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Bacterial Quorum Sensing as a Networked Decision System

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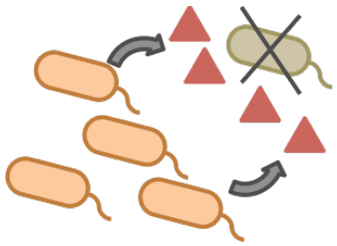
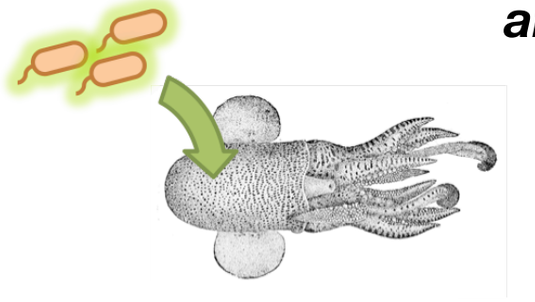
Quorum sensing

Mechanism used by bacteria to coordinate collective behavior

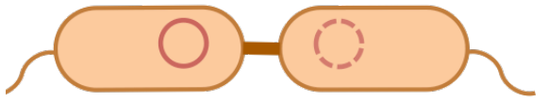


antibiotic production

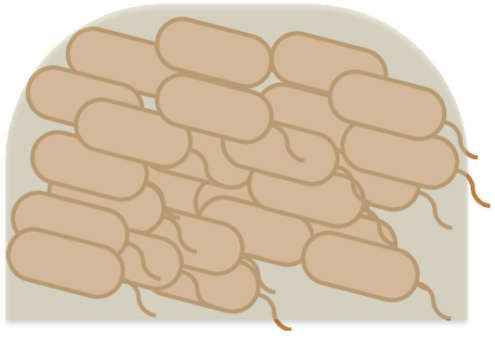


bioluminescence

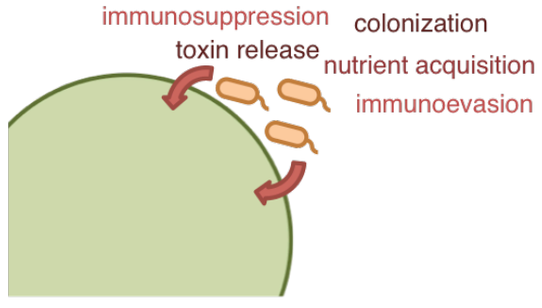
collective behaviors



conjugation



biofilm formation

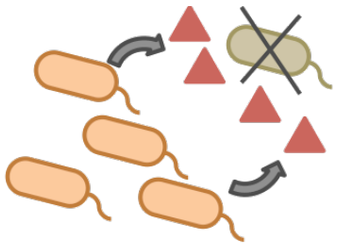


virulence factors

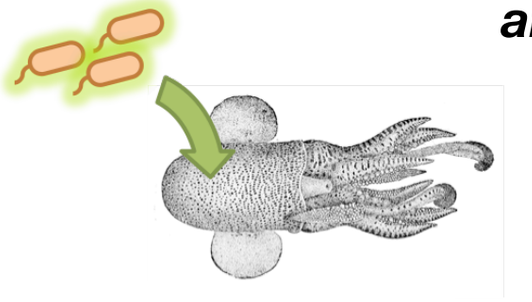
[1] http://sites.tufts.edu/quorumsensing/quorumsensing101

Quorum sensing

Enables bacteria to act as multicellular organisms!

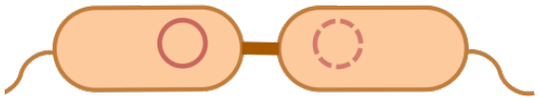


antibiotic production

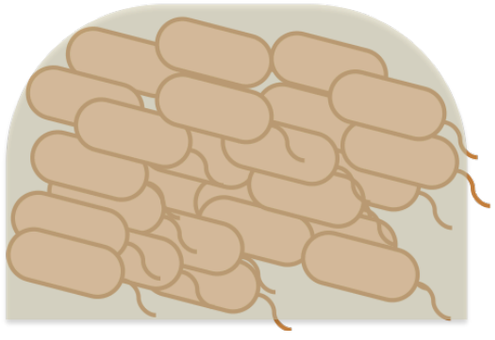


bioluminescence

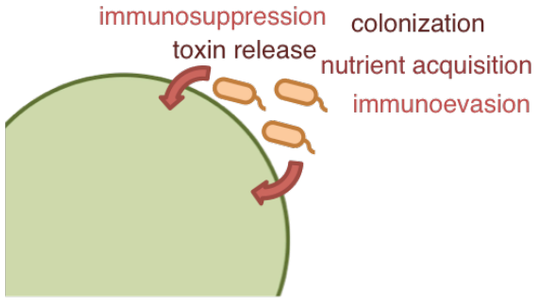
collective behaviors



conjugation



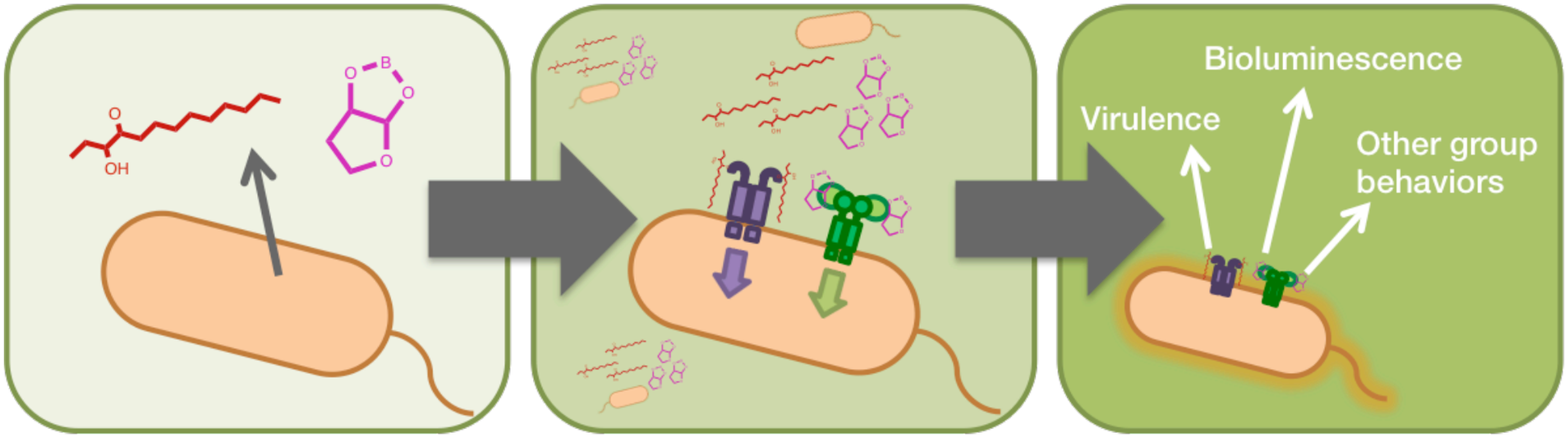
biofilm formation



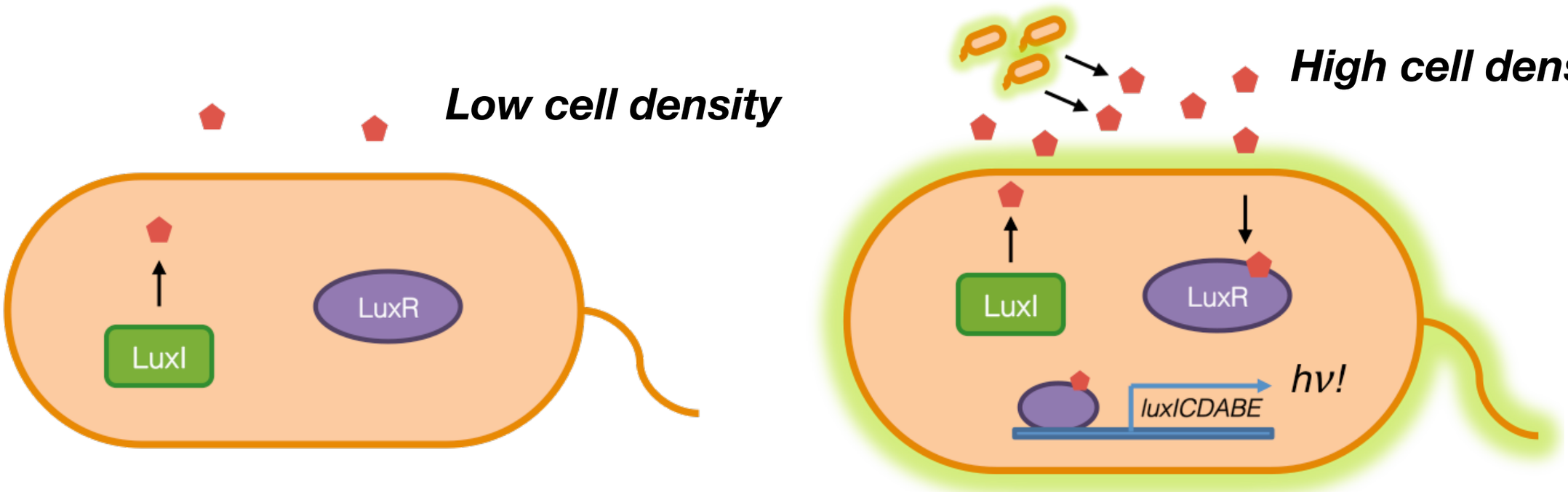
virulence factors

[2] Waters and Bassler (2005)

How does it work?

