Feedbacks in quorum sensing: An evolutionary perspective

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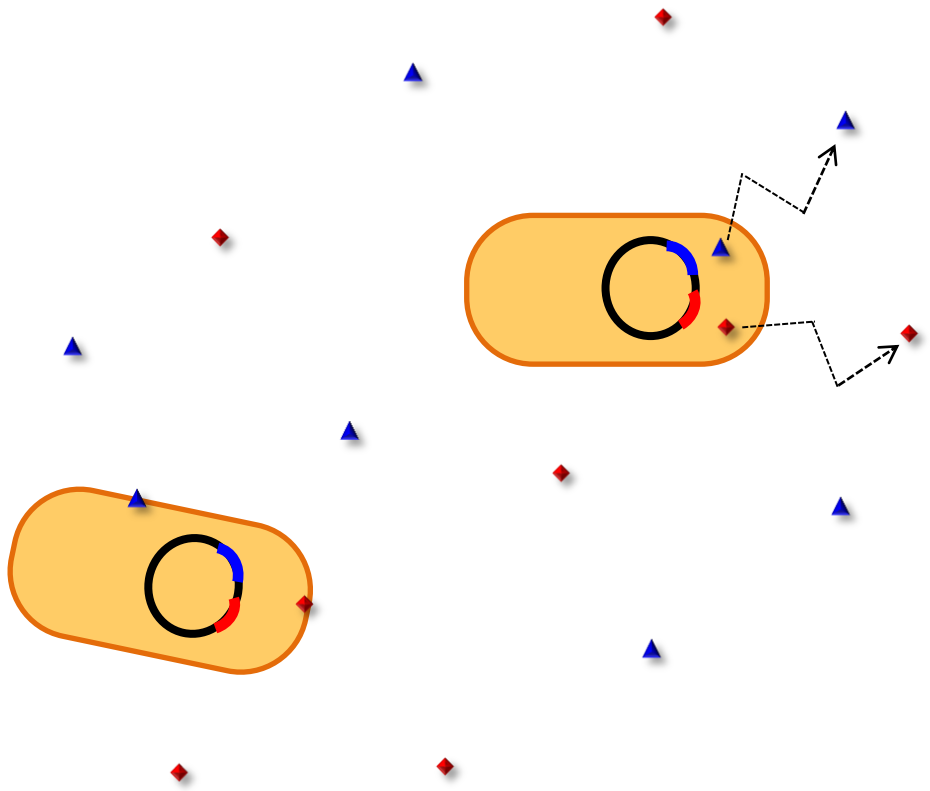
Outline

- **Introduction to quorum sensing**
- **The QS network in *Vibrio harveyi***
- **Why so many feedbacks?**
- **Insights from evolution**

