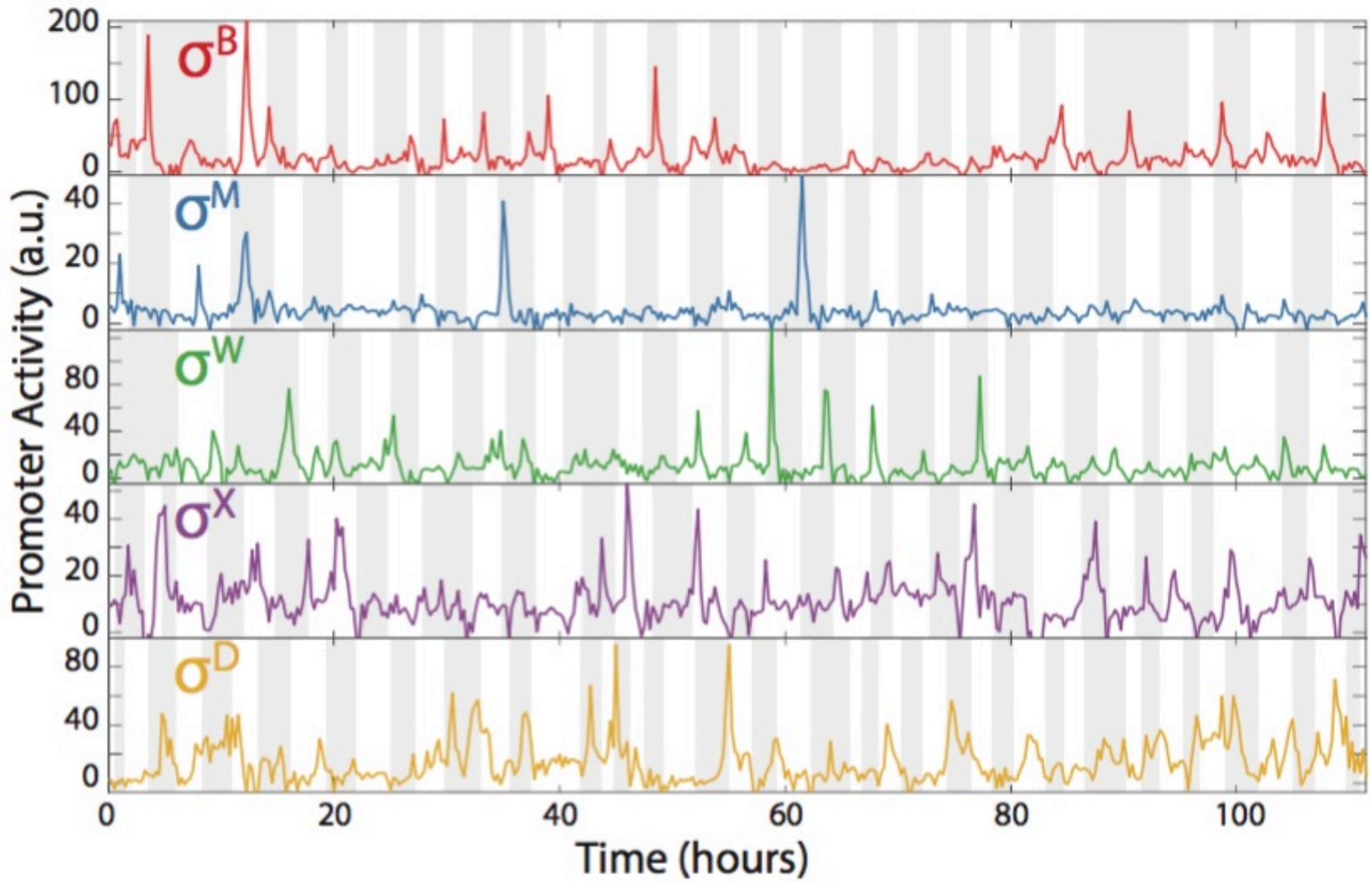
Pairwise cross-correlation of sigma factor activities



Long-term sigma-factor dynamics

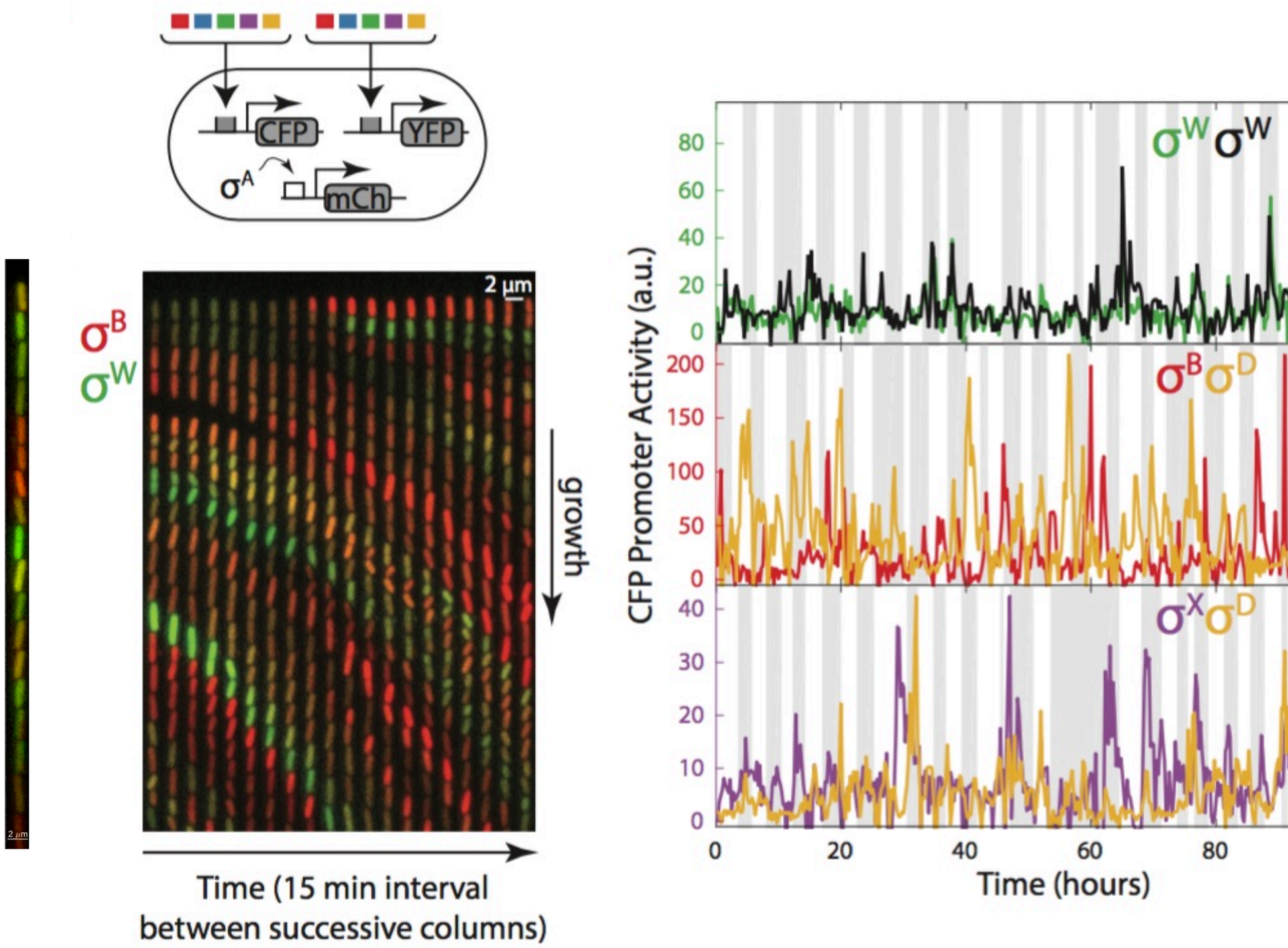






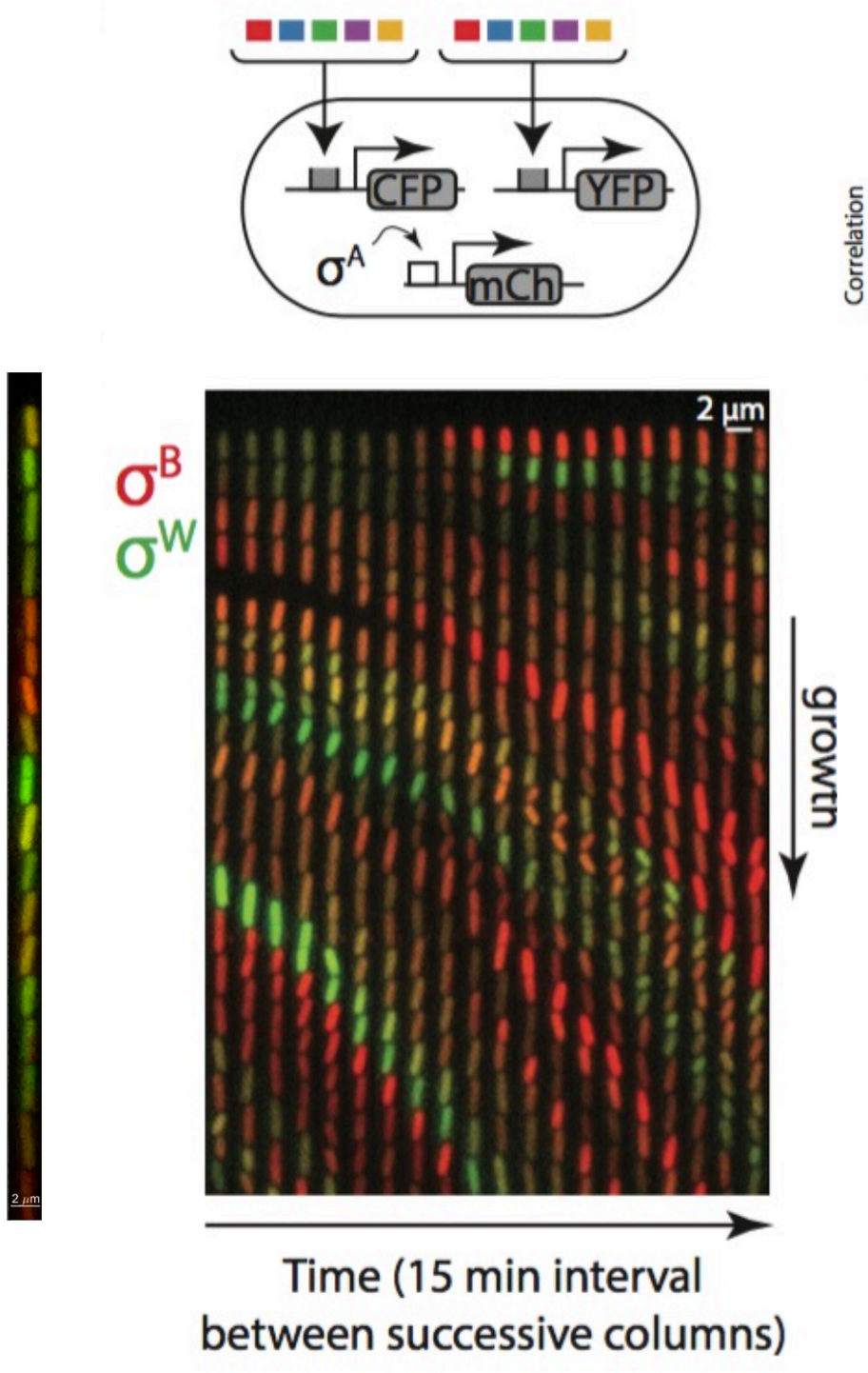
Park et al, Cell Systems **6**, 216 (2018)

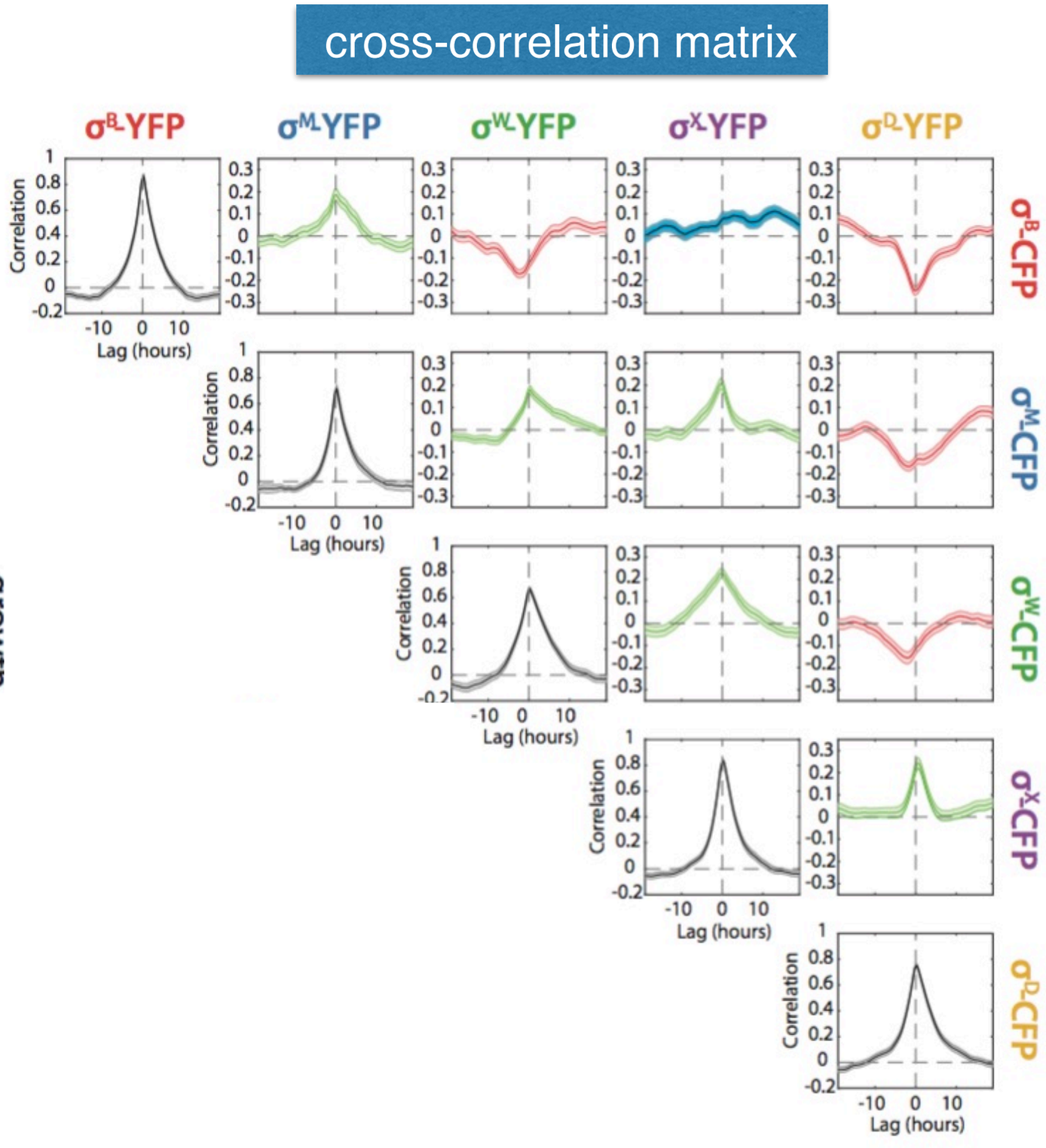
Anticorrelated dynamics of sigma factor pairs



Park et al, Cell Systems **6**, 216 (2018)

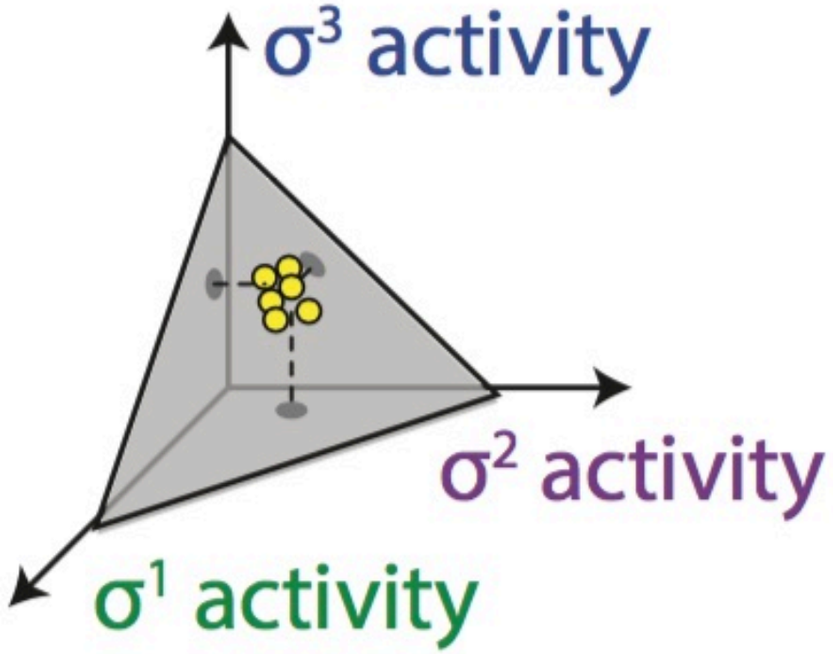
Anticorrelated dynamics of sigma factor pairs

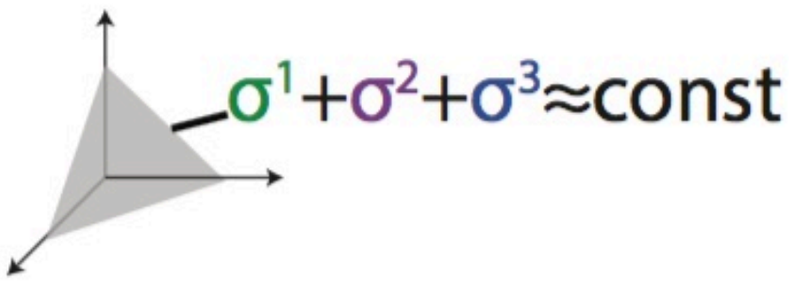




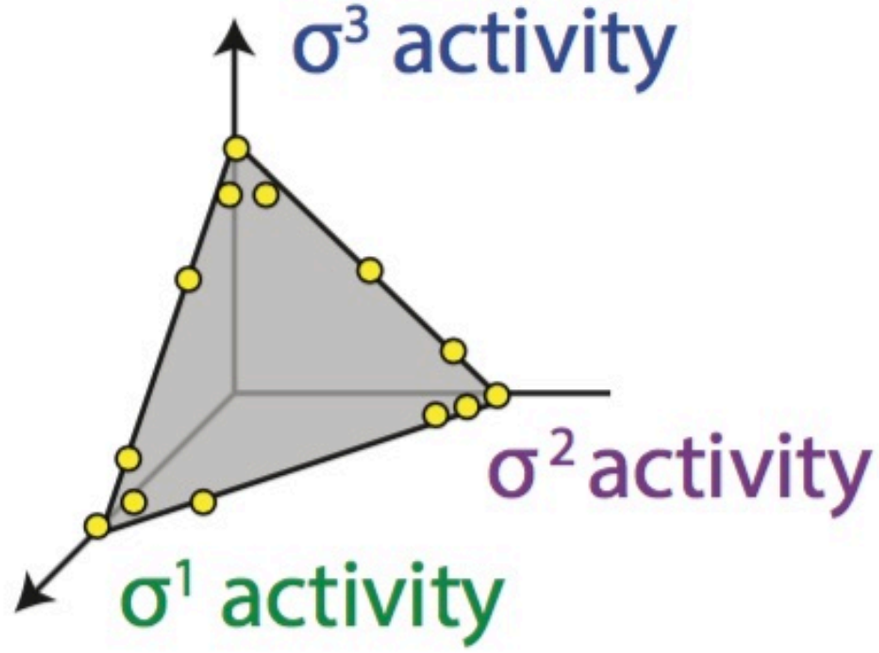
Park et al, Cell Systems **6**, 216 (2018)

Concentration sharing

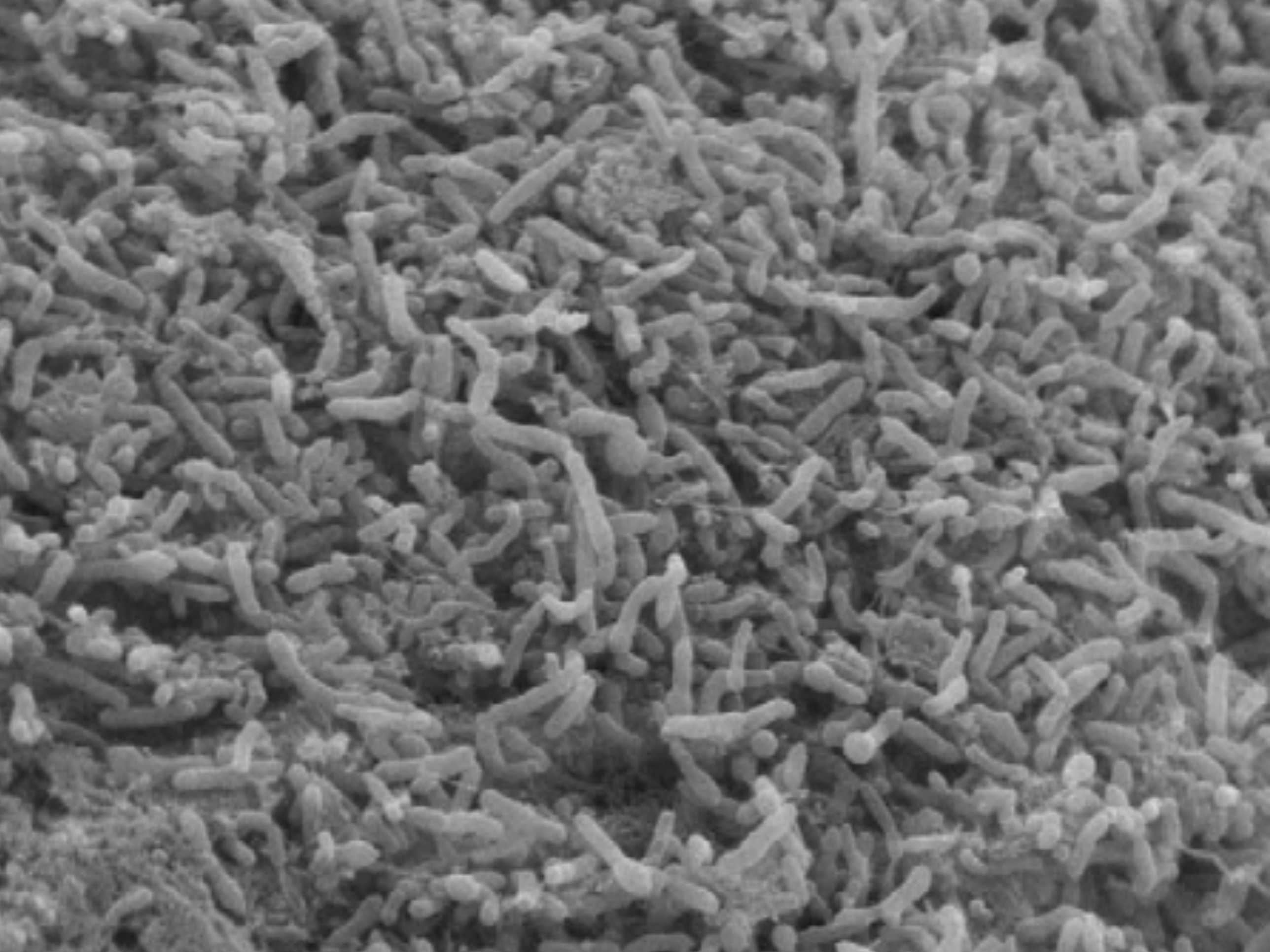




Time-sharing

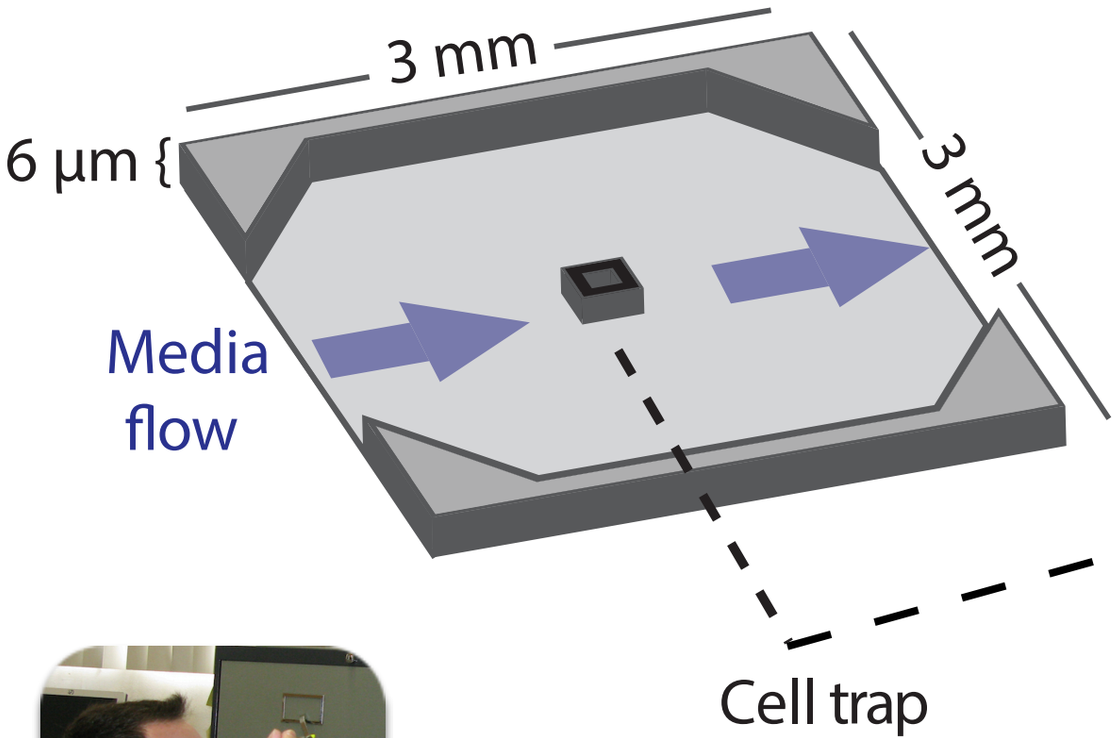


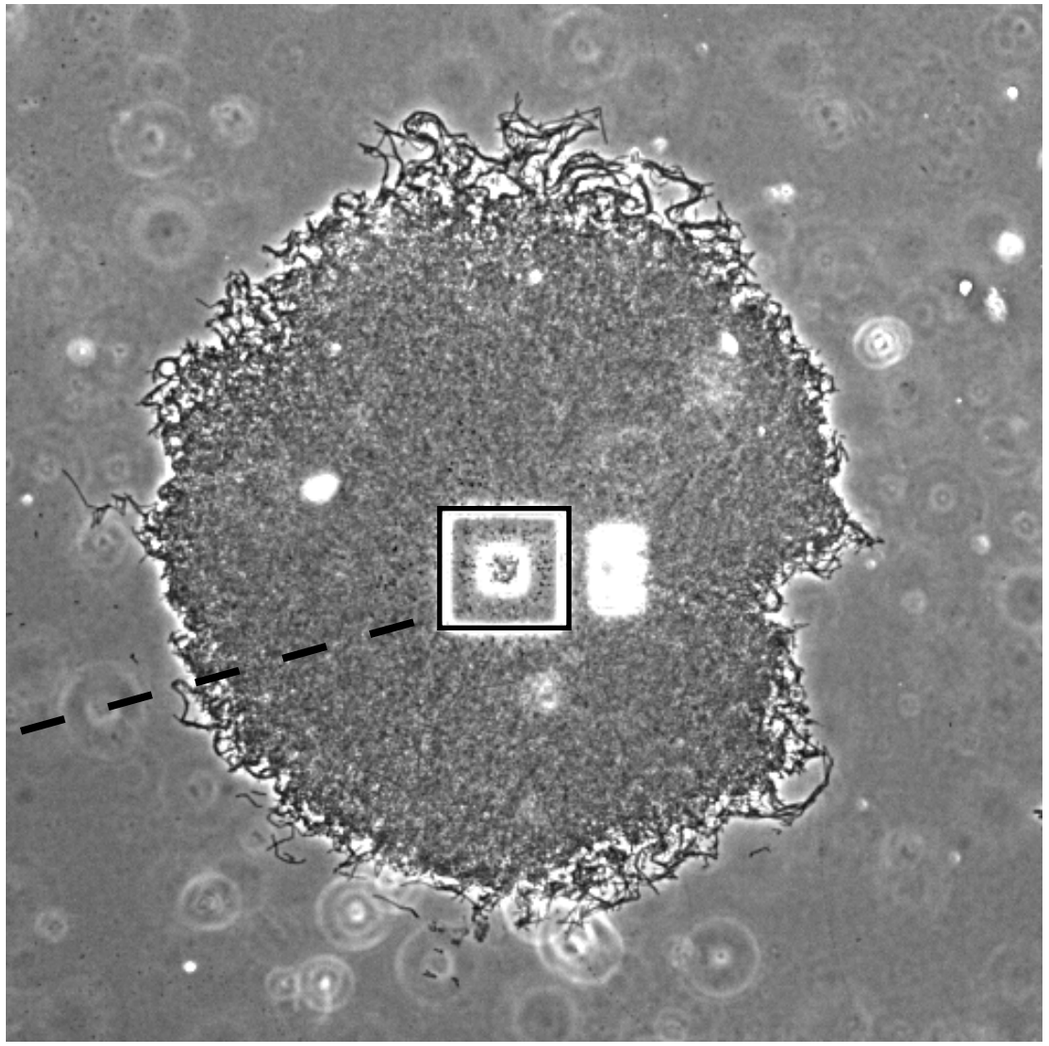
state of an individual cell




Bacterial biofilm (*Bacillus subtilis*)
MUNEHIRO ASALLY

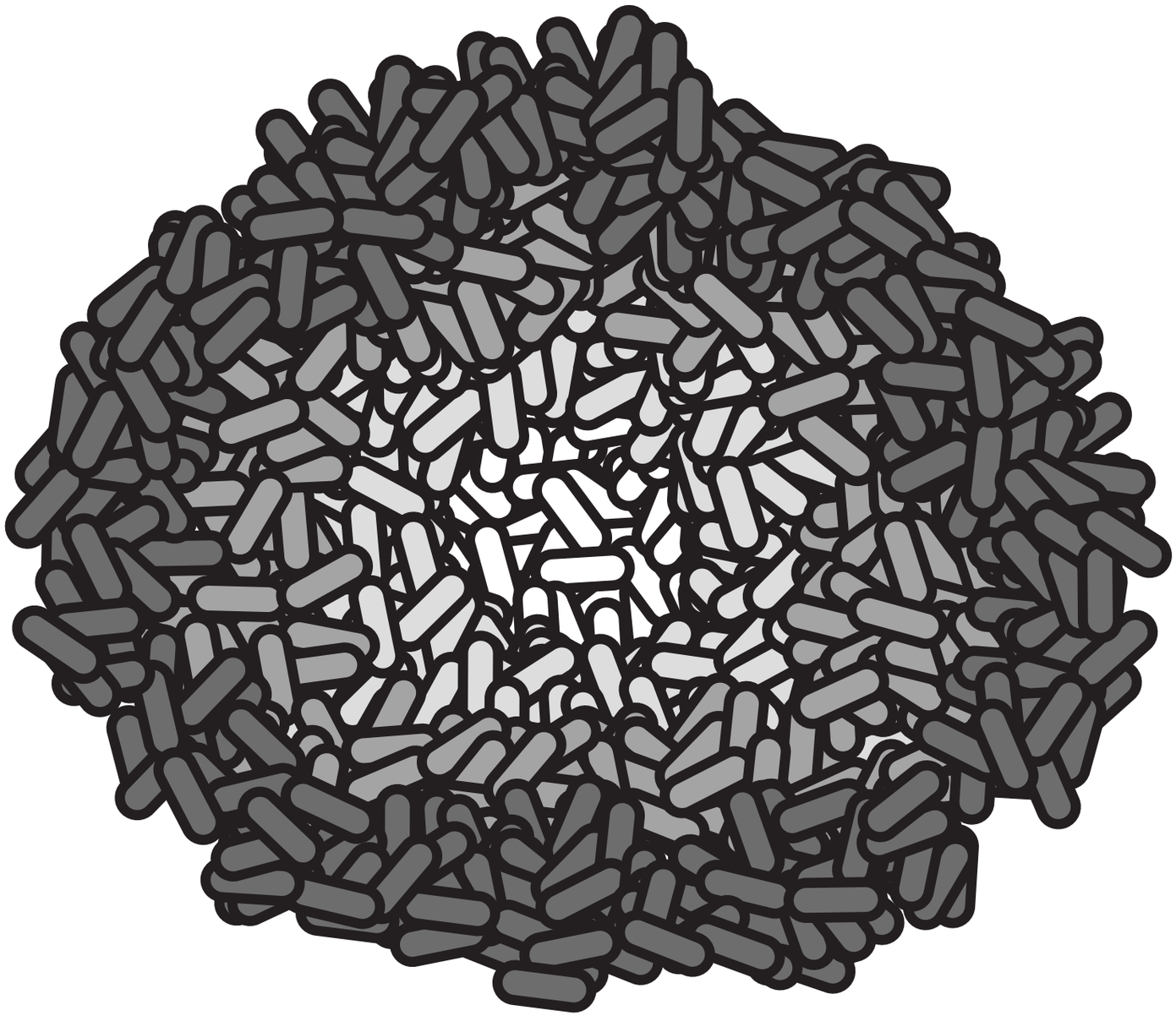
A microfluidics chip for 2D biofilm monitoring