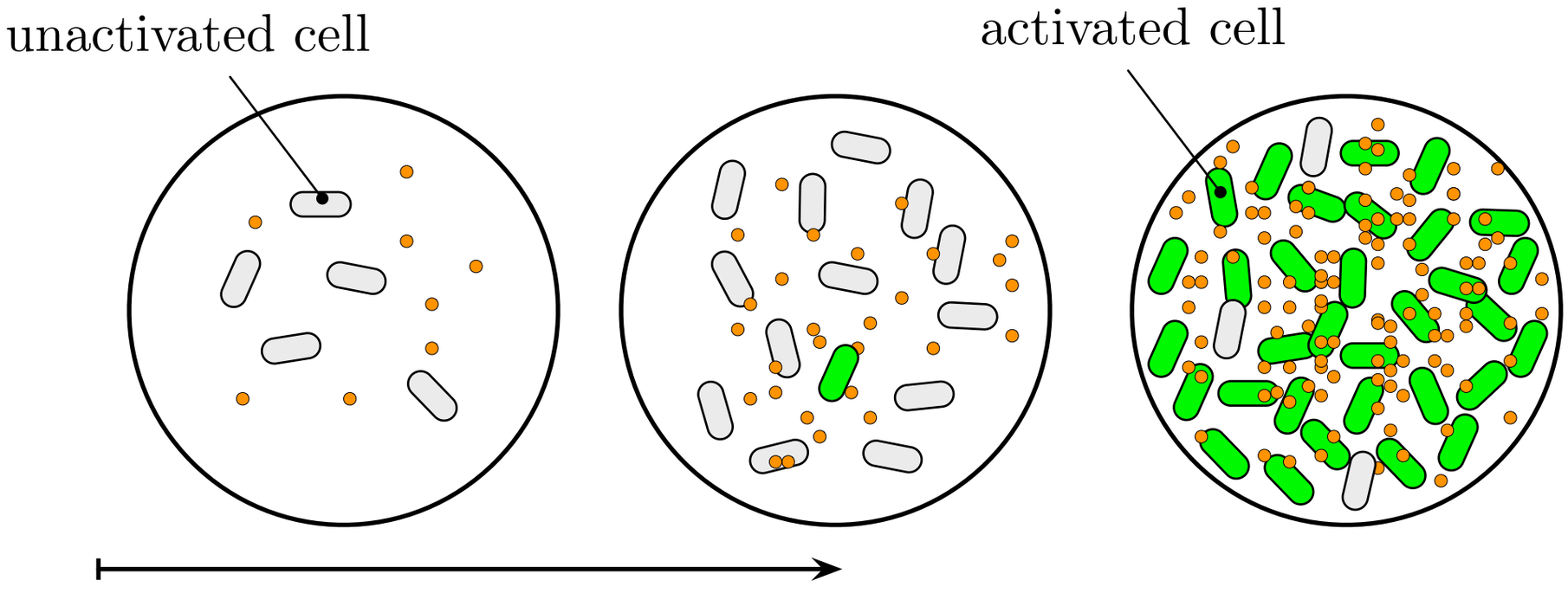


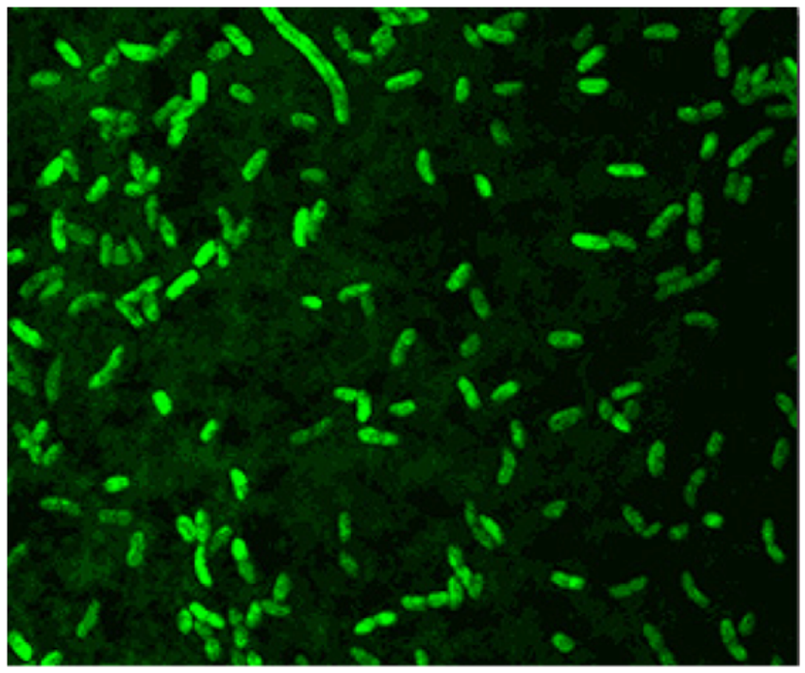
Signaling **Reception** **Activation**

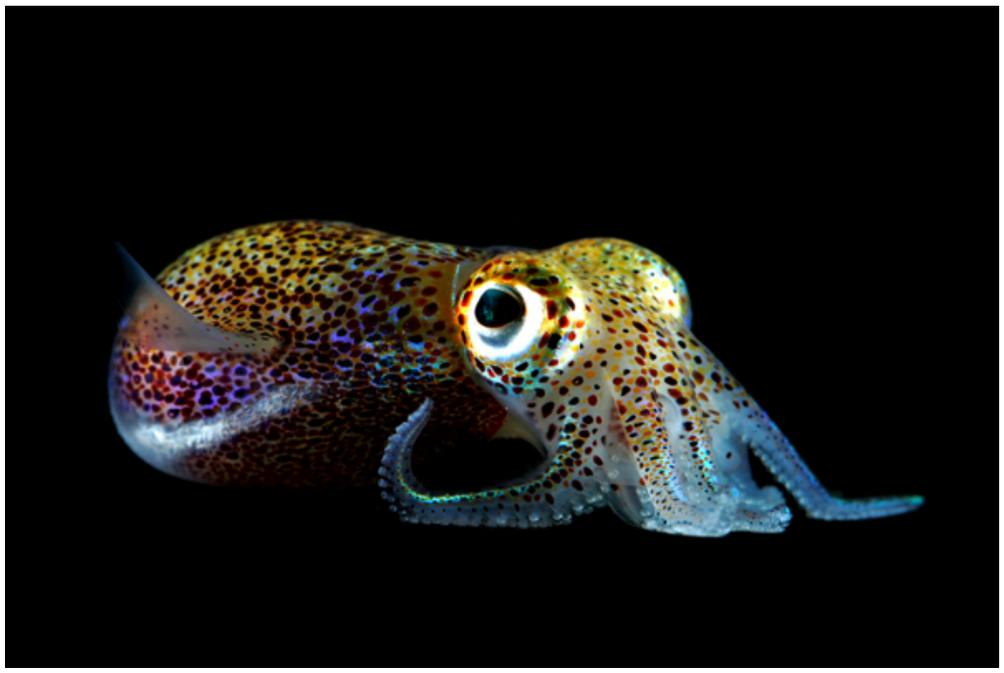


[1] http://sites.tufts.edu/quorumsensing/quorumsensing101

Quorum sensing







[3] Nealson et al. (1970)