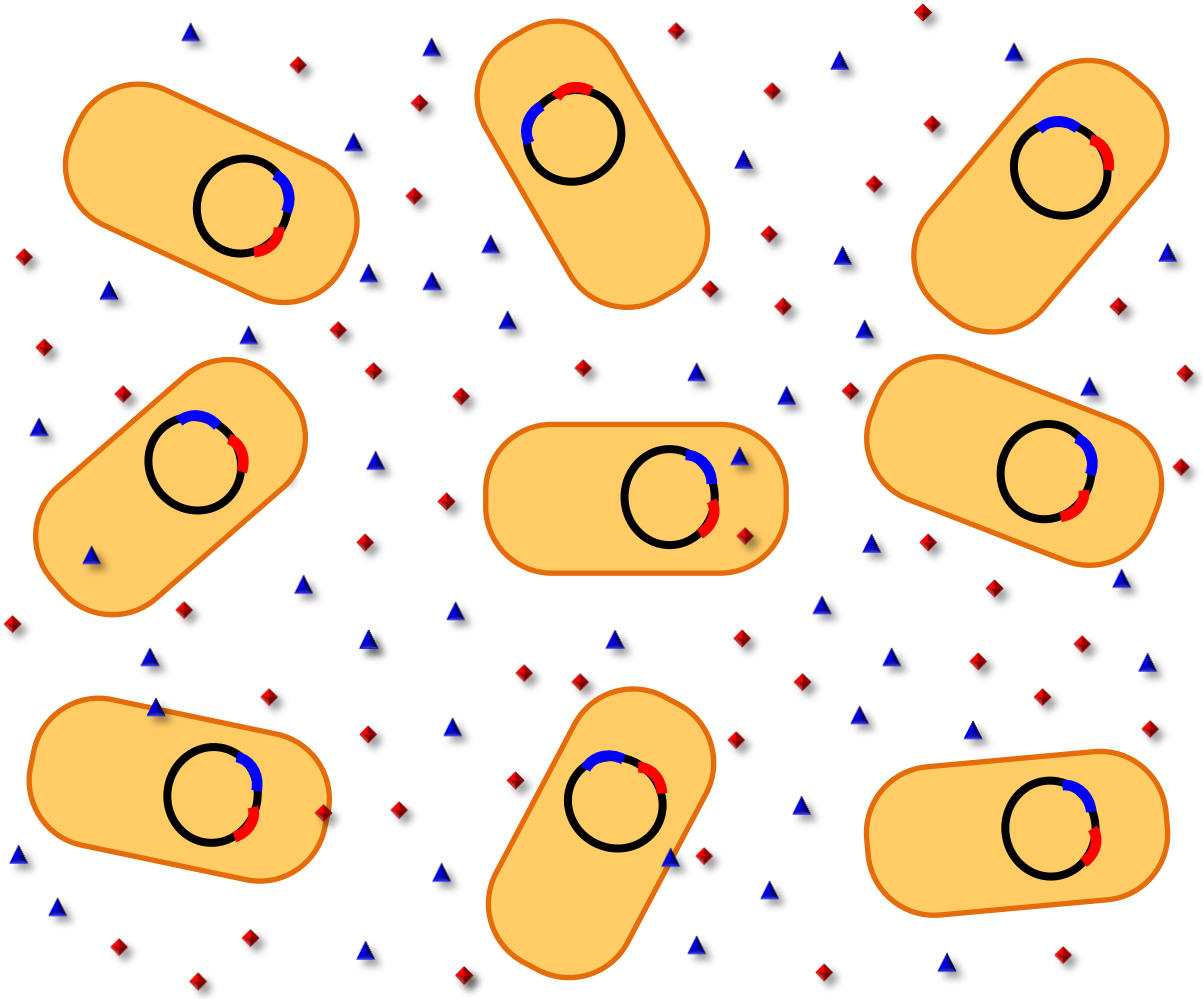
Bacterial Quorum Sensing

Low cell density: low autoinducer (AI) concentration



Bacterial Quorum Sensing

High cell density: high AI concentration

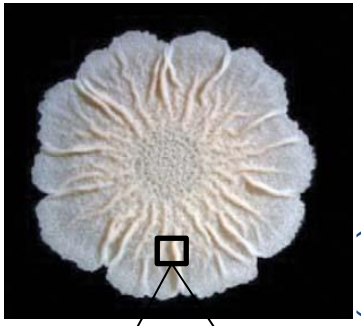


Collective behaviors coordinated by quorum sensing

Quorum Sensing

- Antibiotic production
- Motility
- Conjugation
- Protease production
- Type III secretion

Biofilm



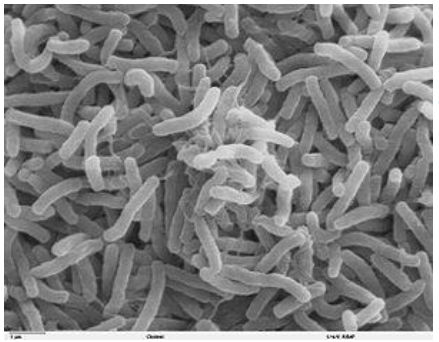
Earl AM et al. (2008)

Bacillus subtilis

Bioluminescence

Vibrio harveyi

Virulence



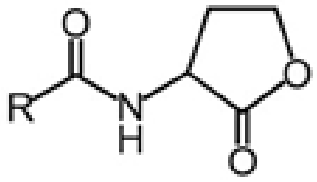
Wikipedia/cholera

Vibrio cholerae

Bacteria are Multilingual

Species-specific signals

Acyl Homoserine Lactone (AHL)



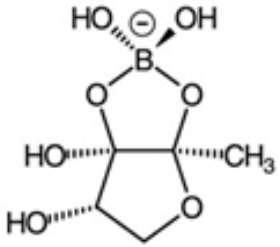
Auto Inducing Polypeptide (AIP)

ADPITRQWGD

ComX (*Bacillus subtilis*)

