Bacterial Quorum Sensing as a Sequential Decision Making System

Marcos Vasconcelos

mvasconc@usc.edu

www-bcf.usc.edu/~mvasconc

Odilon Camara **Urbashi Mitra** **James Boedicker**

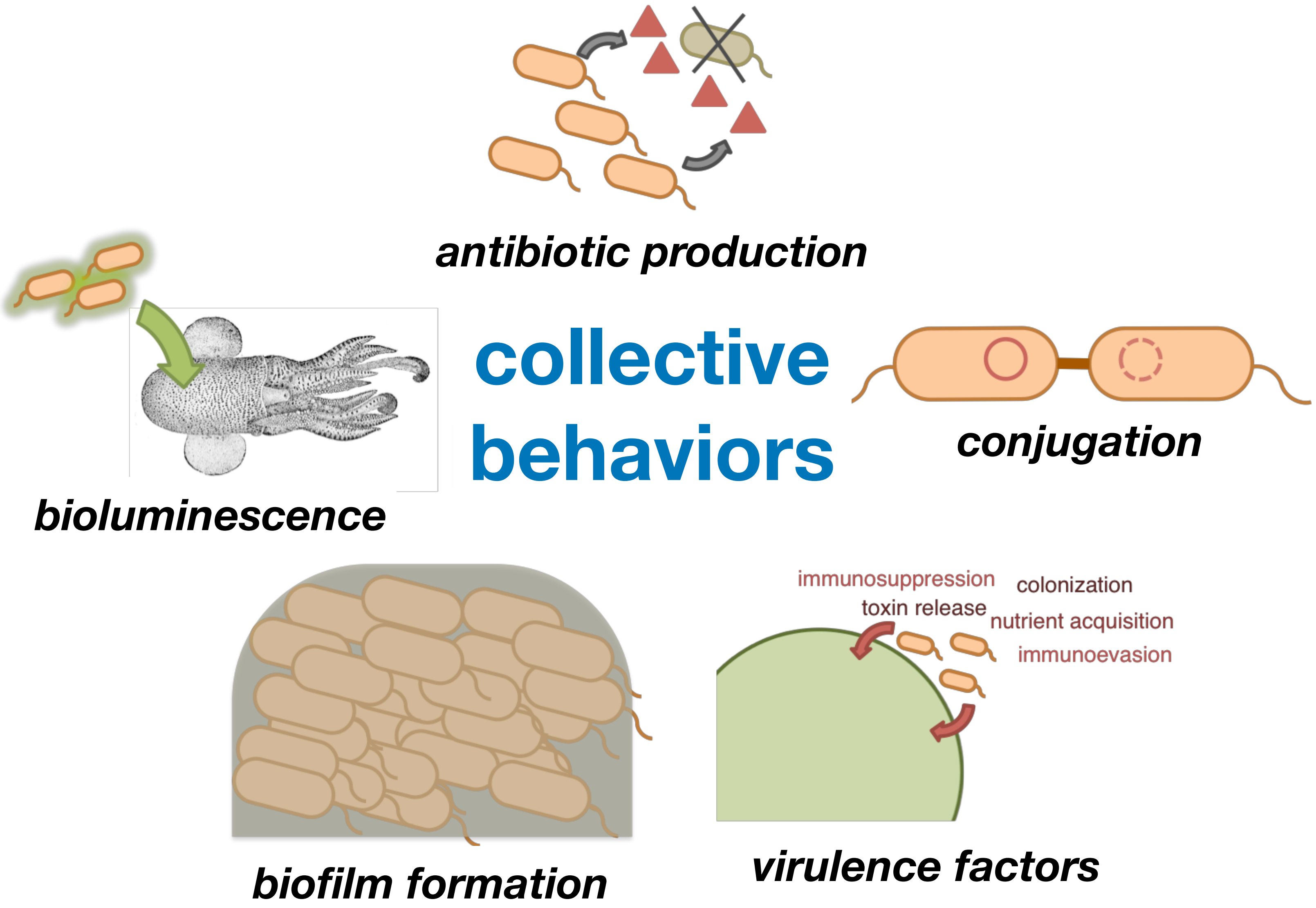
Dept. of Electrical Engineering
University of Southern California

Asilomar Conference on Signals, Systems, and Computers
October 28th-31st, 2018 - Pacific Grove, CA

Quorum sensing

Mechanism used by bacteria to coordinate

density dependent collective behavior



collective behaviors

antibiotic production

bioluminescence

conjugation

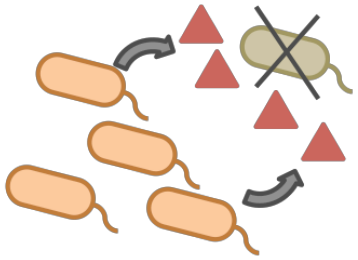
biofilm formation

virulence factors

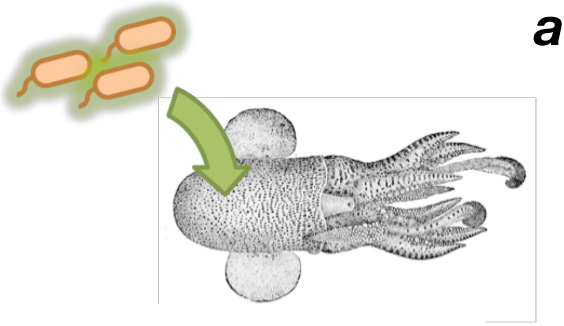
[1] http://sites.tufts.edu/quorumsensing/quorumsensing101

Quorum sensing

Enables bacteria to act as multicellular organisms!

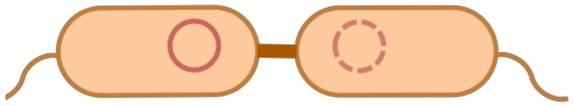


antibiotic production

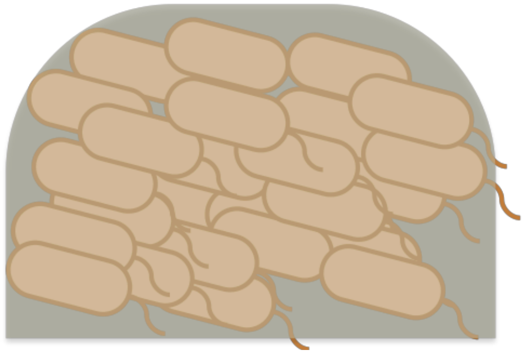


bioluminescence

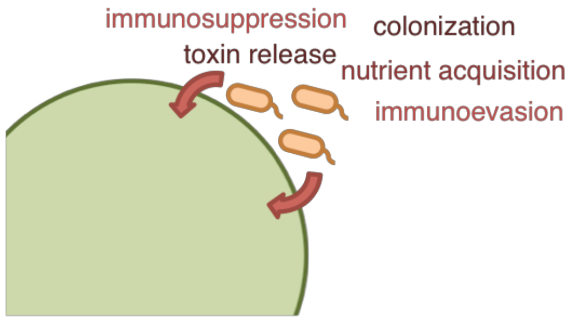
collective behaviors



conjugation



biofilm formation



virulence factors

[2] Waters and Bassler (2005)