Vibrio Fischeri luminescing

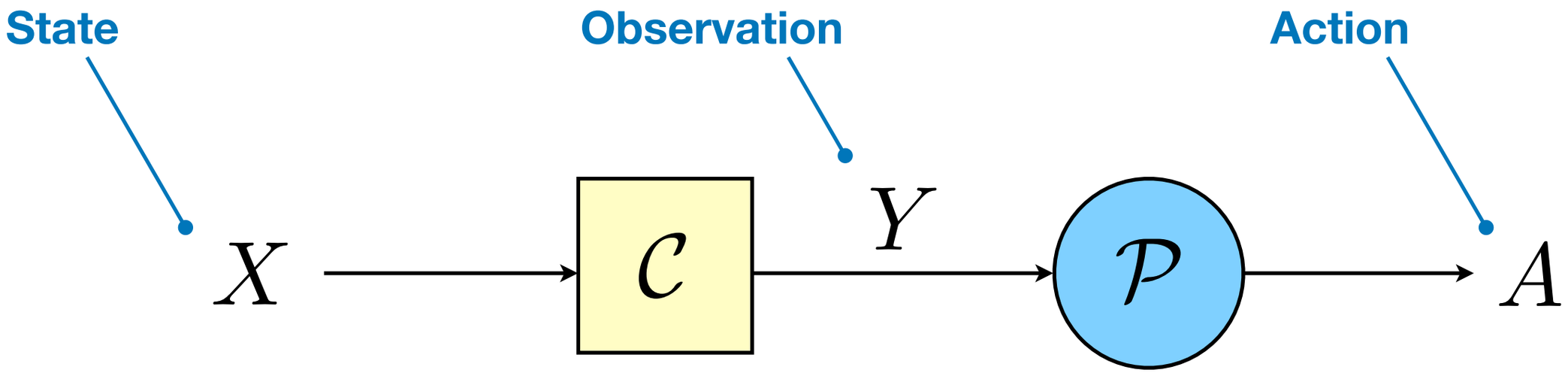
Goal

Cells are decision makers

Propose a new optimization-based model for QS

Calibrate our model from experimental data

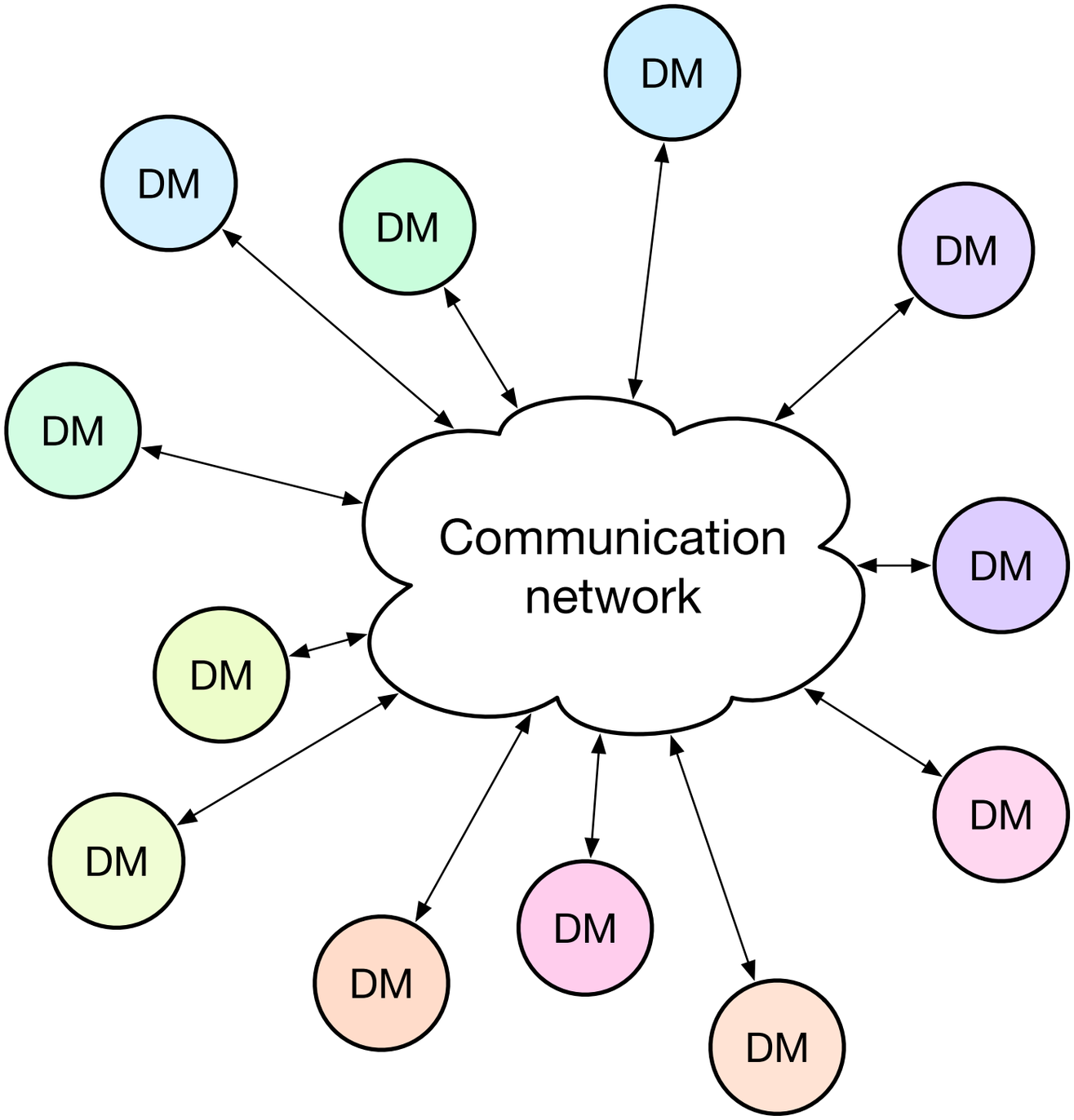
Bayesian decision system



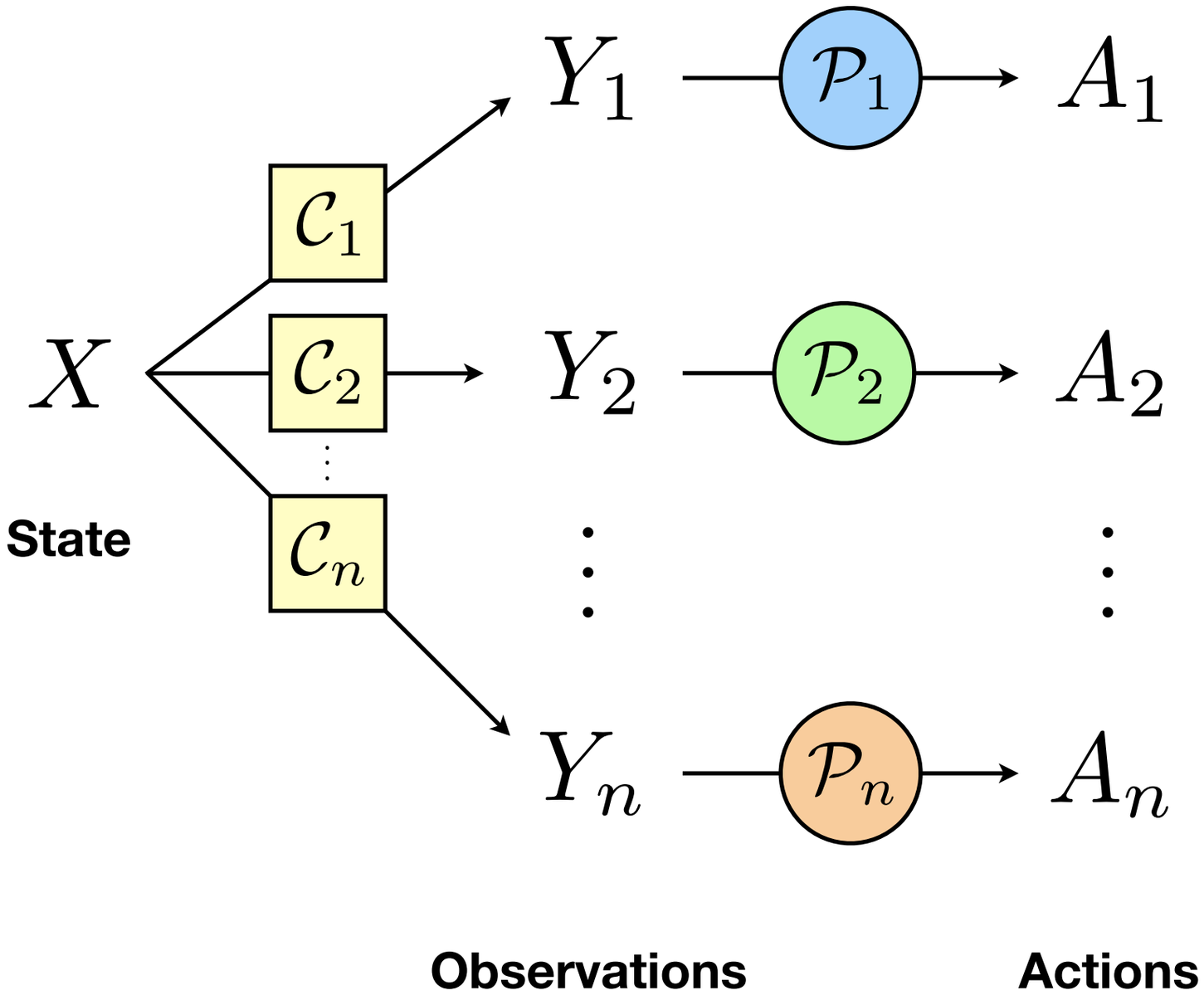
$X \sim f_X$

$$\underset{\mathcal{P}}{\text{maximize}} \quad \mathbf{E}\big[\mathcal{U}(A, X)\big]$$

Network decision system



Local observations, Global actions



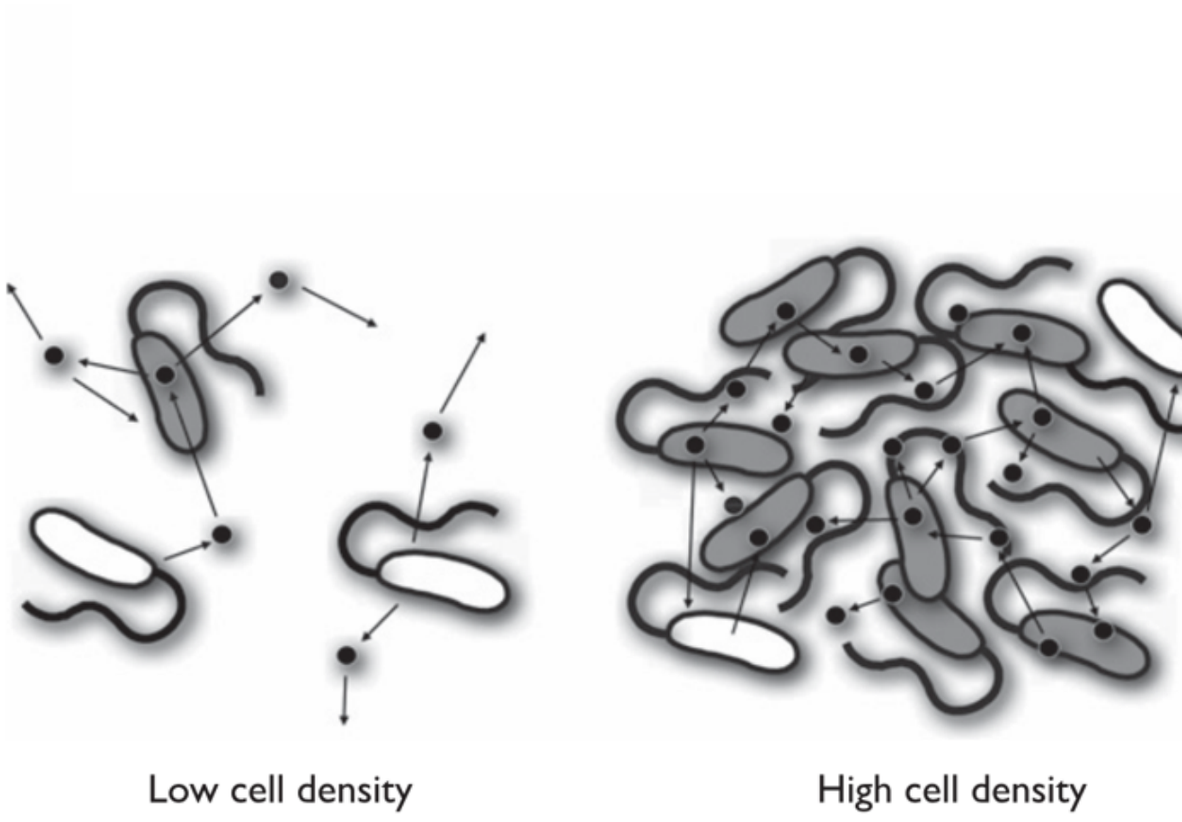
$$\underset{\mathcal{P}_1,\cdots,\mathcal{P}_n}{\text{maximize}} \quad \mathbf{E}\big[\mathcal{U}(A_1,\cdots,A_n,X)\big]$$