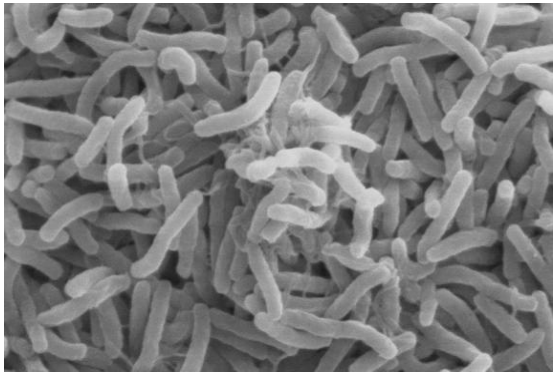
Universal signal

AI-2



Quorum sensing is ubiquitous among bacteria

Virulence



Vibrio cholerae

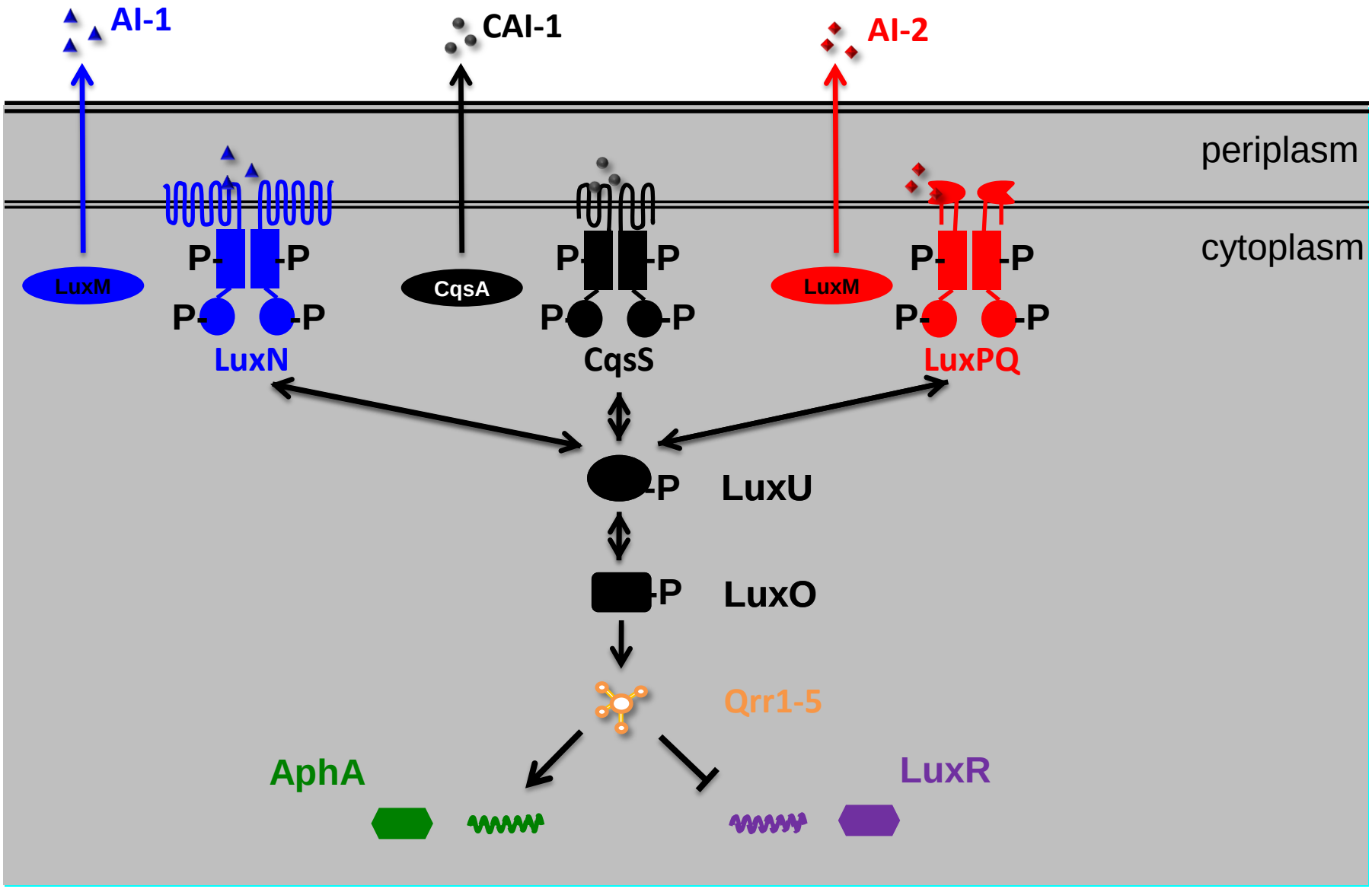
Biofilm formation

Bacillus subtilis

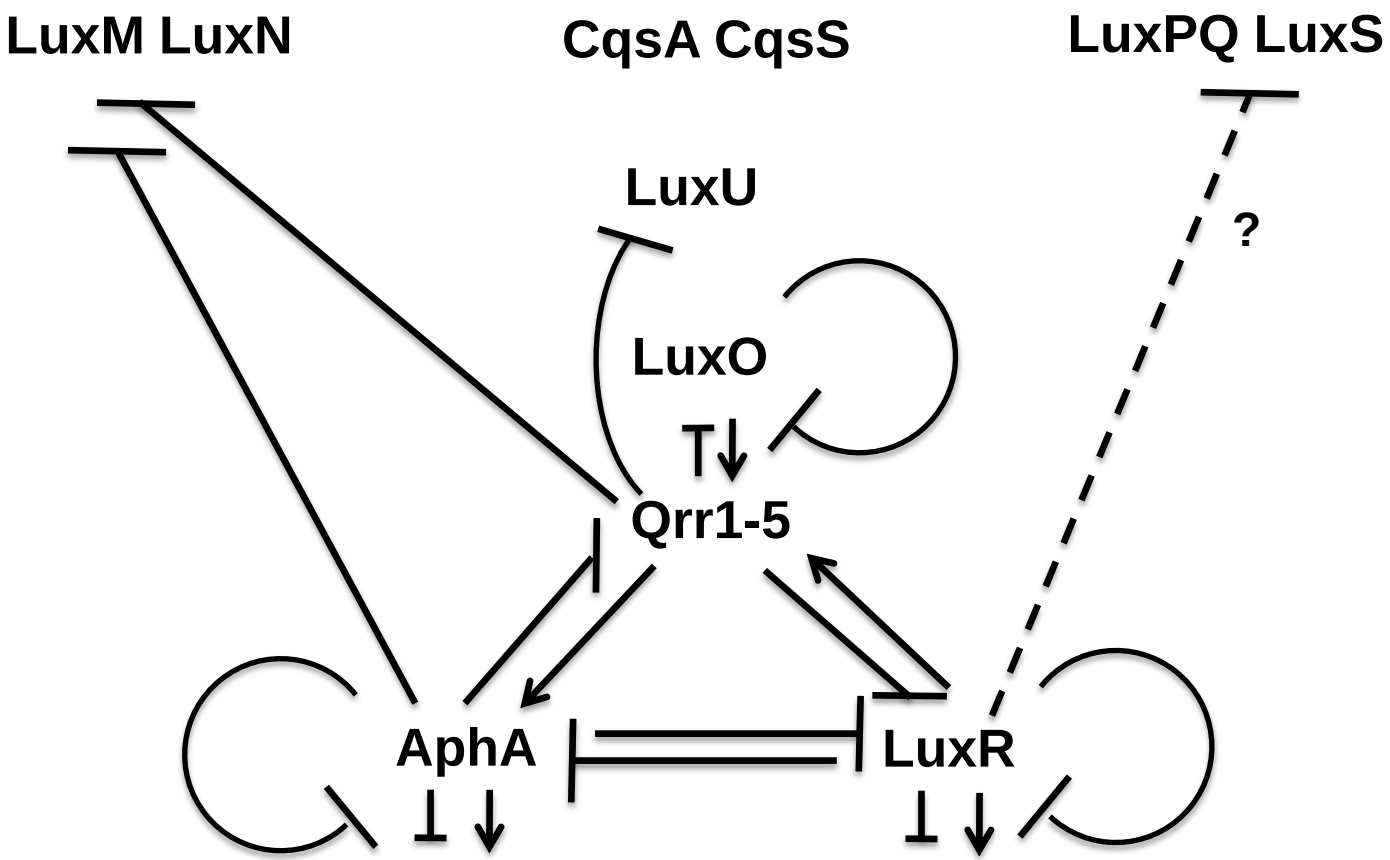
Bioluminescence

Vibrio harveyi