Gürol Süel

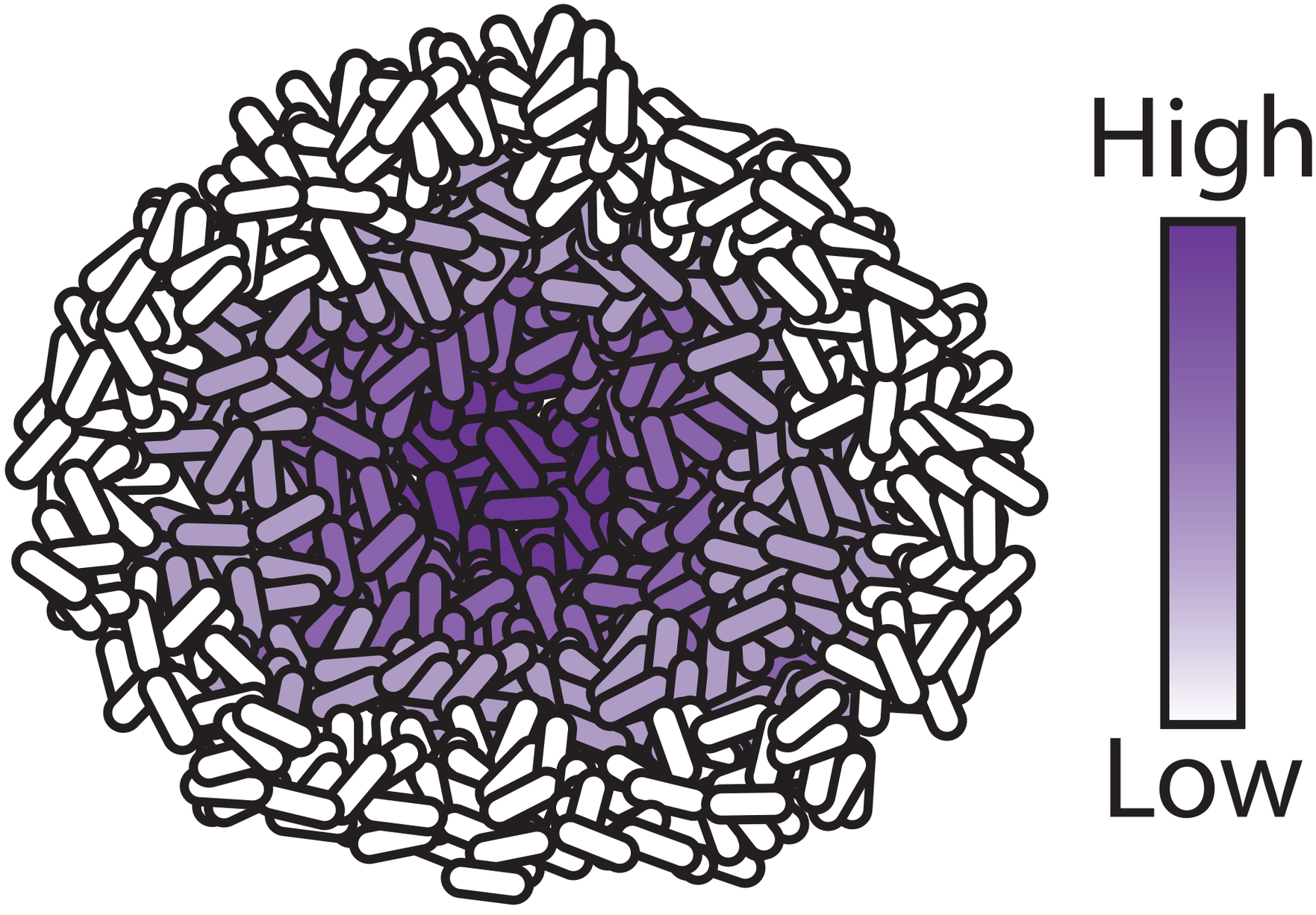
Nutrient Access



High

Low

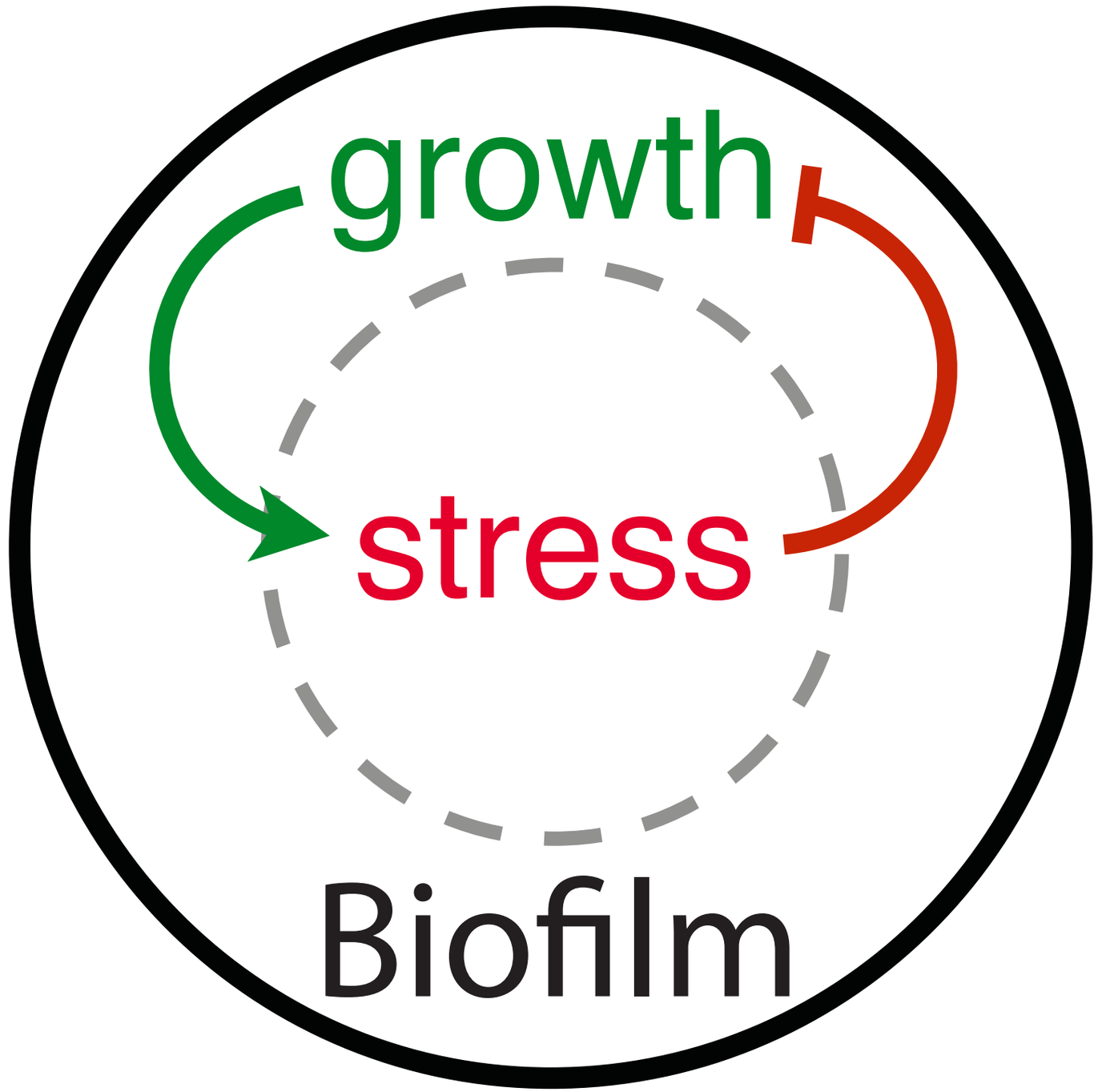
Stress Gradient



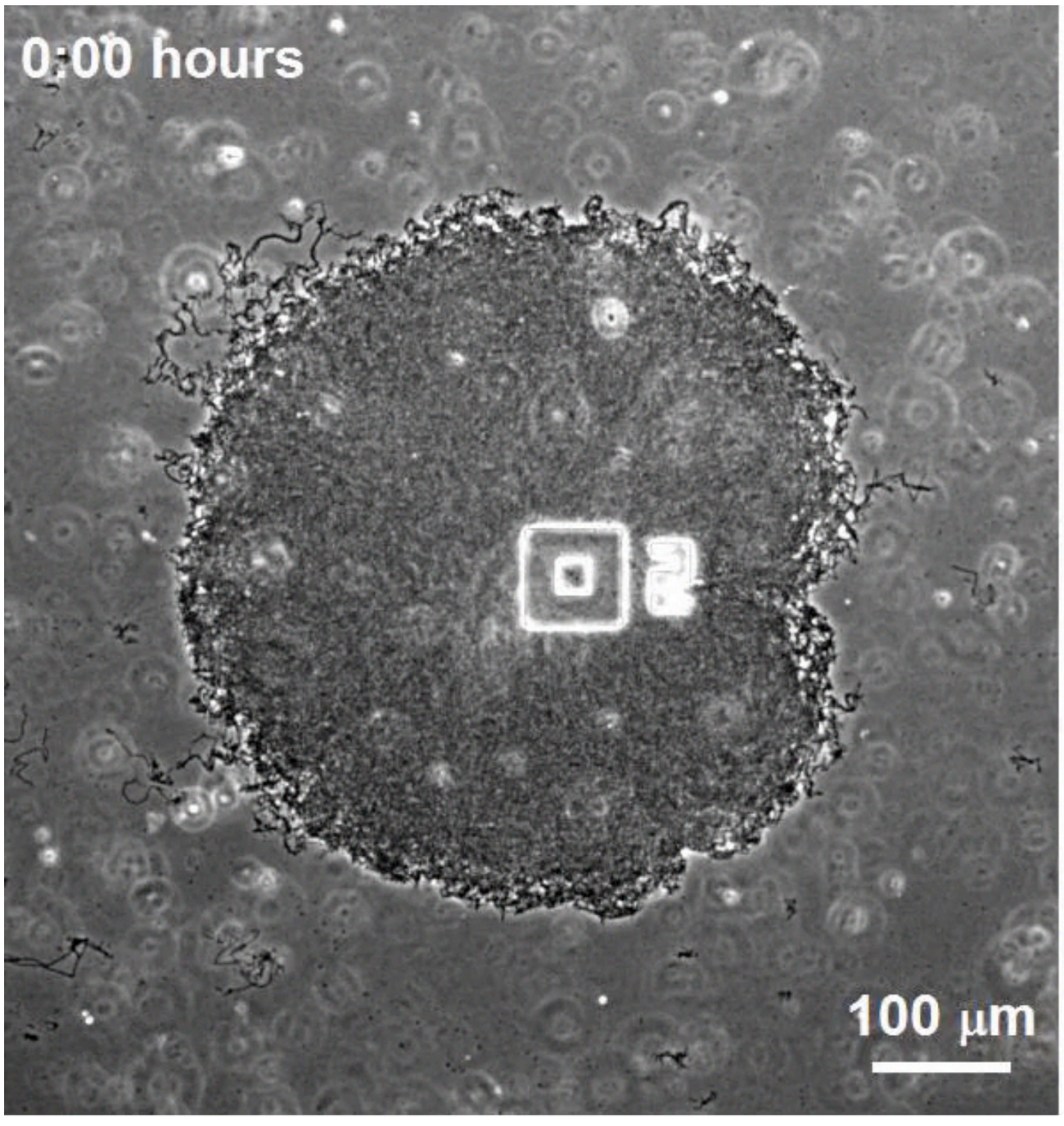
High

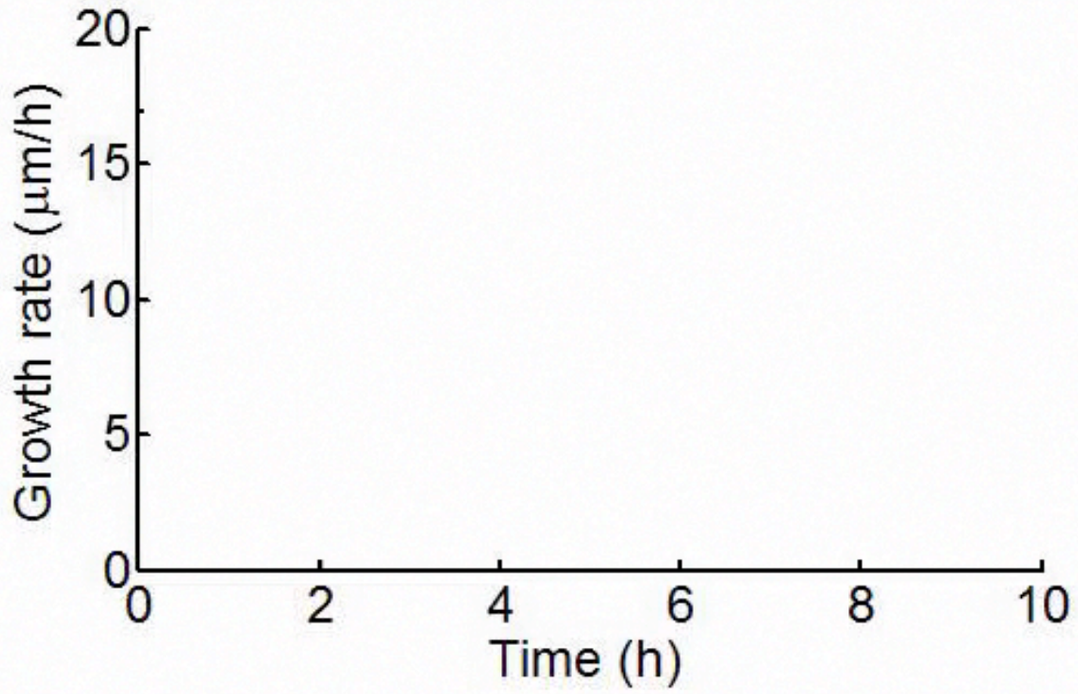
Low

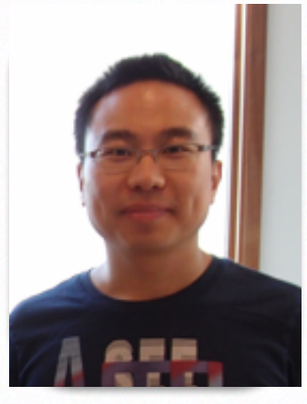
A metabolic negative feedback



Growth-rate oscillations



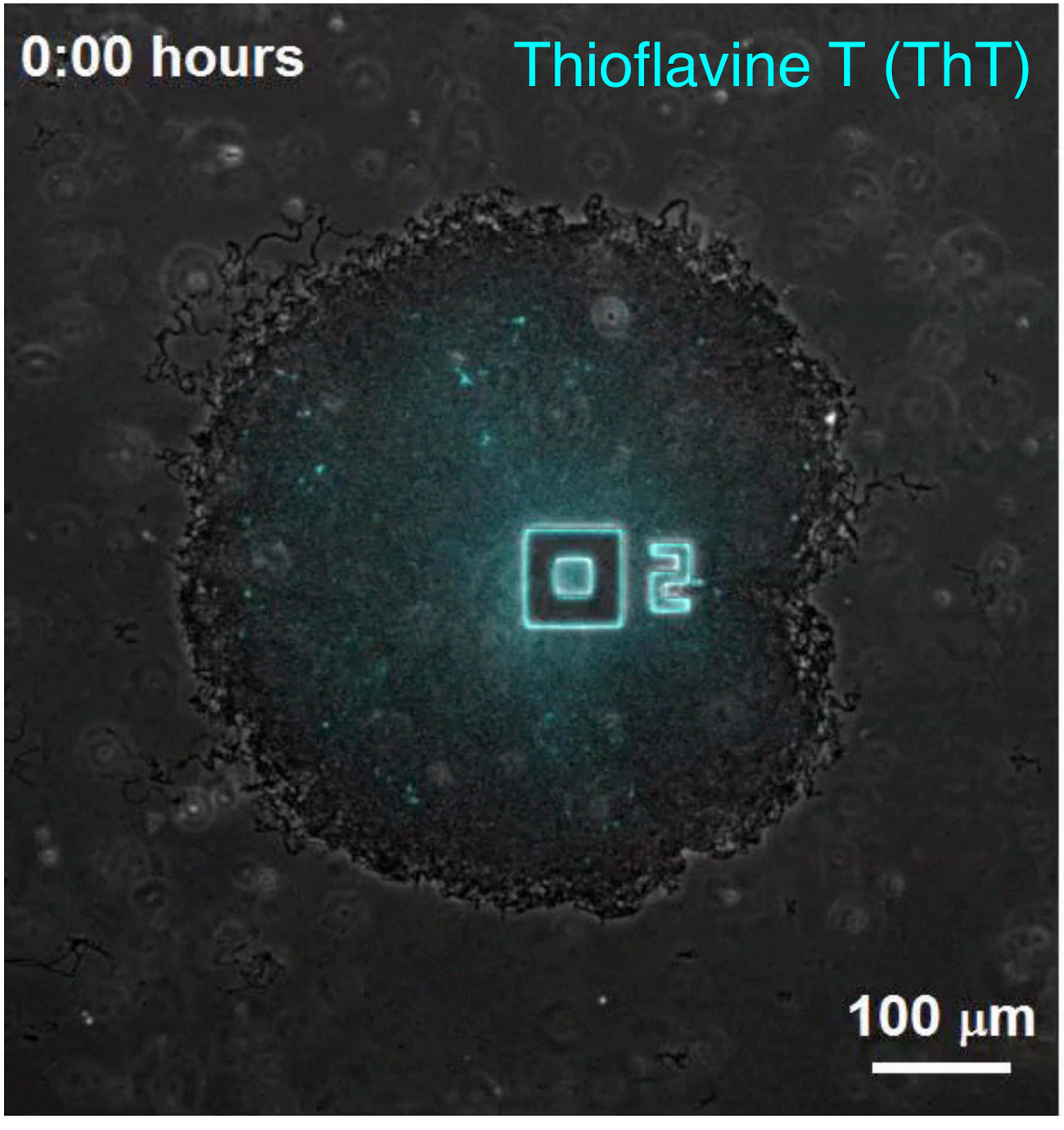


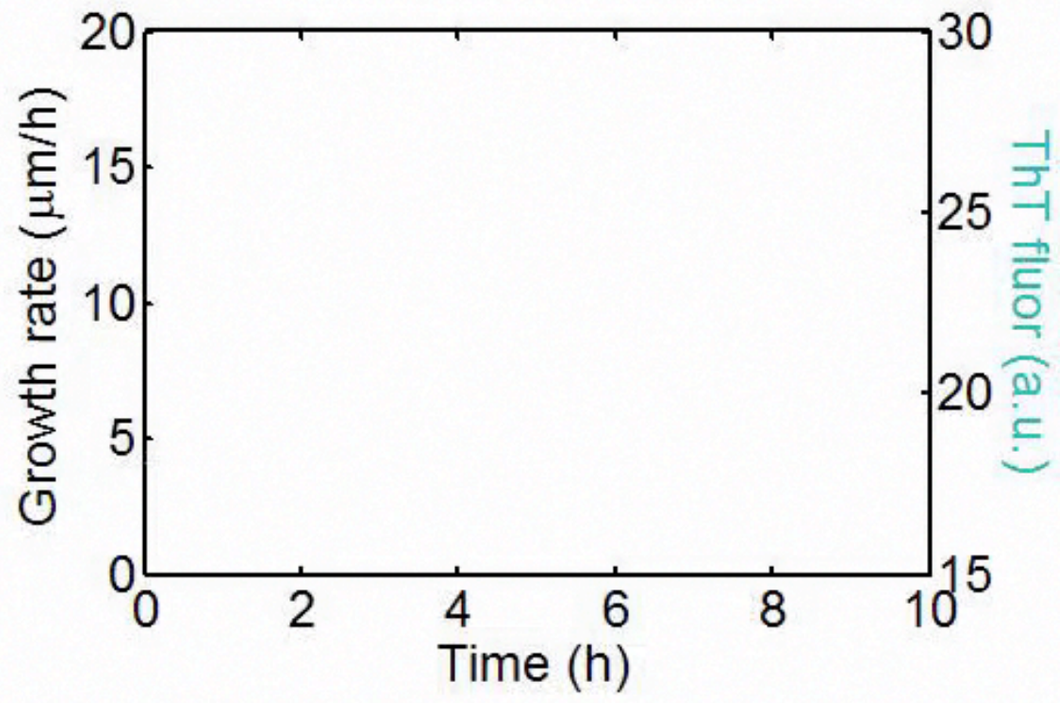


Jintao Liu

Liu et al, Nature **523**, 550-554 (2015)

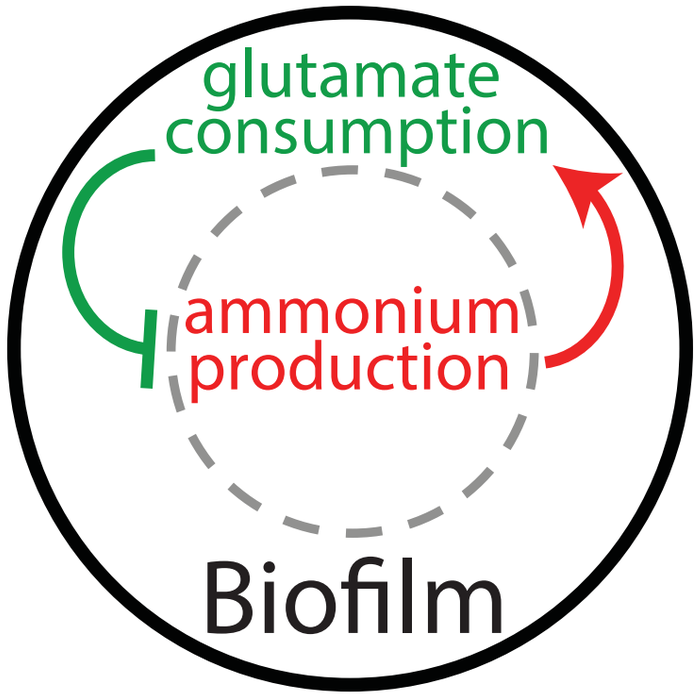
Stress oscillations





Arthur Prindle

Mathematical metabolic model



ammonium

$$\frac{dA}{dt} = \alpha G_i H_i - \delta_A A(r_i + r_p)$$

glutamate

$$\frac{dG_i}{dt} = D\left(G_p - G_i\right) - \alpha G_i H_i - \delta_G G_i r_i$$

$$\frac{dG_p}{dt} = D\left(G_i - G_p\right) + D_E\left(G_E - G_p\right) - \delta_G G_p r_p$$

GDH

$$\frac{dH_i}{dt} = \beta_H \frac{G_i^n}{K_H^n + G_i^n} - \gamma_H H_i$$

biomass

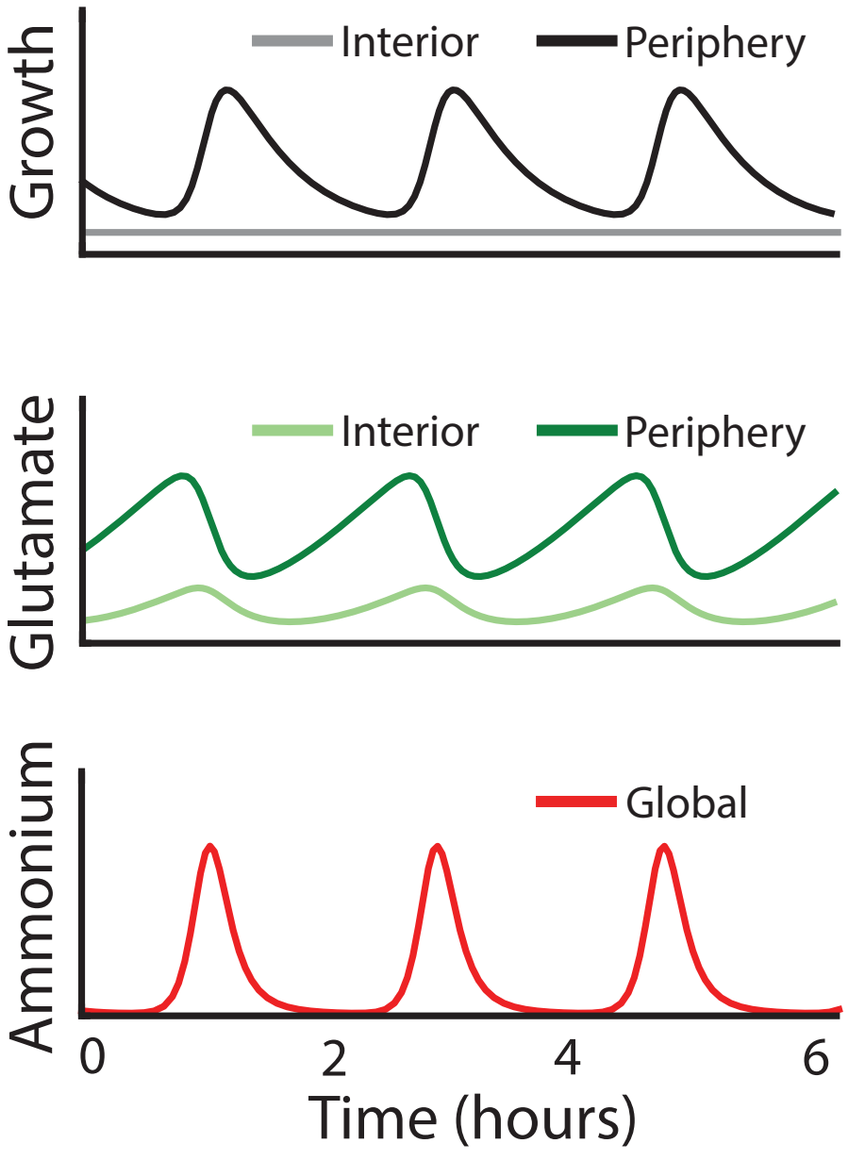
$$\frac{dr_i}{dt} = \beta_r A G_i - \gamma_r r_i$$

$$\frac{dr_p}{dt} = \beta_r A G_p - \gamma_r r_p$$

Marçal Gabaldà

Liu et al, Nature **523**, 550-554 (2015)

Mathematical metabolic model



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GDH

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biomass

$$\frac{dr_i}{dt} = \beta_r A G_i - \gamma_r r_i$$

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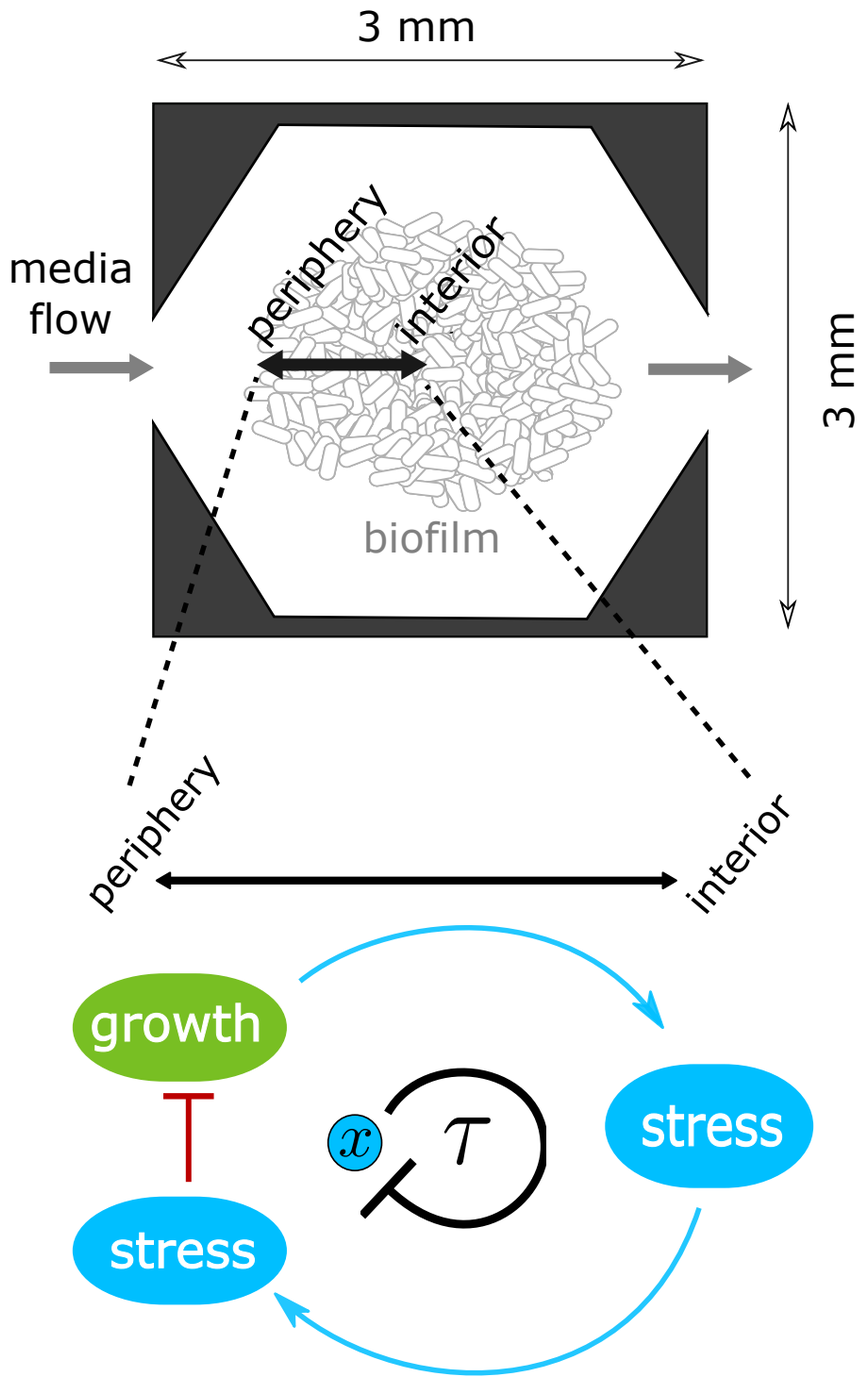
Liu et al, Nature **523**, 550-554 (2015)