The model

State

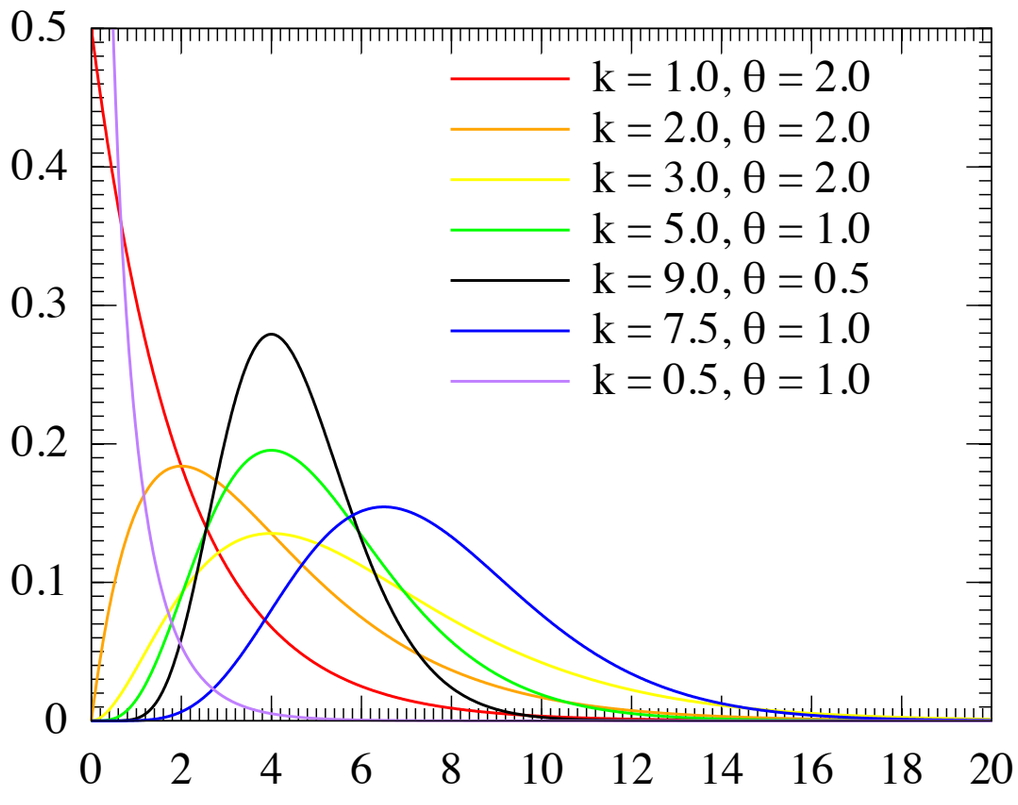
Density of the colony

$$X \sim \text{Gamma}(\kappa, \theta)$$



Low cell density

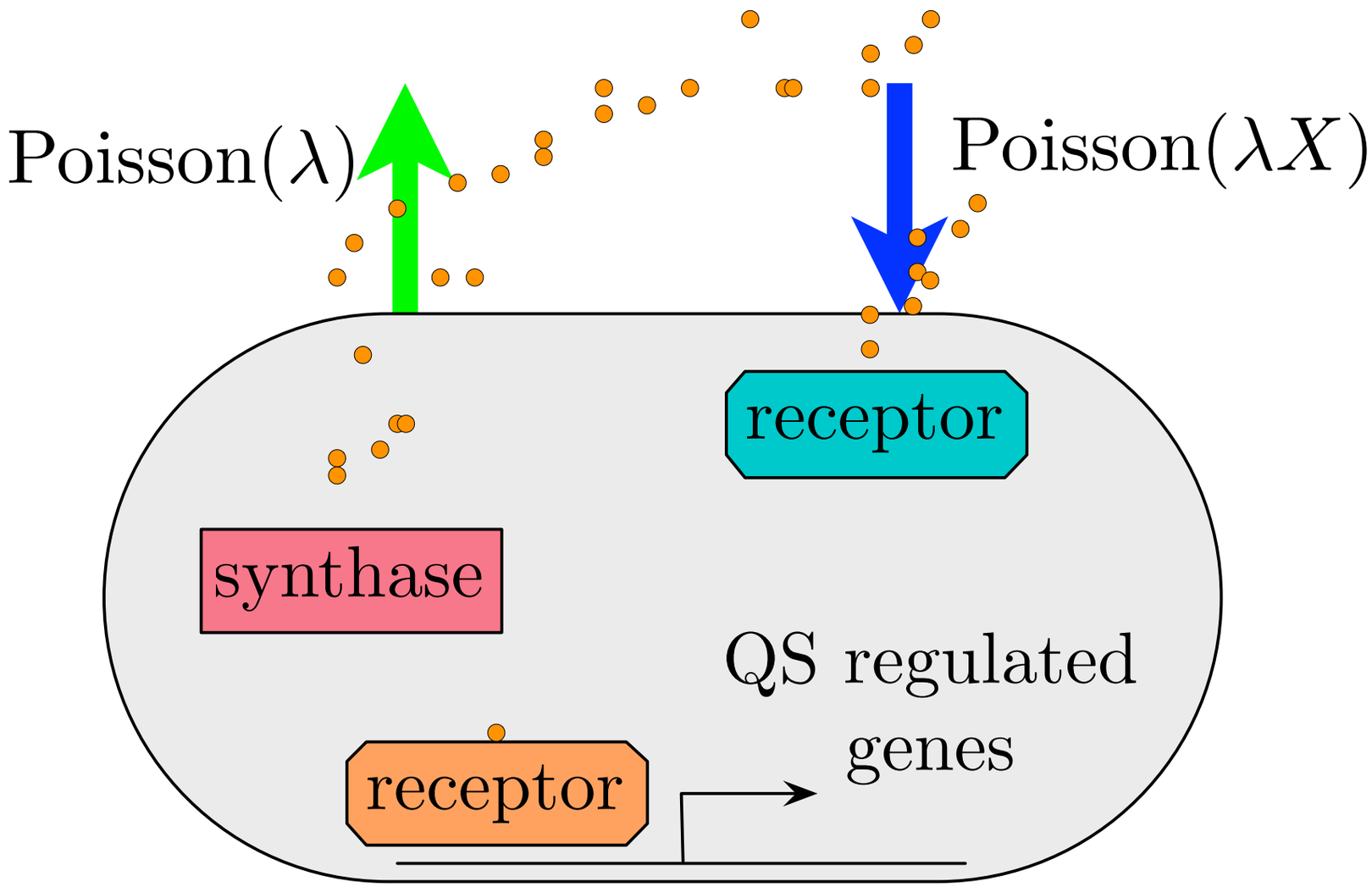
High cell density



[4] Darch et al (2012) - “Density-dependent fitness benefits in quorum-sensing bacterial populations”

[5] Clough et al (2005) - “Quantifying uncertainty associated with microbial count data: A Bayesian approach”

Sensing mechanism



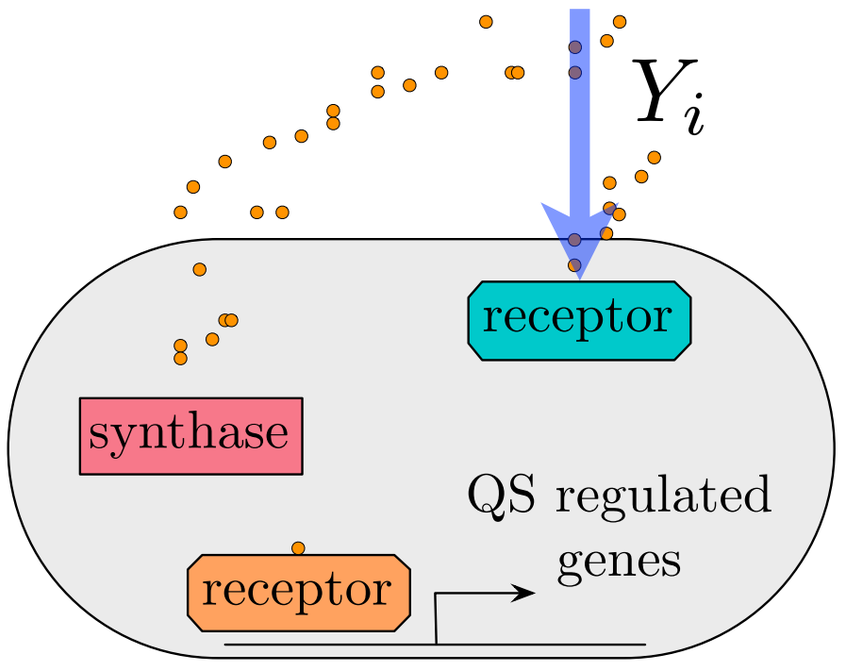
λ depends on the type of bacteria

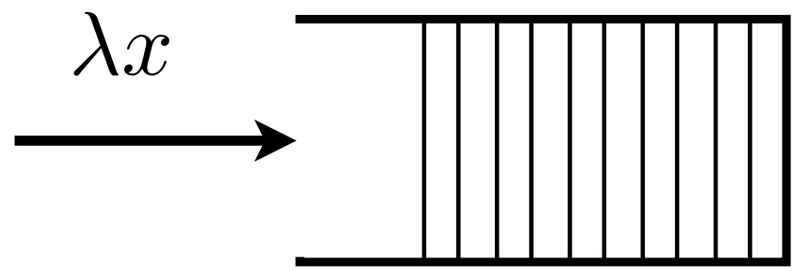
Observations

Assumptions

$$\text{Given } X\text{:} \quad Y_i \perp\!\!\!\perp Y_j, \quad i \neq j$$

$$\text{Given } X = x\text{:} \quad Y_i \sim \text{Poisson}(\lambda x)$$





Queueing analogy[6]

[6] Michelusi et al (2015)

Quorum size

quorum

noun [C] · US /ˈkwɔr·əm, ˈkwoʊr-/

the number of members who must be present at a meeting in order for decisions to be officially made

- Cambridge Dictionary

$$A_i = \begin{cases} 0 & i\text{-th cell is } \textbf{inactive} \\ 1 & i\text{-th cell is } \textbf{active} \end{cases}$$

Colony of N cells

Quorum of size τN

$$\sum_{k=1}^{N} A_k \geq \tau N$$

Public goods interpretation

Exofactor production is a **costly** **investment**

The **public benefit** is enjoyed by the **entire colony**

The benefit only kicks in **if a quorum is reached** (**risk**)

Pay-off

$$\mathcal{U}_i(A_i, A_{-i}, X) = \tau X \cdot \mathbf{1}\left(\sum_{k=1}^{X} A_k \geq \tau X\right) - c \cdot A_i$$