Quorum sensing network in *V. harveyi*

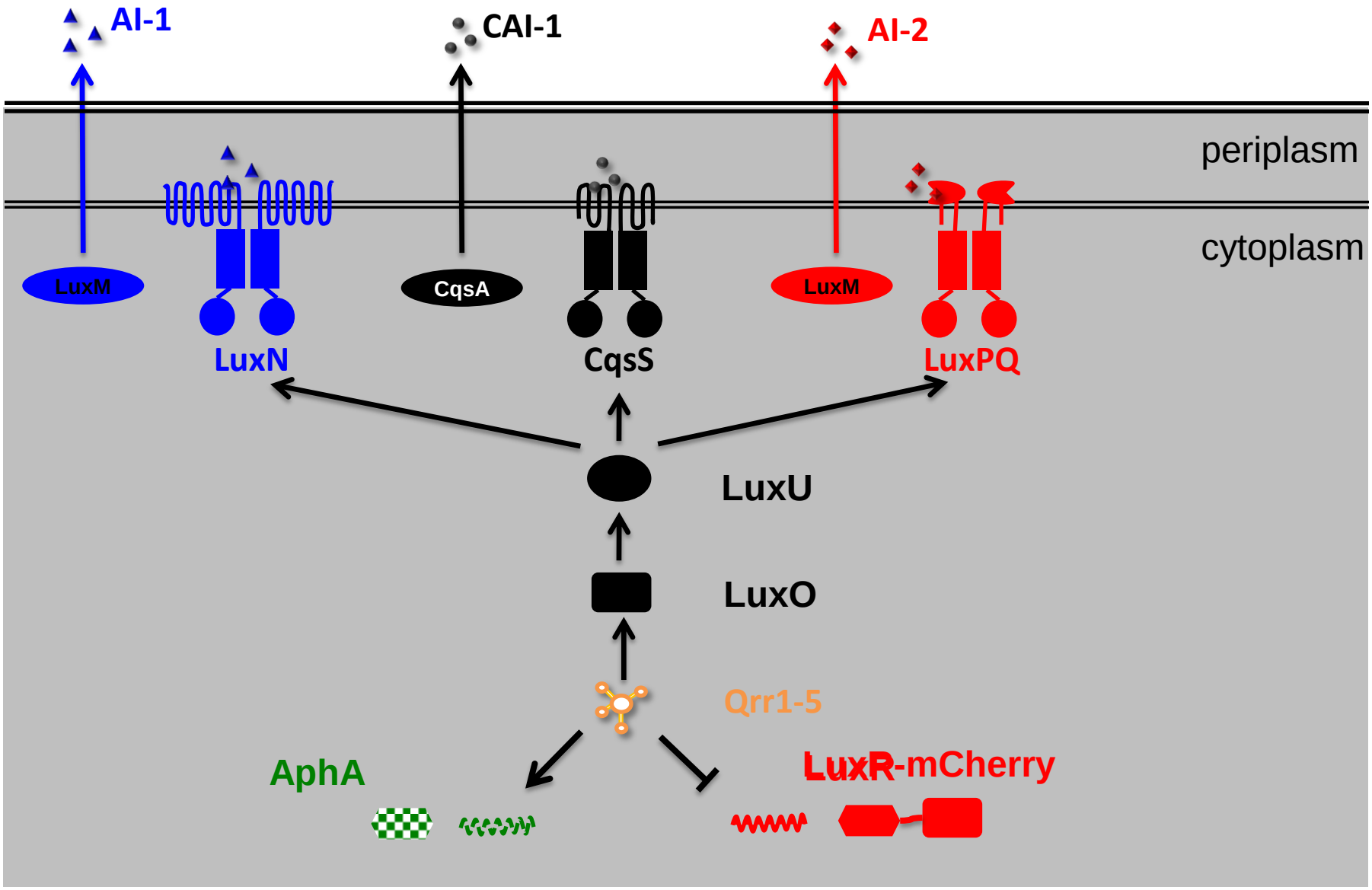


QS network has many internal feedbacks

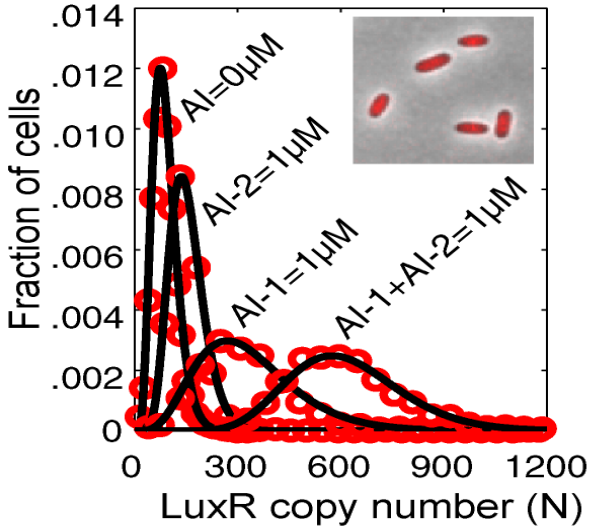


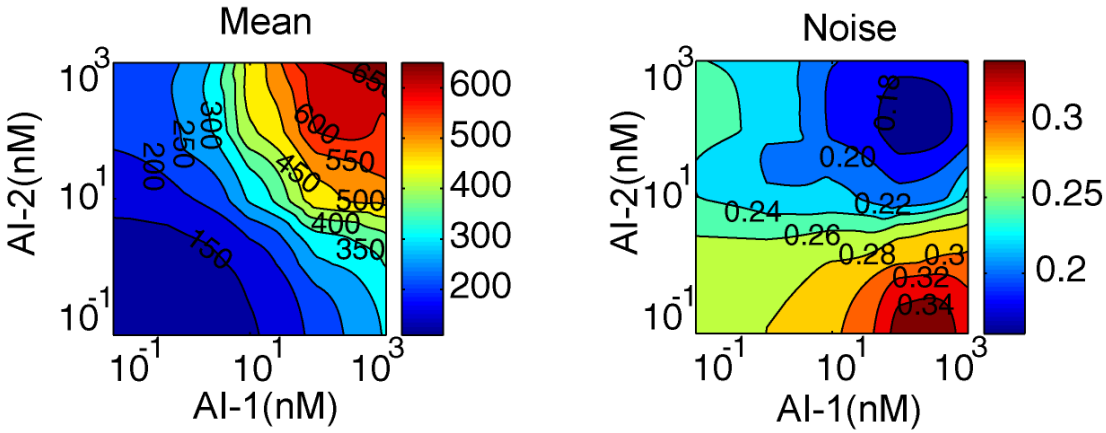
Rutherford *et al., Genes & Dev* (2011)
Shao & Bassler, *Mol Micro* (2012)