A delay-differential model



stress at periphery

delayed stress production

$$\frac{dx}{dt} = f(x(t-\tau)) - \delta x$$

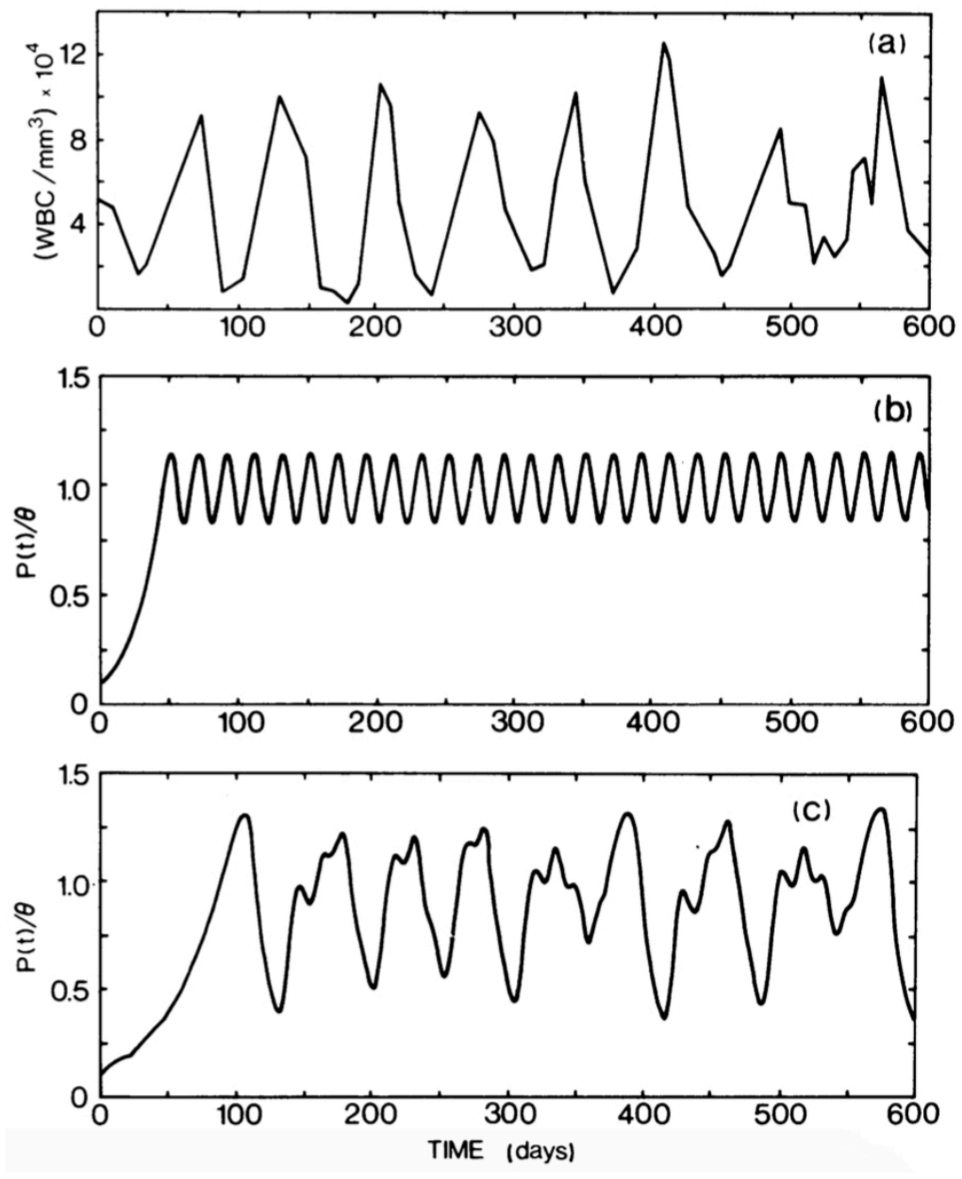
Rosa M.Corral

Oscillation and Chaos in Physiological Control Systems

Abstract. *First-order nonlinear differential-delay equations describing physiological control systems are studied. The equations display a broad diversity of dynamical behavior including limit cycle oscillations, with a variety of wave forms, and apparently aperiodic or "chaotic" solutions. These results are discussed in relation to dynamical respiratory and hematopoietic diseases.*

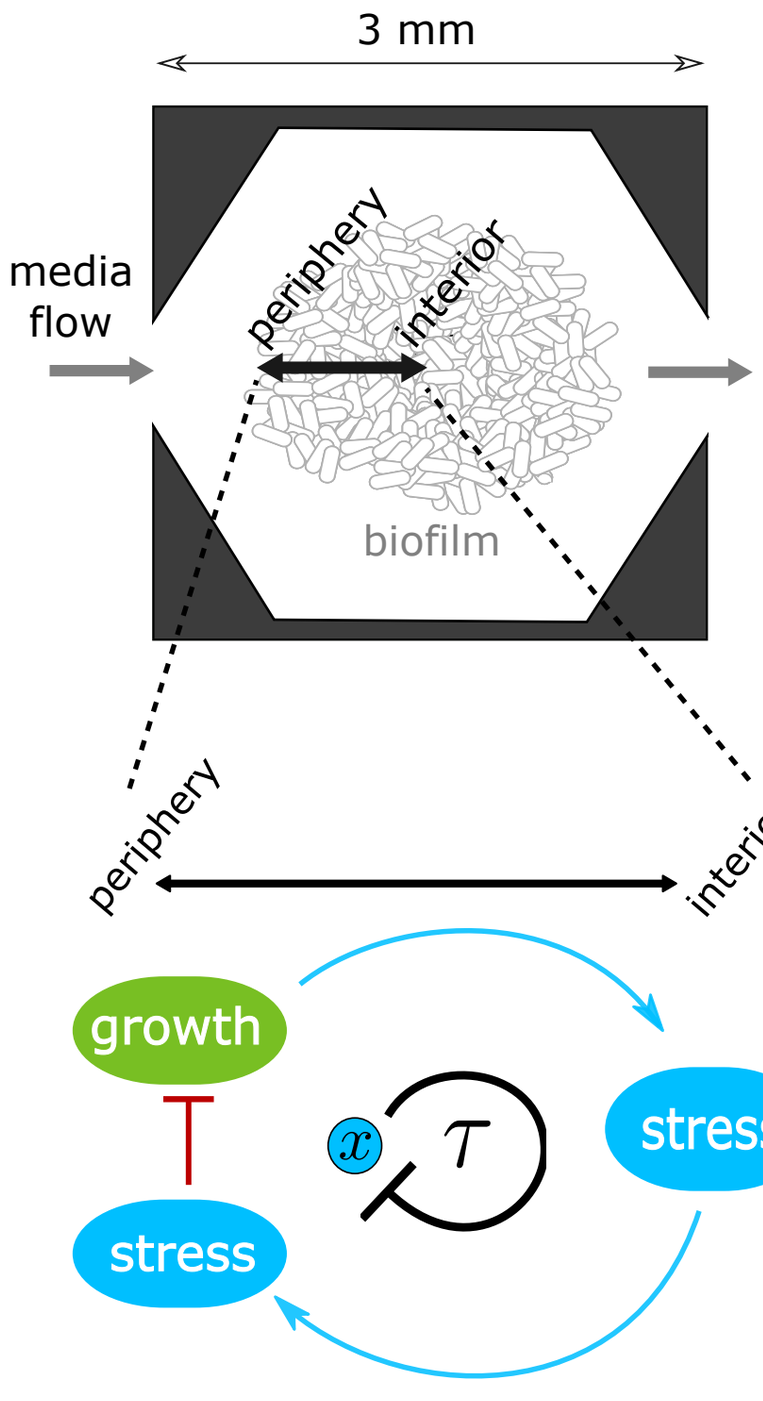
MICHAEL C. MACKEY
LEON GLASS

Department of Physiology,
McGill University,
Montreal, Quebec, Canada H3G 1Y6



$$\frac{dP}{dt} = \frac{\beta_0 \theta^n P_\tau}{\theta^n + P_\tau^n} - \gamma P$$

A delay-differential model

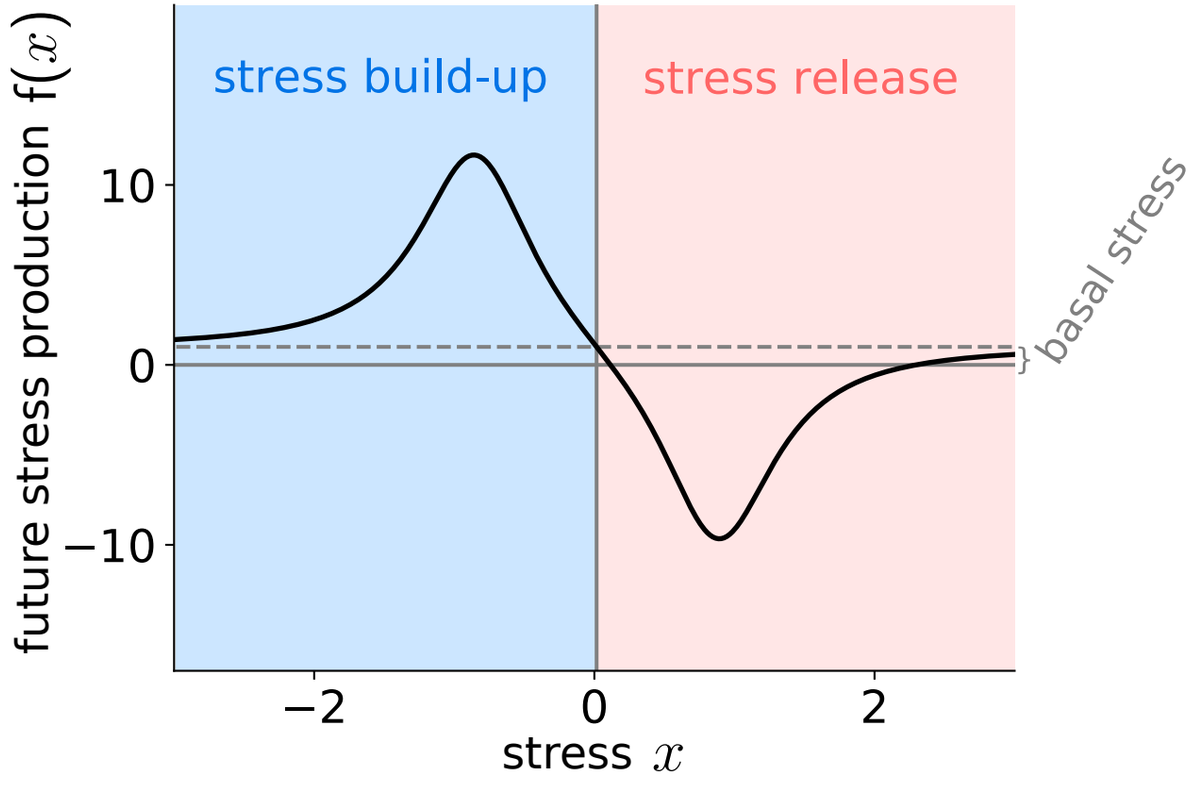


$$\frac{dx}{dt} = f(x(t-\tau)) - \delta x$$

stress dynamics

$$f(x) = C - \frac{\alpha x}{1 - (x/\beta)^2 + (x/\gamma)^4}$$

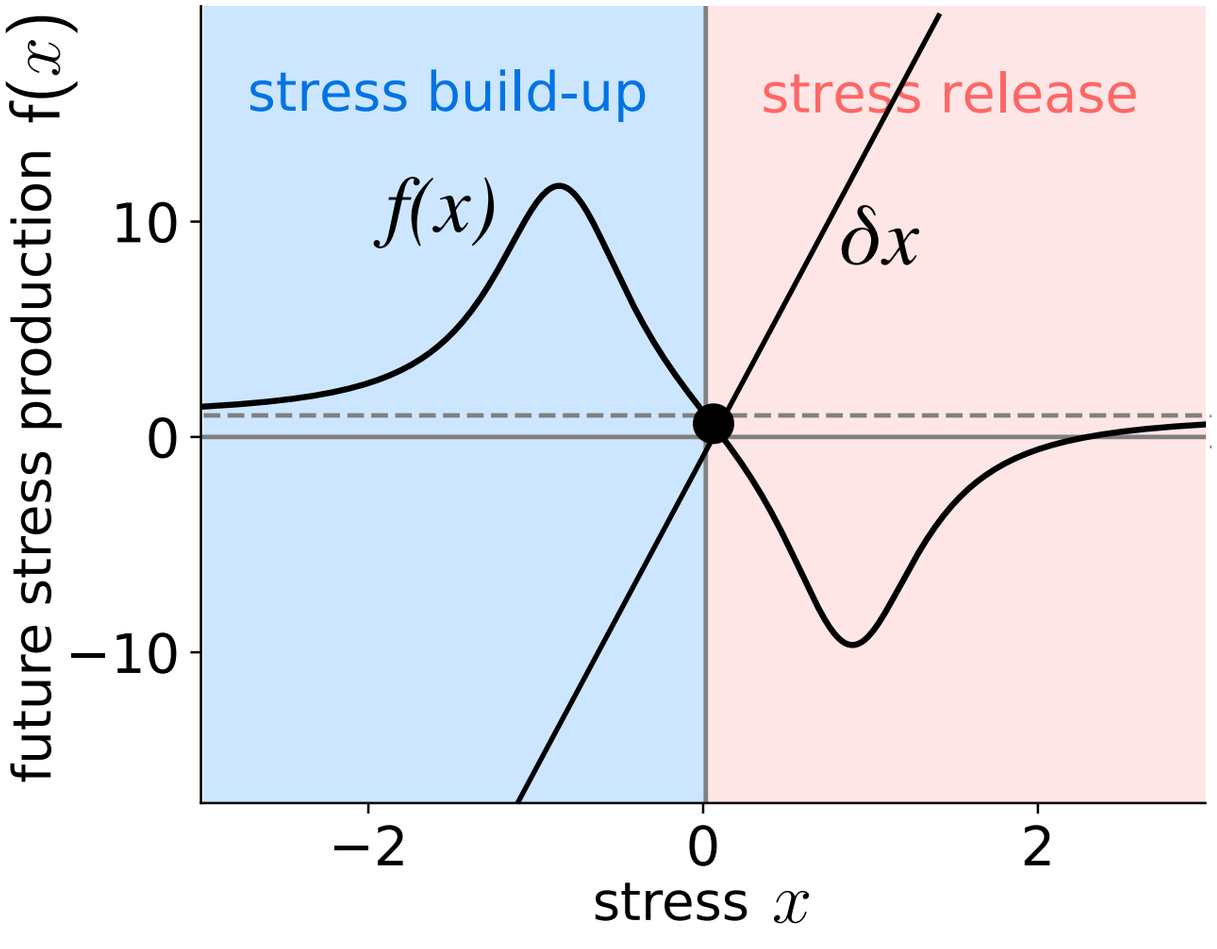
stress production



The fixed point becomes unstable for strong feedback

fixed point:

$$C - \frac{\alpha\, x_s}{1 - x_s^2 + x_s^4} - \delta x_s = 0$$



characteristic equation:

$$J_\tau \exp(-\lambda\,\tau) + J_0 - \lambda = 0$$

$$\lambda \equiv \mu + i\nu$$

instability condition:

$$\mu = 0$$

$$\nu = \sqrt{J_\tau^2 - J_0^2} \approx \sqrt{\alpha^2 - \delta^2}$$

$$\Longrightarrow \alpha > \delta$$

feedback strength

PHYSICAL REVIEW E **69**, 036210 (2004)

Subcritical Hopf bifurcation in dynamical systems described by a scalar nonlinear delay differential equation

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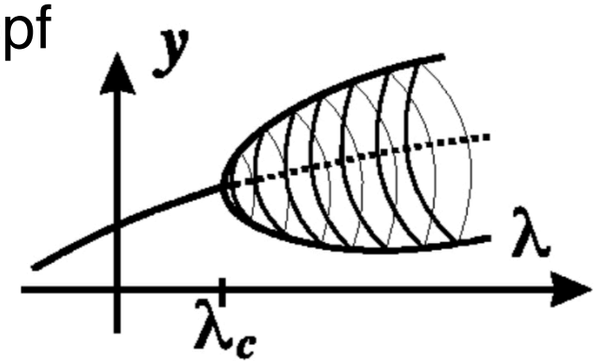
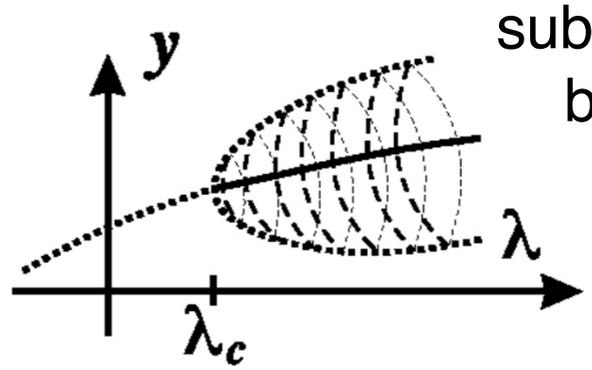
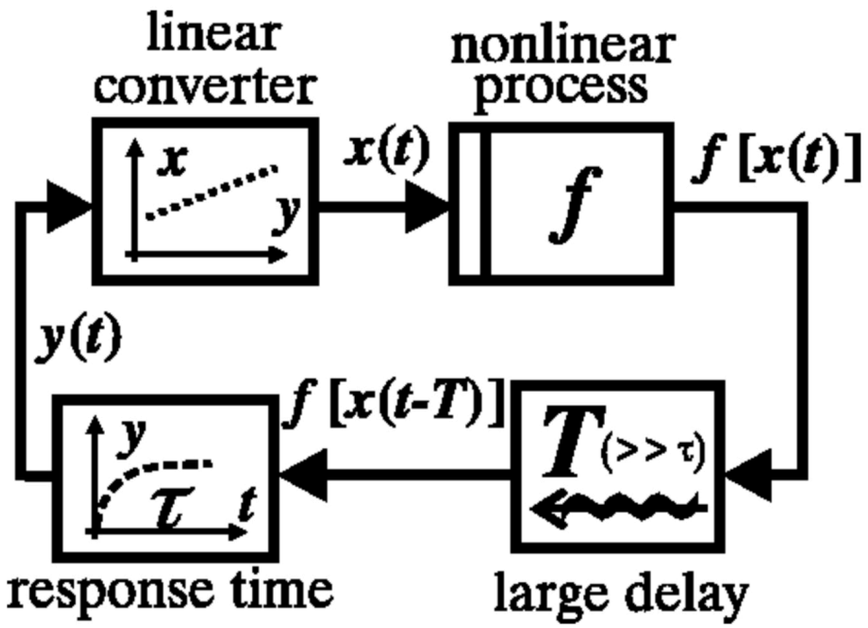
Thomas Erneux
Groupe d'Optique Non Linéaire Théorique, Université Libre de Bruxelles, Campus Plaine, Case Postale 231, 1050 Bruxelles, Belgium

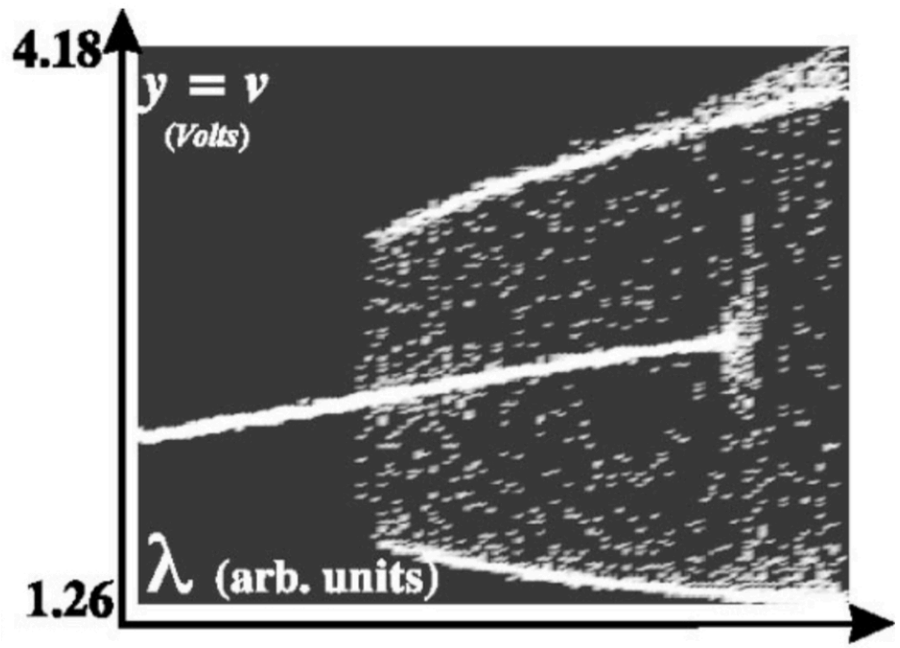
supercritical Hopf bifurcation





subcritical Hopf bifurcation





The system exhibits a Hopf bifurcation

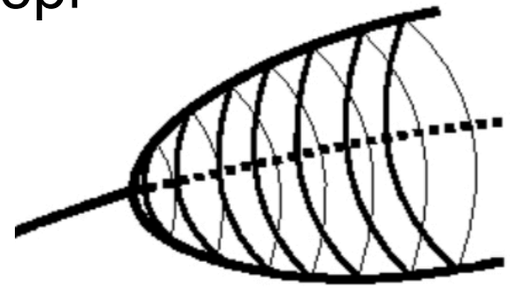
$$\frac{1}{\delta}\frac{dx}{dt} = \widetilde{f}(x(t-\tau)) - x(t) \quad \overset{\text{large } \delta}{\Longrightarrow} \quad x_{n+1} = \widetilde{f}(x_n)$$

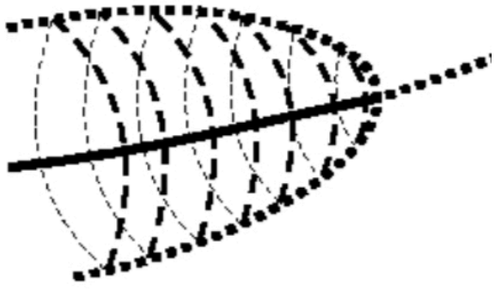
$$\widetilde{f}(x) = \widetilde{C} - \frac{\widetilde{\alpha}x}{1 - x^2 + x^4}, \quad \text{with } \widetilde{C} = \frac{C}{\delta}, \ \widetilde{\alpha} = \frac{\alpha}{\delta}$$

Hopf bifurcation condition: $\widetilde{f}_x\left(\widetilde{\alpha}_c, \widetilde{x}_s(\widetilde{\alpha}_c)\right) = -1$

In our case: $\widetilde{f}_x(\widetilde{\alpha}_c, \widetilde{x}_s) = -\widetilde{\alpha}_c = -1$ ➡ Hopf bifurcation

supercritical Hopf bifurcation





subcritical Hopf bifurcation

The Hopf bifurcation is subcritical

$$\frac{1}{\delta}\frac{dx}{dt} = \widetilde{f}(x(t-\tau)) - x(t) \overset{\text{large } \delta}{\Longrightarrow} x_{n+1} = \widetilde{f}(x_n)$$

Limit cycle: $x_n = \widetilde{f}(\widetilde{f}(x_n)) \implies x_n = \widetilde{x}_s + \sqrt{-a\Lambda/b}$

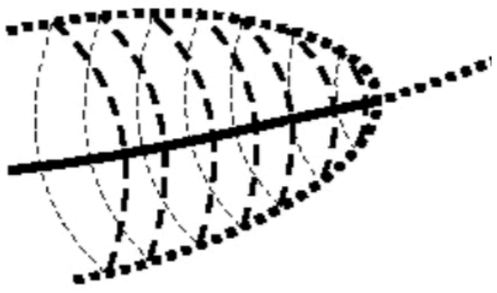
with $a = -f_{xx} f_\alpha - 2\, f_{x\alpha}$

$$b = -\frac{1}{2}\widetilde{f}_{xx}^2 - \frac{1}{3}\widetilde{f}_{xxx}$$

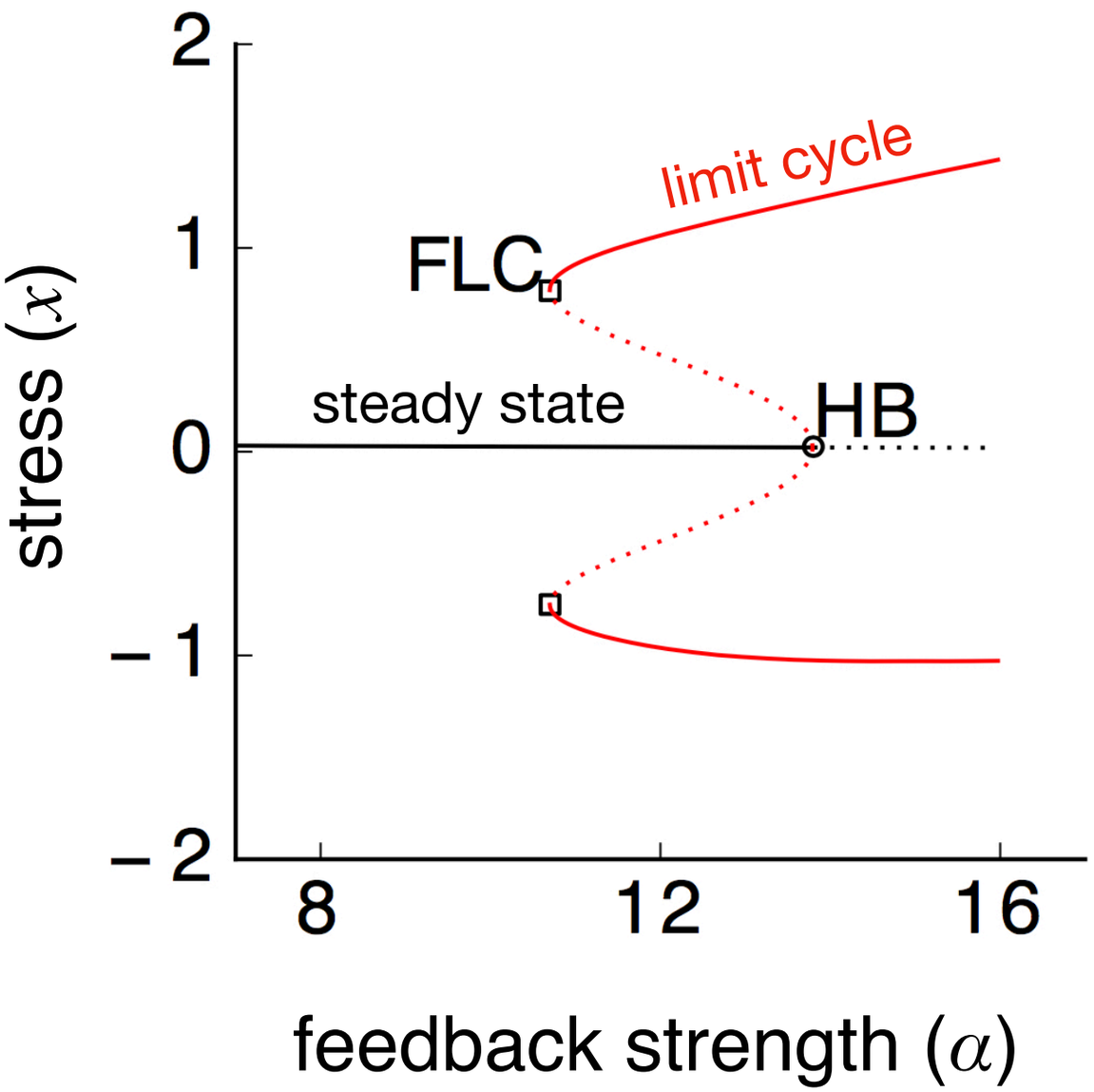
$$\Lambda = \widetilde{\alpha} - \widetilde{\alpha}_c$$