public benefit

activation cost

public benefit is proportional to the **size of the colony**

utility = growth rate of the colony

Optimization problem

Threshold policy

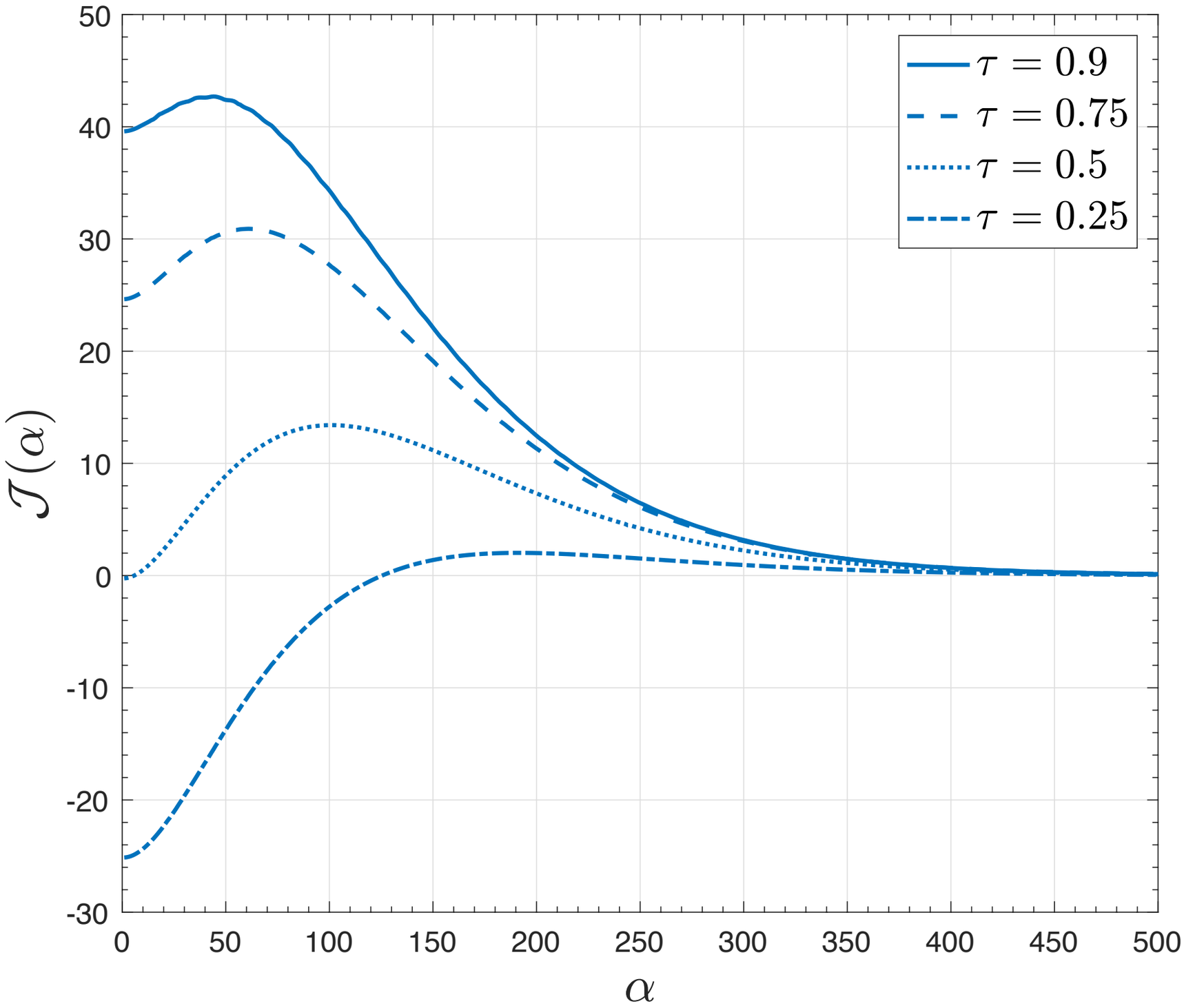
$$A_i = \mathbf{1}(Y_i \geq \alpha)$$

Find α that maximizes the function $\mathcal{J}_i$

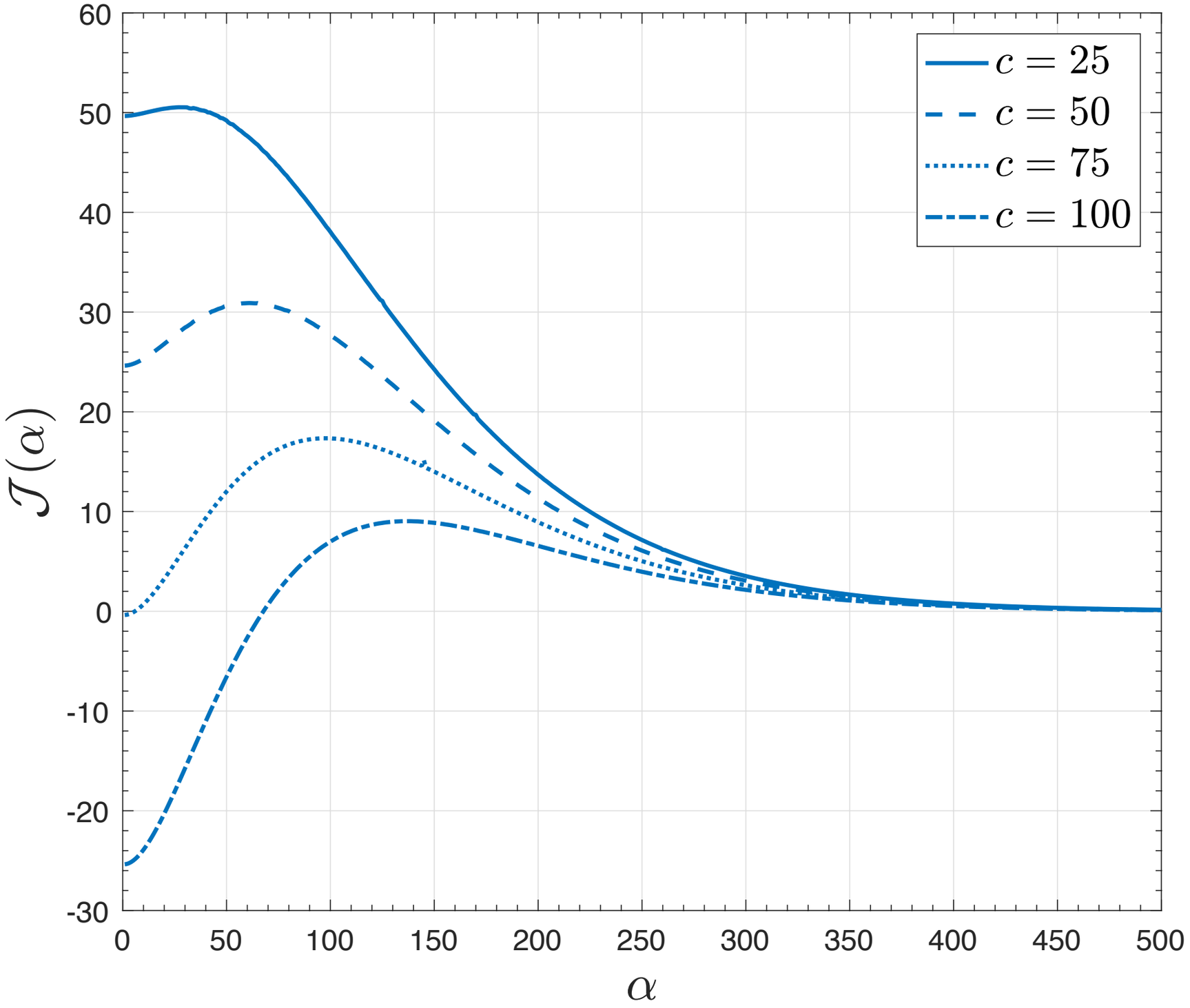
$$\mathcal{J}_i(\alpha) \triangleq \mathbf{E}\Big[\mathcal{U}_i(A_i, A_{-i}, X)\Big]$$