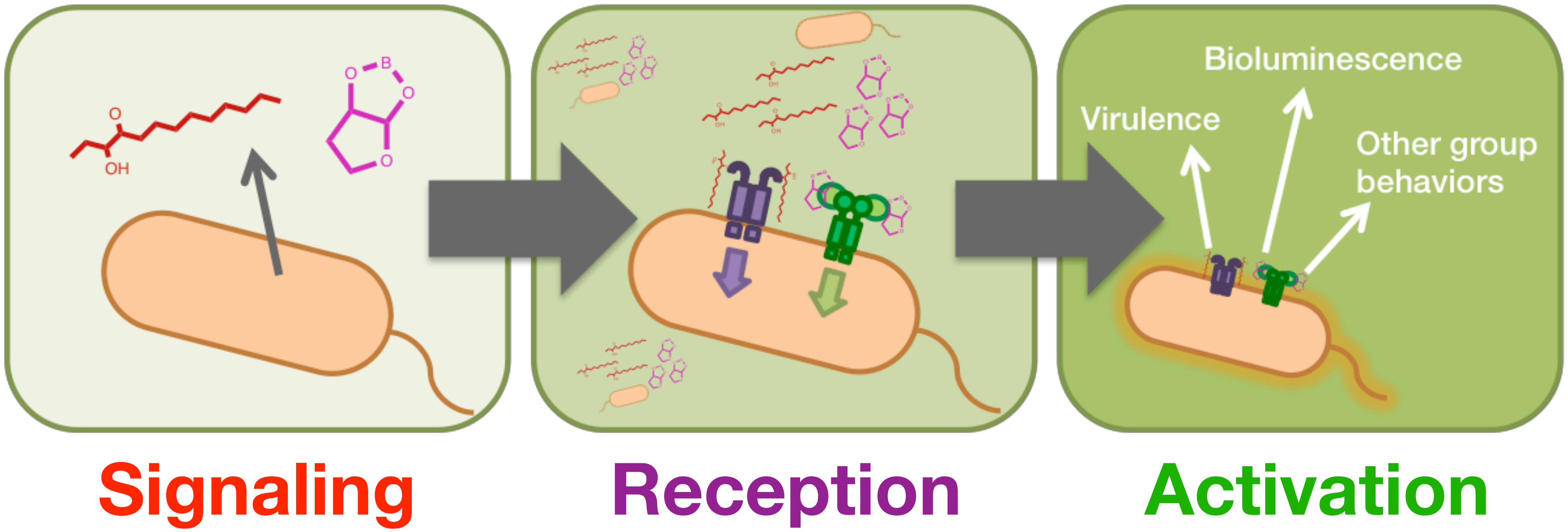
Goal

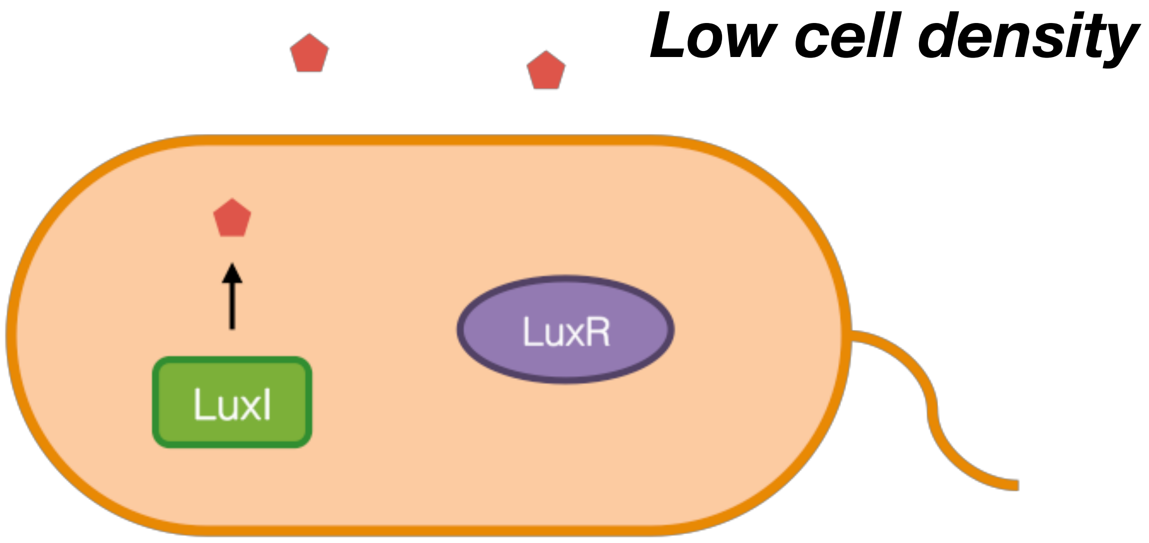
Develop a model for Quorum Sensing

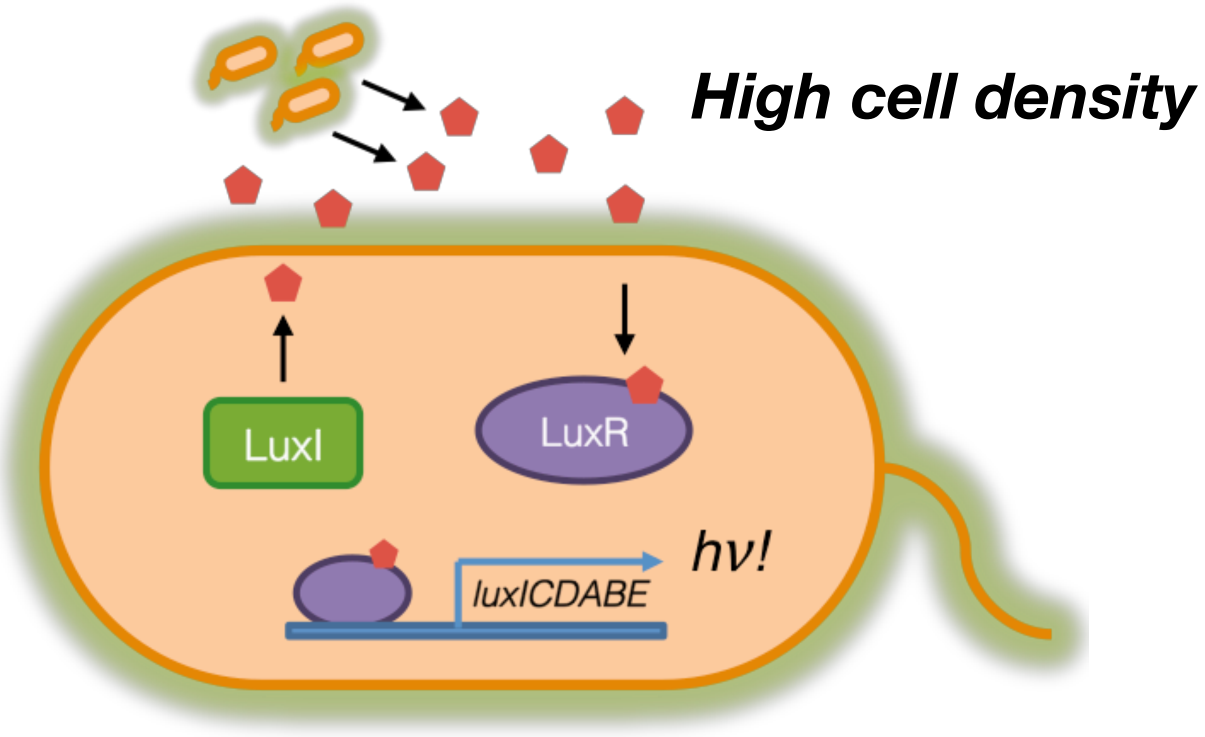
Sequential decision making based on optimal control

Optimality of QS systems

How does it work?