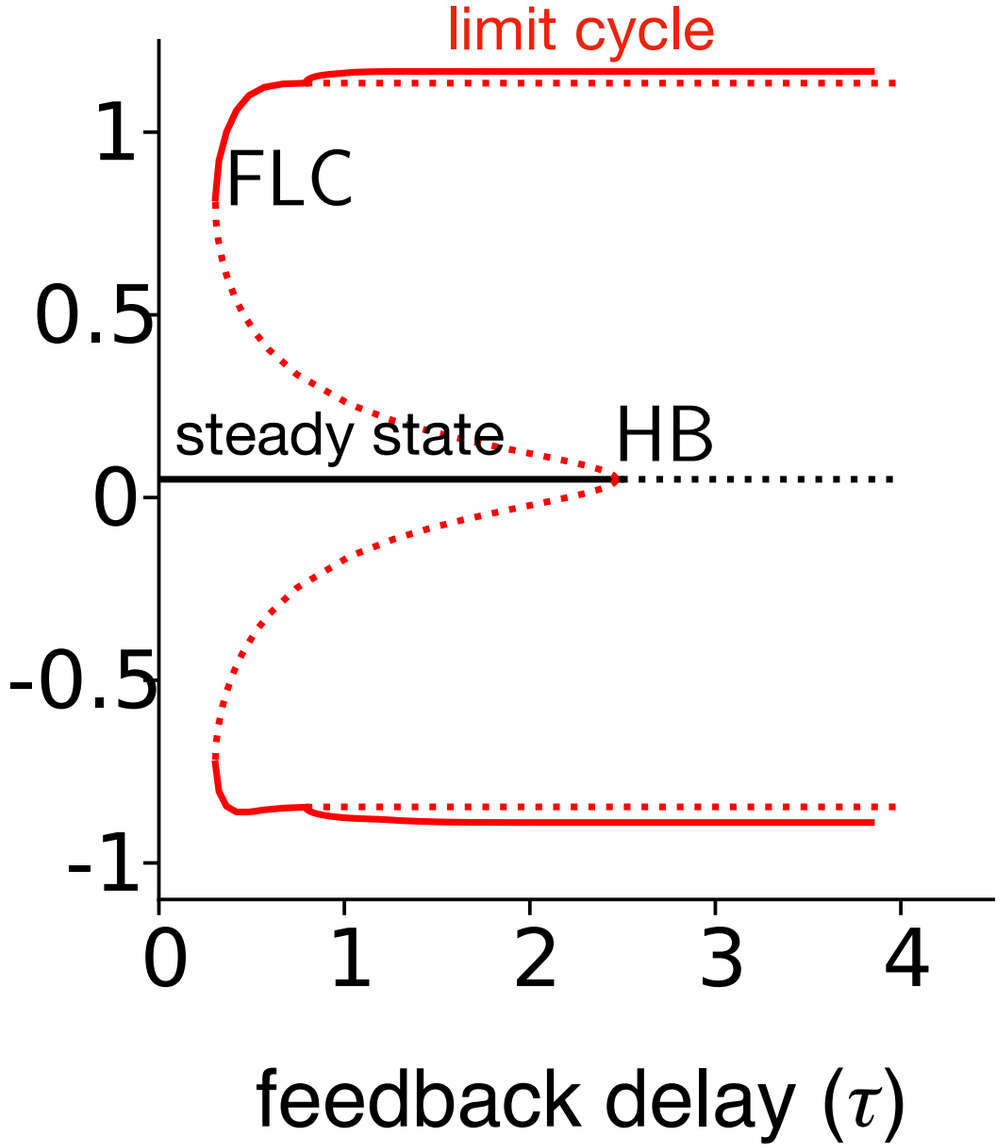
In our case: $a > 0,\ b > 0$

subcritical Hopf bifurcation



The Hopf bifurcation is subcritical

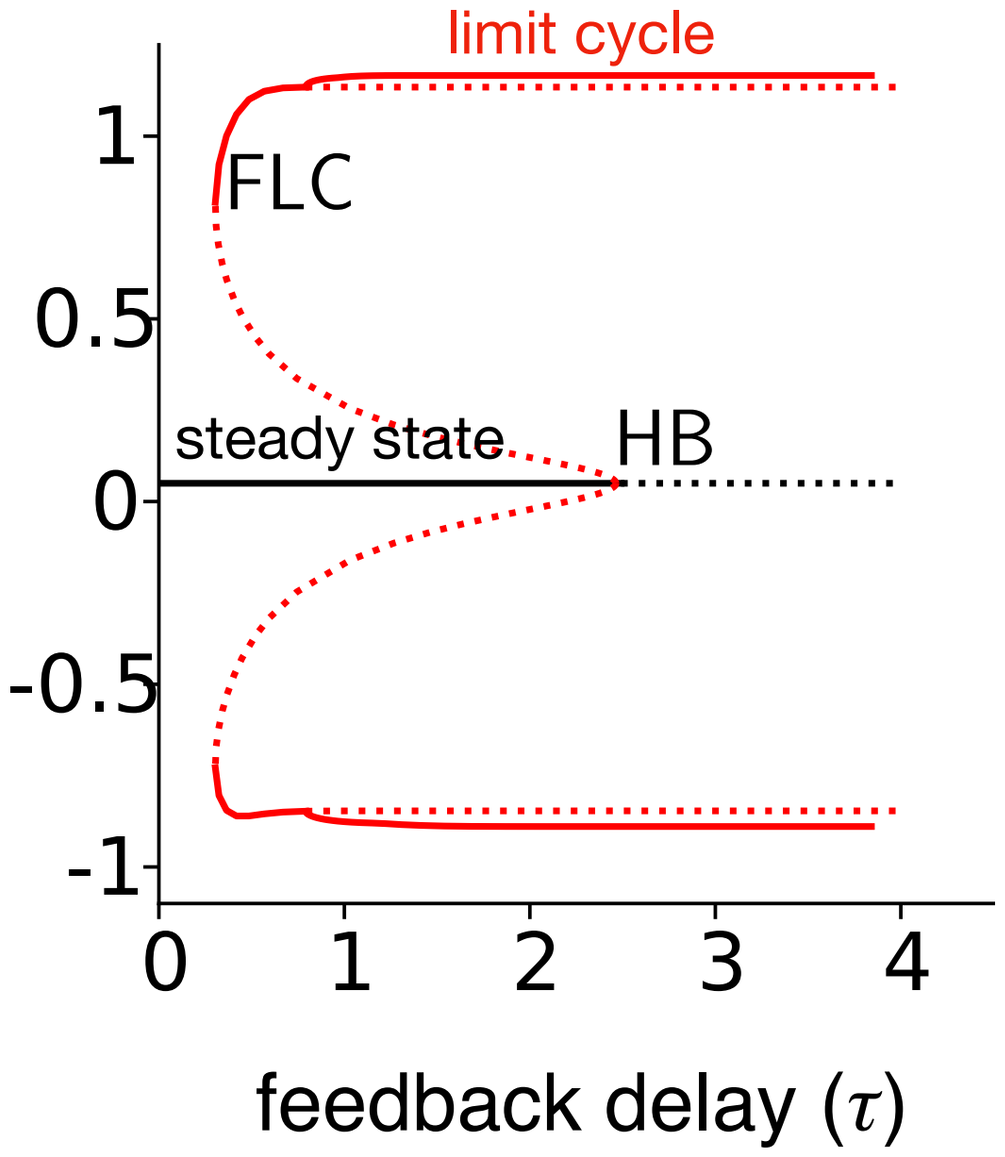




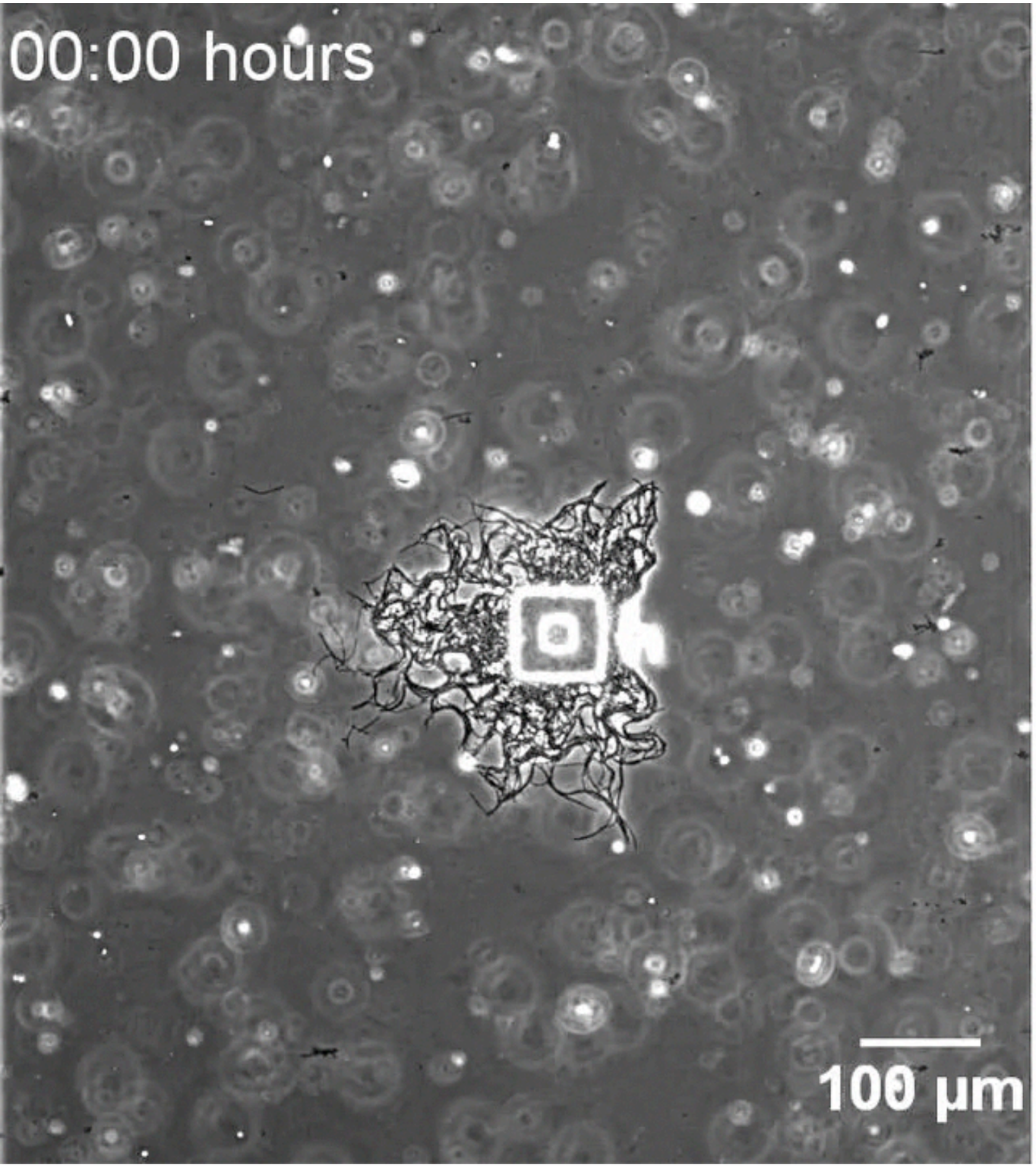
Consequences

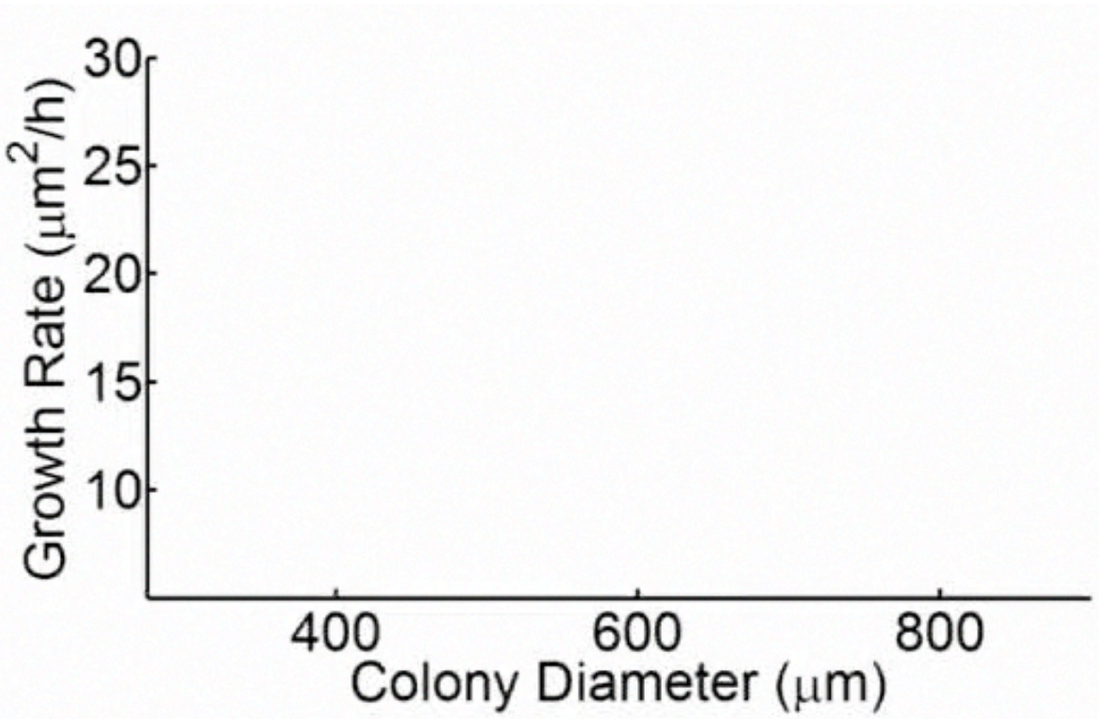
1. Oscillations start when the biofilm reaches a critical size

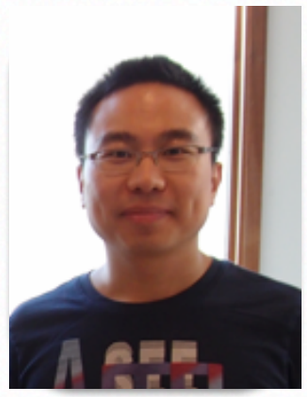
2. Oscillations can be triggered before the critical size by perturbing the system



1. Oscillations start when the biofilm reaches a critical size





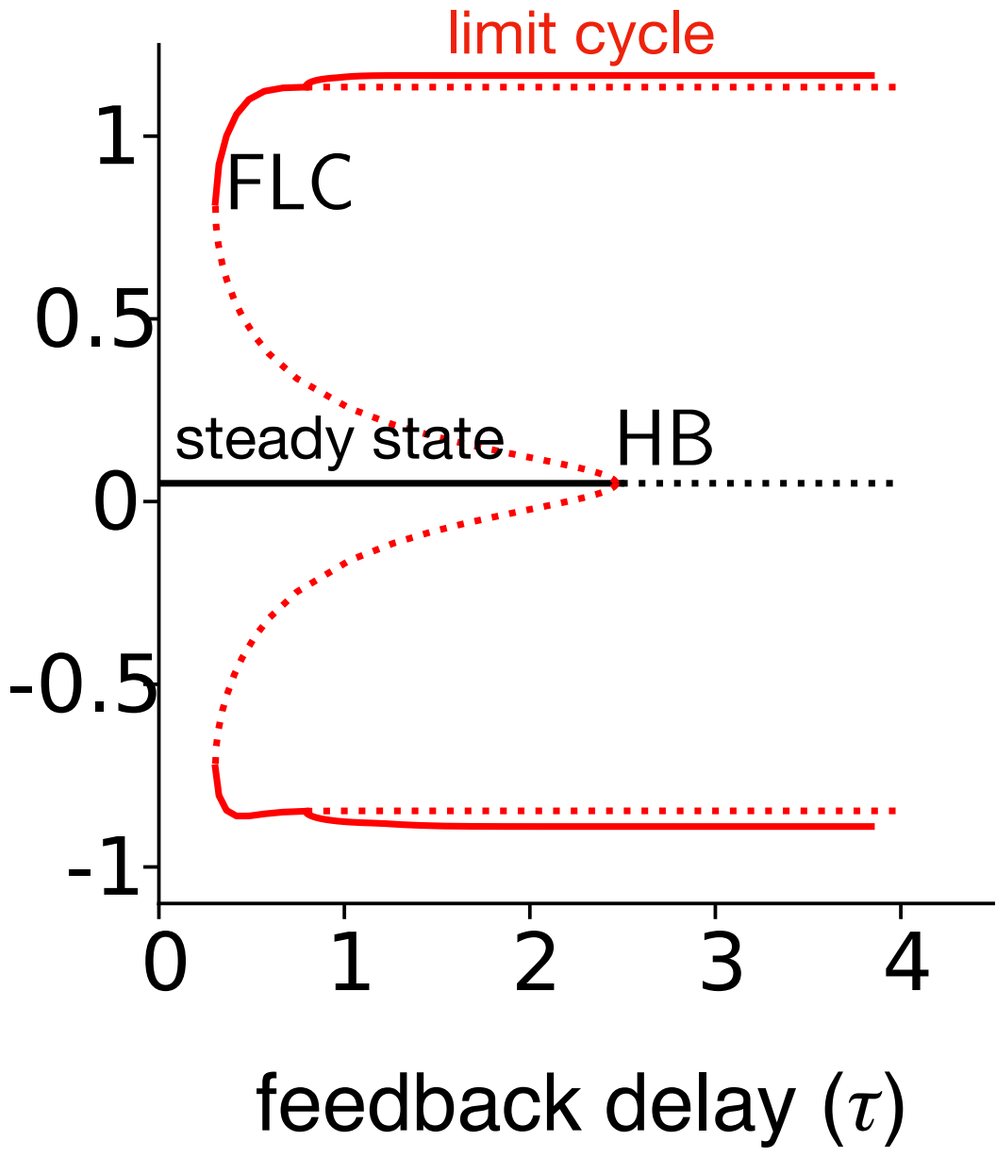


Jintao Liu

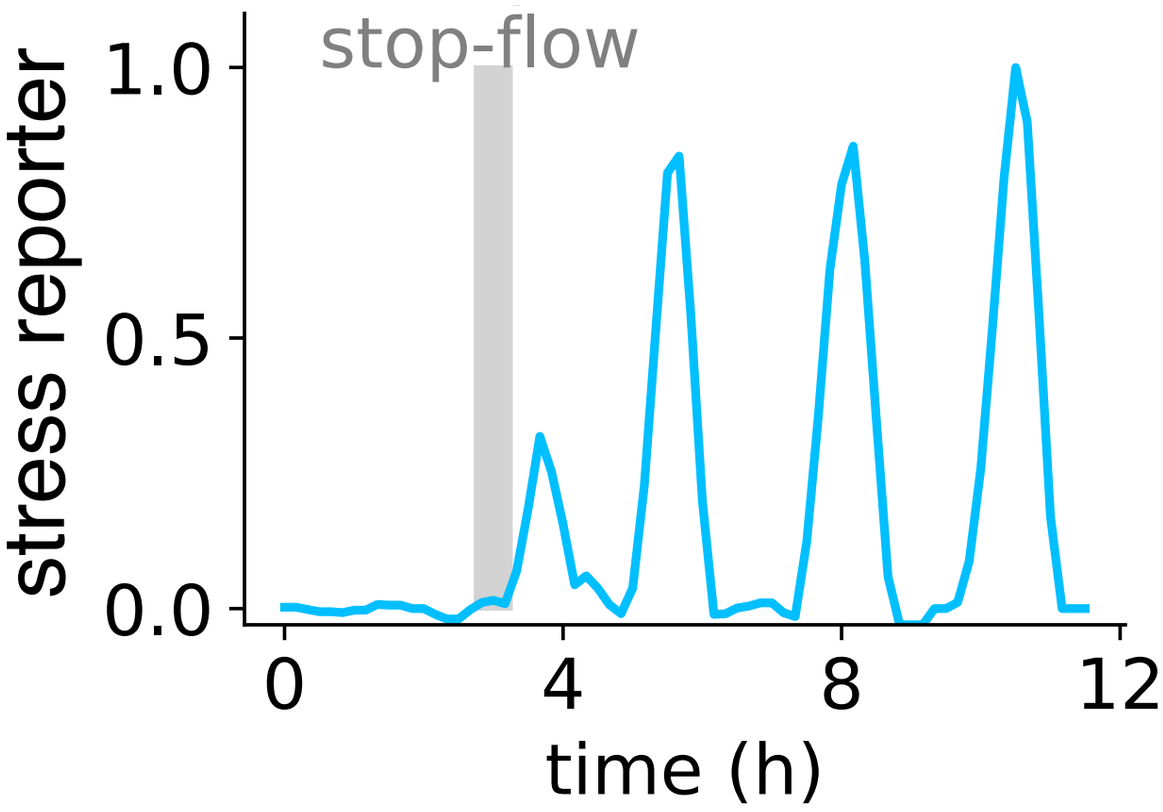
Consequences

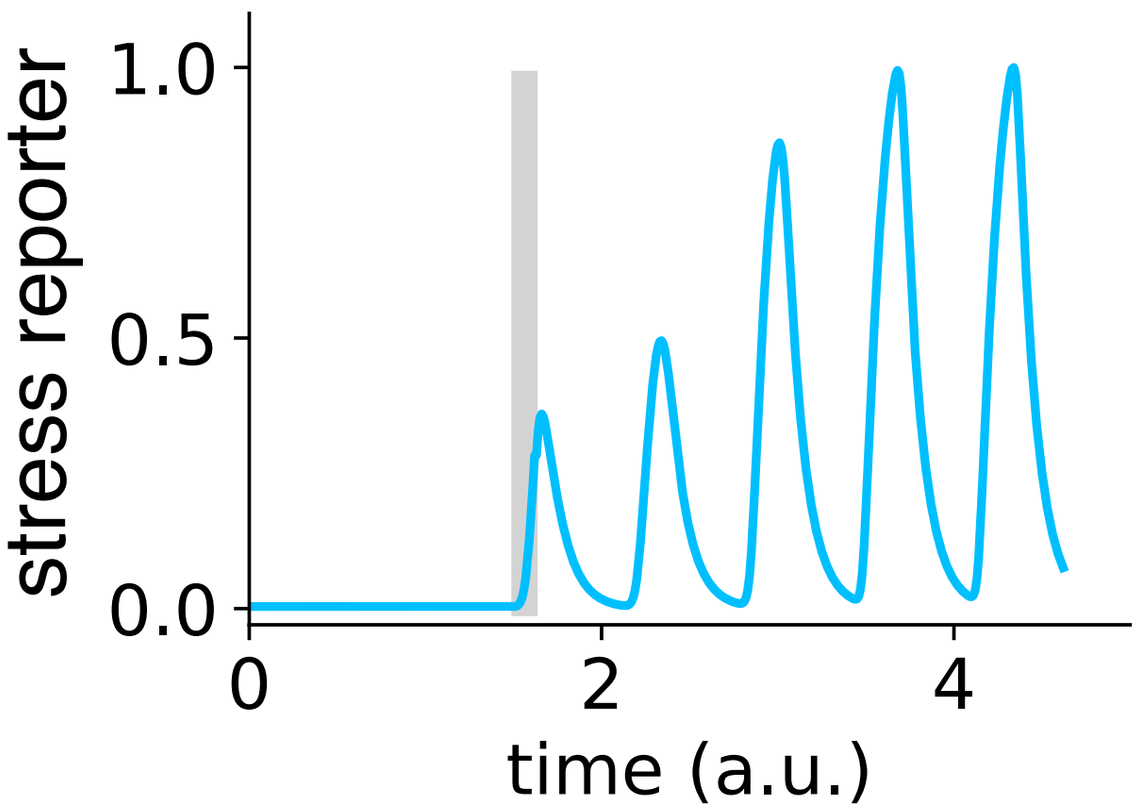
1. Oscillations start when the biofilm reaches a critical size

2. Oscillations can be triggered before the critical size by perturbing the system



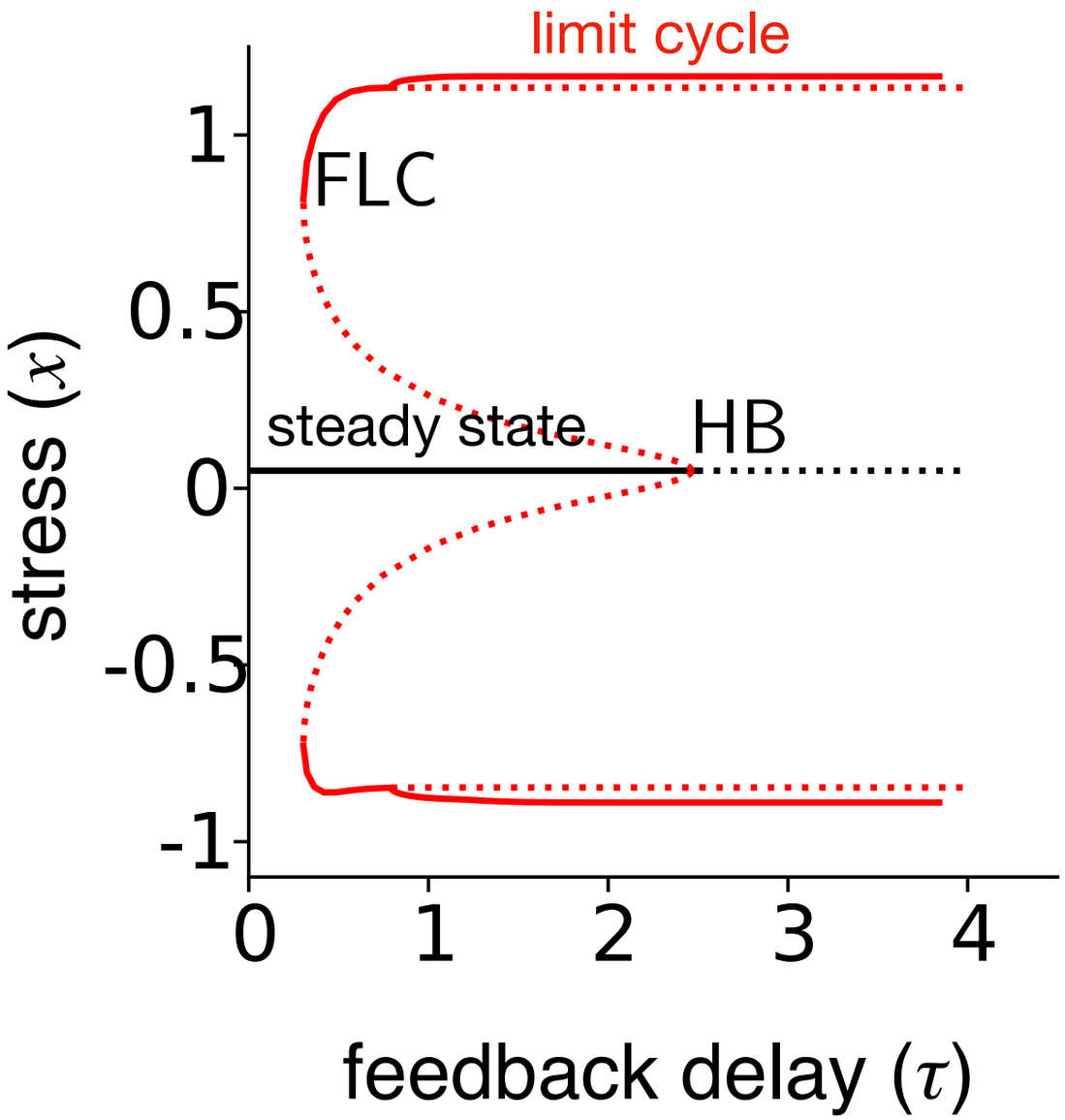
2. Oscillations can be triggered before the critical size



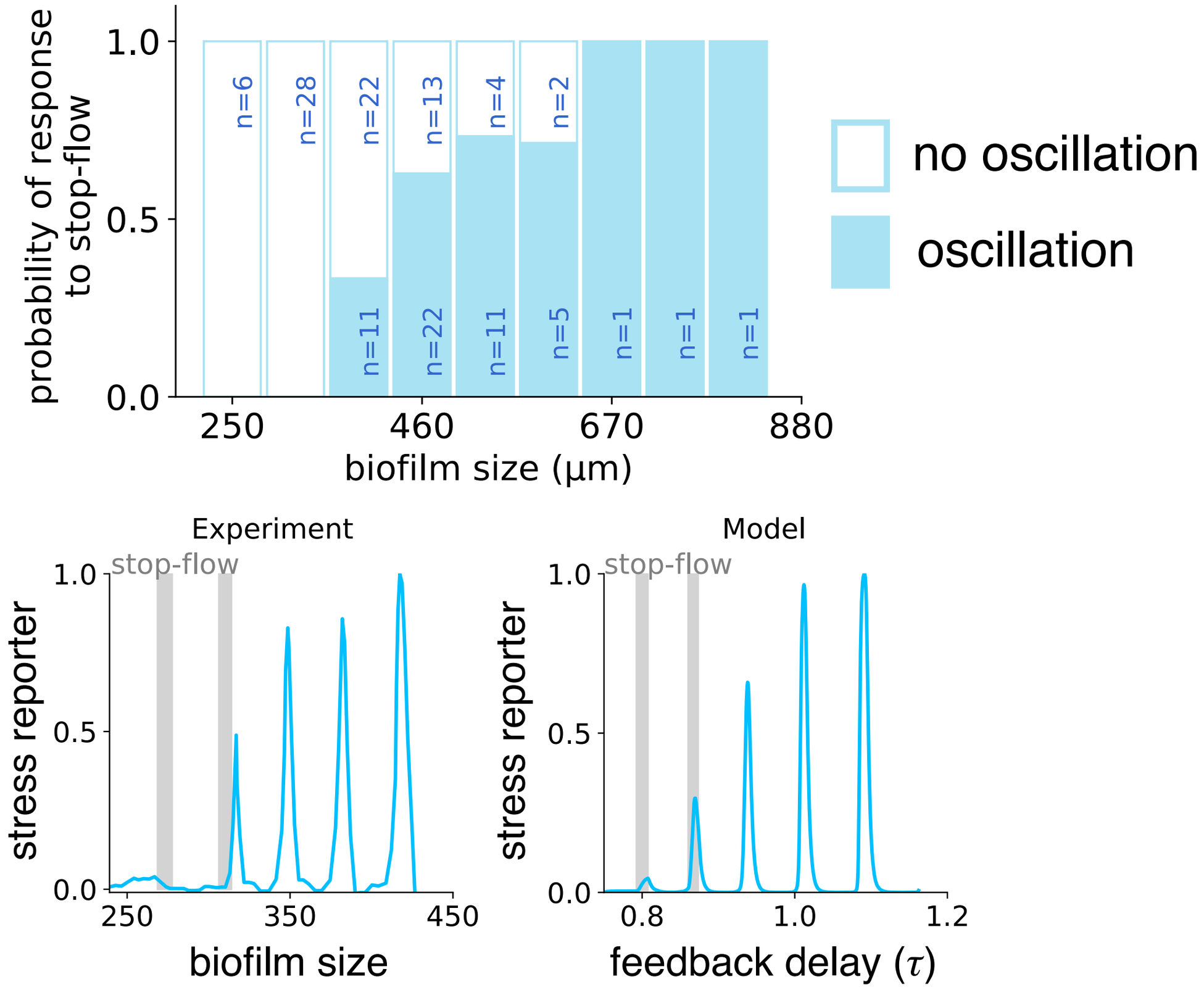


Martinez-Corral et al
bioRxiv (2018)

As the biofilm size increases, it's easier to trigger oscillations

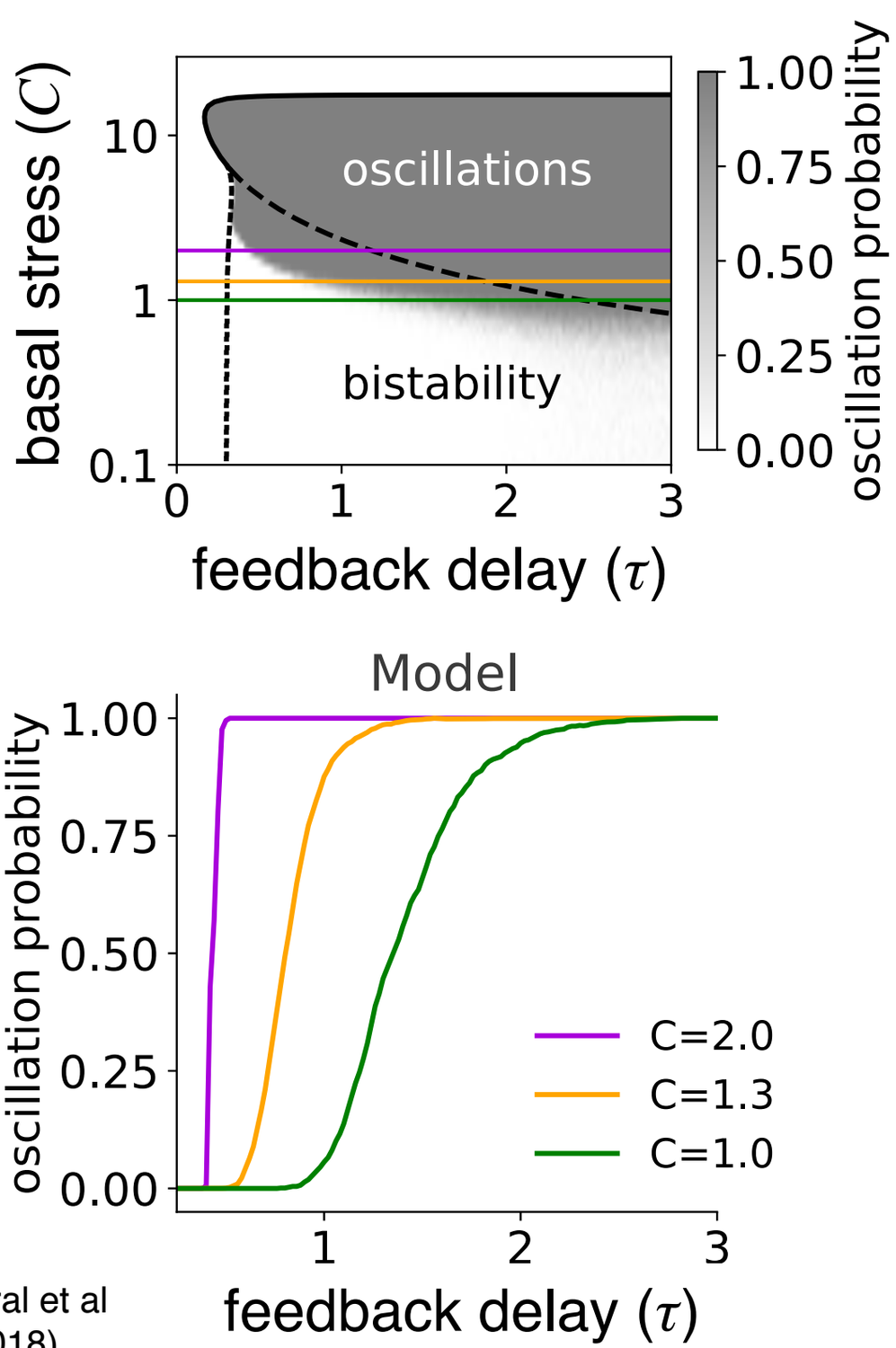


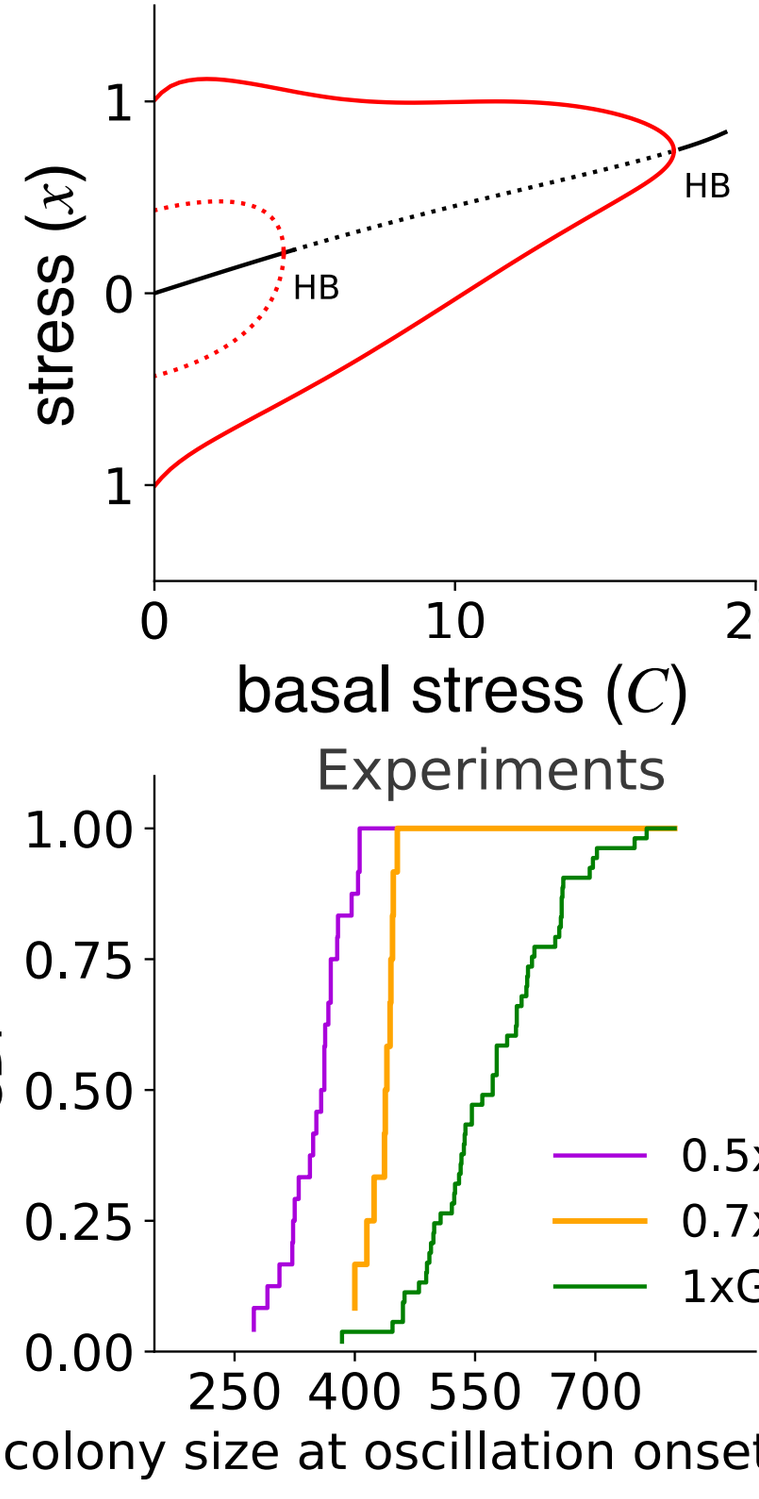
Experimental validation



Martinez-Corral et al
bioRxiv (2018)