Threshold optimization

Quorum sensing

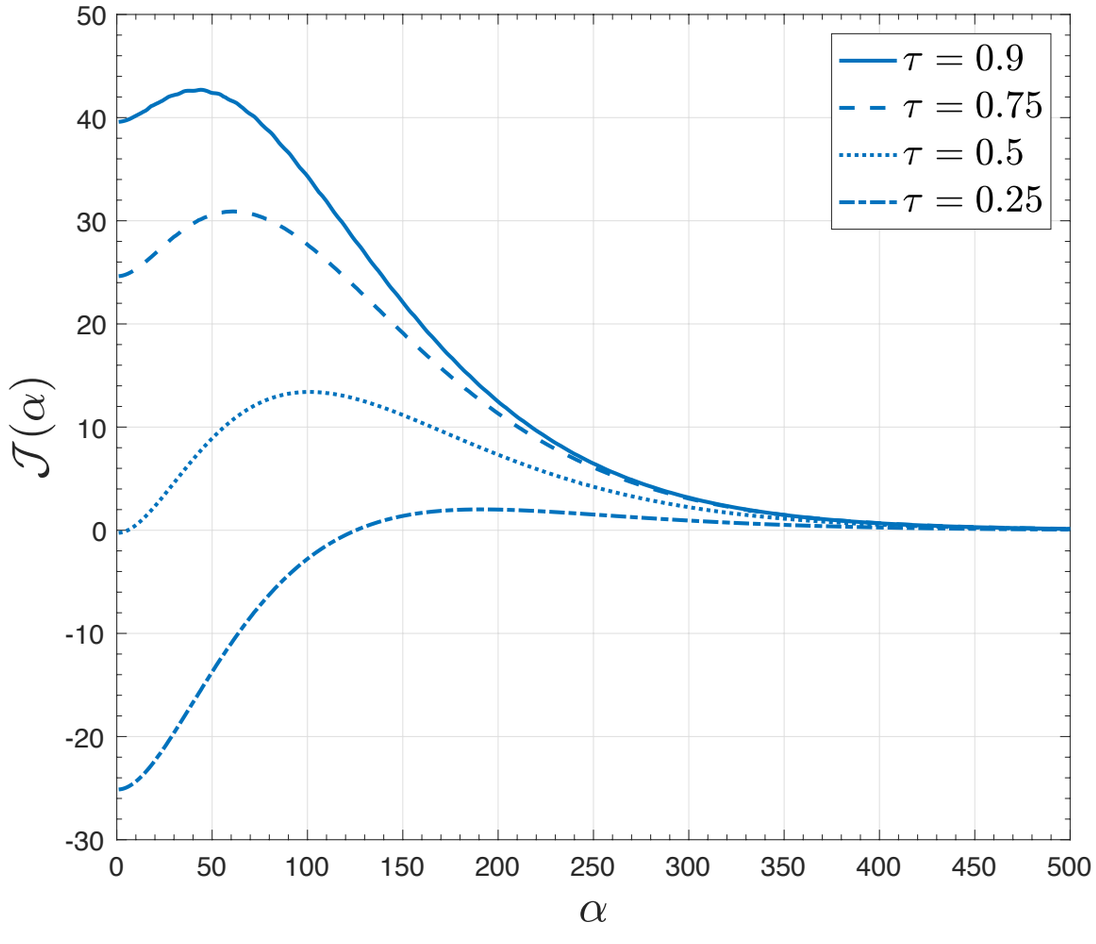


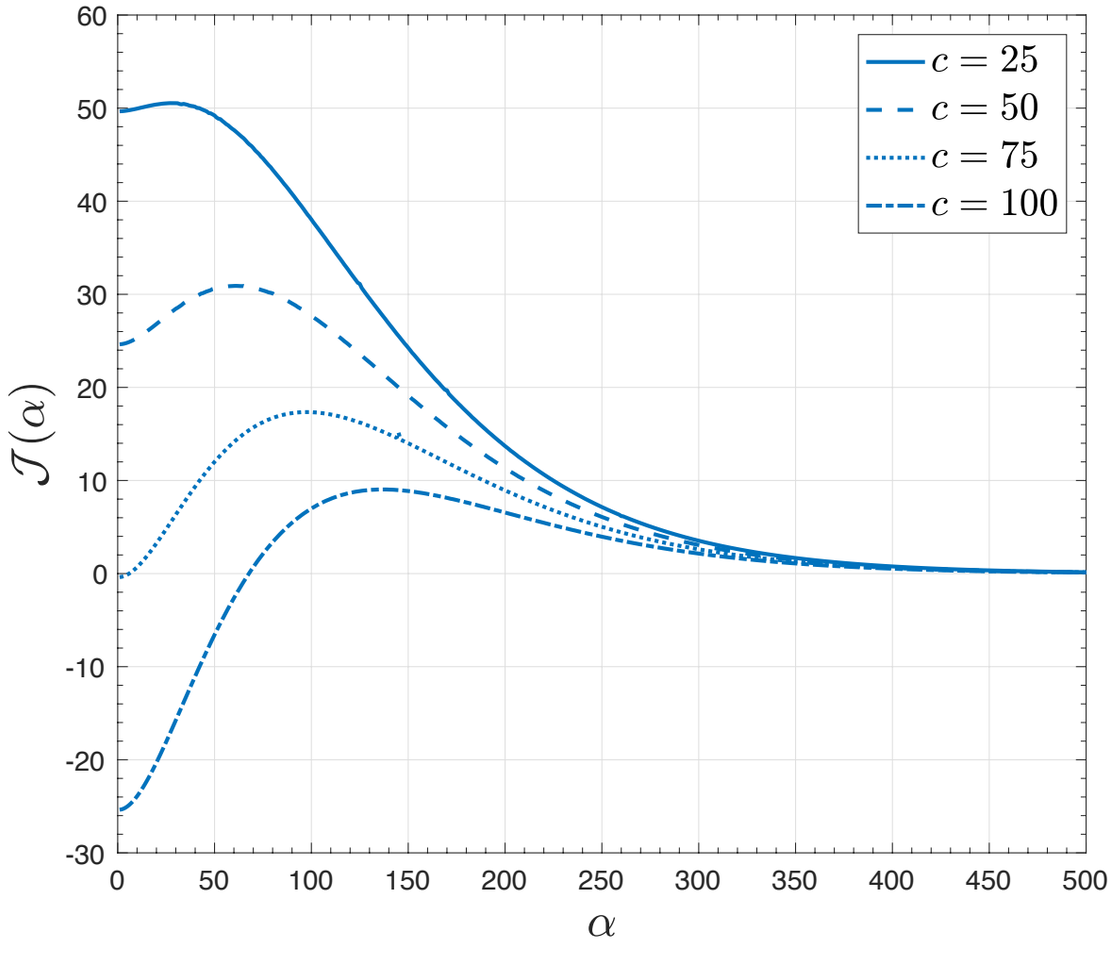
Quorum sensing



Quorum sensing

$\mathcal{J}$ is **unimodal** in α



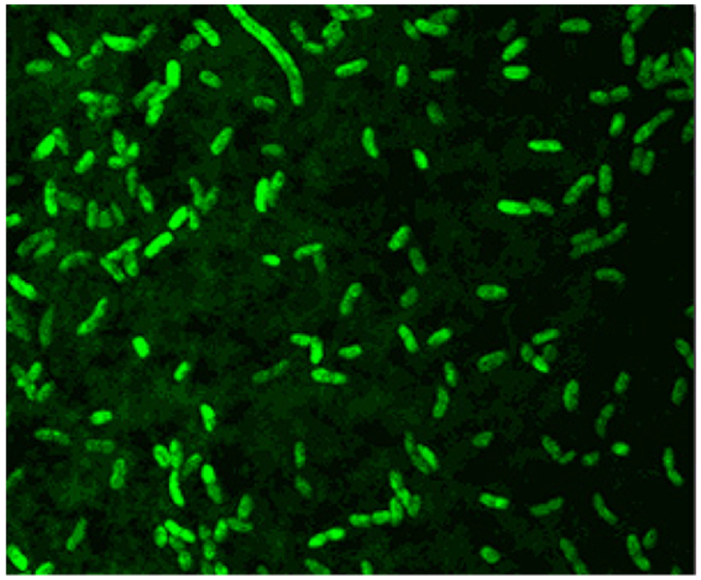


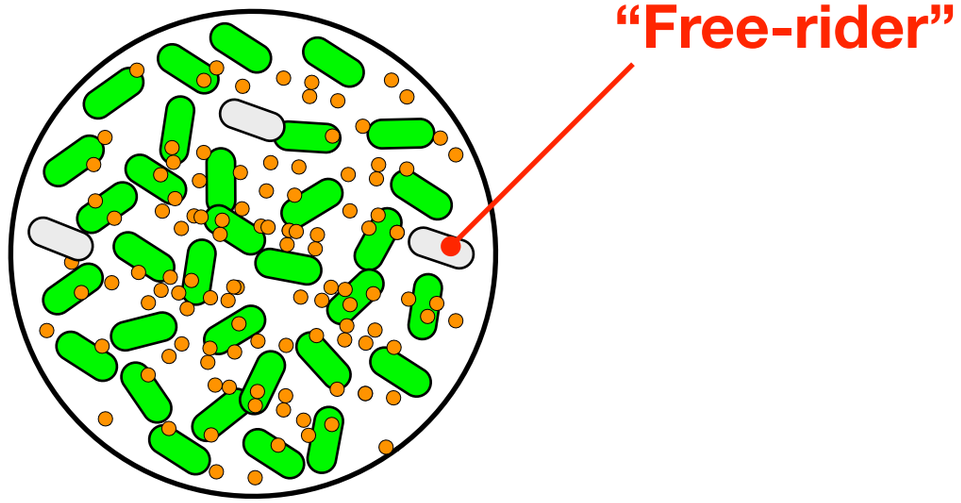
Free-riding bacteria

Free riding (cheating)

Agent that **benefits** from

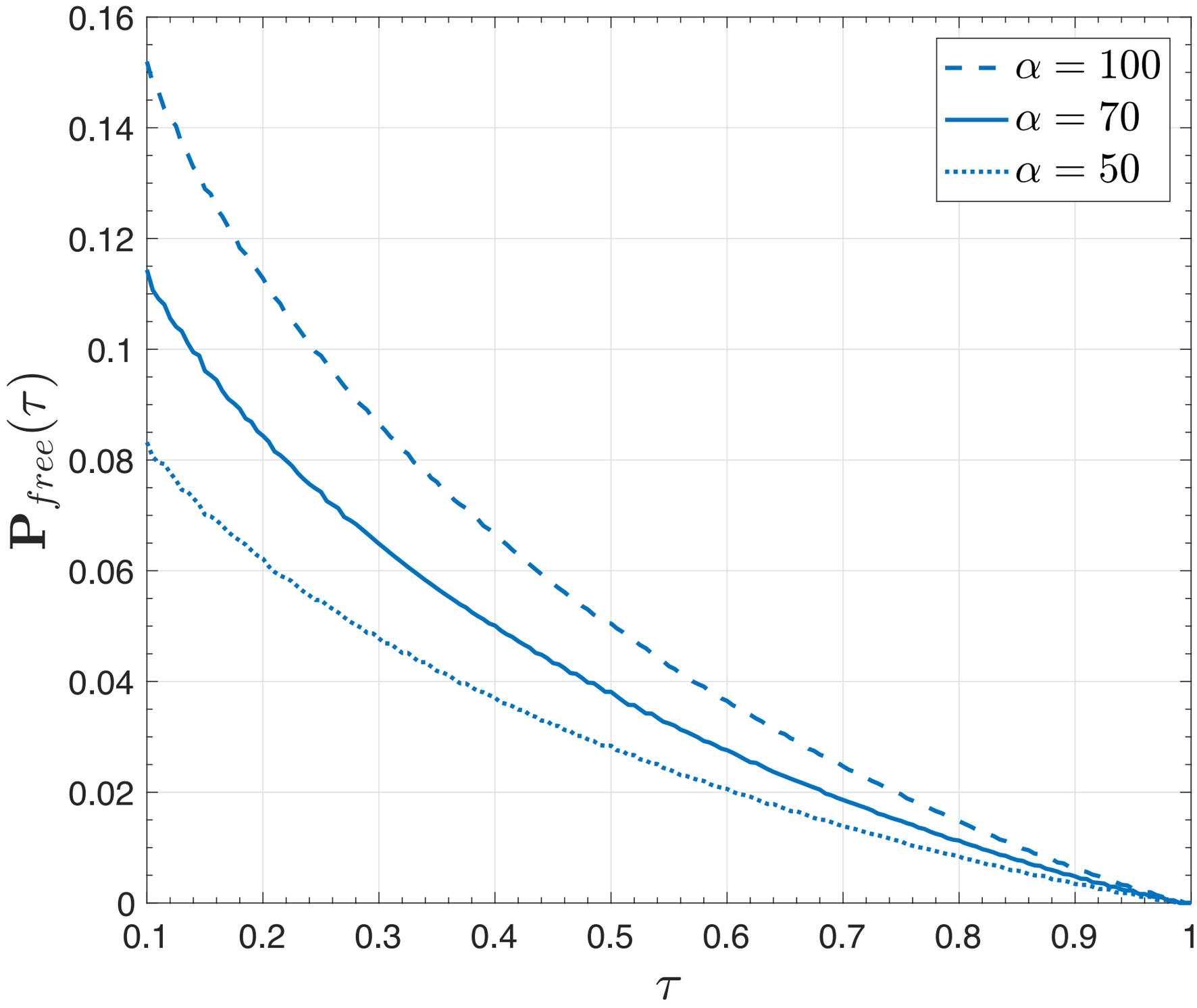
public goods but is **inactive**





$$\mathbf{P}_{free}(\tau) = \mathbf{P}\left(A_i = 0 \;\middle|\; \sum_{k \neq i} A_k \geq \tau X \right)$$

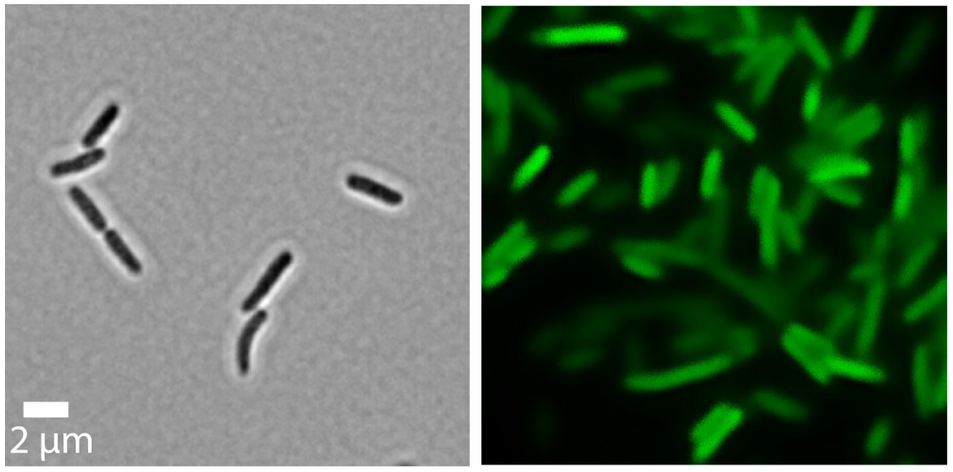
Free riding

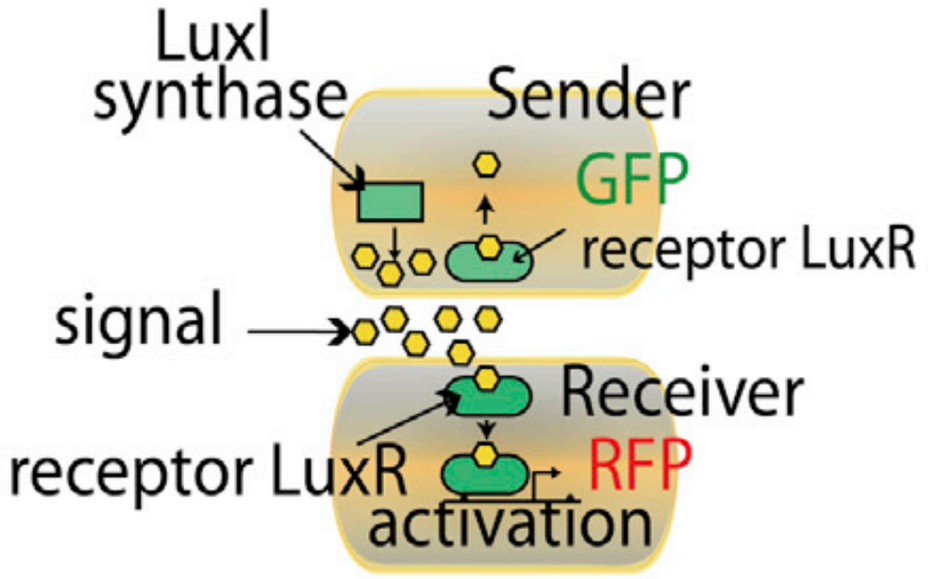

0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
τ
$\mathbf{P}_{free}(\tau)$
$\alpha = 100$
$\alpha = 70$
$\alpha = 50$