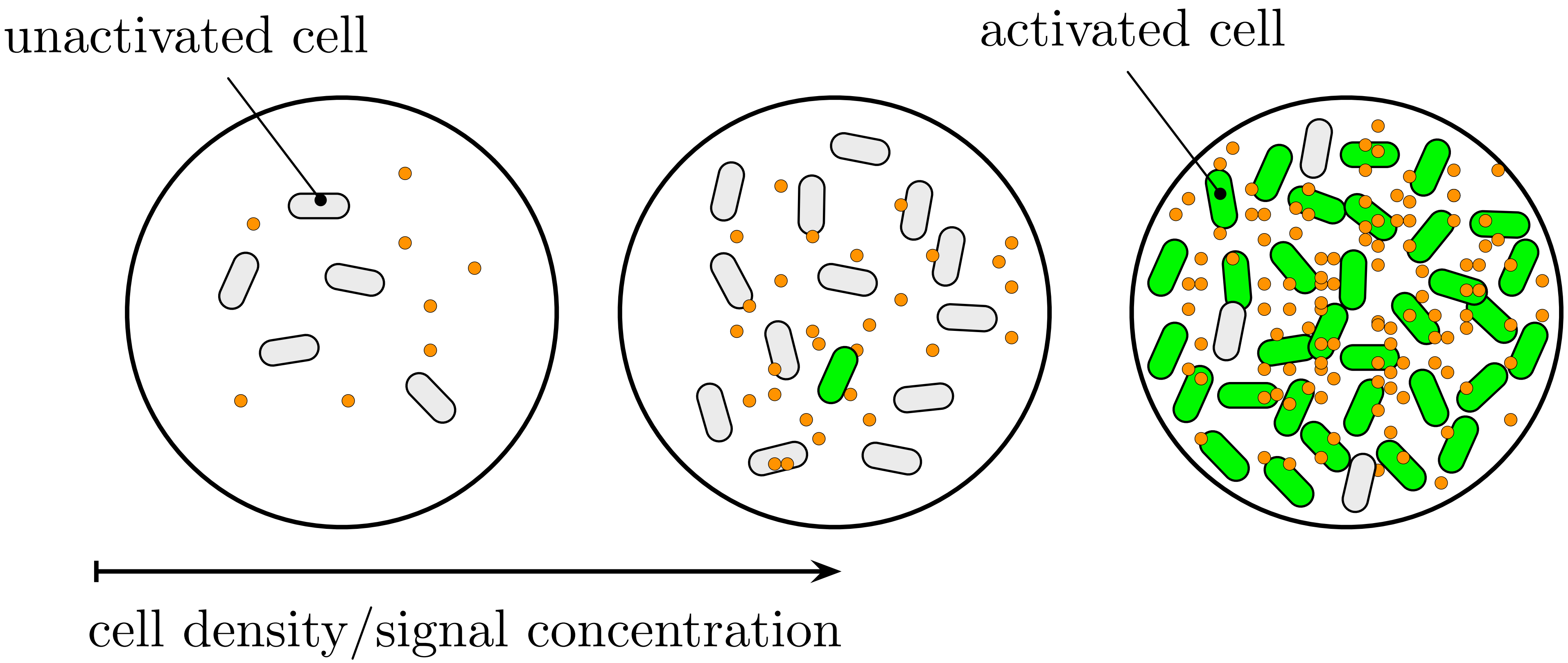


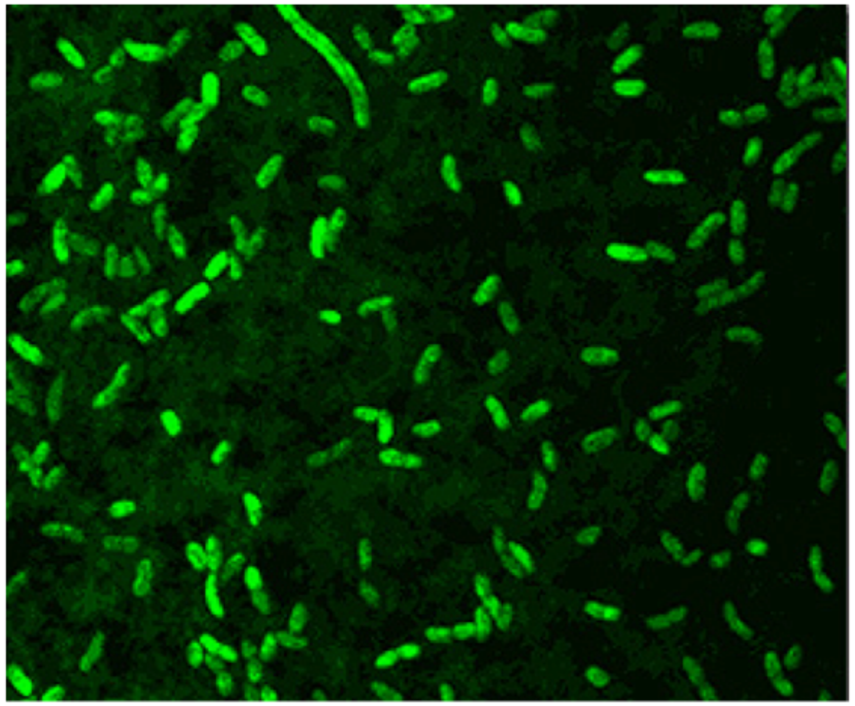


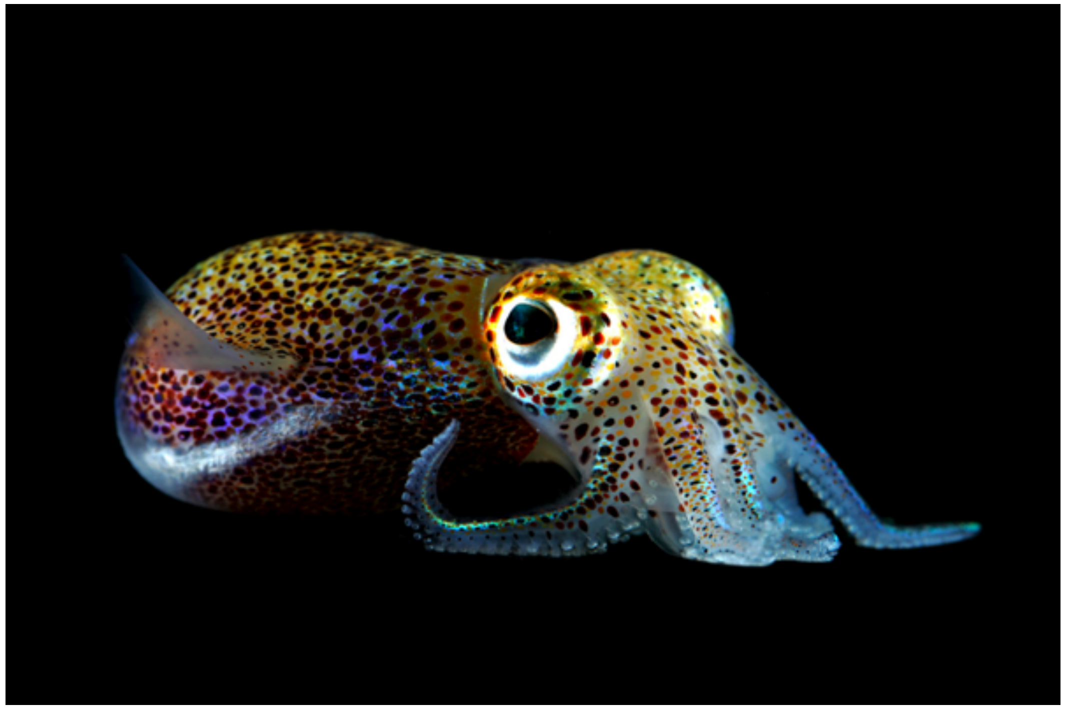


[1] http://sites.tufts.edu/quorumsensing/quorumsensing101

Quorum sensing







[3] Nealson et al. (1970)

Vibrio Fischeri luminescing

Application

Release enzymes responsible for metabolizing food

Enzymes act as public-goods

Food is available for the entire colony

Logistic Growth Model

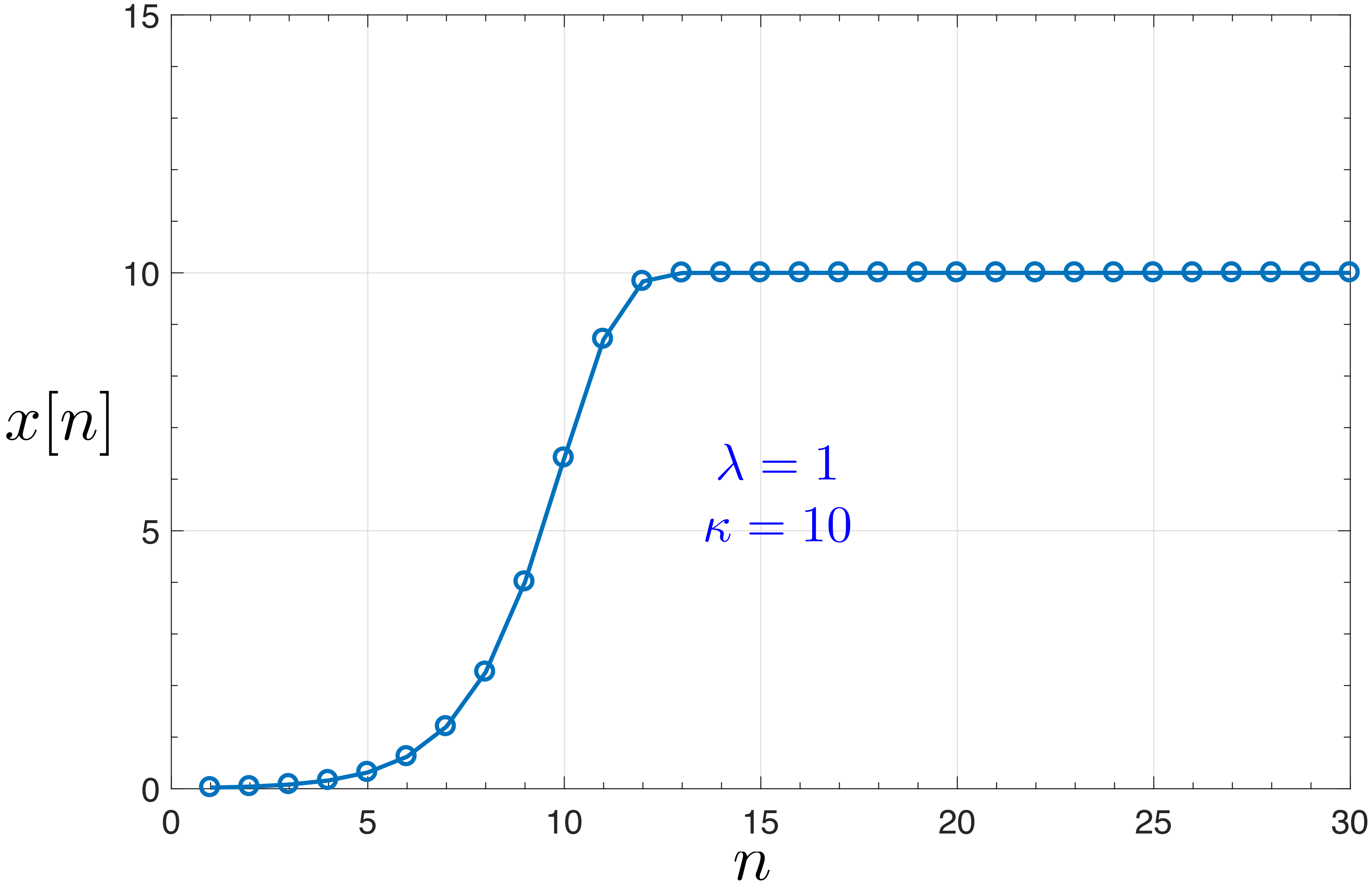
$$x[n+1] = x[n] + \boldsymbol{\lambda} \cdot x[n] \cdot \left(1 - \frac{x[n]}{\boldsymbol{\kappa}}\right)$$