Engineered reporter strains



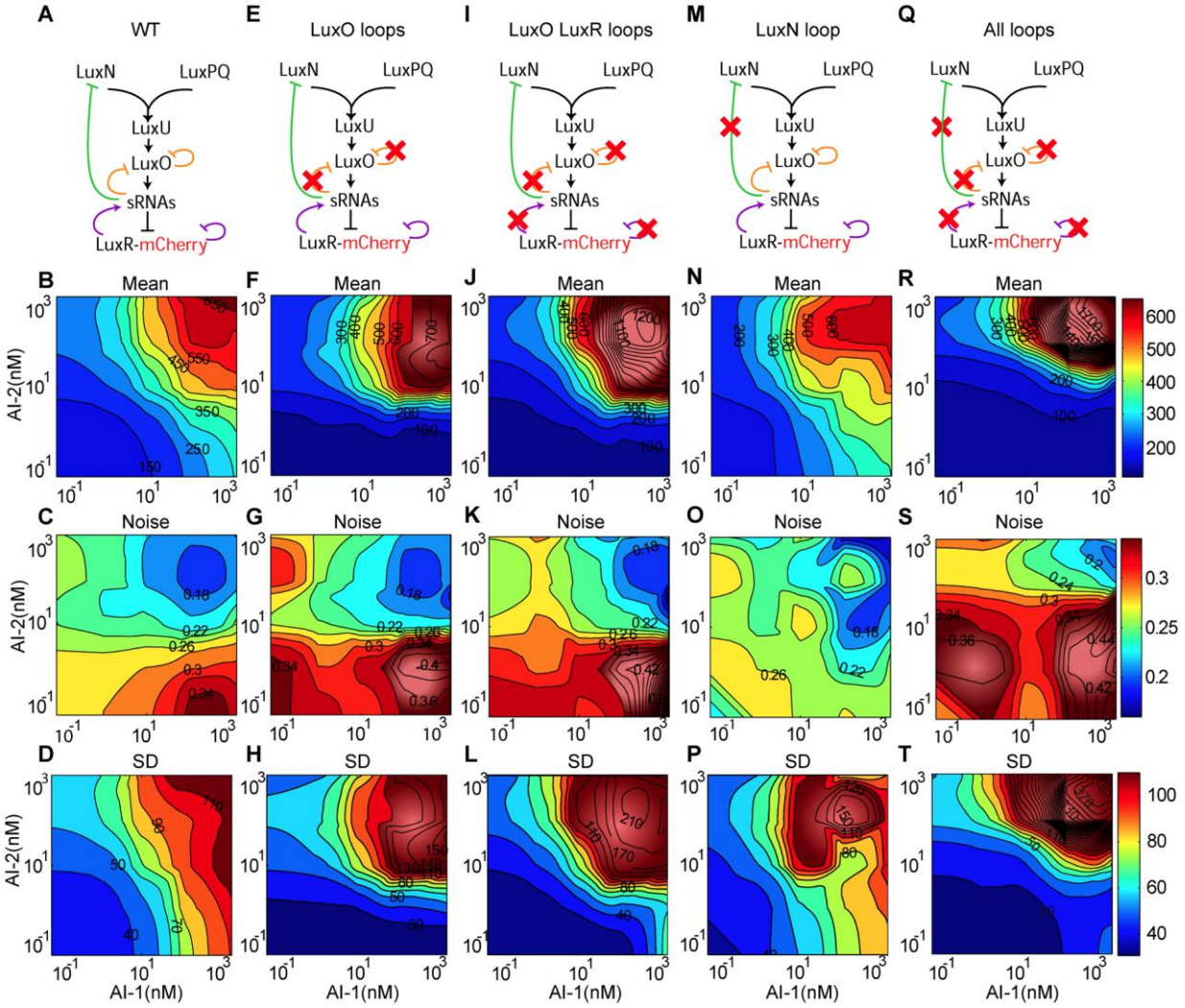
Single-cell measurements





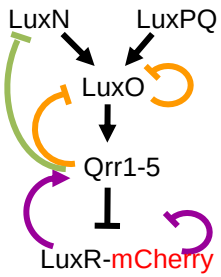
Teng *et al. Mol Sys Biol* (2011)