Experimental results

Bacteria strain

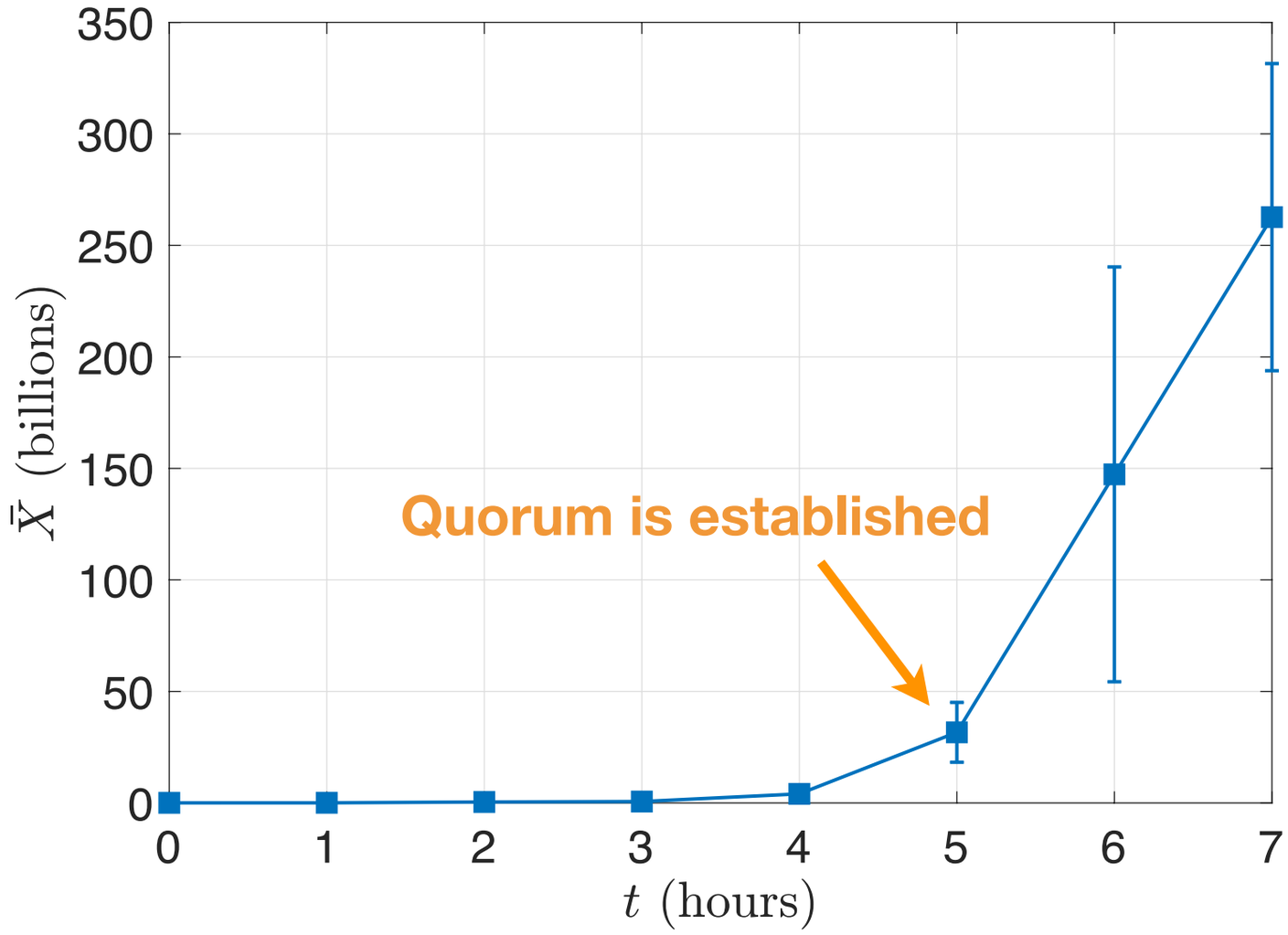
E. Coli ptd103 LuxI/R





Threshold	$\alpha = 70\text{nM}$
Auto-inducer emission rate	$\lambda = 2.3 \times 10^{-9}$ nmol

Experimental data



t (h)	$\bar{X}$ (10^9 cells/L)	σ_X (10^9 cells/L)	$\lambda\bar{X}$ (nM)	p
0	0.0465	0.0140	0.1070	0
1	0.0653	0.0011	0.1503	0
2	0.4267	0.0833	0.9813	0
3	0.6400	0.1637	1.4720	0.0135
4	4.0667	0.5033	9.3533	0.1038
5	**31.6667**	**13.4079**	**72.8333**	**0.8538**
6	147.3333	93.0017	338.8667	0.9953
7	262.6667	68.8573	604.1333	1

Sharp transition happens here!