Intrinsic growth rate

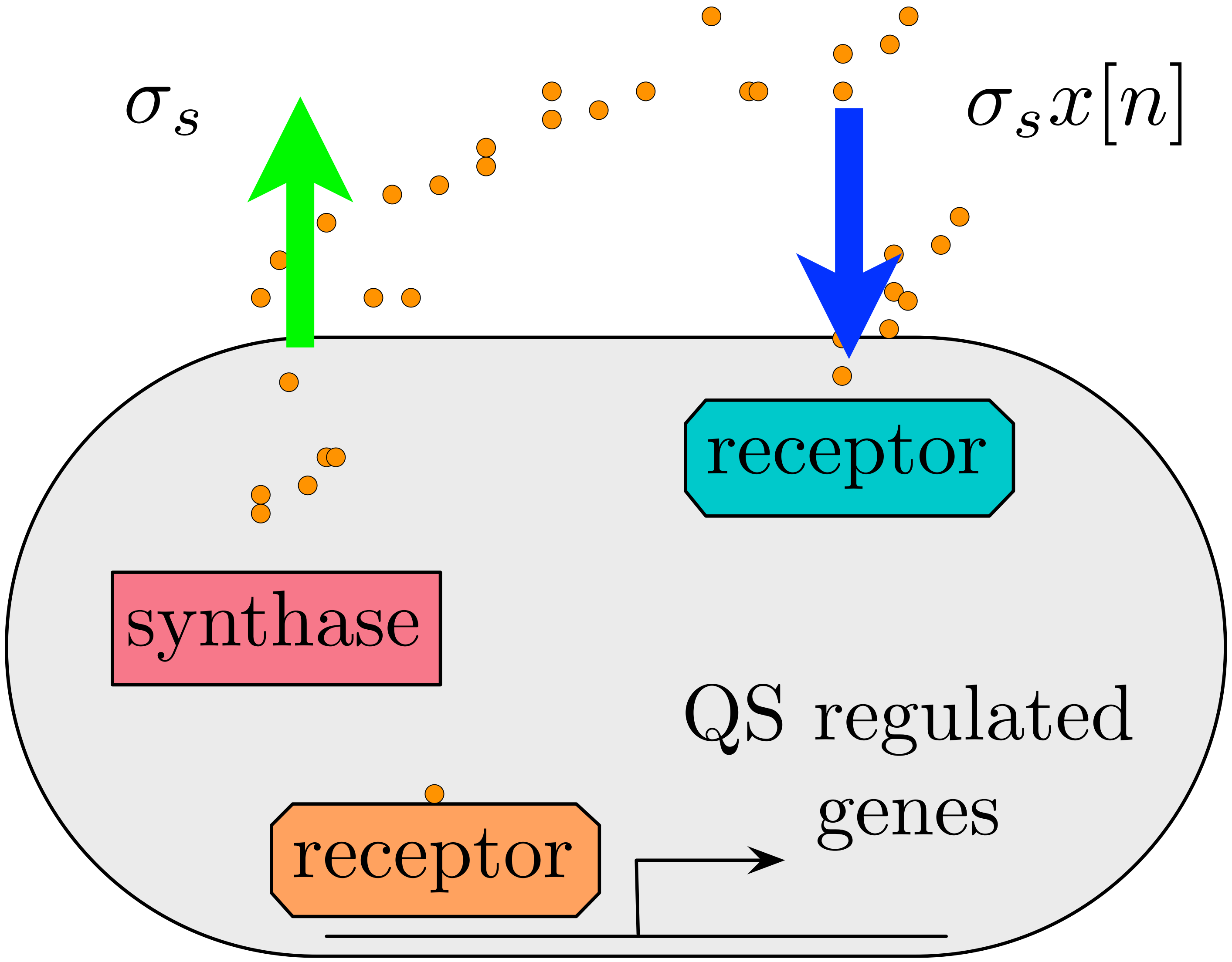
λ

Carrying capacity

κ



Signaling



$$s[n] = \sigma_s x[n]$$

received signal

WLOG $\sigma_s = 1$

Control signal

$$u[n] \in \{0, 1\}$$

Inactive

Active

Active cells produce enzymes

Inactive cells DO NOT produce enzymes

$$u[n] = \mathcal{U}\left(x[n]\right)$$

Control policy

Enzymes

$$e[n] = \sigma_e x[n] u[n]$$

public good

Increase the amount of food available for the colony

$$\Downarrow$$

Increase the Carrying Capacity of the system

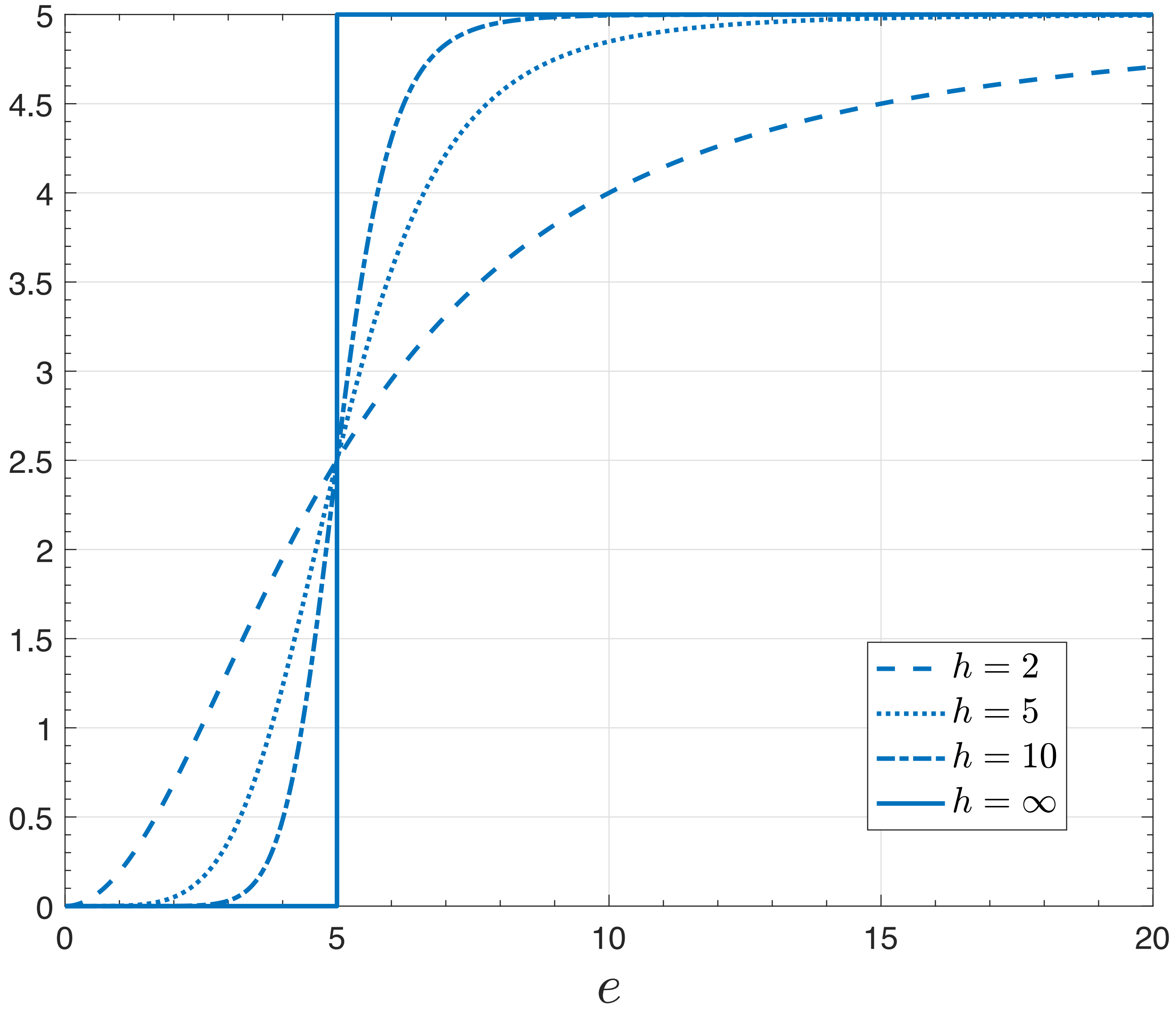
$$\kappa = \kappa_0 + \Delta\kappa(e)$$

public benefit

Public benefit $\Delta\kappa(e)$

1. **The benefit is an increasing function of public-goods**
2. **The benefit saturates at some finite value** $b_{\max}$
3. **The benefit is zero when there is no public-good present**

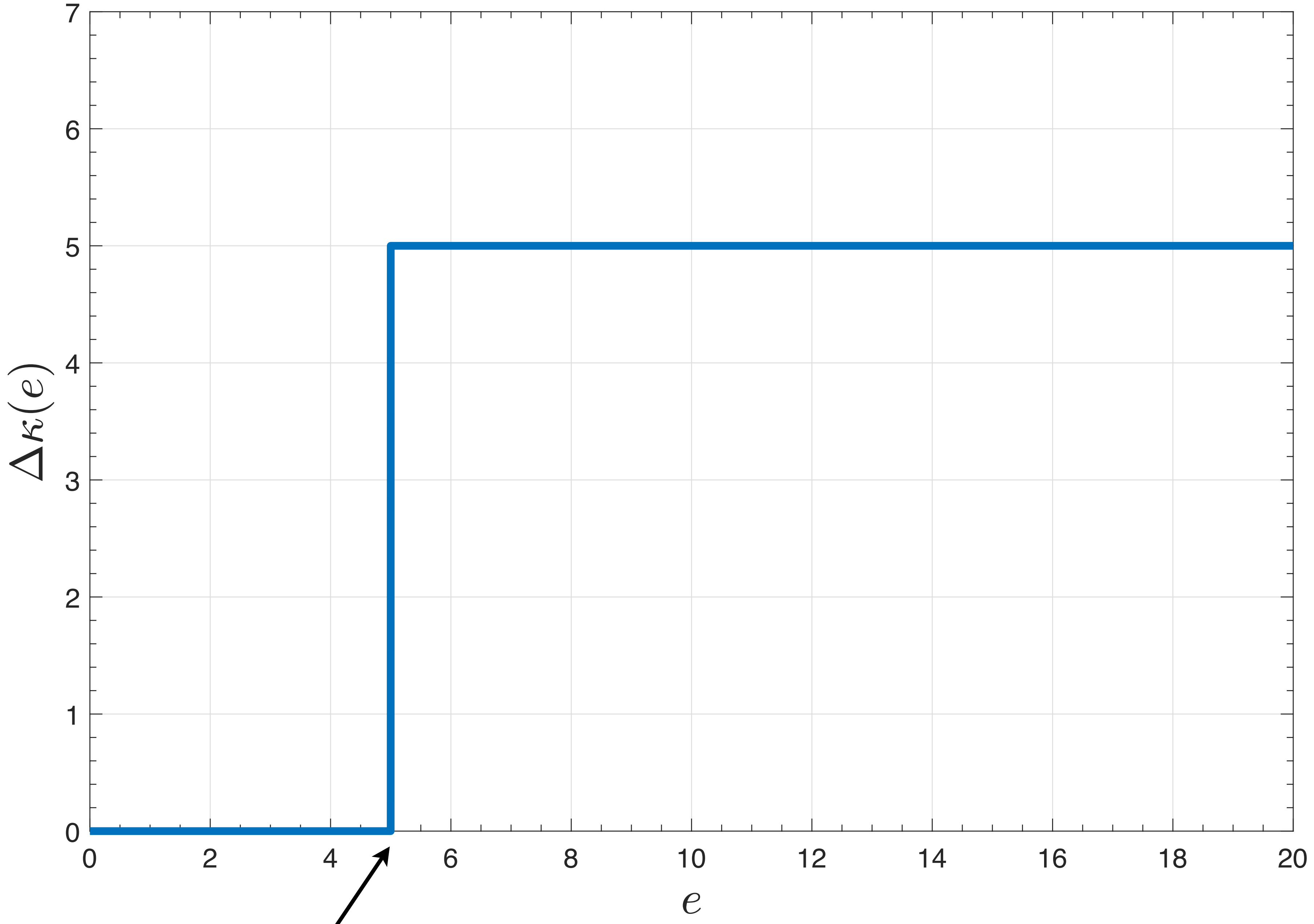
$$\boxed{\Delta\kappa(e) = b_{\max} \cdot \frac{(e/\tau)^h}{1+(e/\tau)^h}}$$