Each feedback does something…

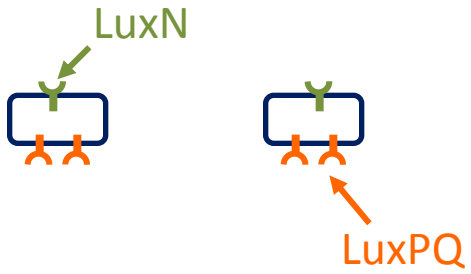


LuxN feedback regulates receptor ratio

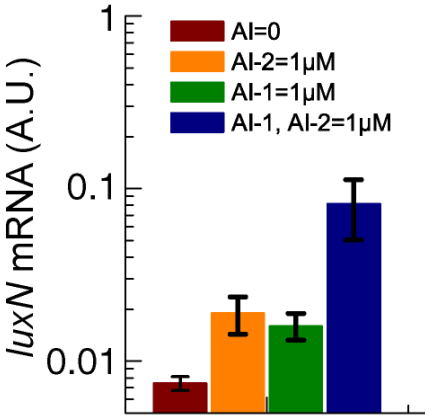
WT



Low Cell Density

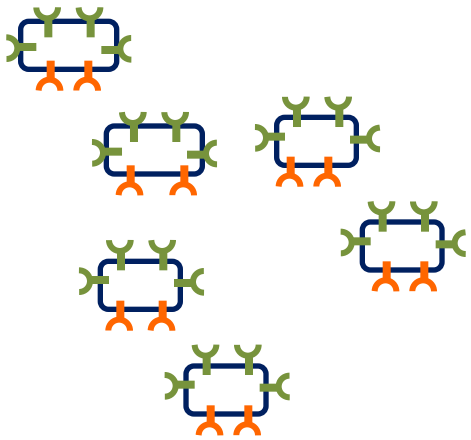


WT

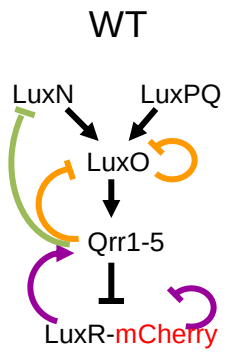


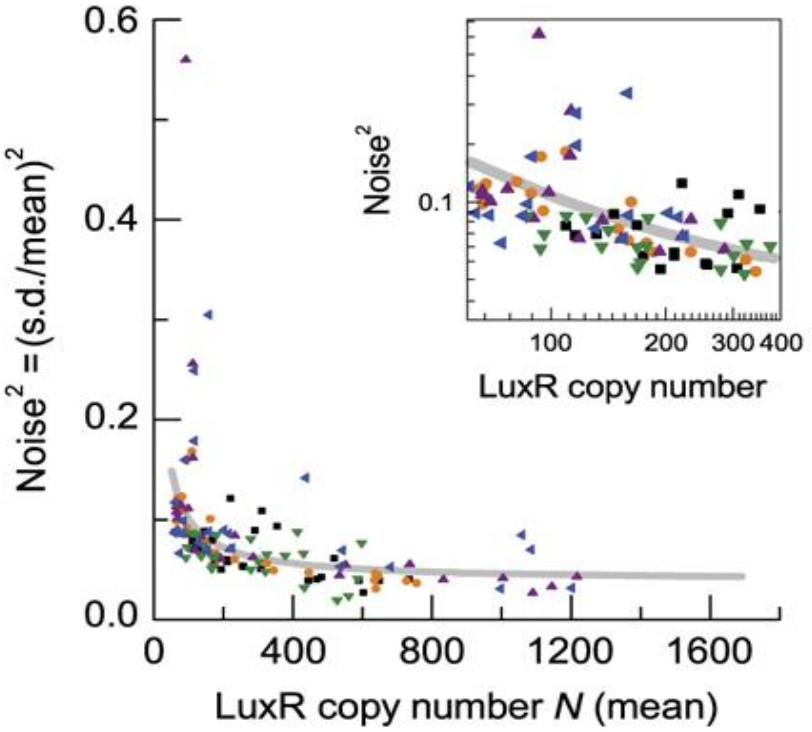
luxN expression

High Cell Density

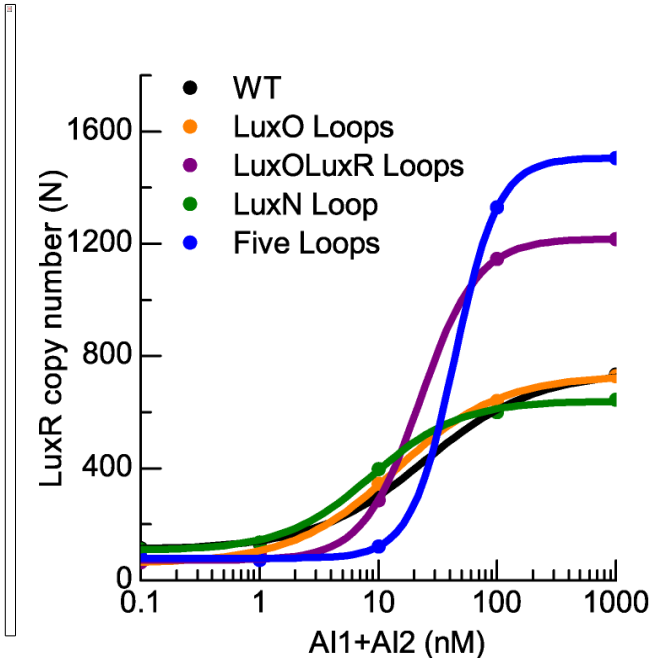


Core feedbacks have little effect on noise



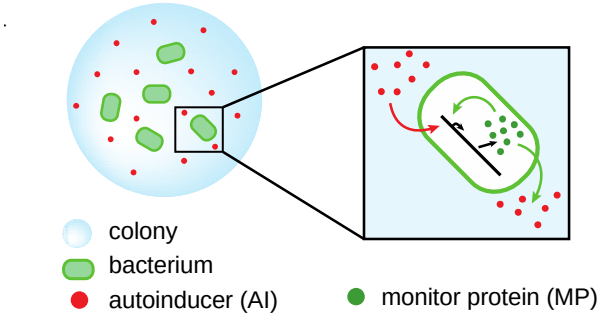


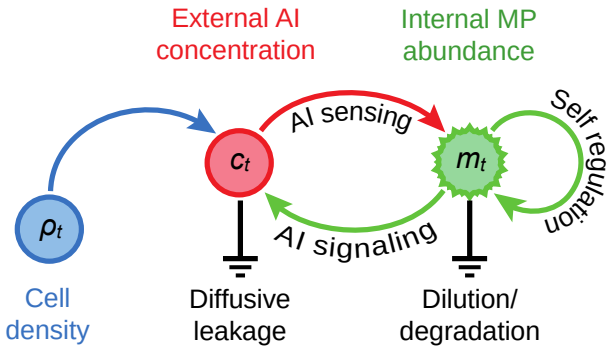
Feedback by LuxR controls input-output relation

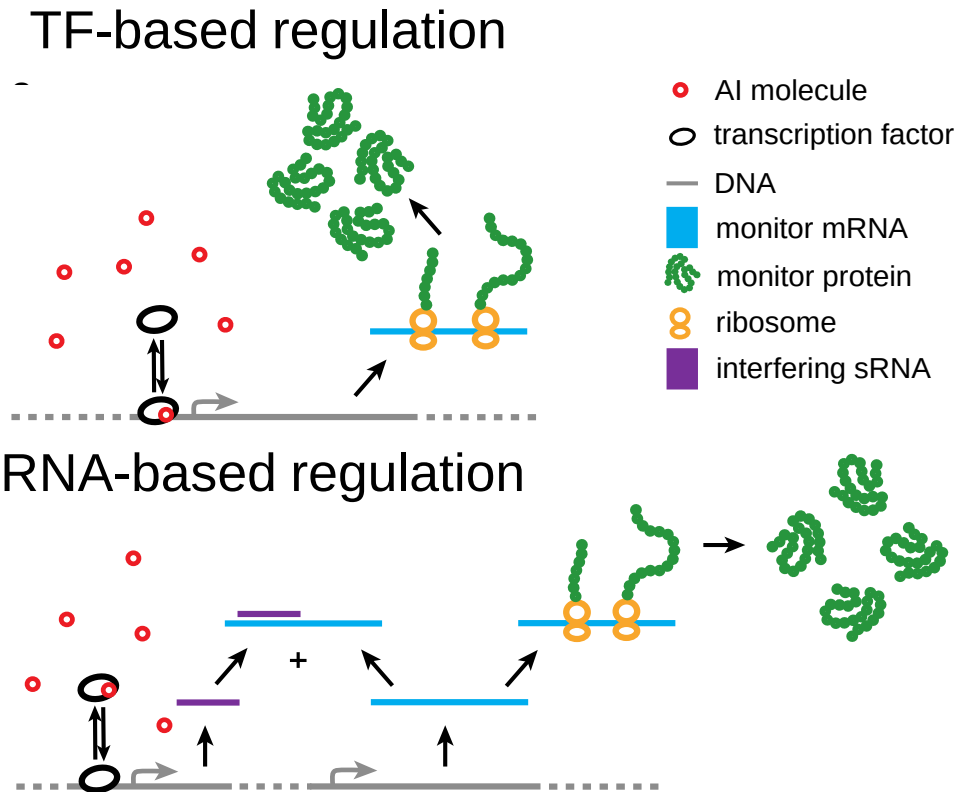


LuxR feedback increases AI input dynamic range and decreases LuxR output dynamic range.