Proportion of activated cells

Calibrating the model

Estimate the quorum coefficient

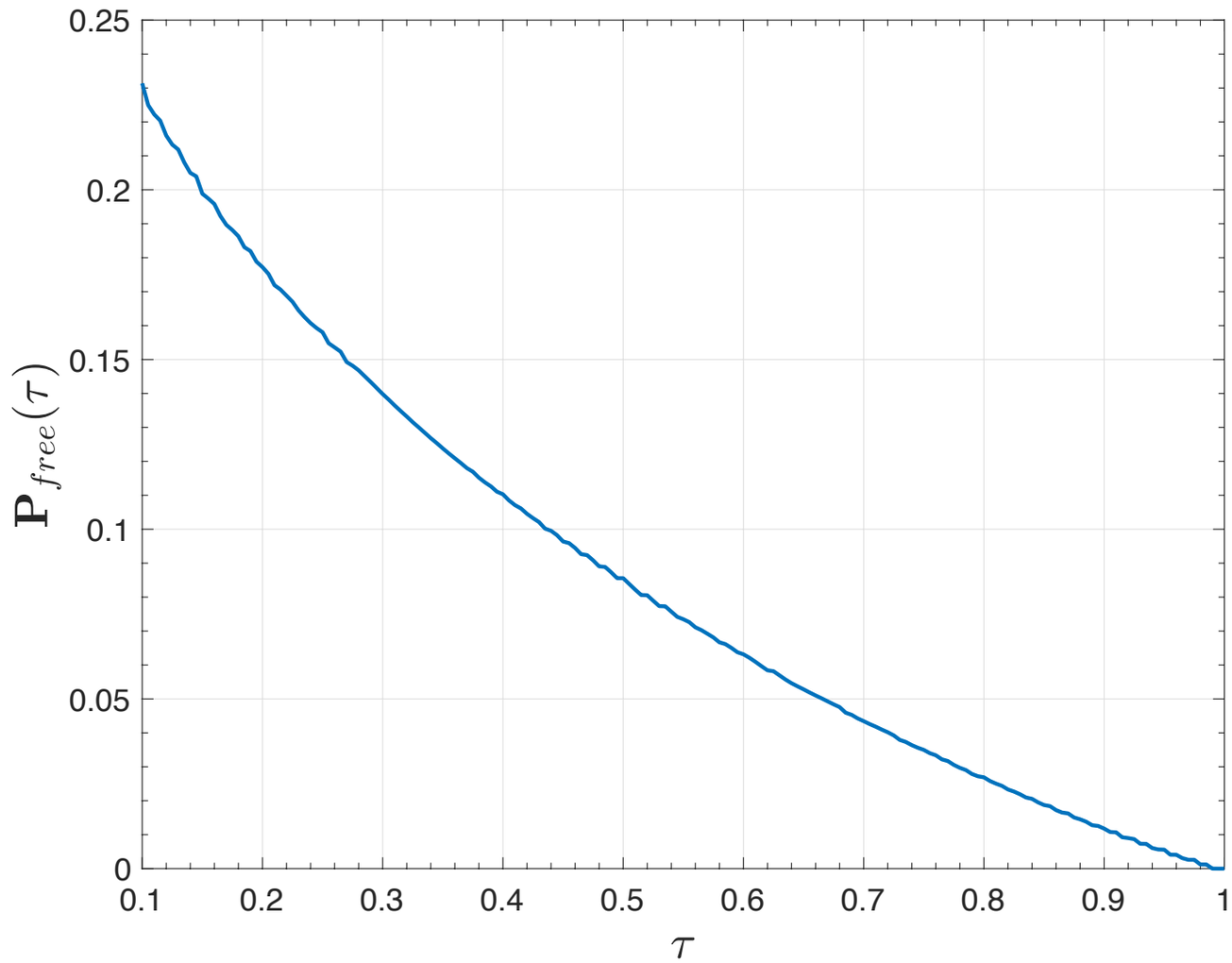
$$\bar{X} = 31.6667$$

$$\sigma = 13.4079$$

$$\kappa = 5.5780$$

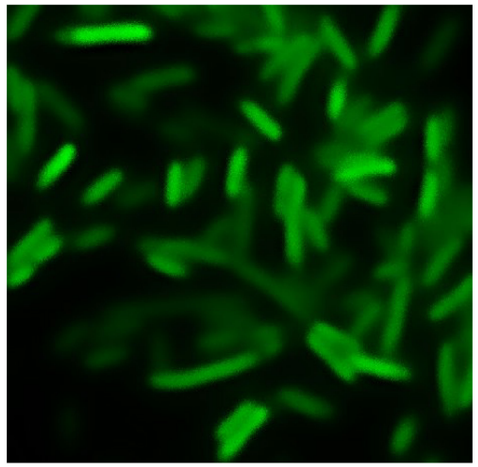
$$\theta = 5.6770$$

$$X \sim \text{Gamma}(\kappa, \theta)$$



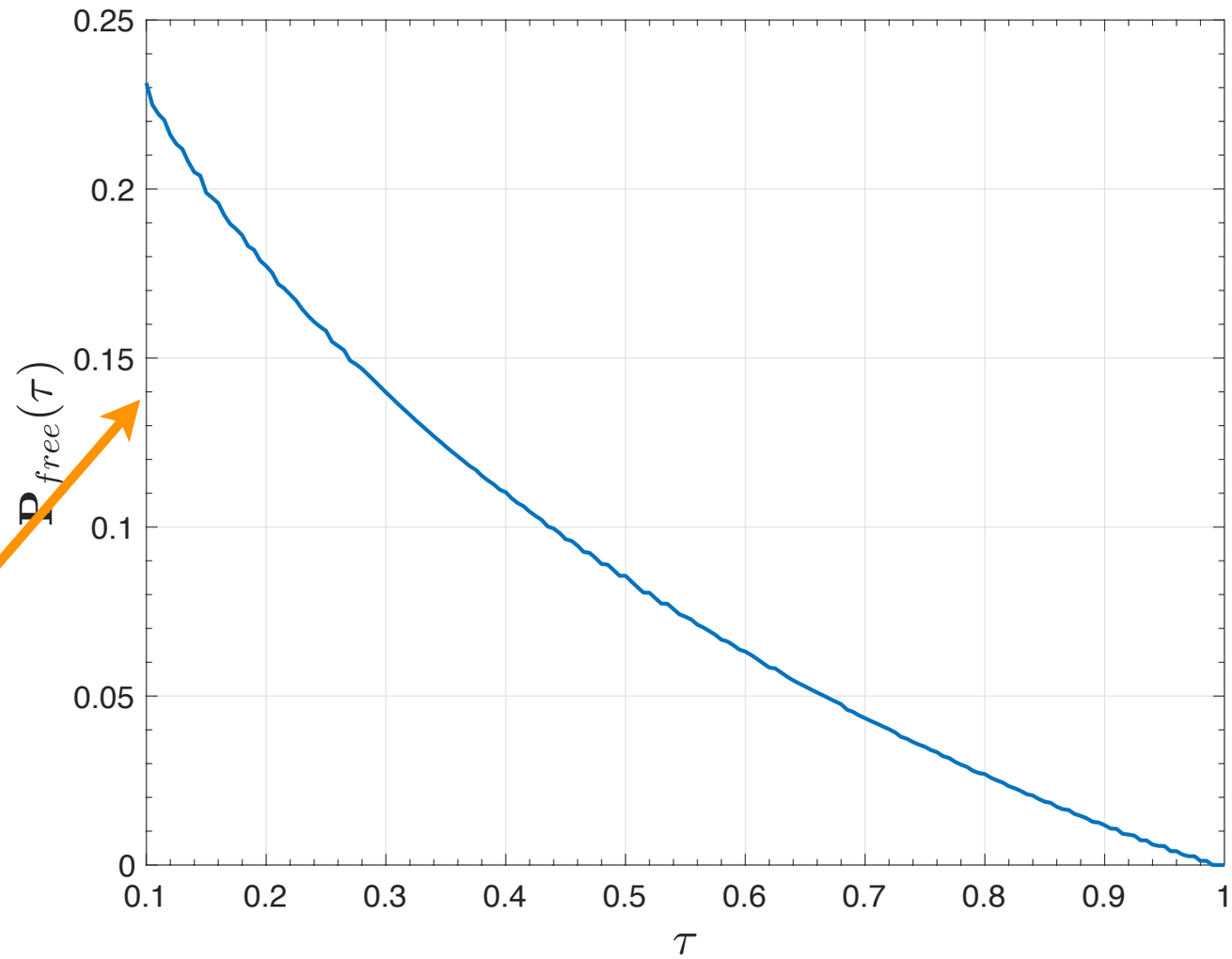
Calibrating the model

Estimate the quorum coefficient



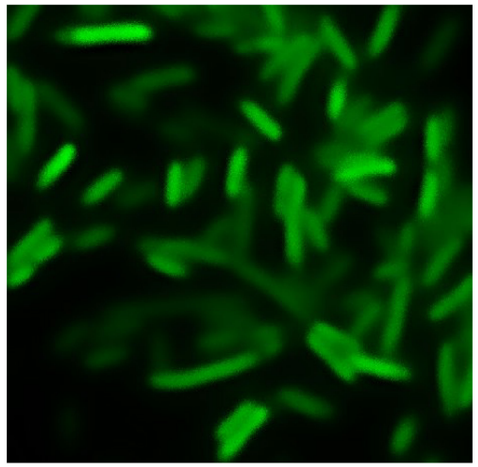
Frequency of free-riders

$$\boldsymbol{p} \approx 0.14$$



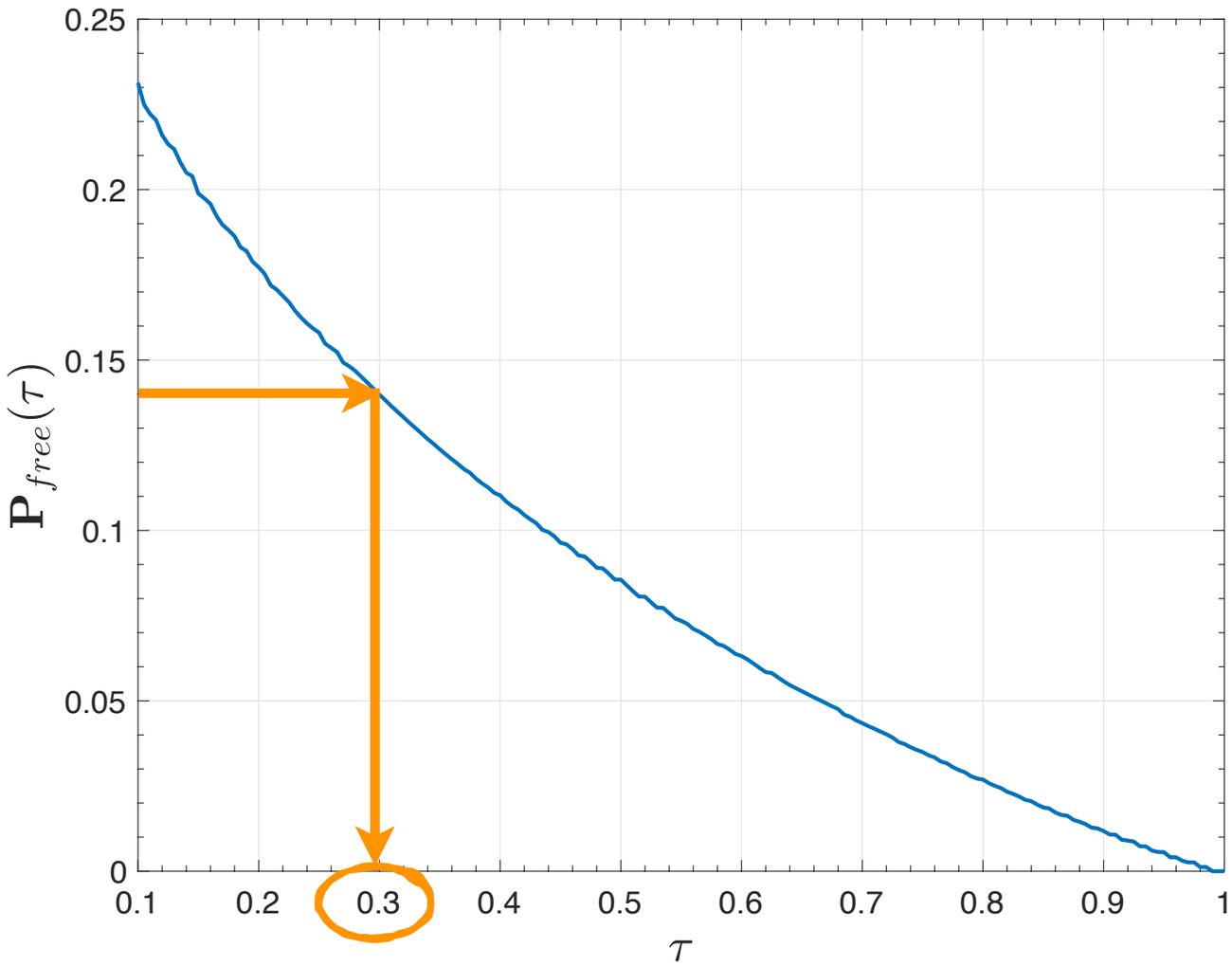
Calibrating the model

Estimate the quorum coefficient



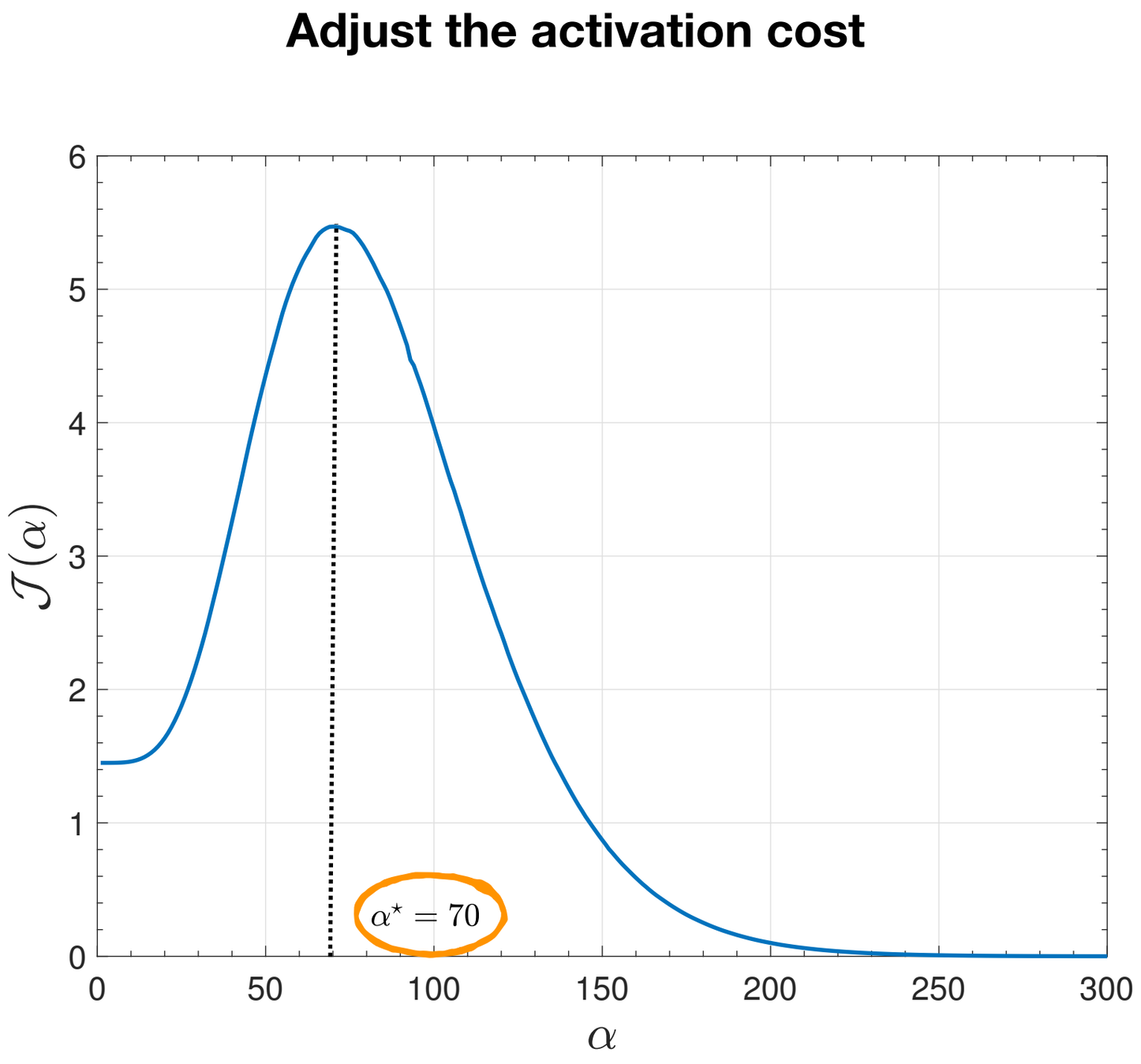
Frequency of free-riders

$$\boldsymbol{p} \approx 0.14$$



$$\hat{\boldsymbol{\tau}} = 0.3$$

Calibrating the model



$$\hat{\boldsymbol{c}} \approx 20.25$$

Summary

New decision theoretic model of Quorum Sensing

Cells are decision makers

Nature is the “system designer”

Formulate new hypothesis on the trade-offs between:

1. growth rate vs. activation cost

2. growth rate vs free-riding (cheating)

Future work

Our model <u>does not</u> account for dynamics

<u>Sequential model</u>

1. Signal accumulation/degradation

2. Population dynamics

<u>Open questions</u>

How do cells aggregate information?

How do bacteria avoid the "Tragedy of the Commons"?