[4] Heilmann et al (Frontiers in Microbiology 2015)

Simplified public benefit function

$$\boxed{\Delta\kappa(e) = b_{\max} \cdot \mathbf{1}(e \geq \tau)}$$



$b_{\max}$

Threshold τ

Activation cost

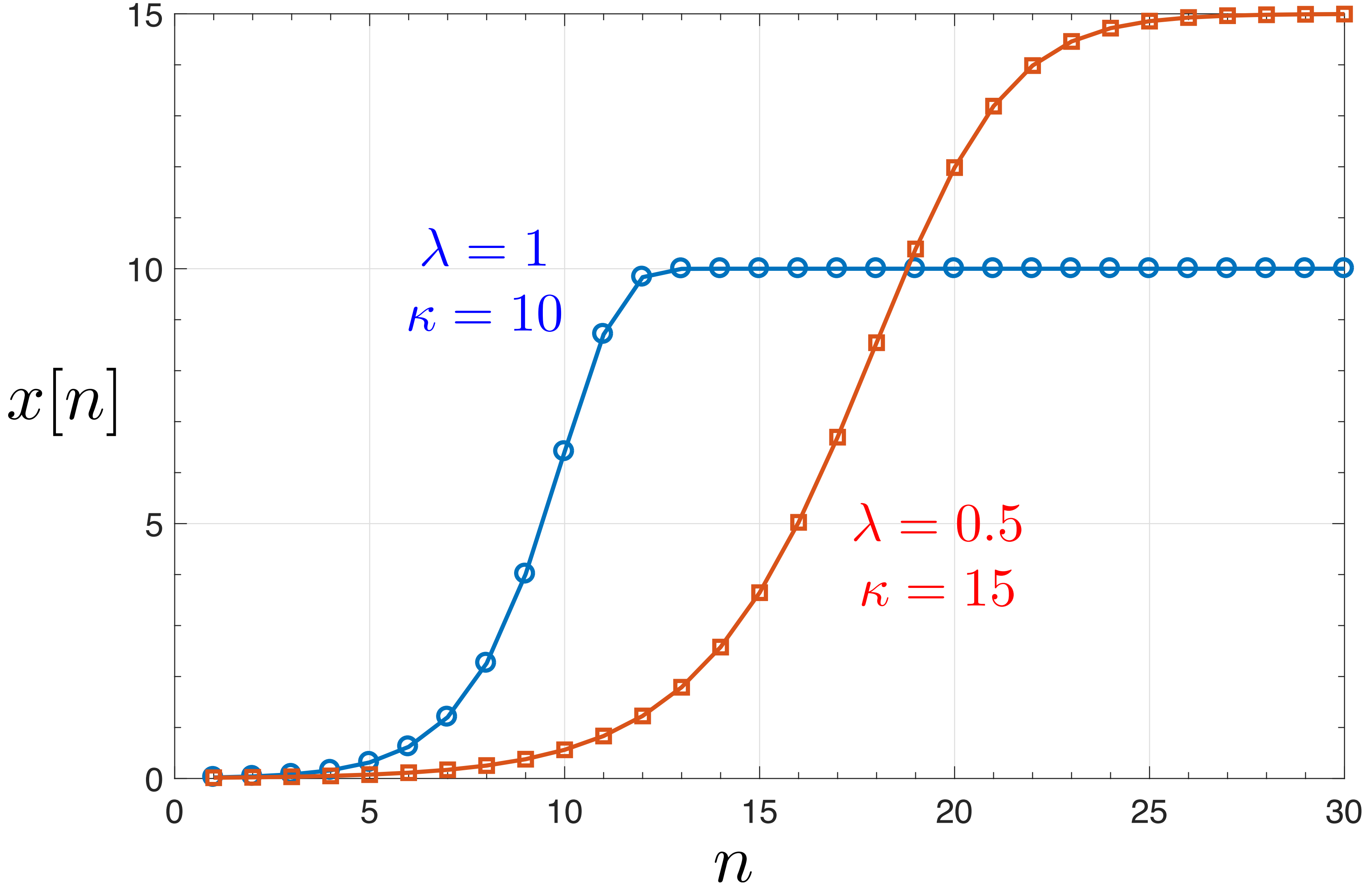
Enzymes are costly to make!

Energy spent on making enzymes $\Rightarrow$ **Less energy for reproduction**

Slow down the intrinsic growth-rate

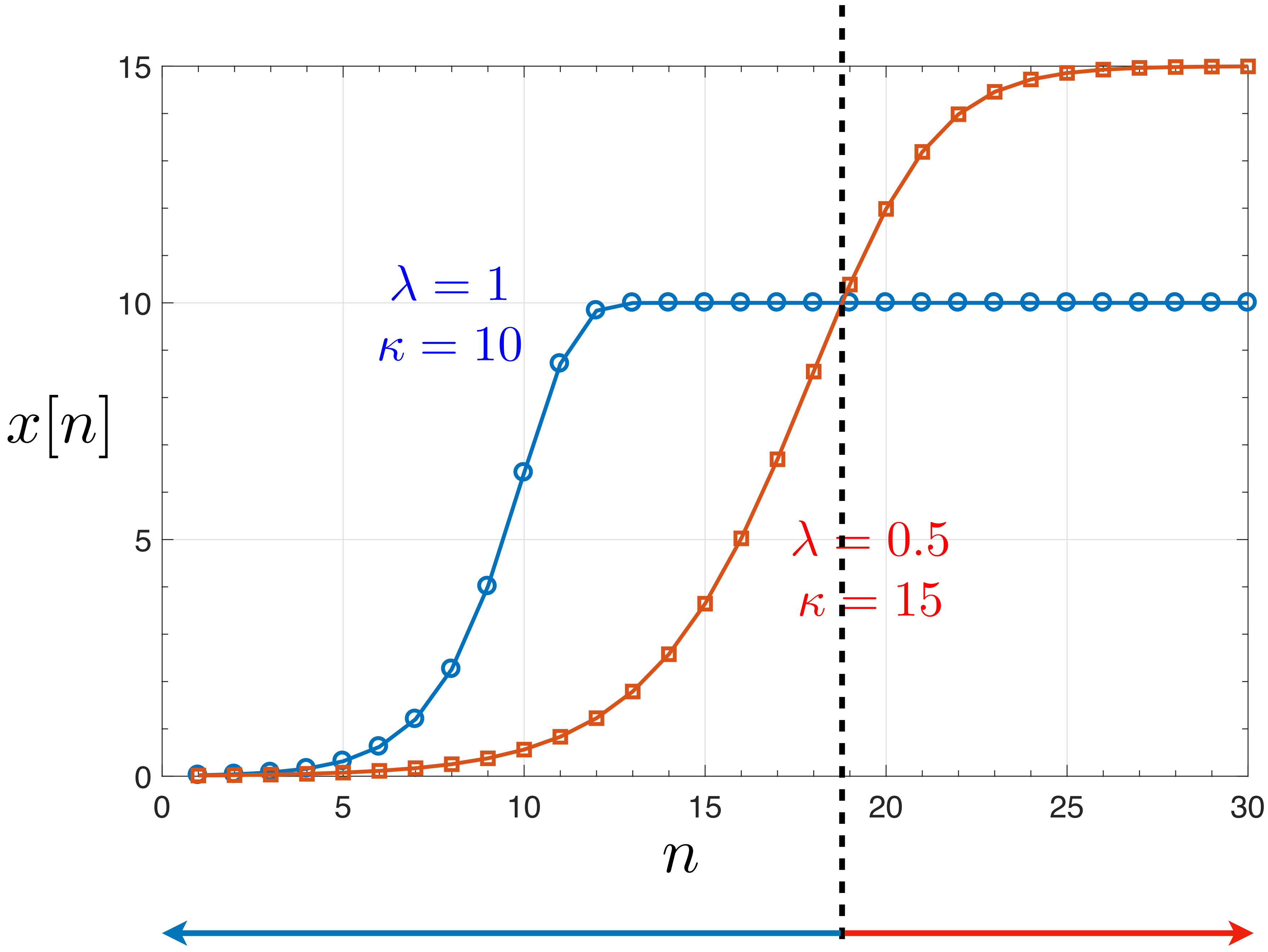
$$\boxed{\lambda = \rho - cu[n]}$$

Intrinsic growth-rate vs carrying capacity



What is the best growth curve?