Quorum-sensing feedbacks and mutual information







Taillefumier & NSW *PLoS Comp Biol* (2015)

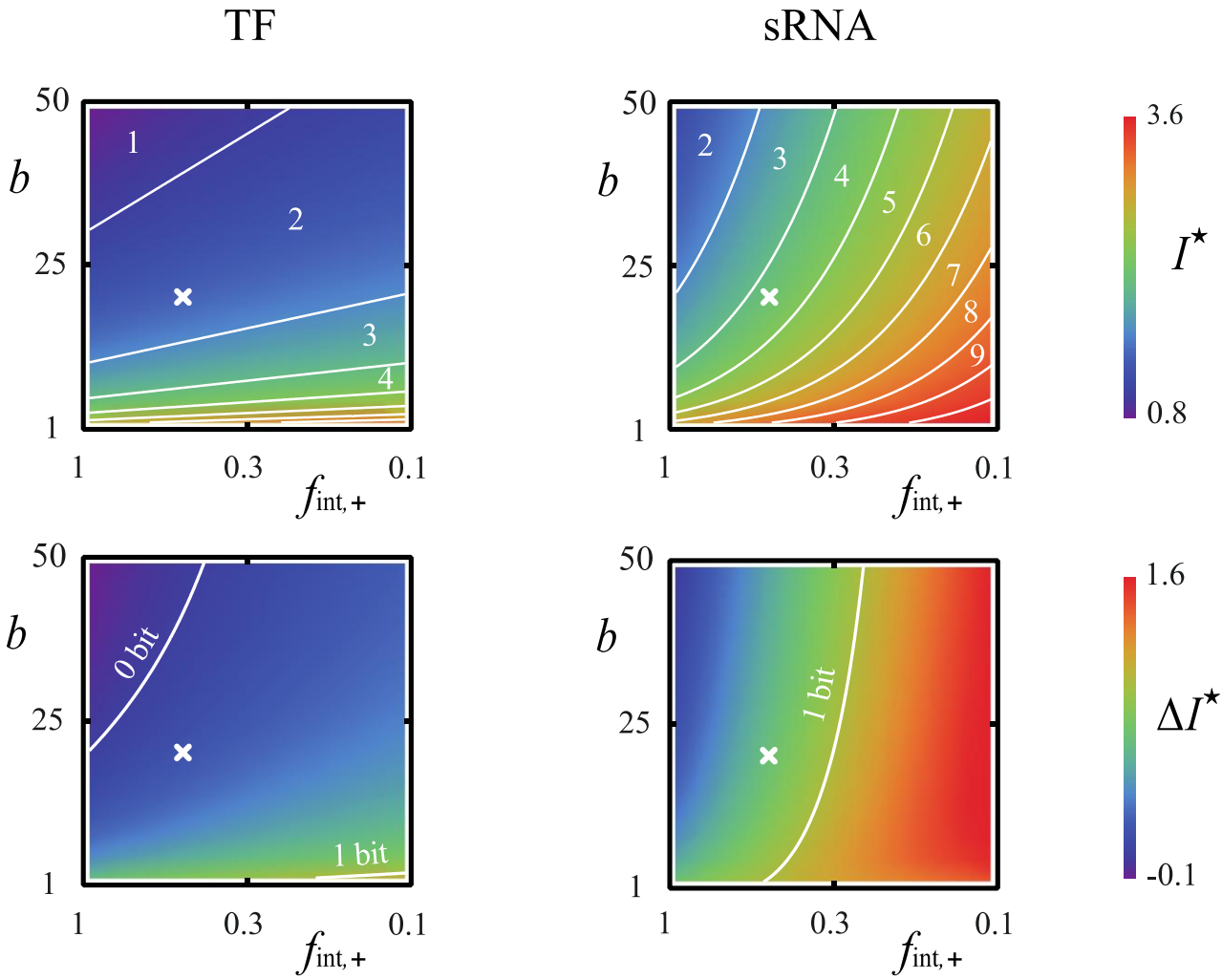
Feedbacks can optimize available information about cell density