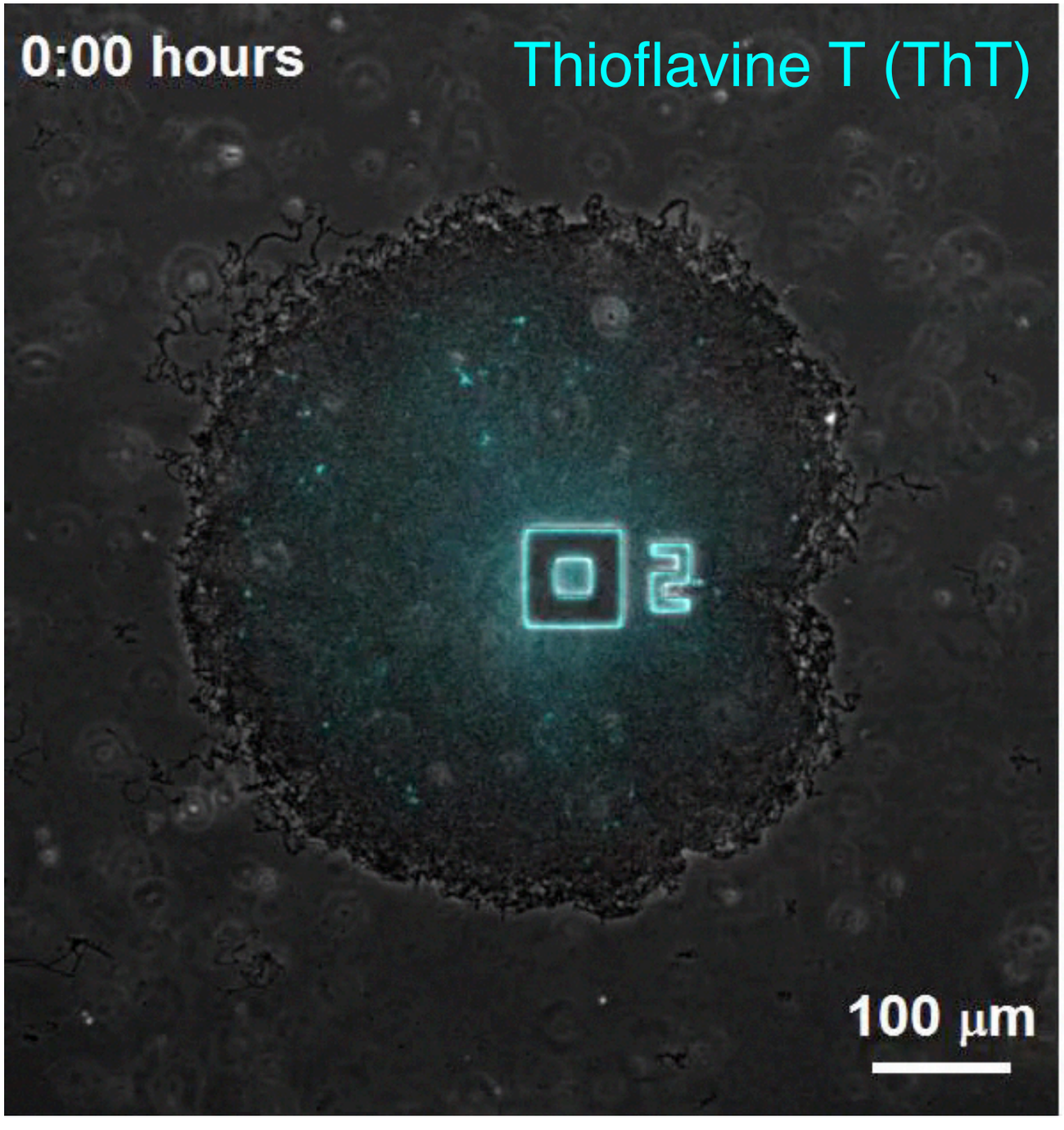
Experimental validation

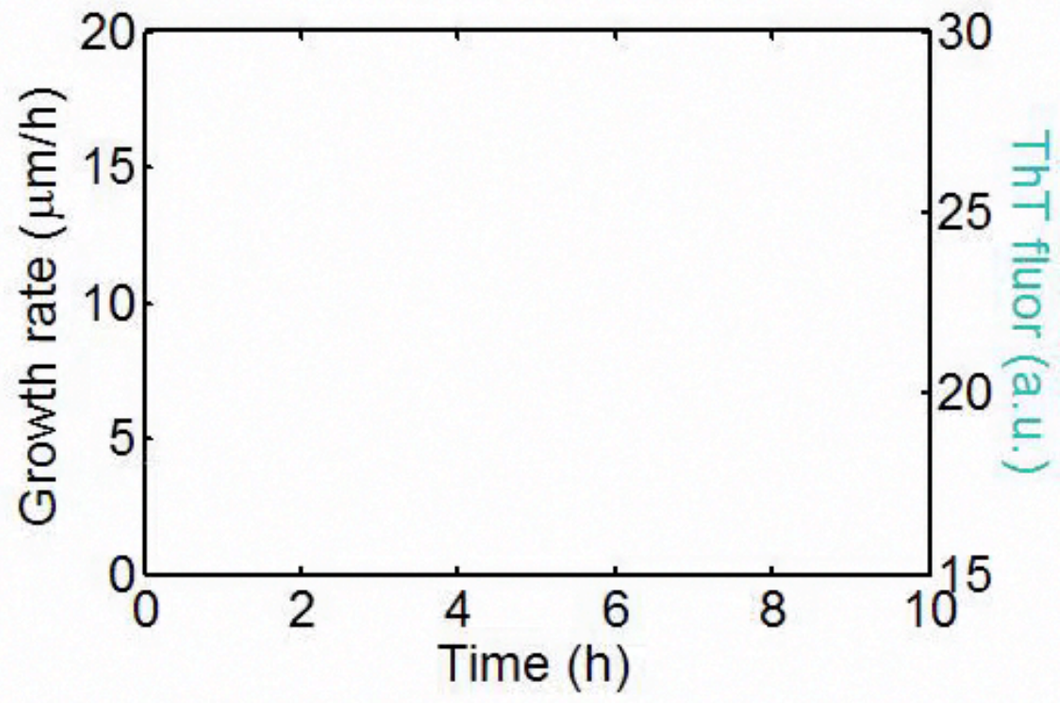




Martinez-Corral et al
bioRxiv (2018)

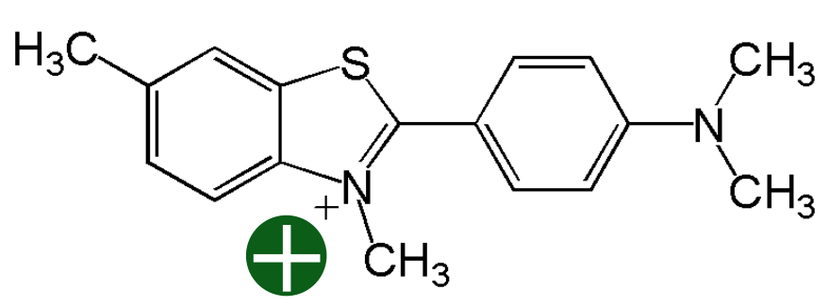
Stress oscillations





Arthur Prindle

ThT is positively charged and cells are negatively polarized



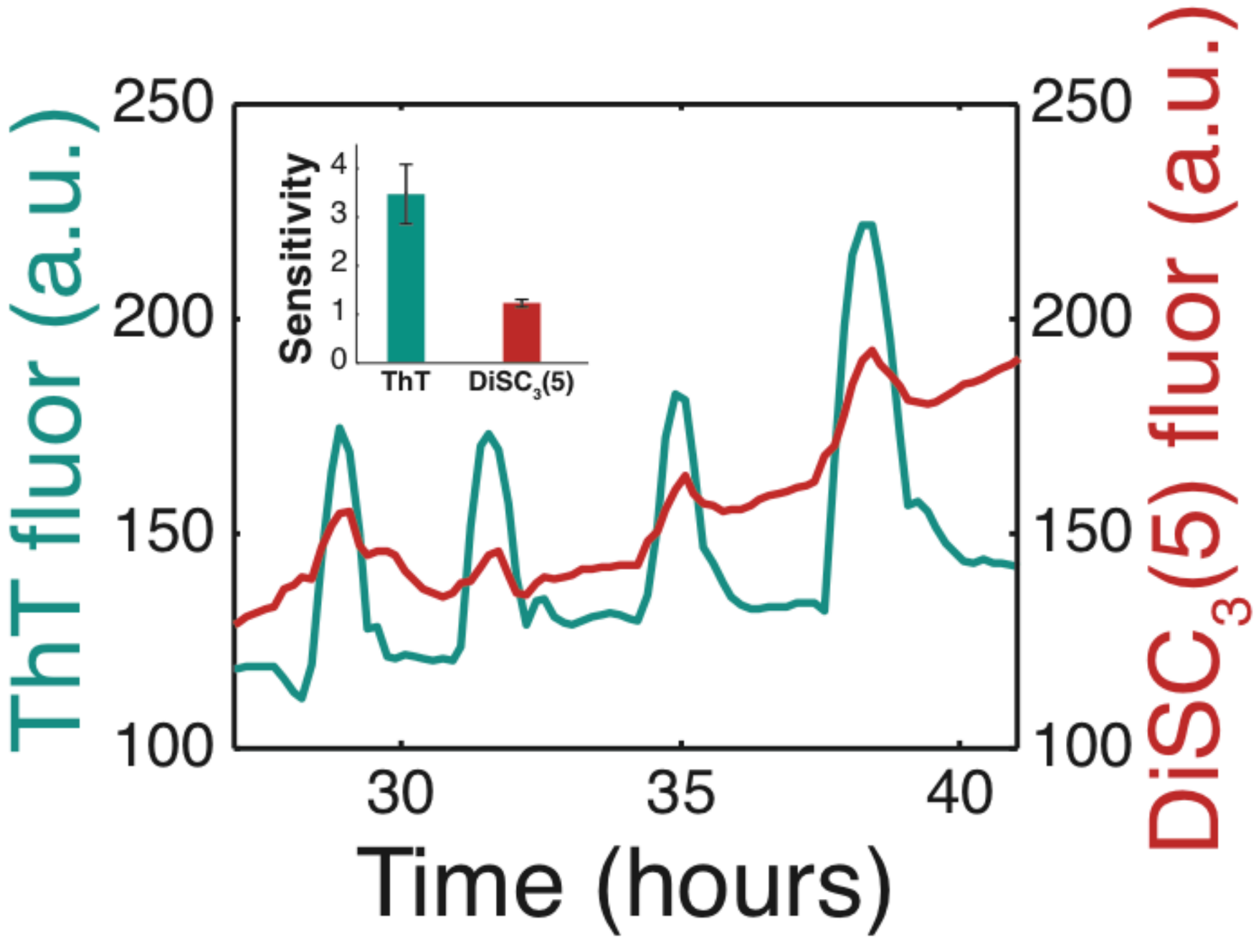
Thioflavine T
(ThT)

membrane potential ~
-150 mV

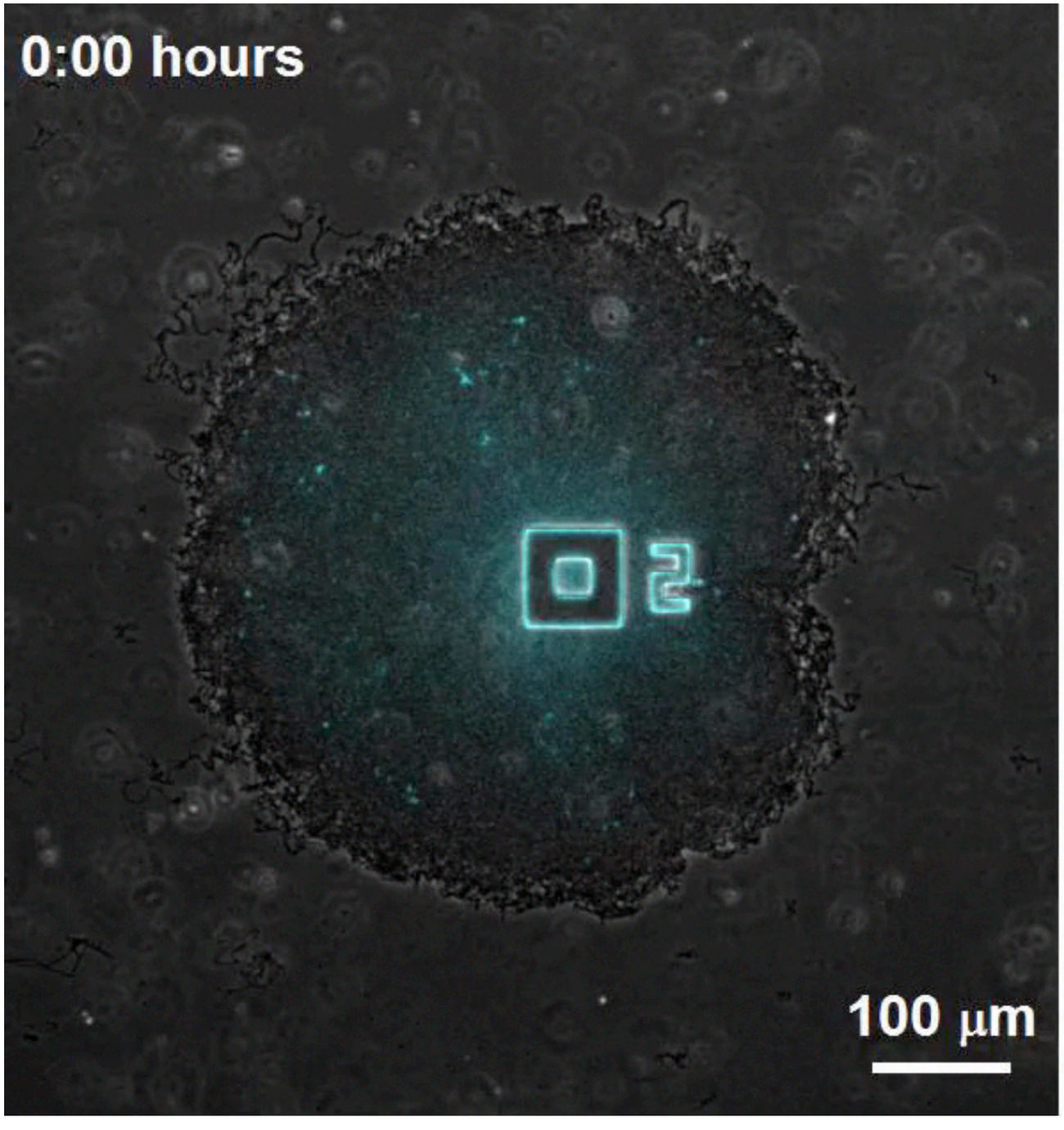
(intracellular ThT
signal is **high** when
cell is hyperpolarized)

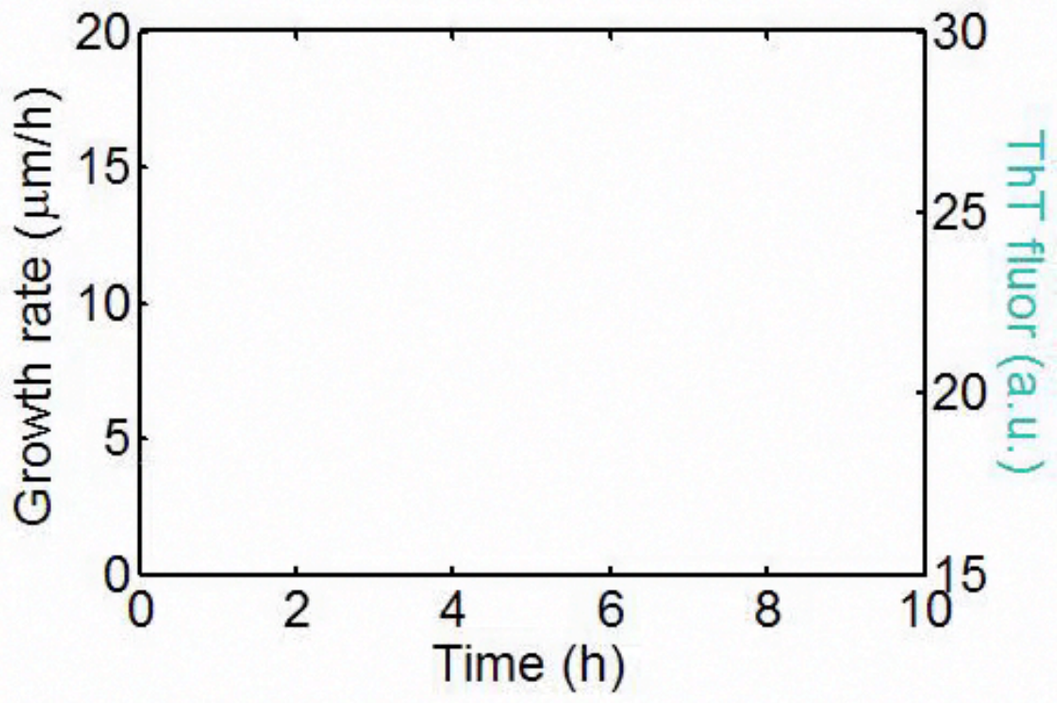
cytoplasm

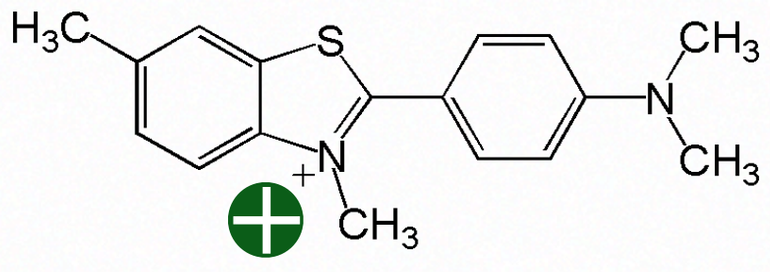
Comparison with a standard voltage-sensing dye



ThT oscillations reflect membrane potential oscillations



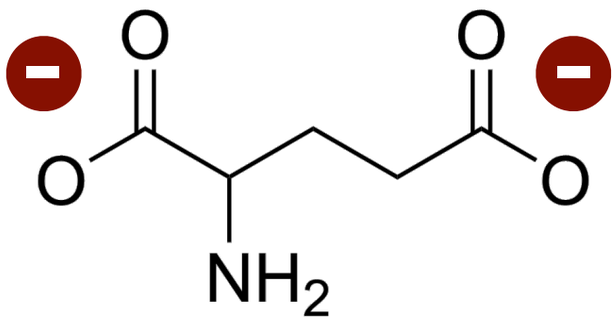


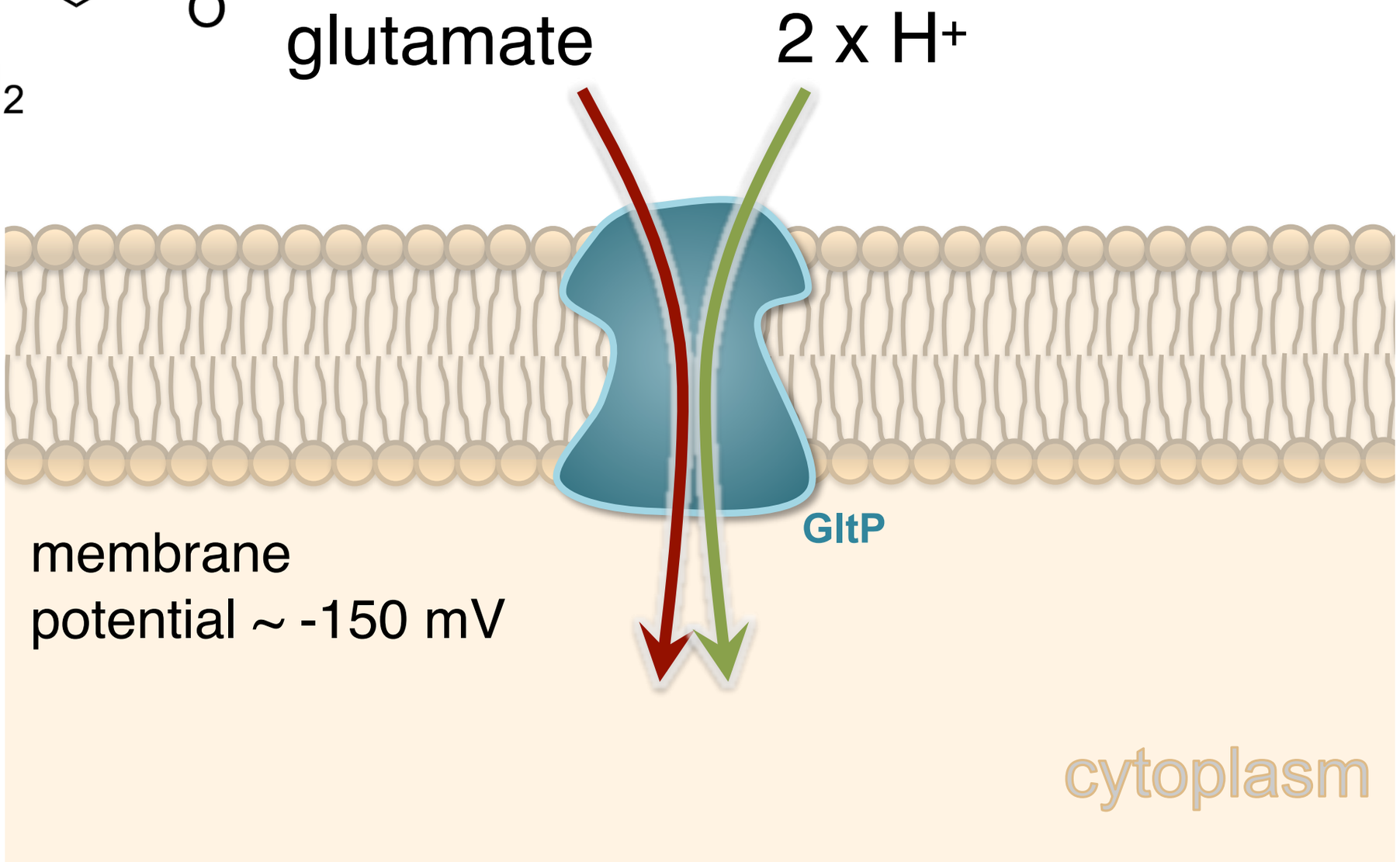


Thioflavine T (ThT)

(high when cell is hyperpolarized)

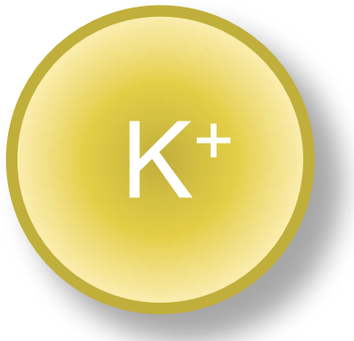
Membrane potential modulates nutrient uptake



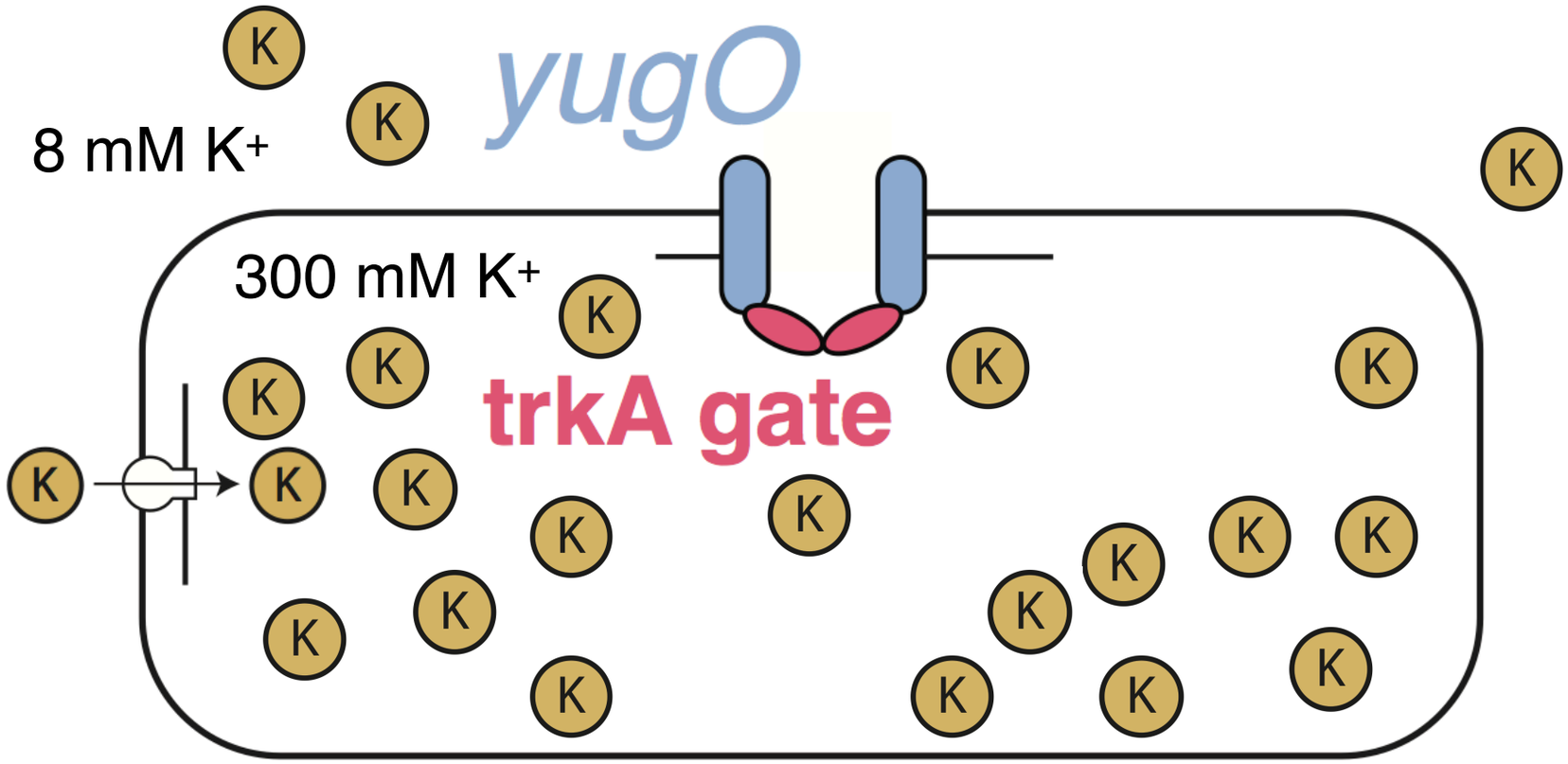


→ glutamate uptake is increased if the cell hyperpolarizes

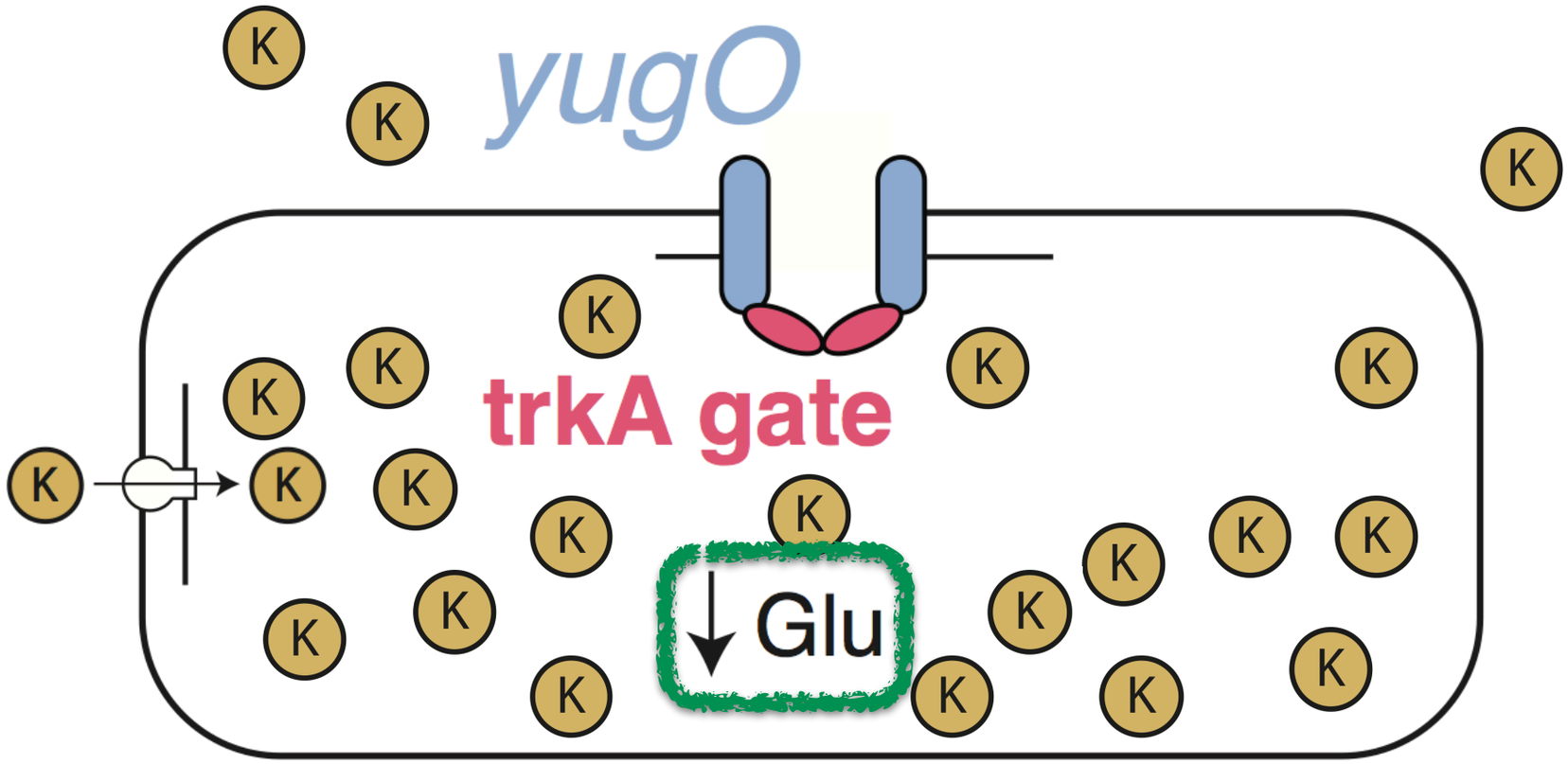
Potassium is involved in the membrane potential oscillations