Intrinsic growth-rate vs carrying capacity



maximize instantaneous population $x[n]$

[5] Pai et al. (PNAS 2012)

Objective function

$$\boxed{\mathcal{V}(\mathcal{U}) = \sum_{n=0}^{\infty} \beta^n \big(1 - \alpha u[n]\big) x[n]}$$

β

Intertemporal trade-off

α

Energetic cost

Low β **we prioritize the present**

High β **we prioritize the future**

Optimal control problem

maximize
$$\mathcal{V}(\mathcal{U}) = \sum_{n=0}^{\infty} \beta^n \big(1 - \alpha u[n]\big) x[n]$$

subject to
$$x[n+1] = \mathcal{F}\big(x[n], u[n]\big)$$

$$\mathcal{F}(x,u) = x + (\rho - cu)x\left(1 - \frac{x}{\kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(xu \geq \tau/\sigma_e)}\right)$$

Intrinsic growth rate

Carrying capacity

Results

The optimal control is a threshold policy

$$\mathcal{U}^*(x) = \mathbf{1}(x \geq x^*)$$

$$\alpha = 0$$

Optimal threshold is computed in closed form

$$x^* = \max\left\{\frac{c\kappa_0\kappa_1}{(\kappa_1 - \kappa_0)\rho + c\kappa_0}, \frac{\tau}{\sigma_e}\right\}$$

$$\alpha > 0$$

Optimal threshold is computed numerically

Sketch of proof

Bellman Eq

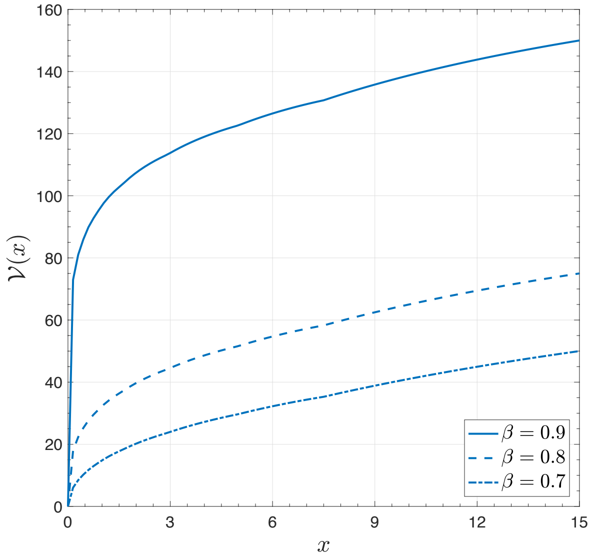
$$\mathcal{V}(x) = \max_{u \in \{0,1\}} \Big\{ (1 - \alpha u)x + \beta \mathcal{V}\big(\mathcal{F}(x,u)\big) \Big\}$$

$$\alpha = 0$$

$$\mathcal{V}(x) = x + \beta \max_{u \in \{0,1\}} \Big\{ \mathcal{V}\big(\mathcal{F}(x,u)\big) \Big\}$$

Lemma

$\mathcal{V}(x)$ is monotone increasing



Value function iteration

+

Real analysis

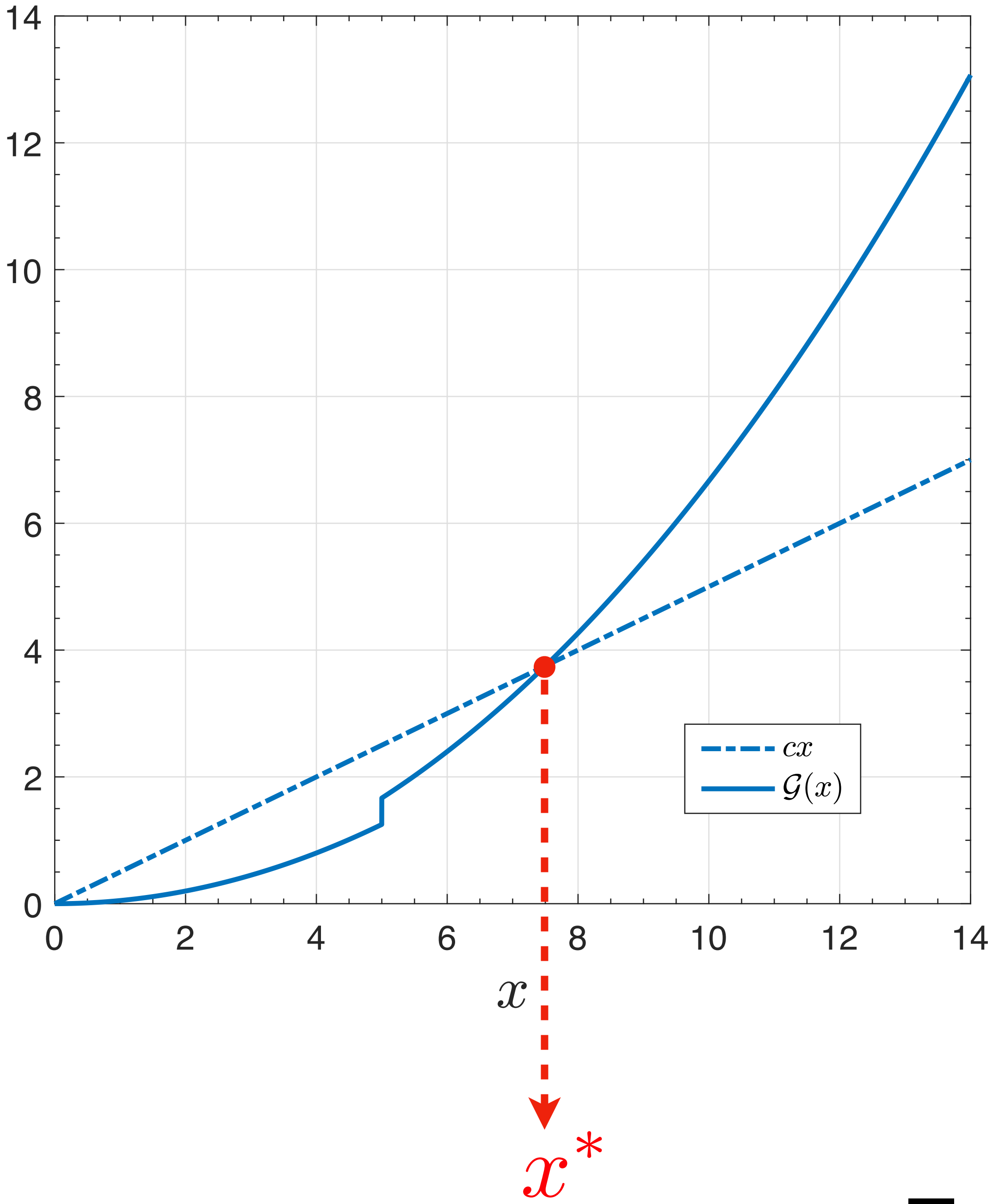
$$\mathcal{U}^*(x) = 1 \iff \mathcal{F}(x,1) \geq \mathcal{F}(x,0)$$