Potassium is concentrated inside the cell

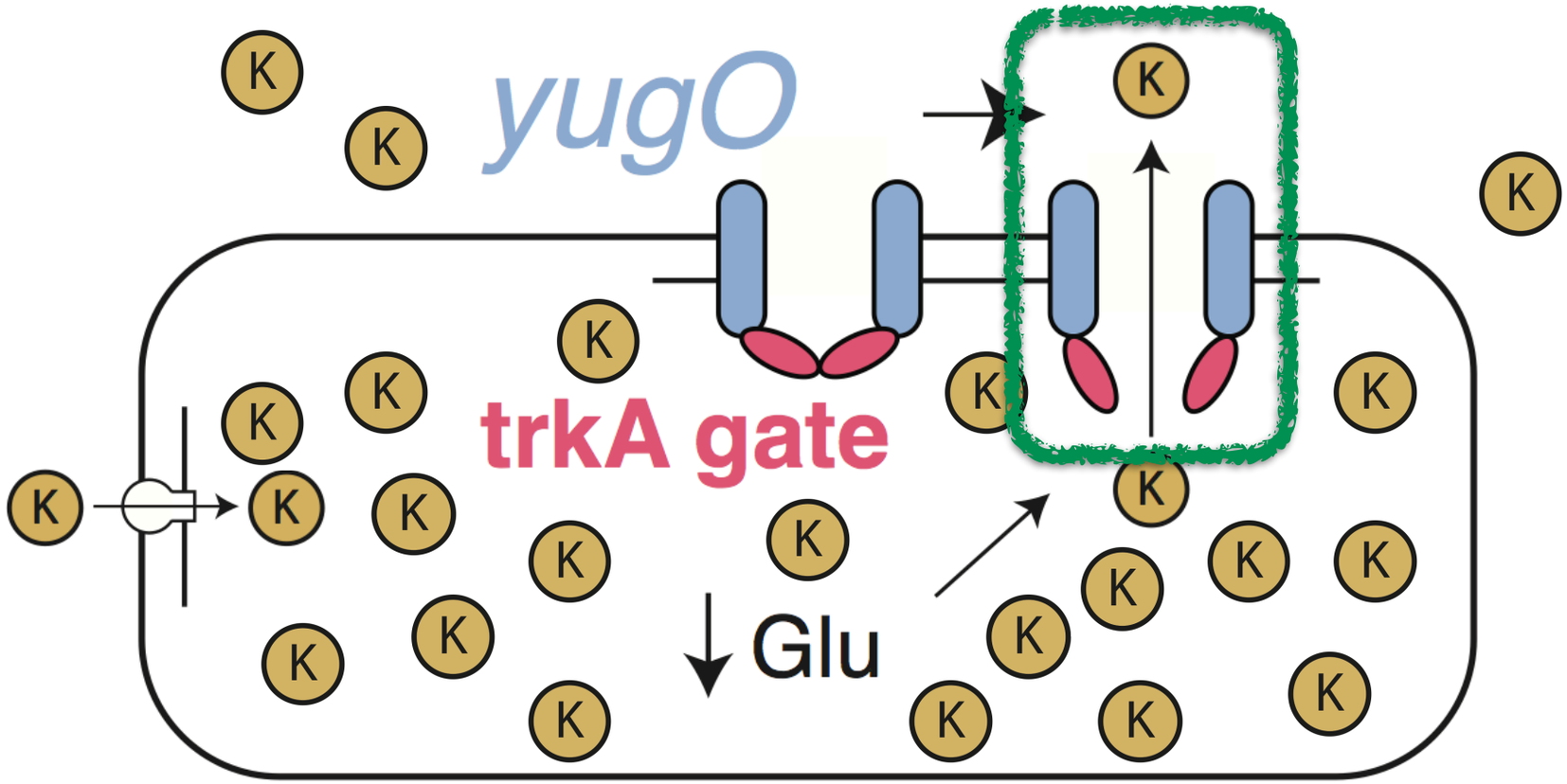


Potassium is released via a stress-gated ion channel



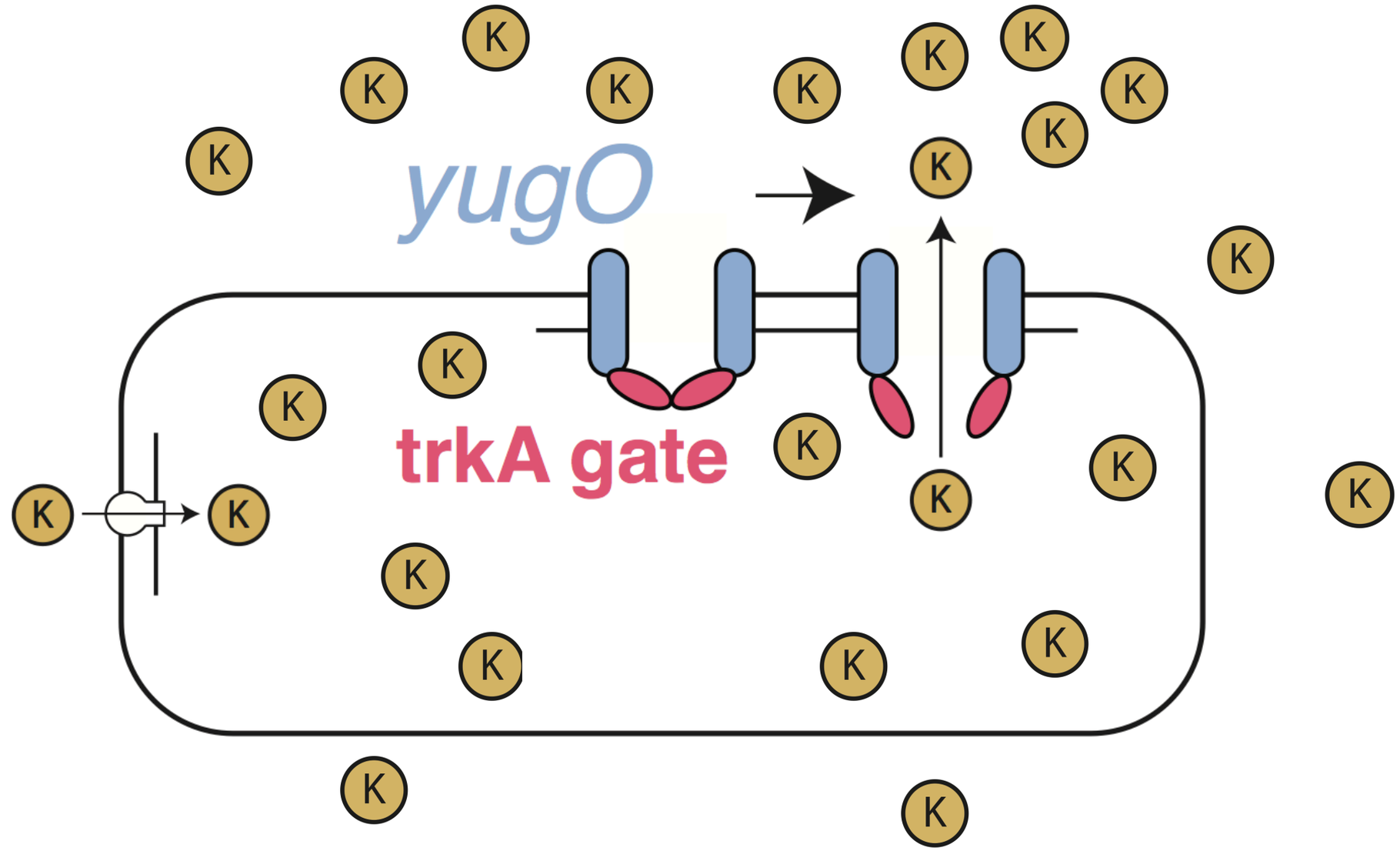
glutamate
decrease

Potassium is released via a stress-gated ion channel



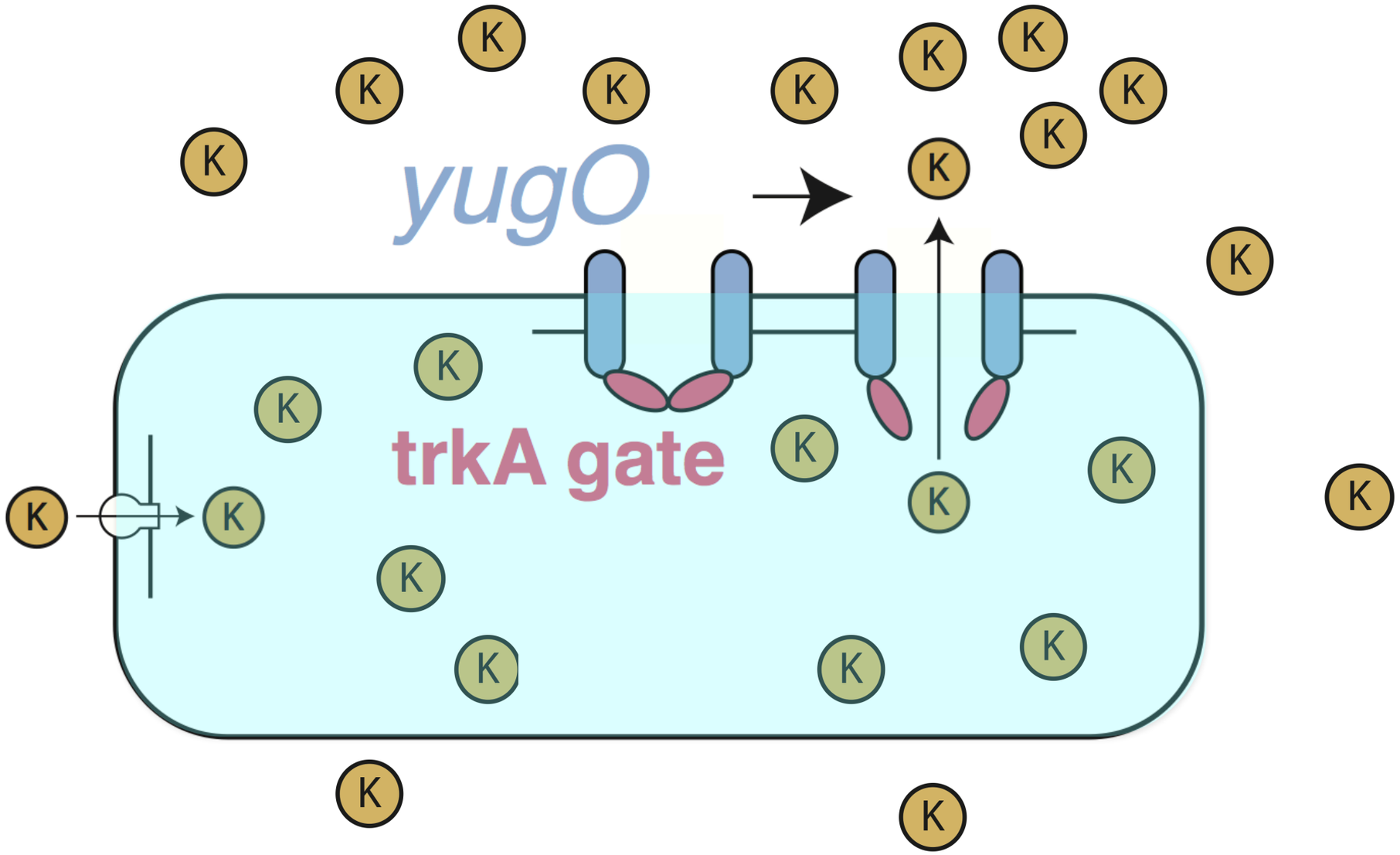
glutamate decrease → channel opens →

Potassium is released via a stress-gated ion channel



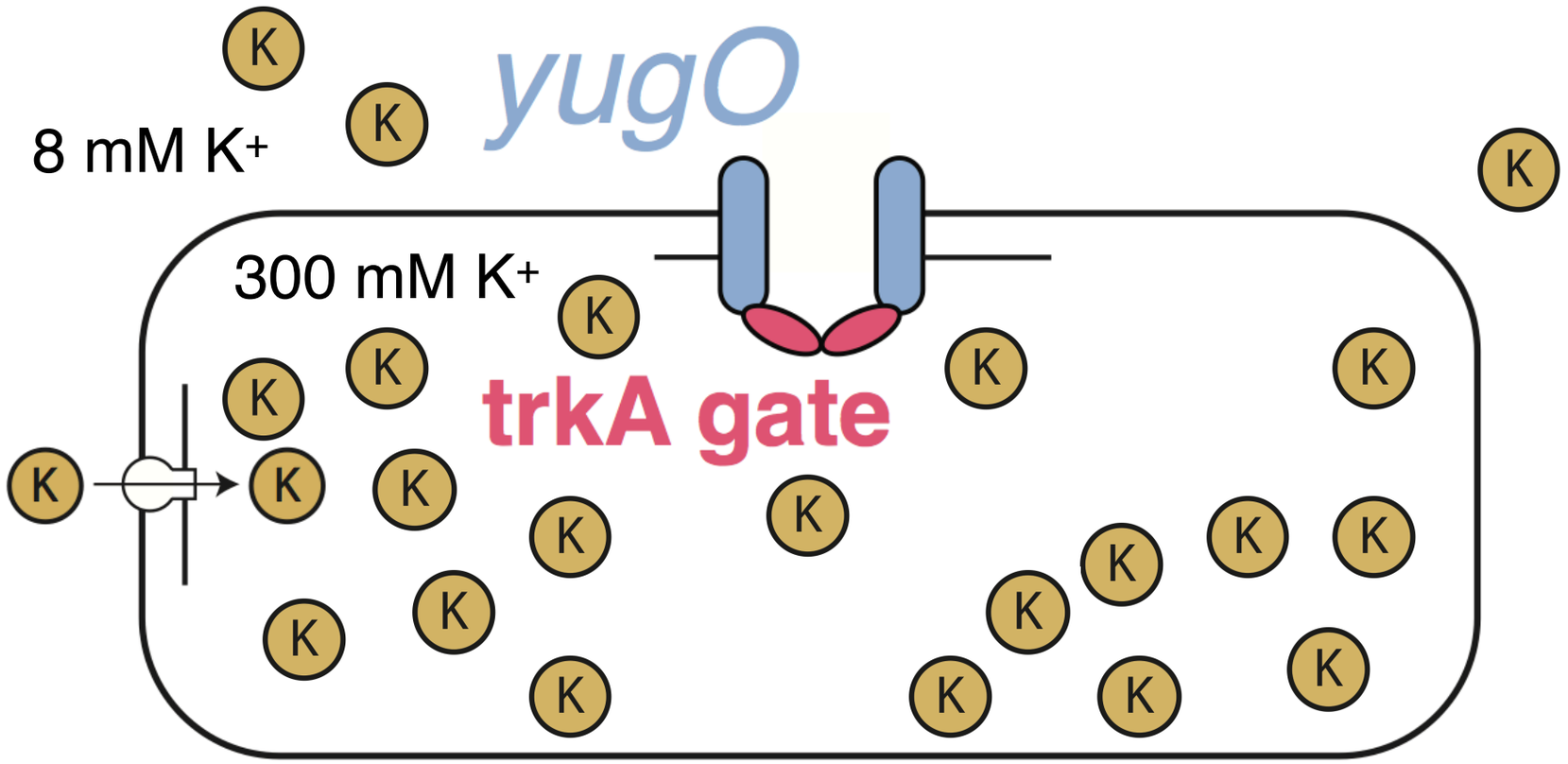
glutamate decrease → channel opens → potassium released →

Potassium release hyperpolarizes the cell



glutamate decrease → channel opens → potassium released → cell hyperpolarizes → (high ThT)

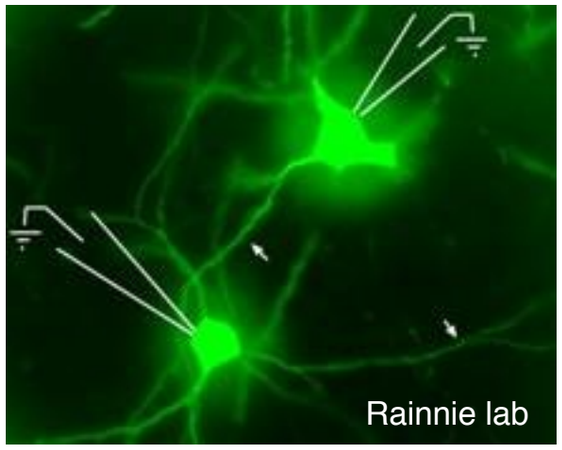
Hyperpolarization allows glutamate uptake again

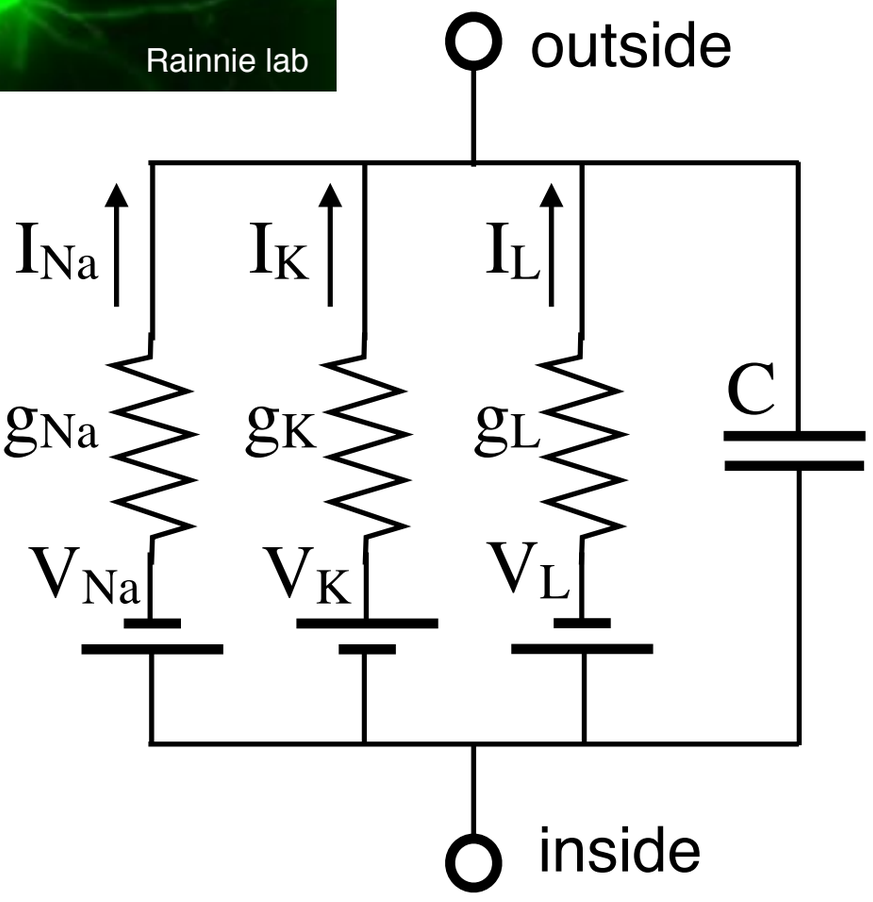


glutamate decrease → channel opens → potassium released → cell hyperpolarizes → glutamate uptake

(high ThT)

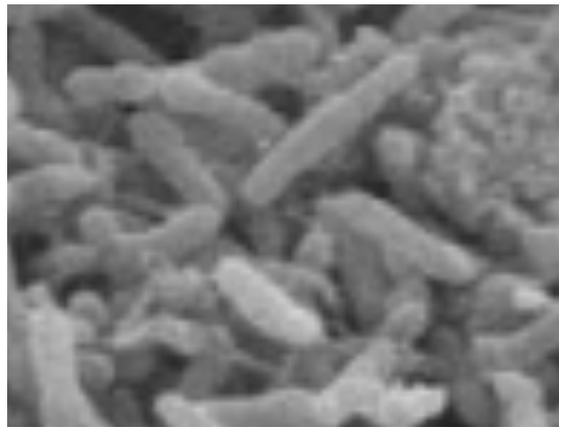
Hodgkin-Huxley model of neuronal electrophysiology

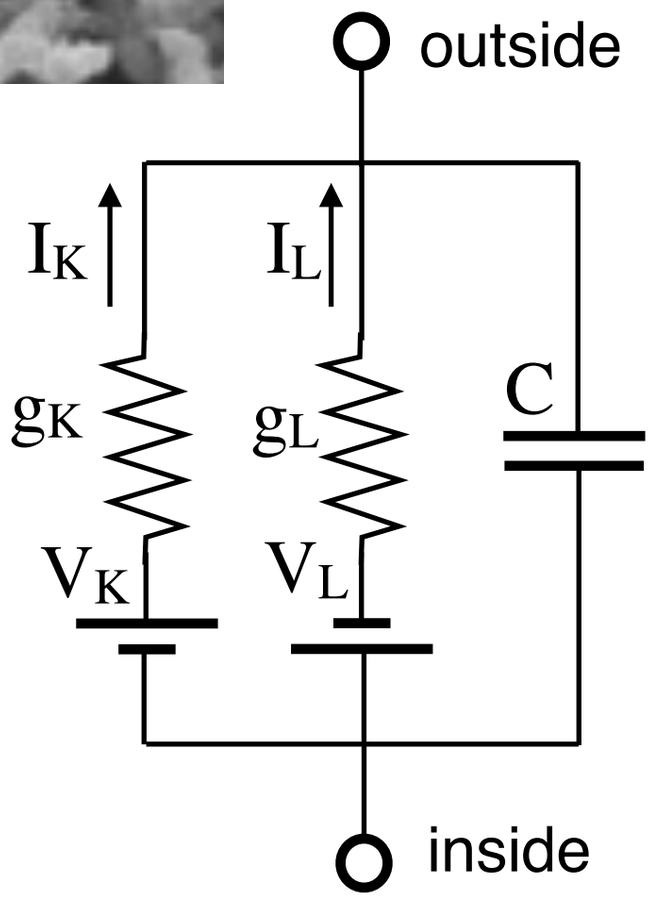




$$C\frac{dV}{dt} = \underbrace{-g_{\mathrm{Na}}m^3h(V-V_{\mathrm{Na}})}_{\text{sodium current}} \underbrace{- g_{\mathrm{K}}n^4(V-V_{\mathrm{K}})}_{\text{potassium current}} \underbrace{- g_{\mathrm{L}}(V-V_{\mathrm{L}})}_{\text{leak current}}$$

K-channel model of bacterial electrophysiology

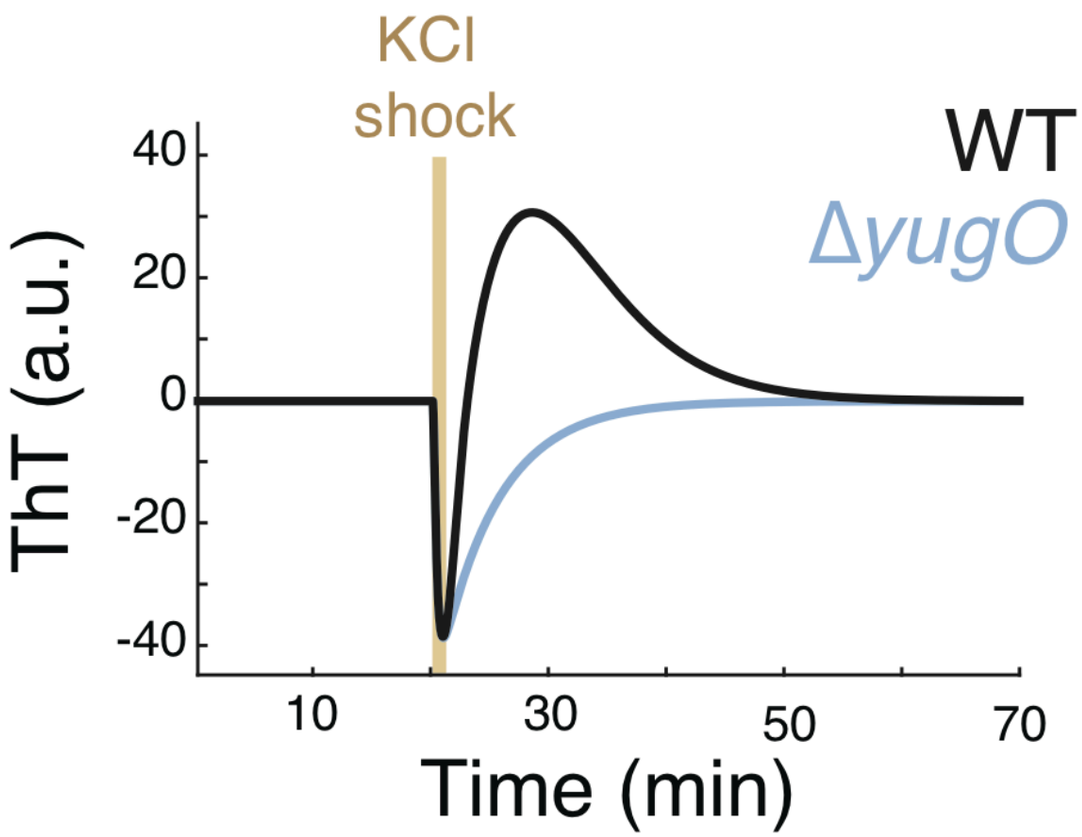




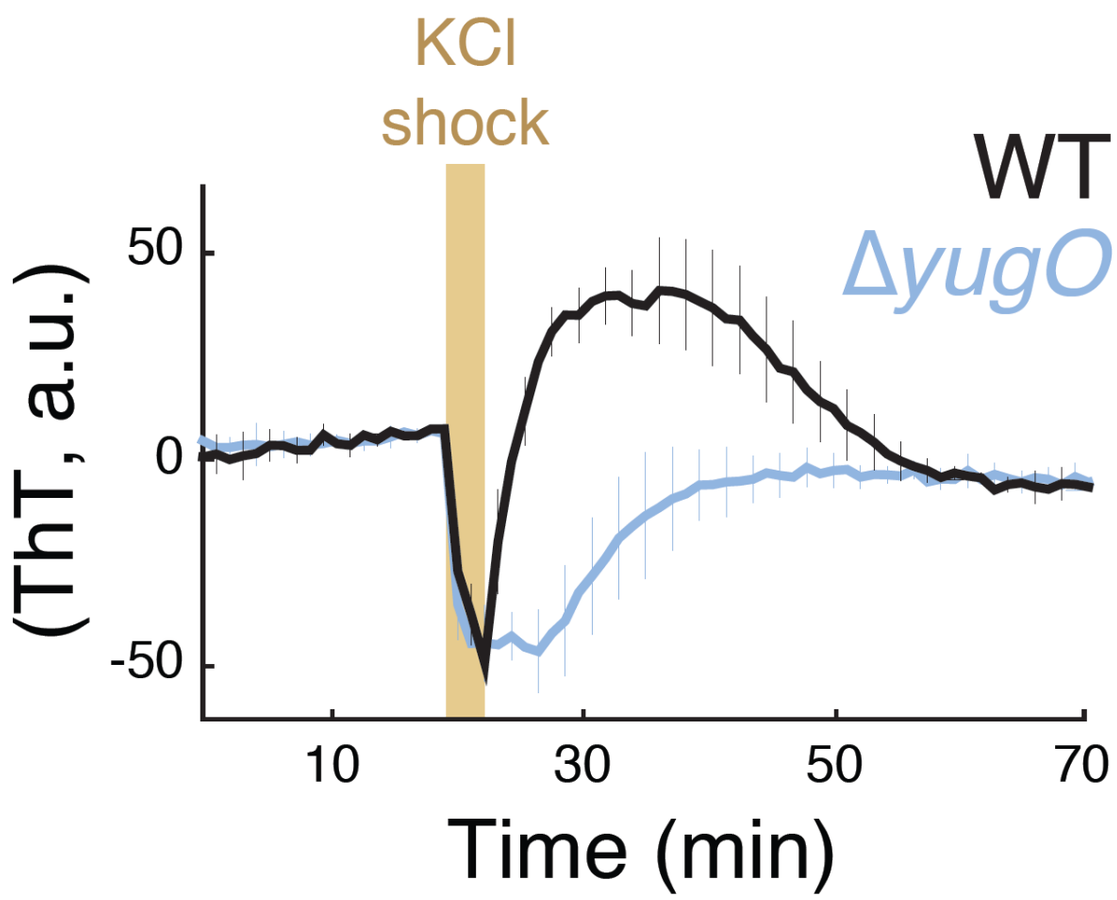
$$C\frac{dV}{dt} = \underbrace{-g_{\mathrm{K}}n^4(V-V_{\mathrm{K}})}_{\text{potassium current}} \underbrace{- g_{\mathrm{L}}(V-V_{\mathrm{L}})}_{\text{leak current}}$$

Comparison with experiments

Model

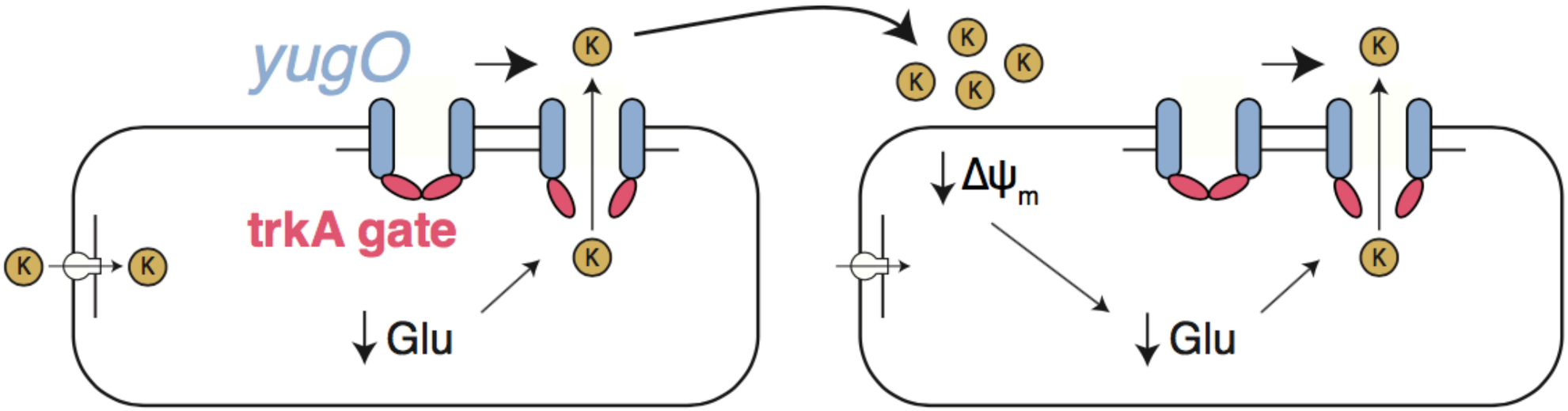


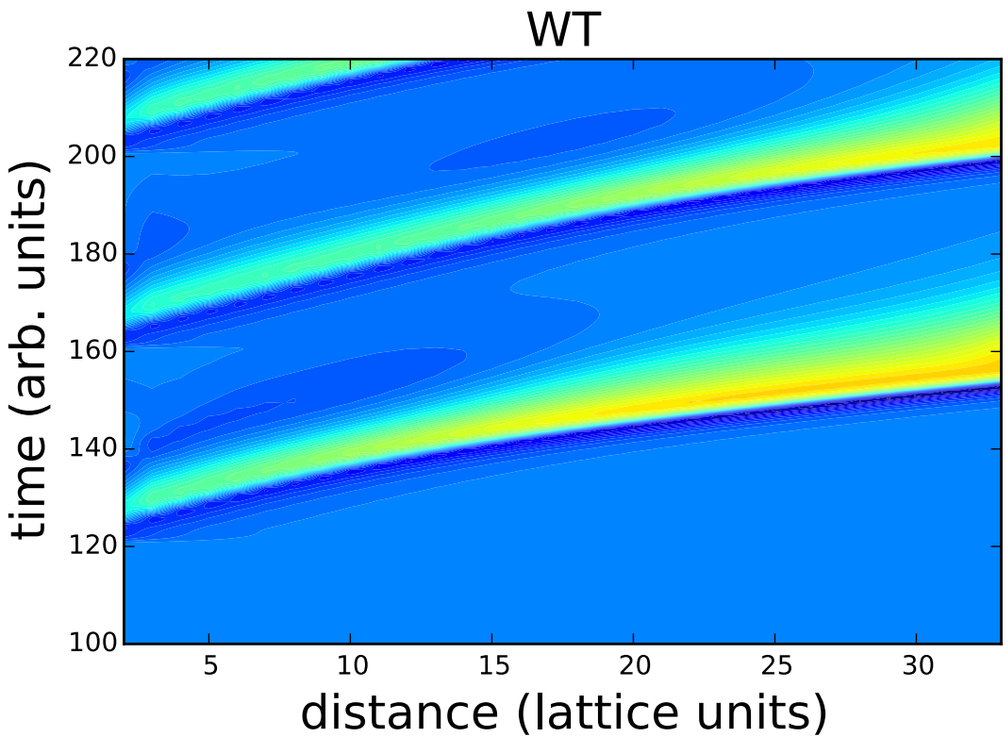
Experiment

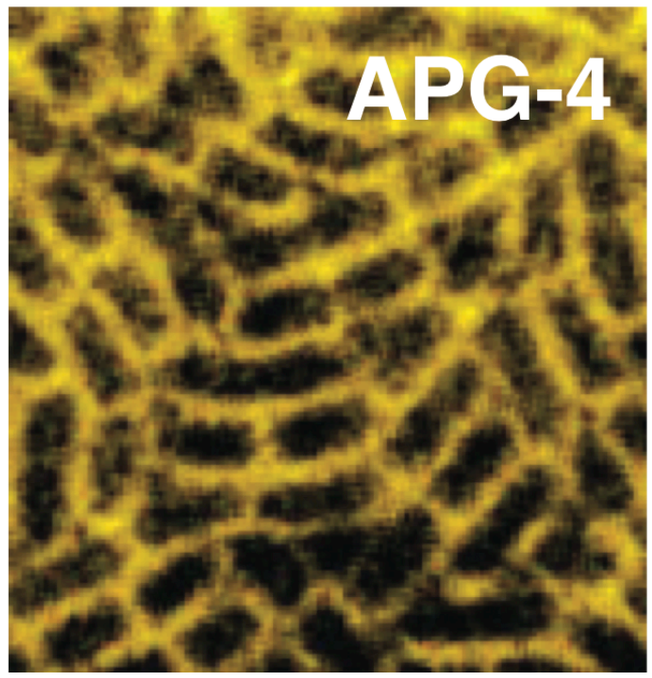


Prindle et al, Nature **527**, 59 (2015)