Sketch of proof

$$\mathcal{F}(x^*, 1) = \mathcal{F}(x^*, 0)$$

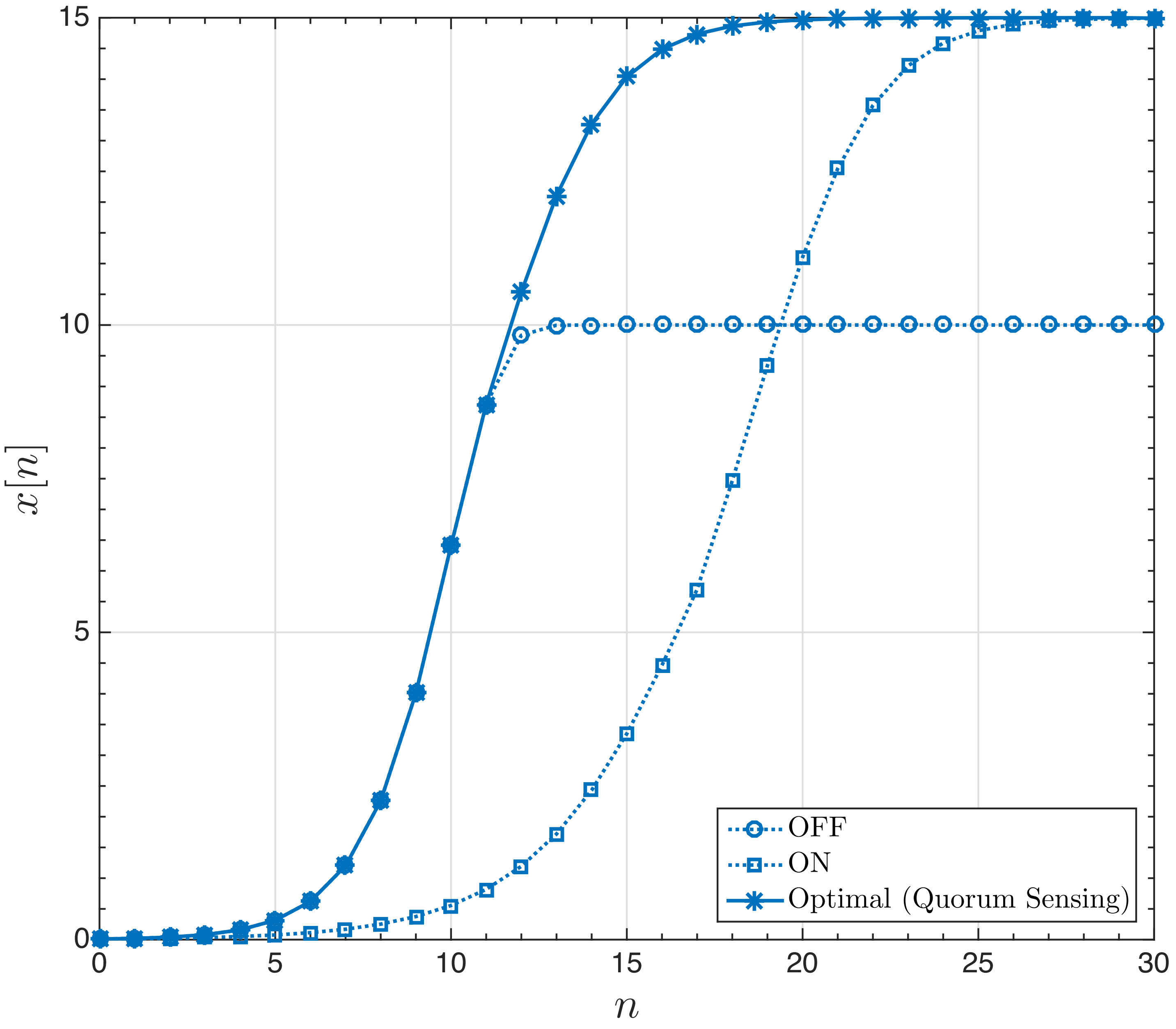
unique nonzero solution

$$x^* = \max\left\{ \frac{c\kappa_0\kappa_1}{(\kappa_1 - \kappa_0)\rho + c\kappa_0}, \frac{\tau}{\sigma_e} \right\}$$



∎

Example



$$x^* = \max\left\{\frac{c\kappa_0\kappa_1}{(\kappa_1 - \kappa_0)\rho + c\kappa_0}, \frac{\tau}{\sigma_e}\right\}$$

Optimal solution is independent of the discount factor

The role of the discount factor

$$\alpha = 0 \qquad \mathcal{V}(\mathcal{U}) = \sum_{n=0}^{\infty} \beta^n x[n]$$

Inst. loss in rate and gain in capacity

$$\lambda[n] = \rho - cu[n]$$

$$\kappa[n] = \kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(e[n] \geq \tau)$$

Given the population today, maximize the population tomorrow

Myopic policy is optimal

$$\alpha > 0 \qquad \mathcal{V}(\mathcal{U}) = \sum_{n=0}^{\infty} \beta^n \big(1 - \alpha u[n]\big) x[n]$$

Invest some of your population today to maximize future populations

The general case

Bellman Eq

$$\mathcal{V}(x) = x + \beta \max \left\{ \mathcal{V}\big(\mathcal{F}(x,0)\big), \mathcal{V}\big(\mathcal{F}(x,1)\big) - \frac{\alpha}{\beta} x \right\}$$

STEP 1

$$\mathcal{V}^{(0)}(x) = x$$

$$\mathcal{V}^{(n+1)}(x) = x + \beta \max \left\{ \mathcal{V}^{(n)}\big(\mathcal{F}(x,0)\big), \mathcal{V}^{(n)}\big(\mathcal{F}(x,1)\big) - \frac{\alpha}{\beta} x \right\}$$

STEP 2

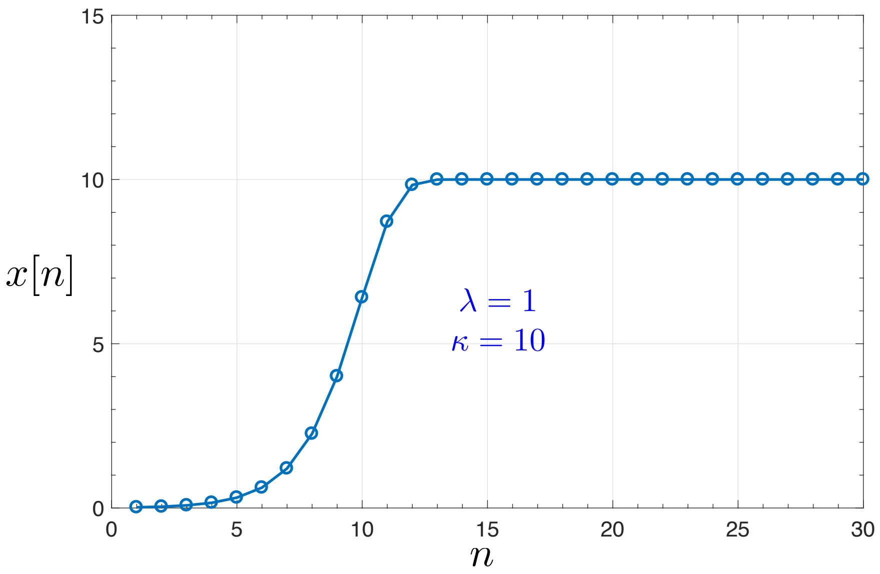
$$\mathcal{V}\big(\mathcal{F}(x^*,0)\big) = \mathcal{V}\big(\mathcal{F}(x^*,1)\big) - \frac{\alpha}{\beta} x^*$$