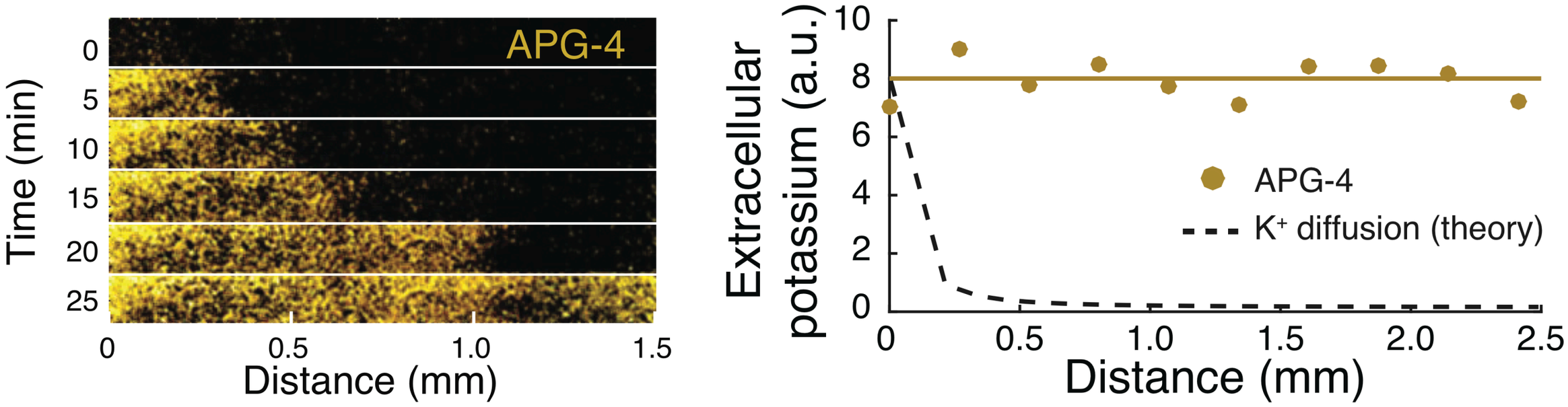
A bucket brigade of potassium

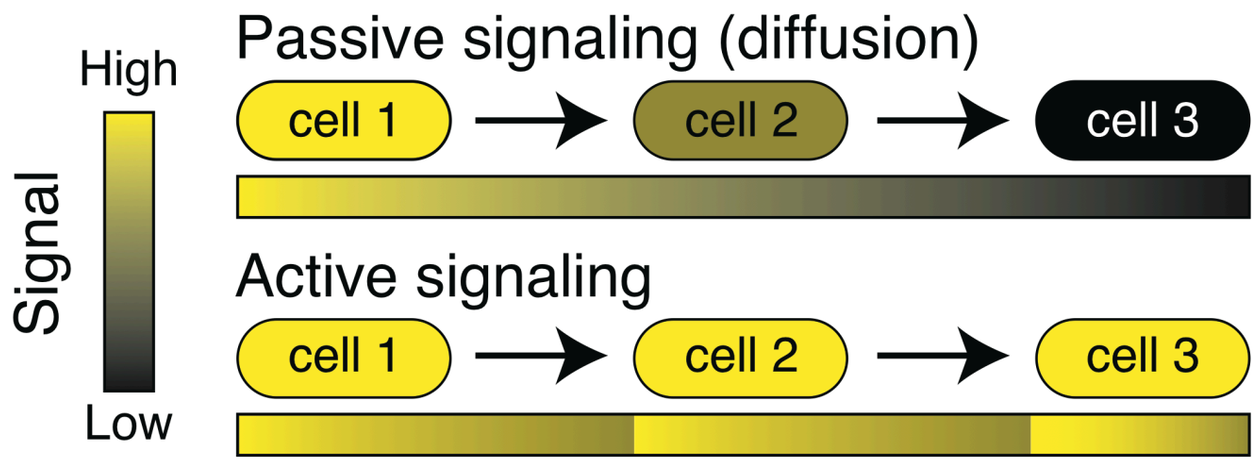






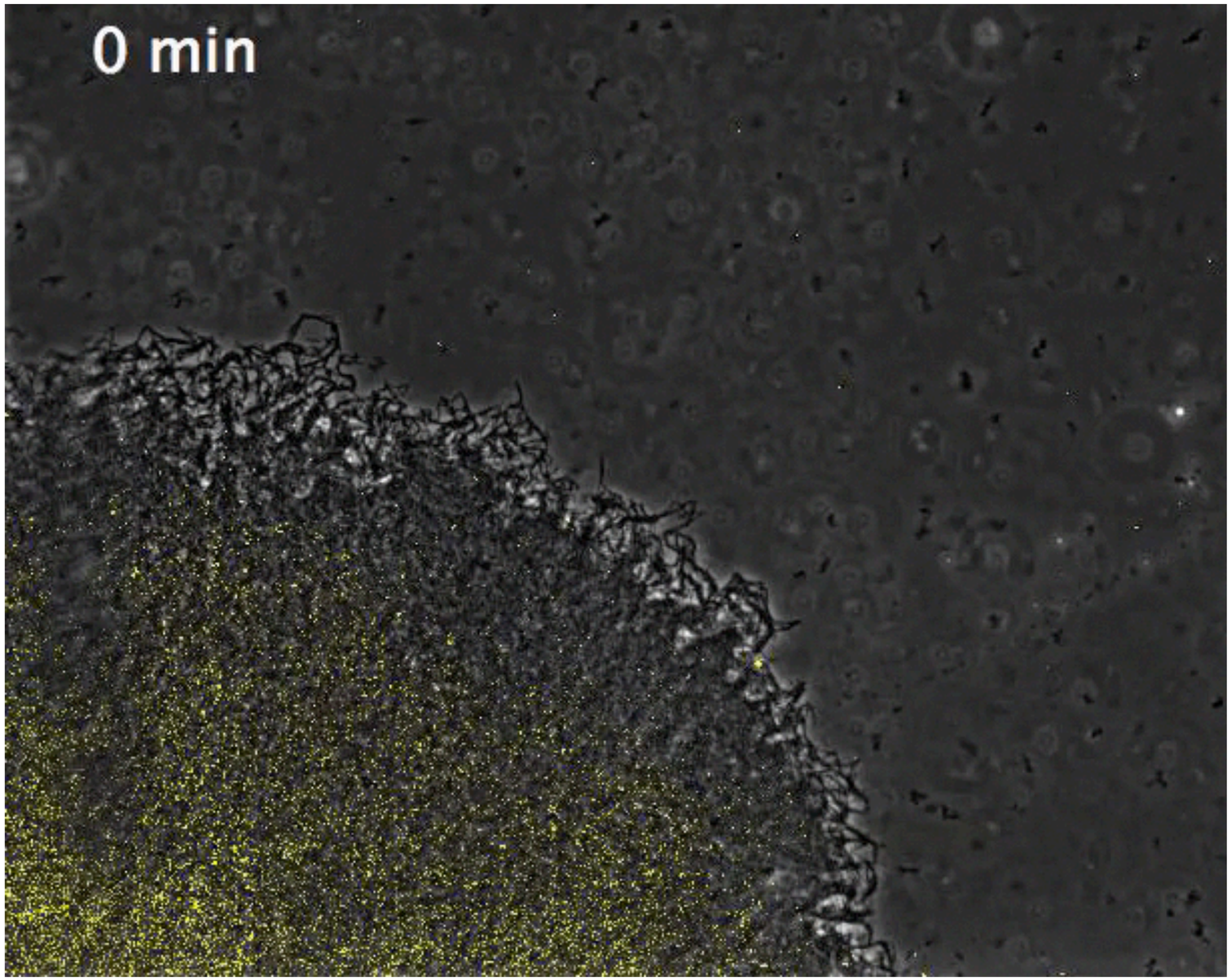
Active propagation of potassium





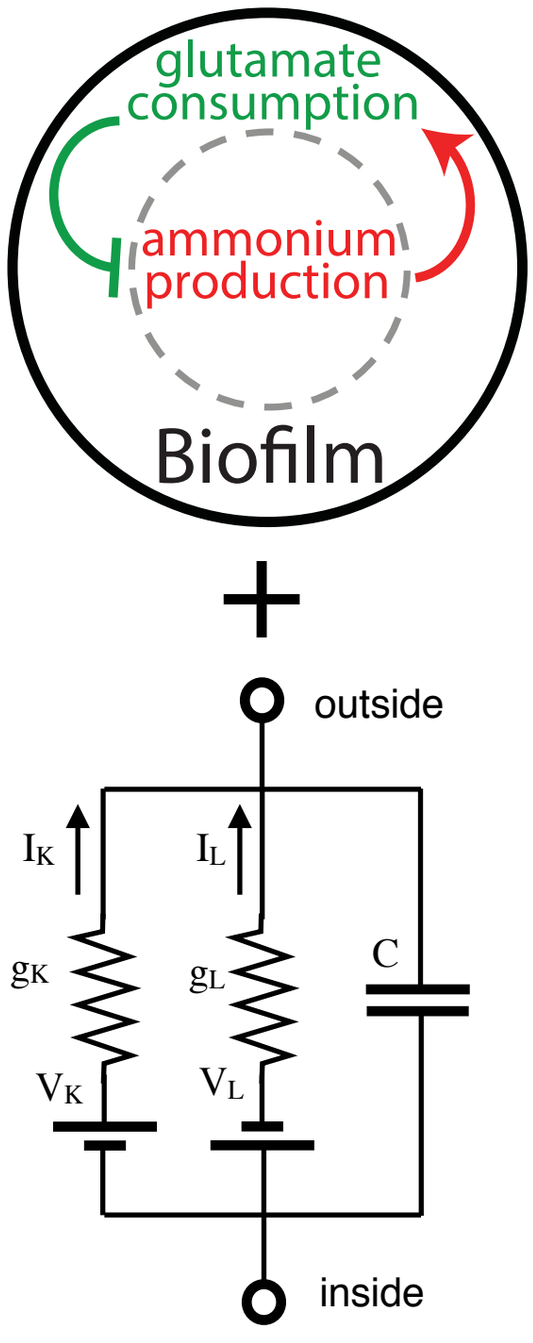
Prindle et al, Nature **527**, 59 (2015)

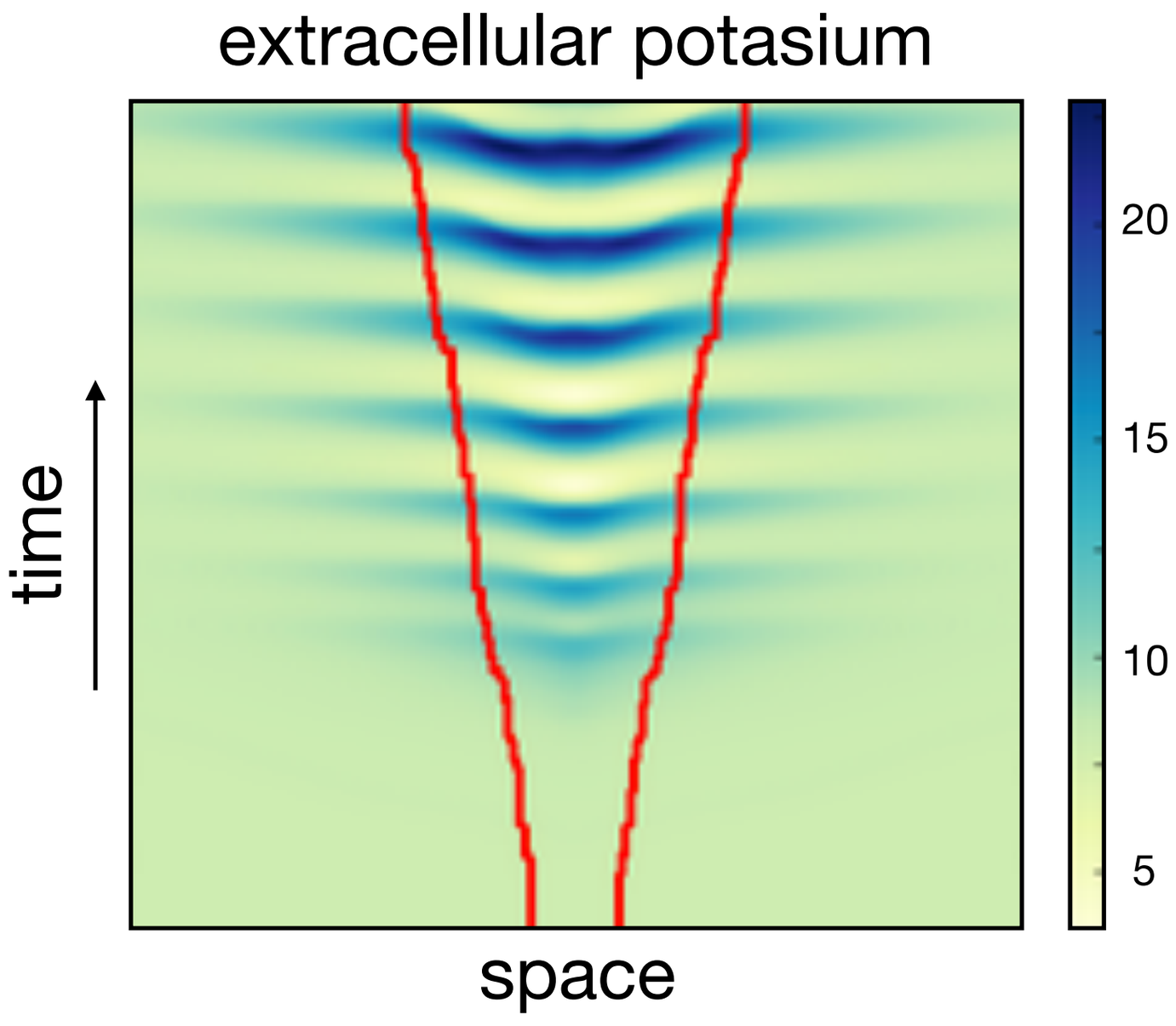
Propagating dynamics of the extracellular potassium



A combined metabolic-electrochemical model

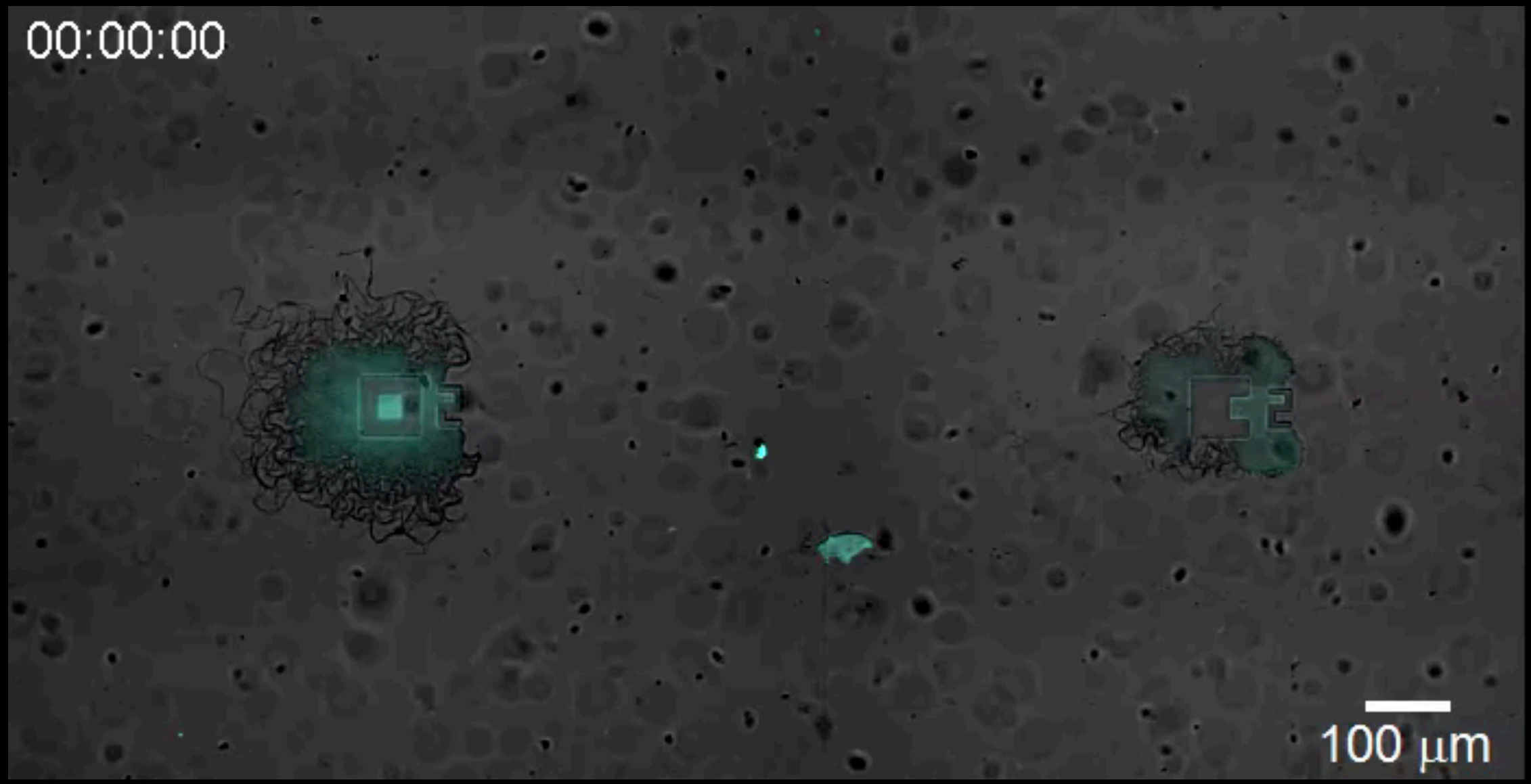
Rosa M.Corral





Can electrical signaling couple entire populations?

Two biofilms coexisting within the same chamber



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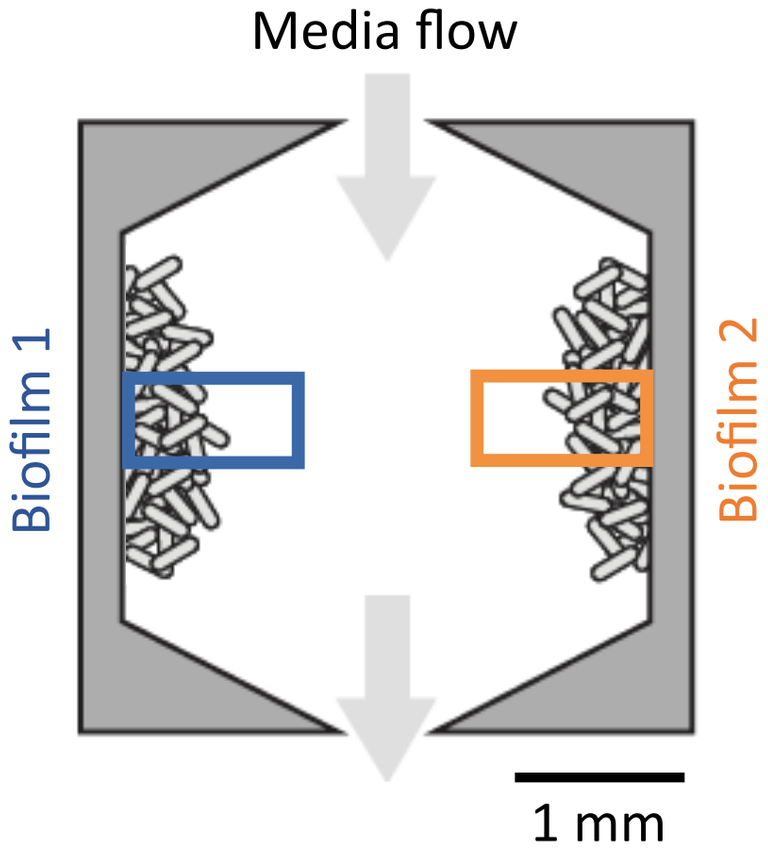
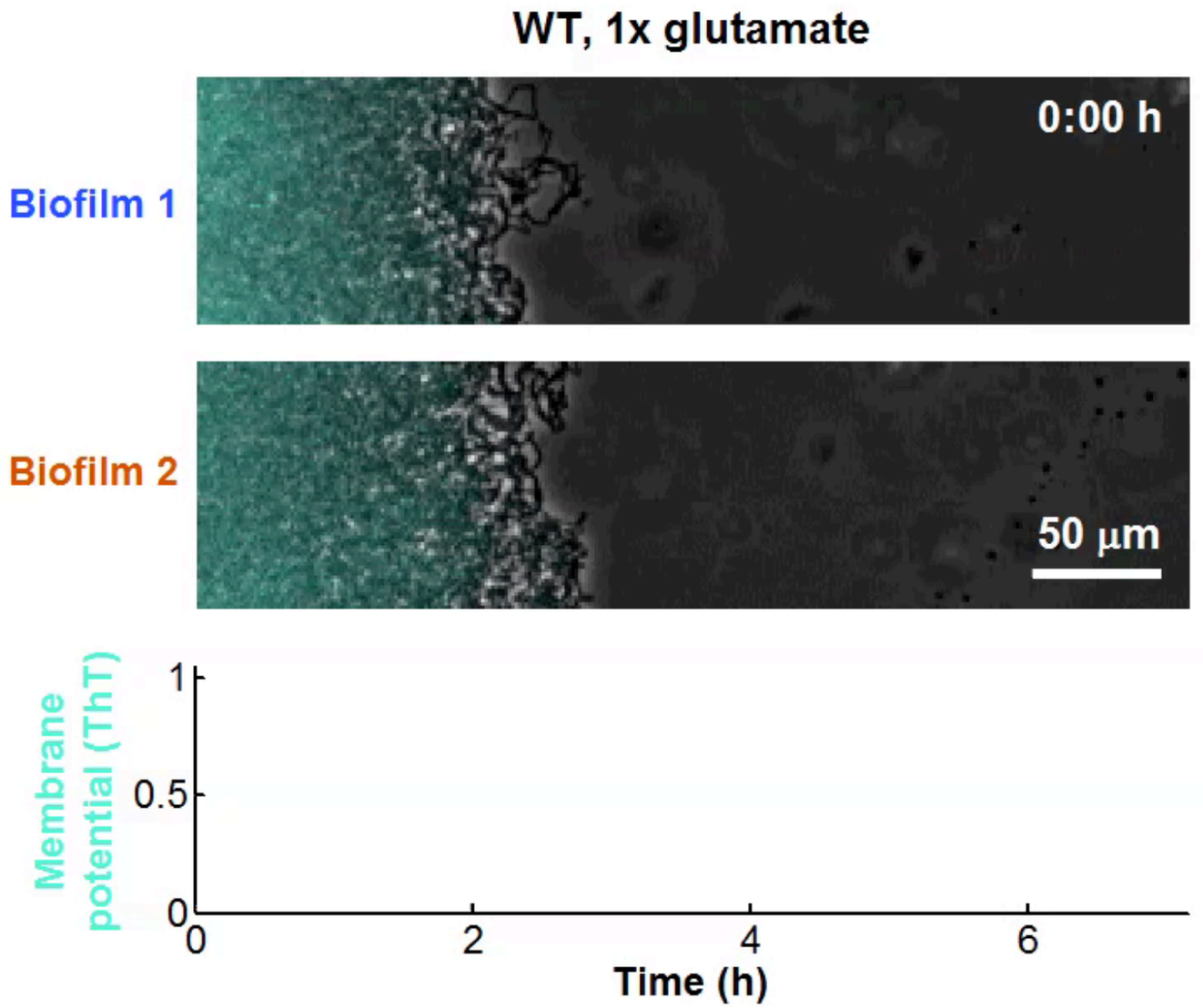
Synchronization via electrical coupling





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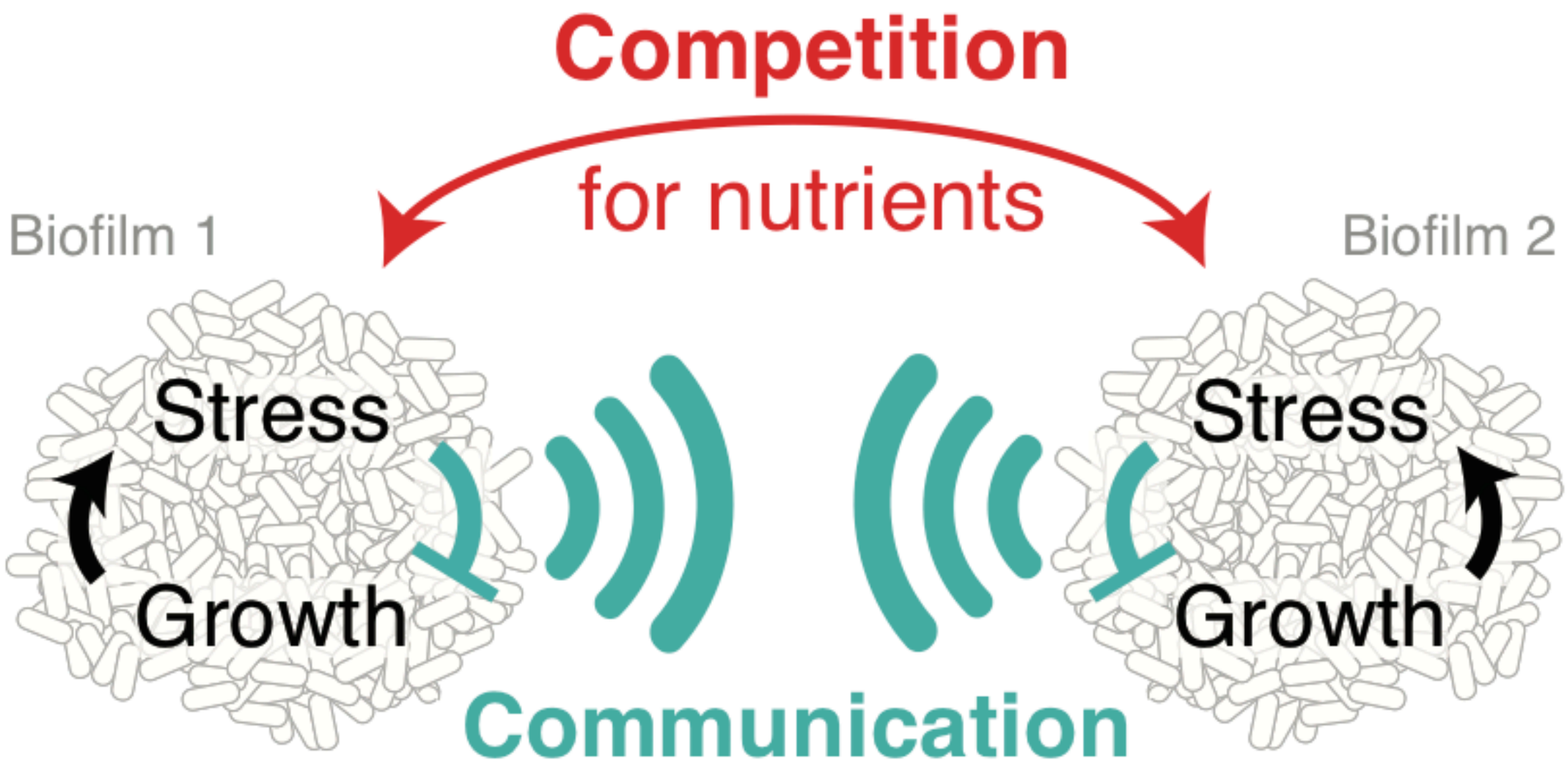
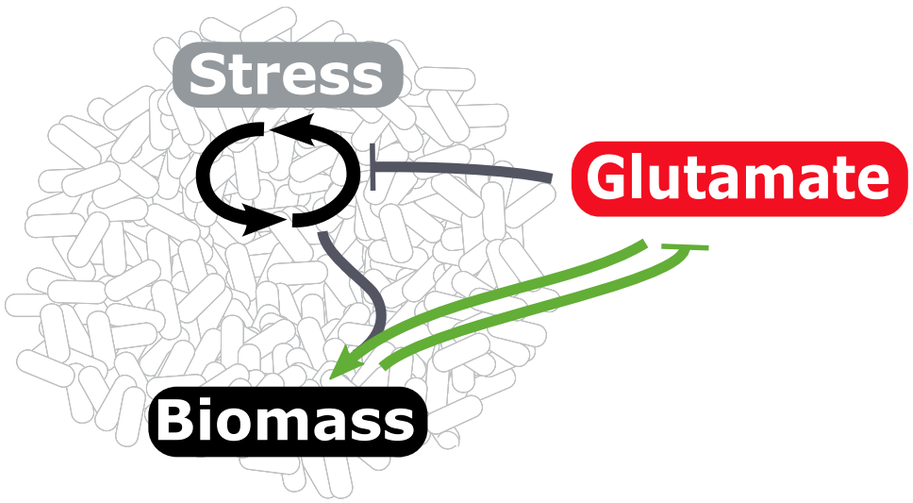
But biofilms are also coupled through nutrient sharing

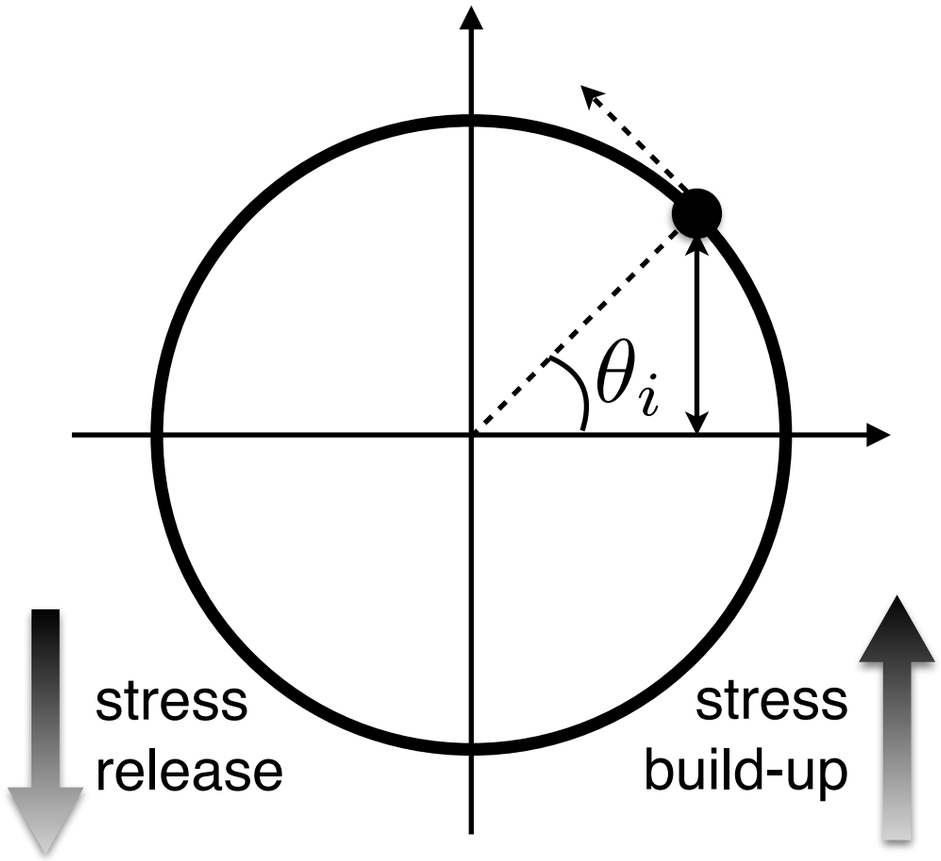


Oscillator frequency and glutamate consumption



stress $\quad \dfrac{d\theta_i}{dt} = \omega_0 + \Delta\omega(G, \theta_i)$

biomass production $\quad \dfrac{dr_i}{dt} = C(G, \theta_i) - \dfrac{\delta_r r_i}{k_r + r_i}$