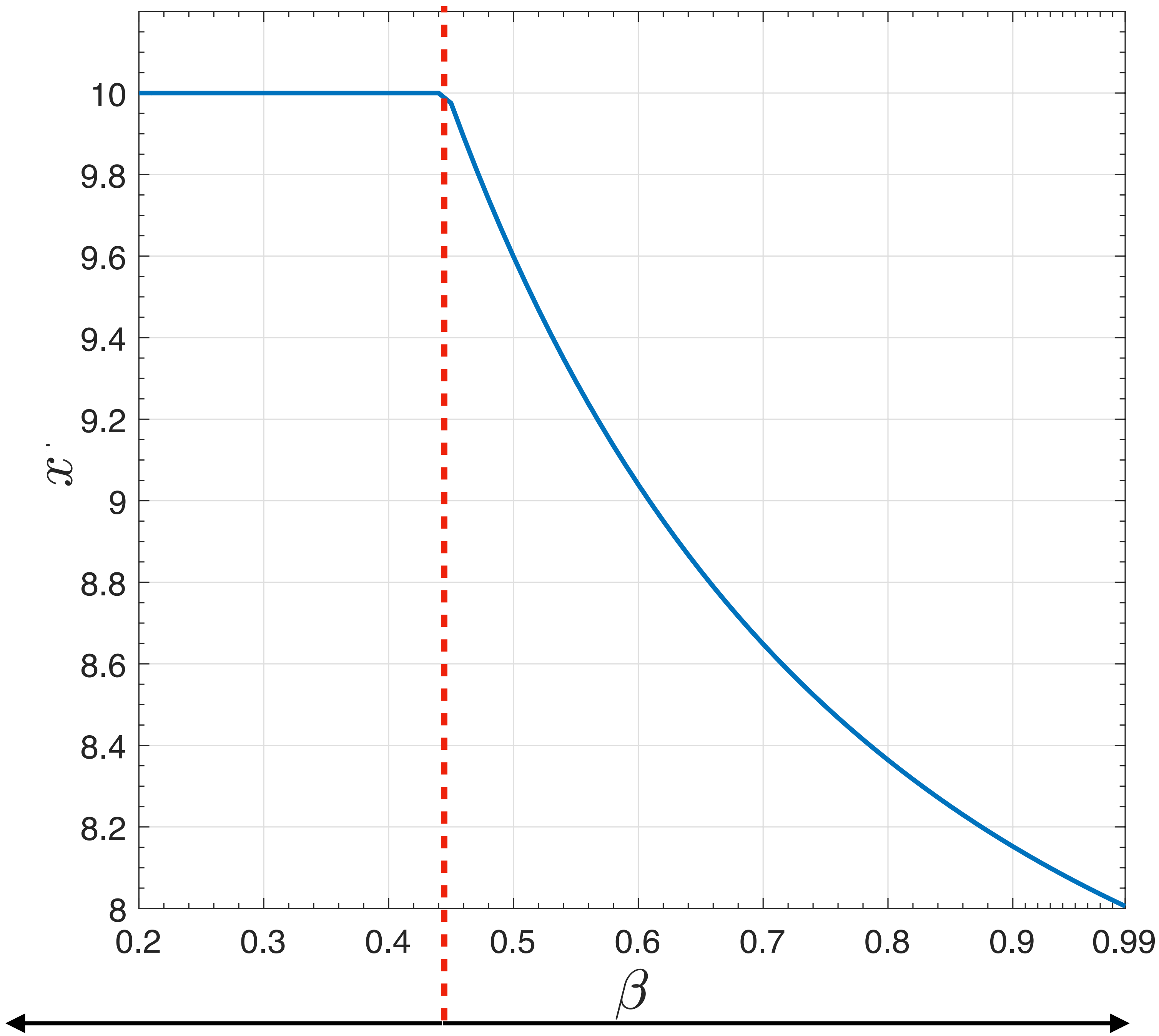
Need to be done numerically

Optimal threshold vs discount factor

$$\alpha = 0.1$$

$$\kappa_0 = 10$$





$\bar{\beta} = 0.44$

OFF policy is optimal

Earlier activation

Conclusion

First principles approach to QS using optimal control

Simple notions and tools from Economics

Public-goods, public-benefit, local cost, investment, etc…

Main result

Optimality of threshold policy

1. **Closed form when** $\alpha = 0$
2. **Numerical when** $\alpha > 0$

Future work

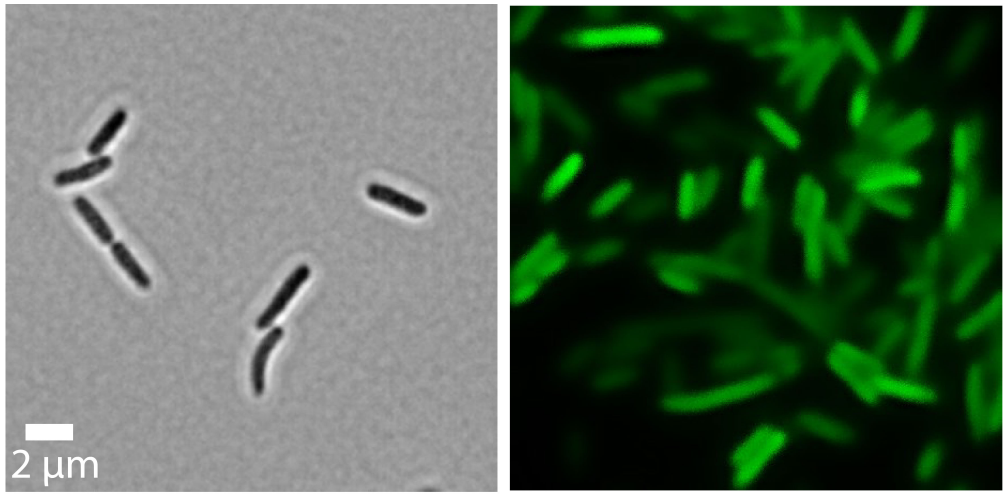
Signal & enzyme dynamics

$$s[n] = (1-\gamma_s)s[n-1] + x[n]\big(1+\sigma_s u[n]\big)$$
$$e[n] = (1-\gamma_e)e[n-1] + x[n]\sigma_e u[n]$$

Instantaneous cost delayed benefit

$$\lambda[n] = \rho - cu[n]$$
$$\kappa[n+1] = \kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(e[n] \geq \tau)$$

Validate results using experimental data



Future work

Signal & enzyme dynamics

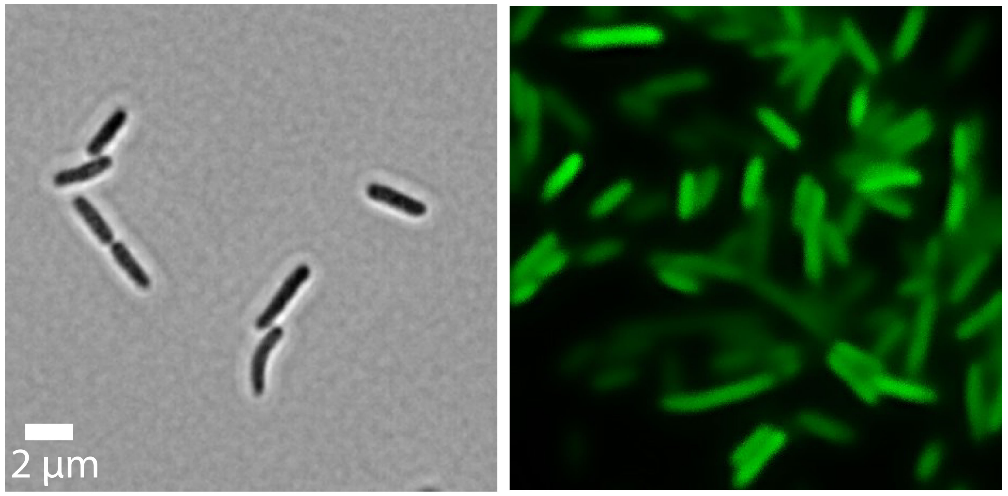
$$s[n] = (1-\gamma_s)s[n-1] + x[n]\big(1+\sigma_s u[n]\big)$$
$$e[n] = (1-\gamma_e)e[n-1] + x[n]\sigma_e u[n]$$

Instantaneous cost delayed benefit

$$\lambda[n] = \rho - cu[n]$$
$$\kappa[n+1] = \kappa_0 + (\kappa_1 - \kappa_0)\mathbf{1}(e[n] \geq \tau)$$

Validate results using experimental data

To be continued…

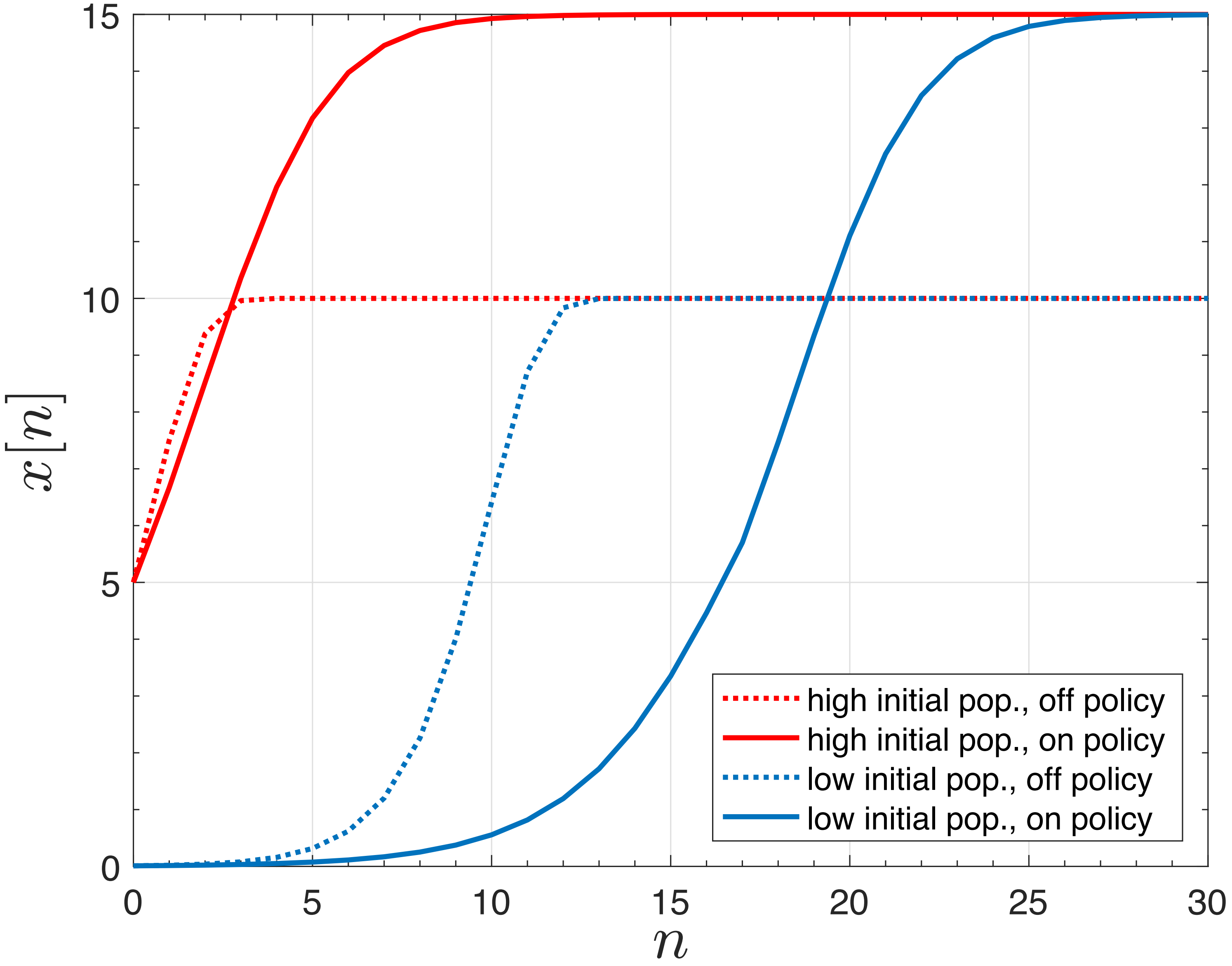


Appendix

Trivial policies

$$\mathcal{U}^{\text{off}}(x) = 0$$

$$\mathcal{U}^{\text{on}}(x) = 1$$



Trivial policies

$$\alpha = 0.1$$

$$\mathcal{U}^{\text{off}}(x) = 0$$

$$\mathcal{U}^{\text{on}}(x) = 1$$

$\boldsymbol{x_0}$	$\boldsymbol{\beta}$	$\boldsymbol{\mathcal{V}_{\text{off}}}$	$\boldsymbol{\mathcal{V}_{\text{on}}}$
0.01	0.5	0.1108	0.0356
5	0.5	13.5889	12.0276
0.01	0.9	37.0031	21.9538
5	0.9	92.2152	107.7870

There should be a transition from OFF to ON