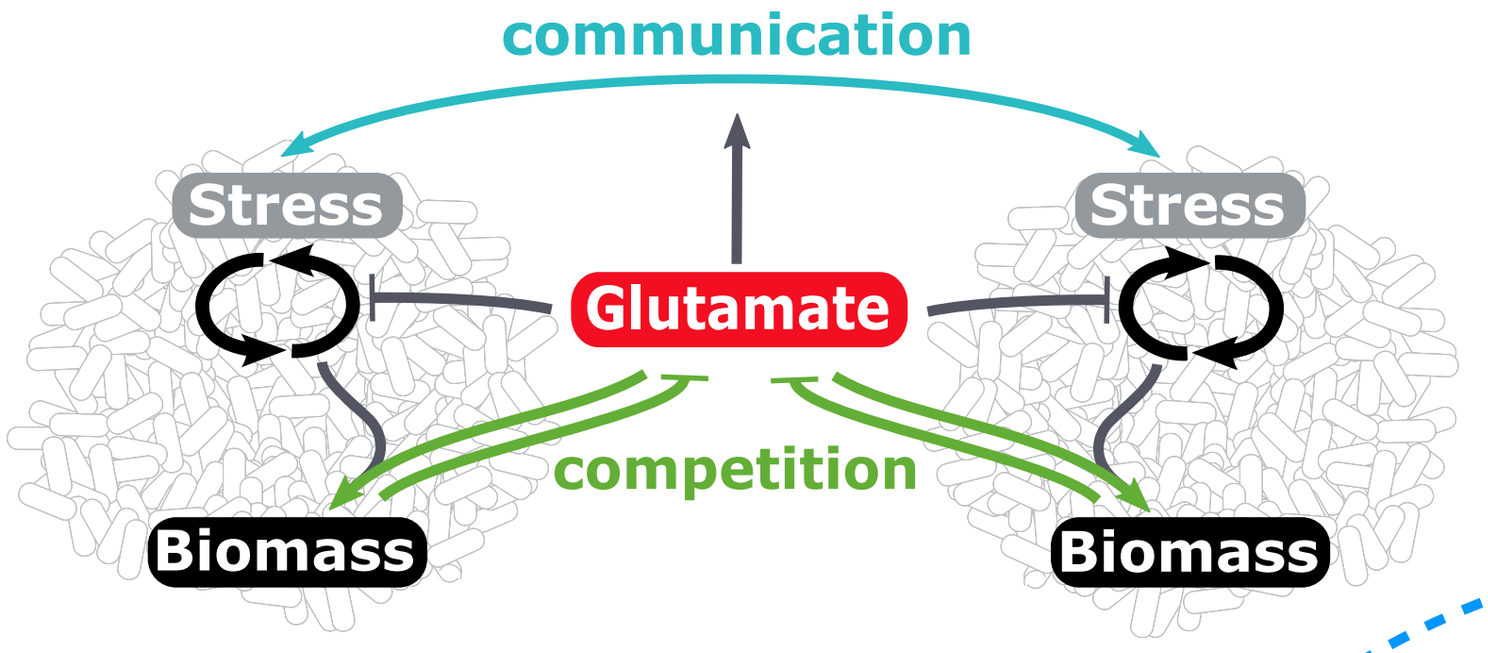
Intrinsic frequency:

$$\Delta\omega(G, \theta_i) = \begin{cases} \dfrac{\Delta\omega_o}{1 + G/k_\omega} \cos\theta_i & \text{if stress is increasing} \\ 0 & \text{if stress is decreasing} \end{cases}$$

Glutamate consumption:

$$C(G, \theta_i) = \frac{aG}{k_G + G}(1 - \sin\theta_i)$$

Communication and competition between coupled biofilms



Communication strength:

$$K(G) = \frac{K_0 G}{k_\theta + G}$$

stress

$$\frac{d\theta_i}{dt} = \omega_0 + \Delta\omega(G, \theta_i) + \underbrace{K(G)\sin(\theta_j - \theta_i)}_{\text{communication}}$$

biomass production

$$\frac{dr_i}{dt} = \underbrace{C(G, \theta_i)}_{\text{competition}} - \frac{\delta_r r_i}{k_r + r_i}$$

glutamate

$$\frac{dG}{dt} = b(G_{\text{ext}} - G) - \underbrace{C(G, \theta_1)}_{\text{competition}} - \delta_G r_1 G - \underbrace{C(G, \theta_2)}_{\text{competition}} - \delta_G r_2 G$$

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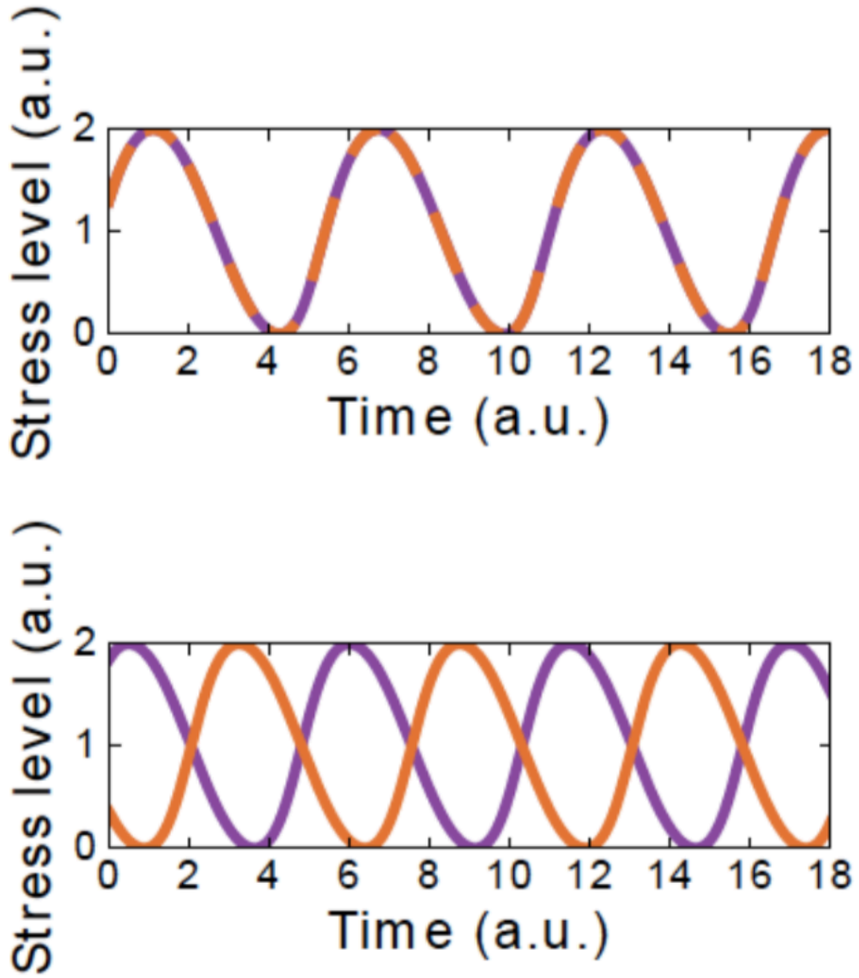
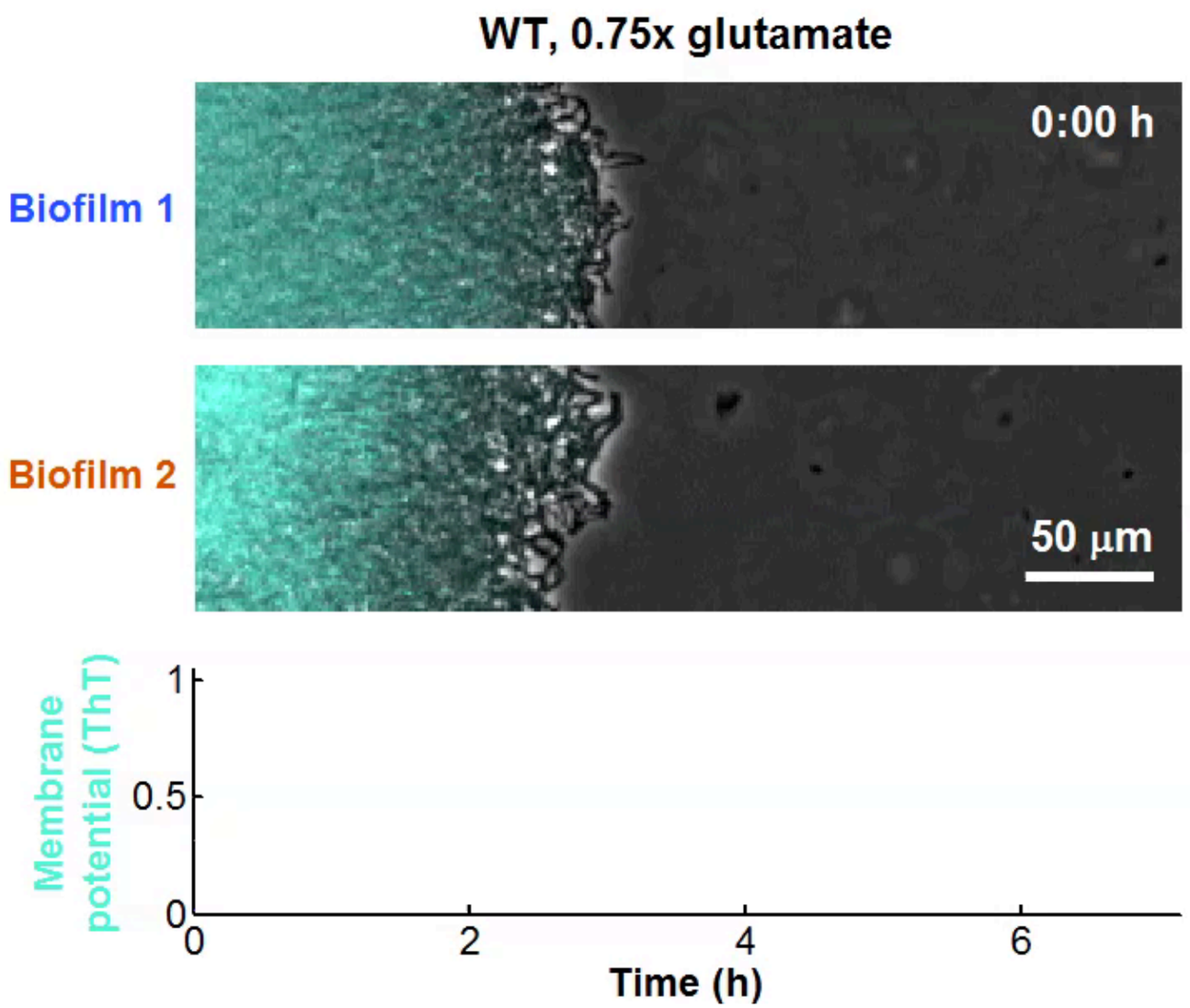
Validation: competition promotes anti-phase dynamics

glutamate





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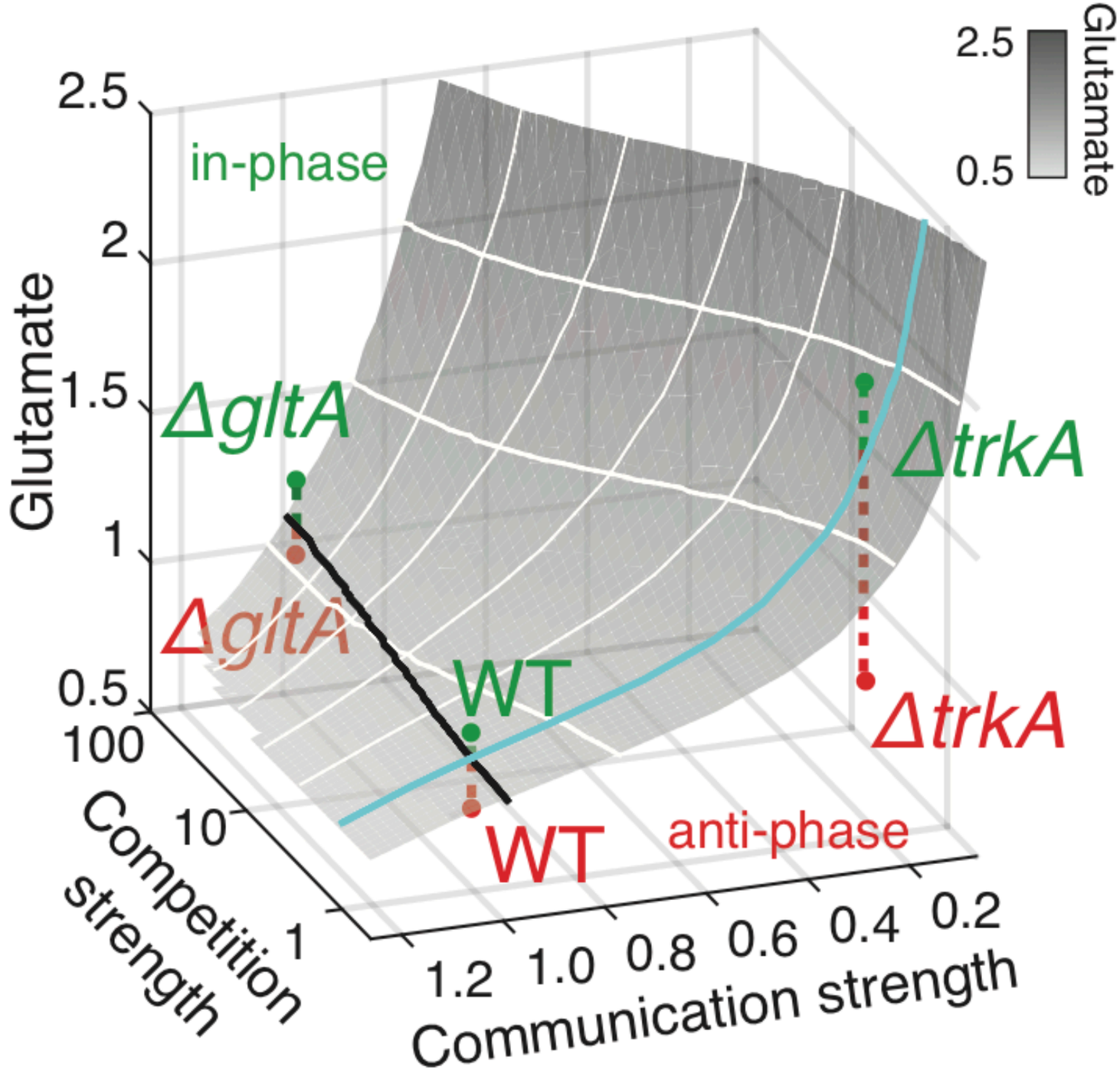
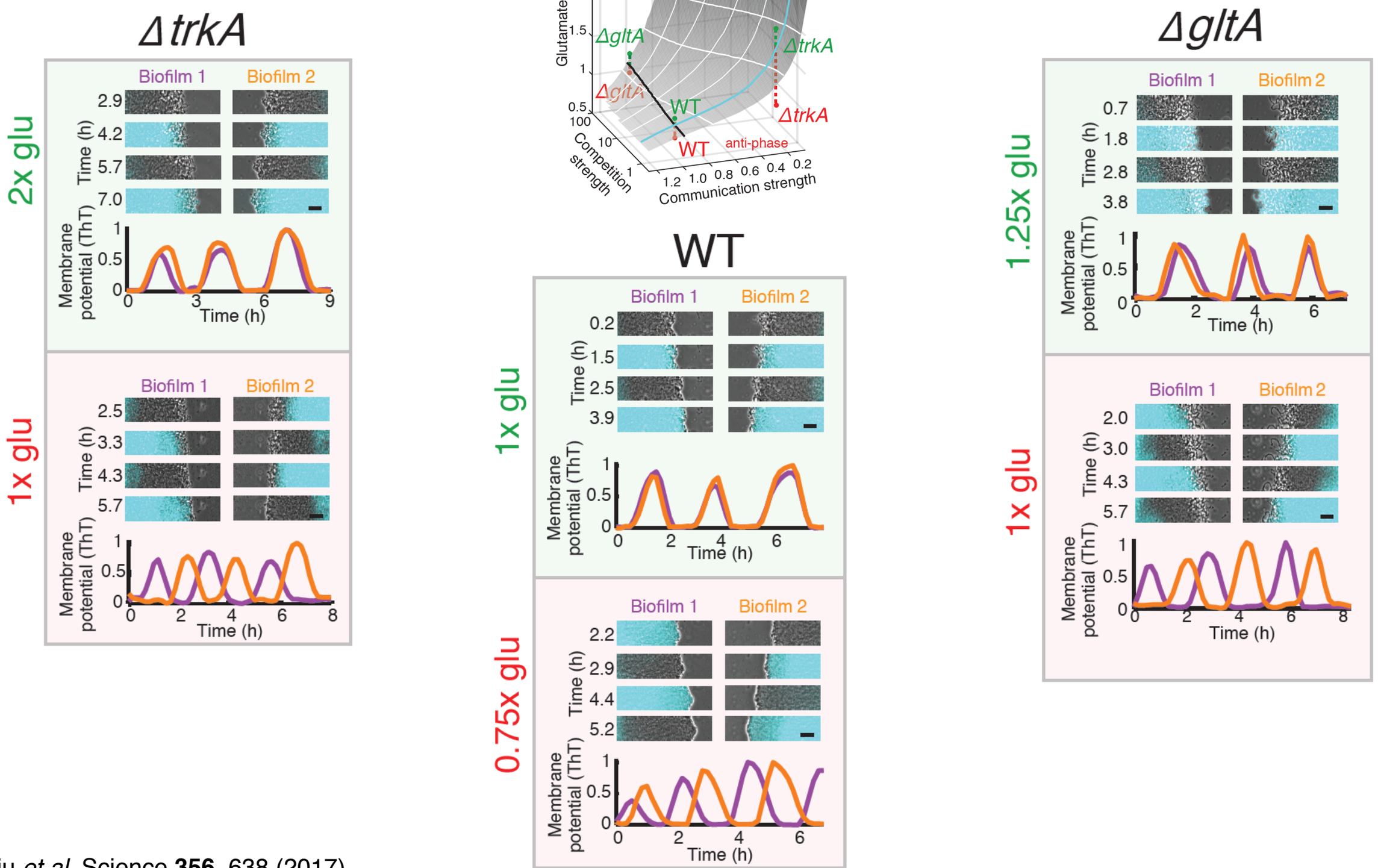
Summary of perturbations



Experimental validation



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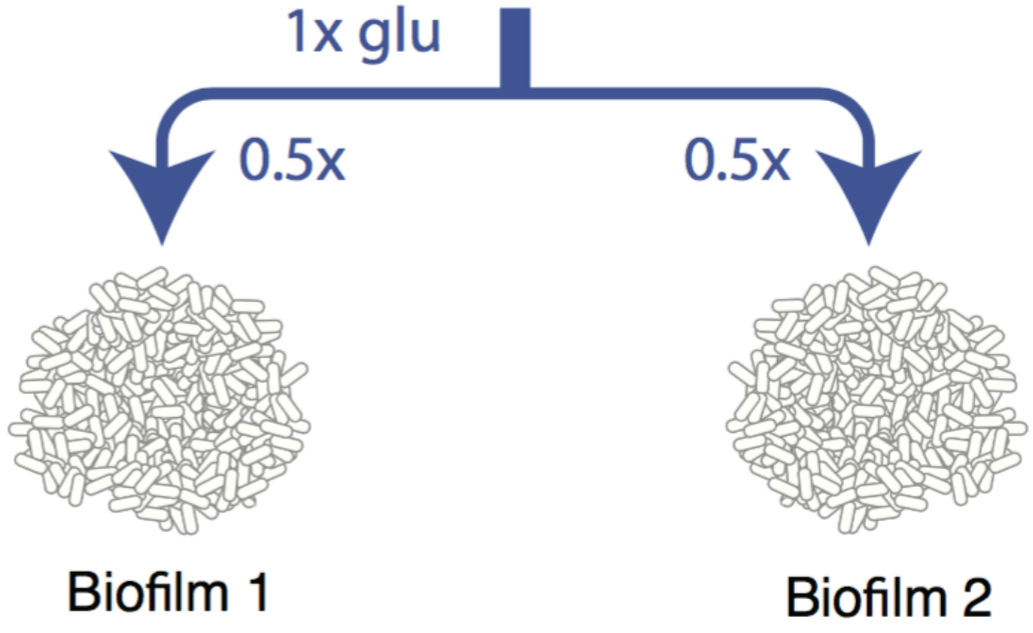
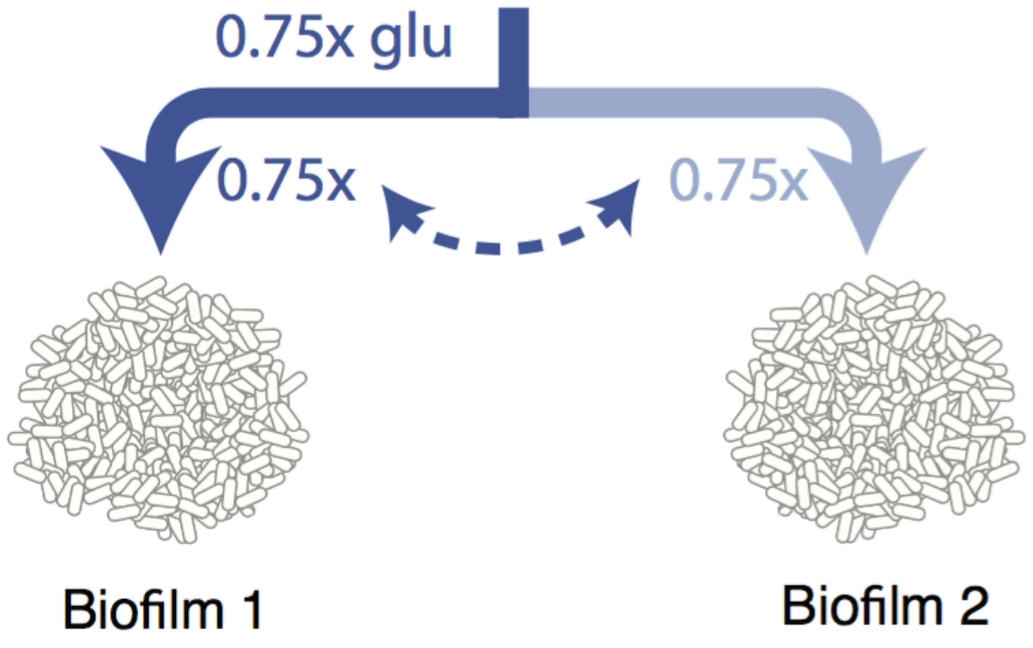
Two different sharing strategies

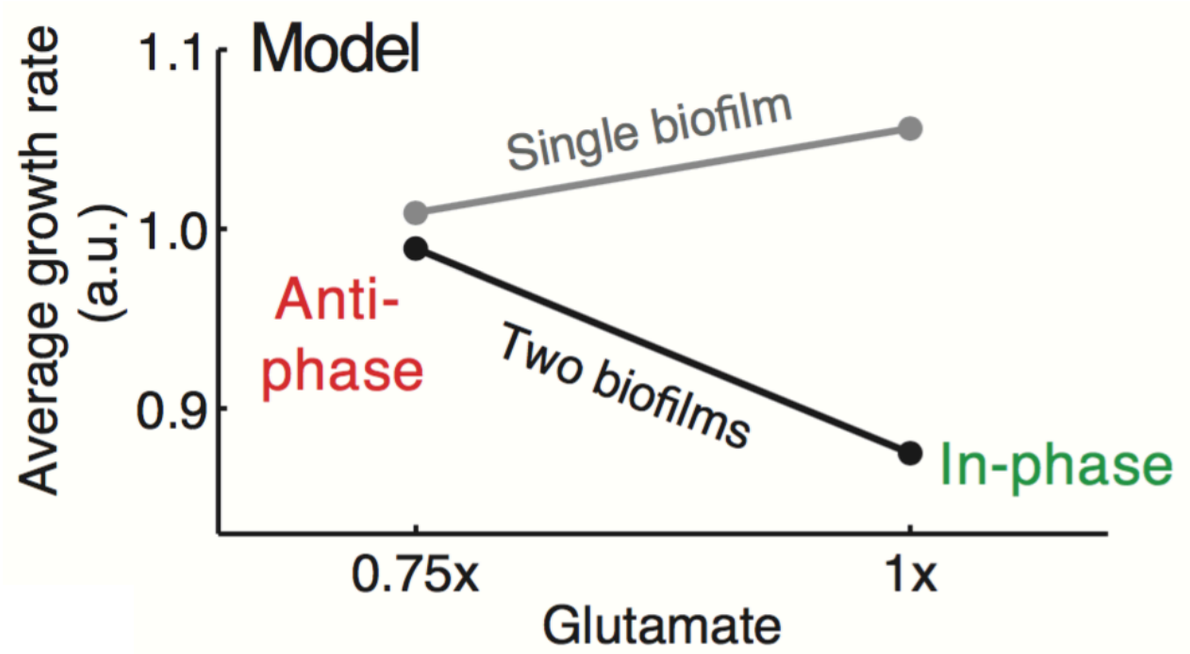
In-phase, resource-splitting

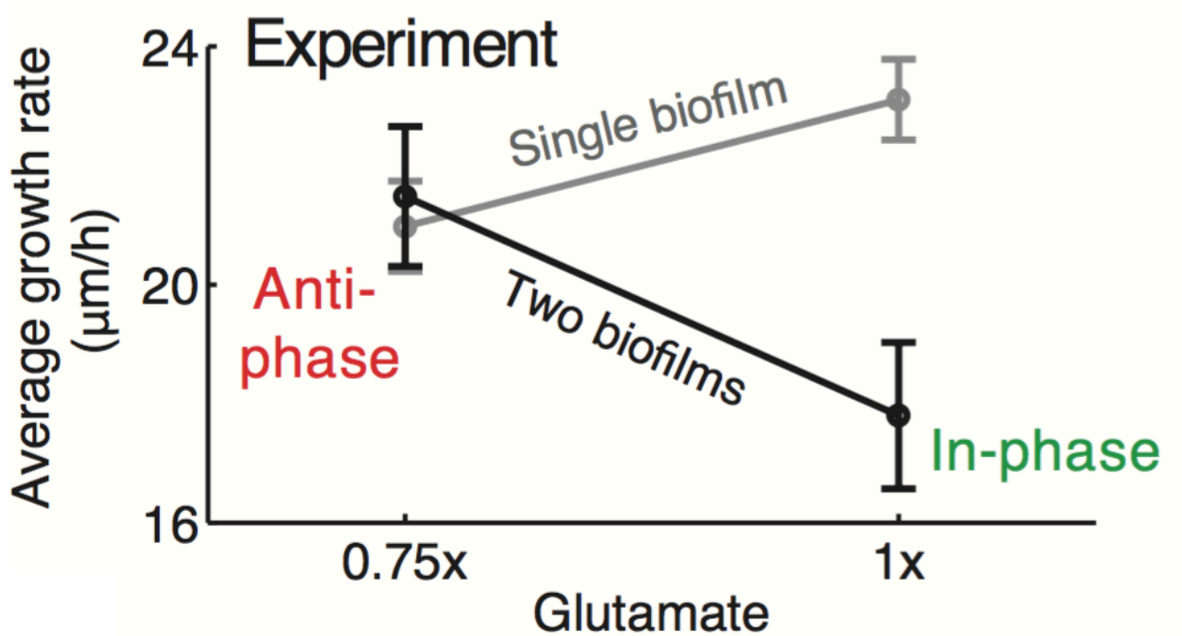


Anti-phase, time-sharing



Effect of timeshare on average growth: experiments





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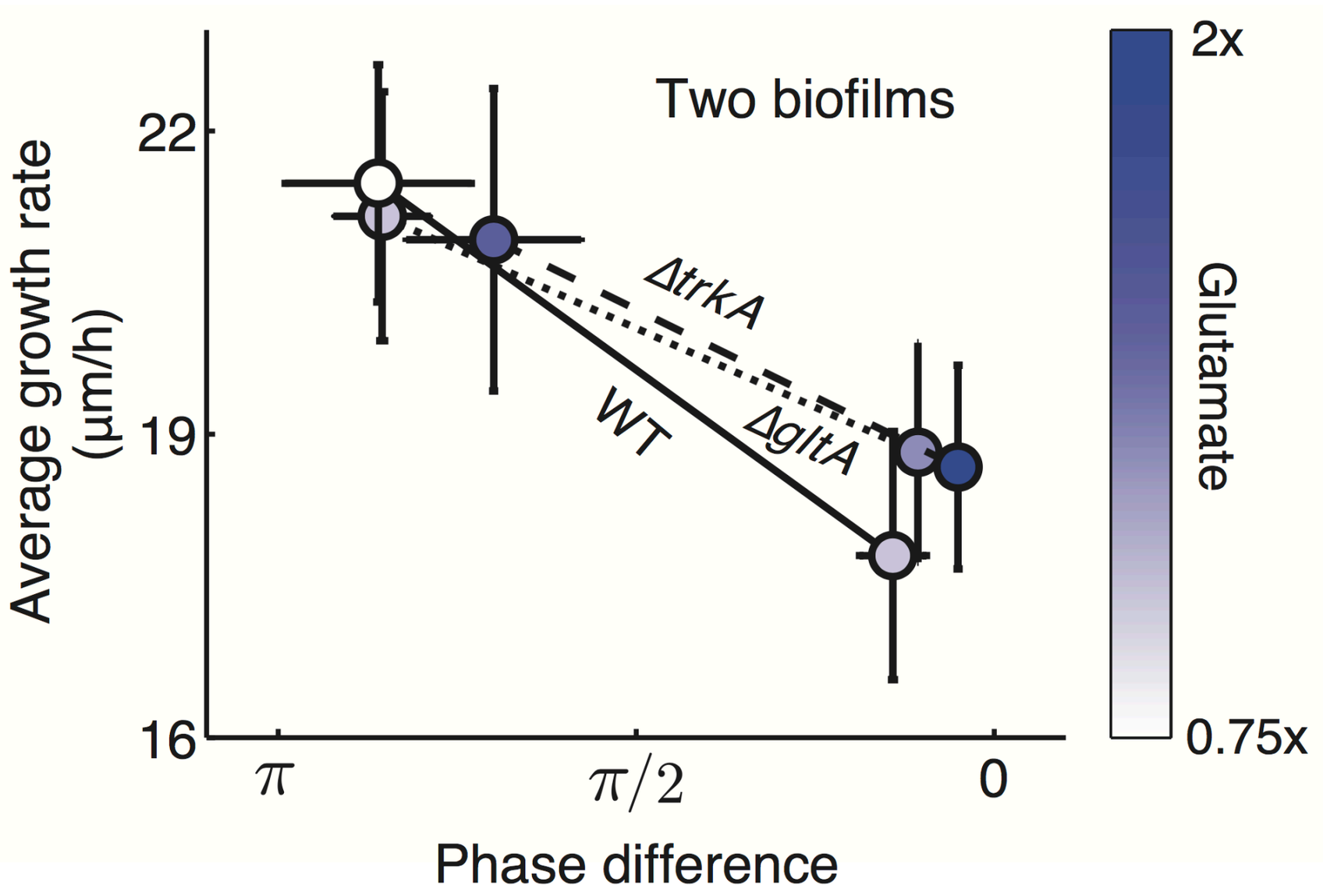
Phase difference accounts for all growth results



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Summary

- Bacterial biofilms undergo growth and stress oscillations driven by delayed negative feedback
- The transition to oscillations is discontinuous
- Stress is communicated via electrical signaling
- Electrical signals extend outside the population
- Synchronization between biofilms mediates time-sharing of limited resources

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