Mutual information

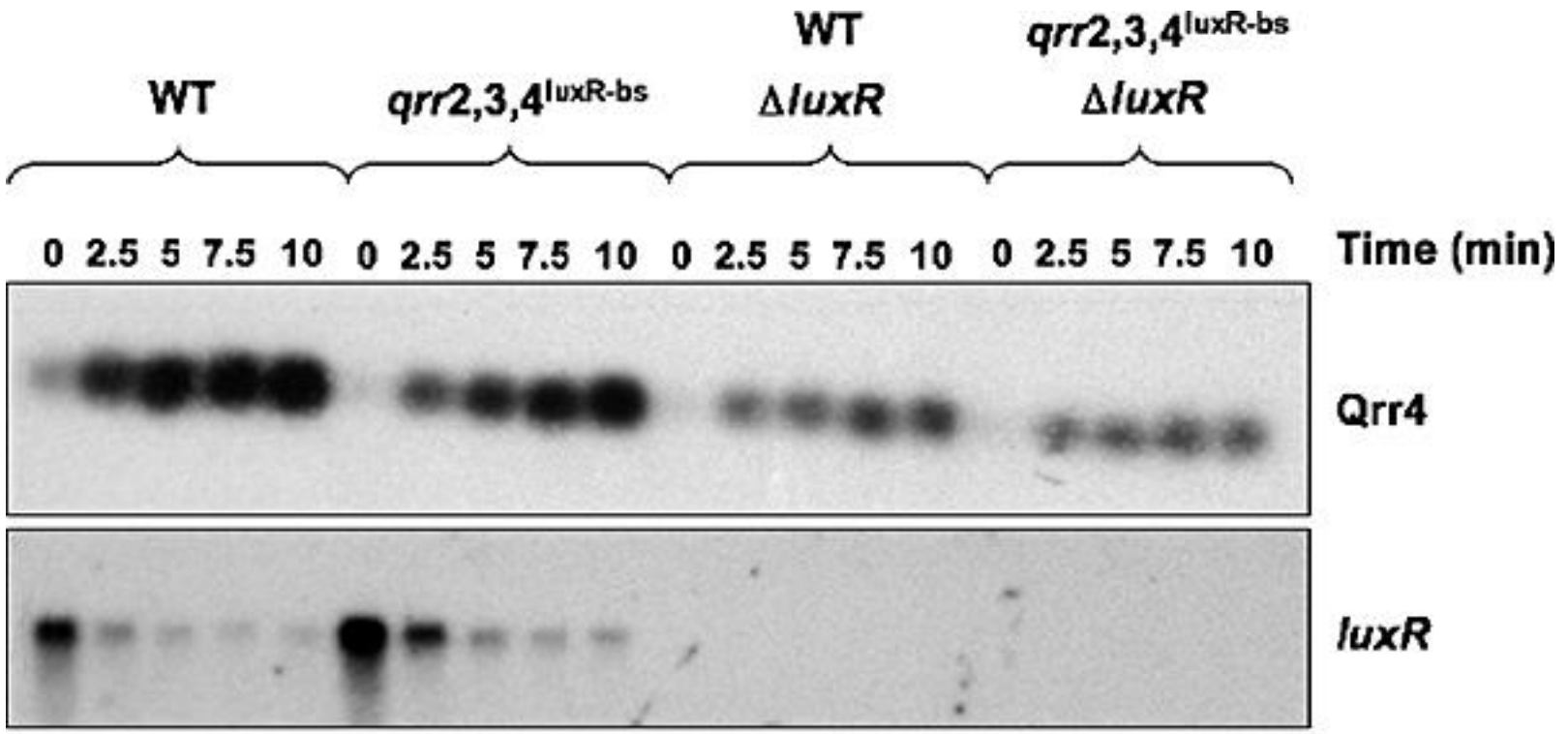
MI increase due to feedbacks

b = protein “burst size”

$f_{\text{int+}}$ = feedback inhibition



Feedback from LuxR speeds Qrr production at HCD ➔LCD transition



Tu *et al., Mol Micro* (2008)

Simple model for network dynamics

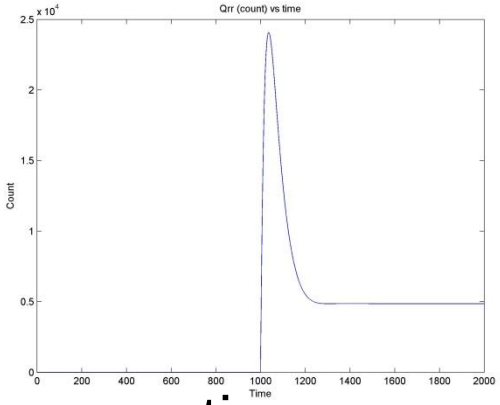
E.g. equations for Qrrs and *luxR* / LuxR:

$$\frac{d[Qrr]}{dt} = Q * V_{tscr}\left(\frac{[\text{LuxO}\sim\text{P}]}{K_M^{OP} + [\text{LuxO}\sim\text{P}]}\right)\left(\frac{K_I^A}{K_I^A + [\text{AphA}]}\right)\left(\frac{K_M^R + A_R^Q[\text{LuxR}]}{K_M^R + [\text{LuxR}]}\right)$$
$$-k_{qn}[Qrr][luxN]$$
$$-k_{qo}[Qrr][luxO]$$
$$-k_{qr}[Qrr][luxR]$$
$$-k_{qa}[Qrr][aphA]$$
$$\frac{d[luxR]}{dt} = V_{tsla}\left(\frac{K_M^A + A_A^R[\text{AphA}]}{K_M^A + [\text{AphA}]}\right)\left(\frac{K_I^R}{K_I^R + [\text{LuxR}]}\right) - k_{qr}[Qrr][luxR] - D_{mRNA}[luxR]$$
$$\frac{d[\text{LuxR}]}{dt} = V_{prot}[luxR] - D_{prot}[\text{LuxR}]$$

Simulate transitions:
LCD ➔HCD and HCD➔ LCD.

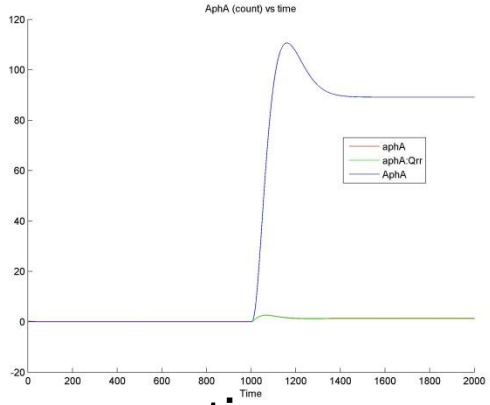
Model results for HCD➔LCD transition

Qrrs



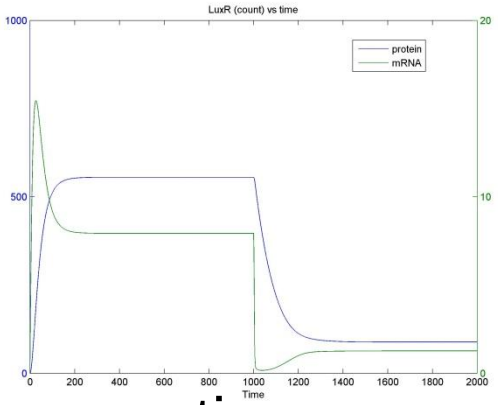
time

AphA



time

luxR / LuxR



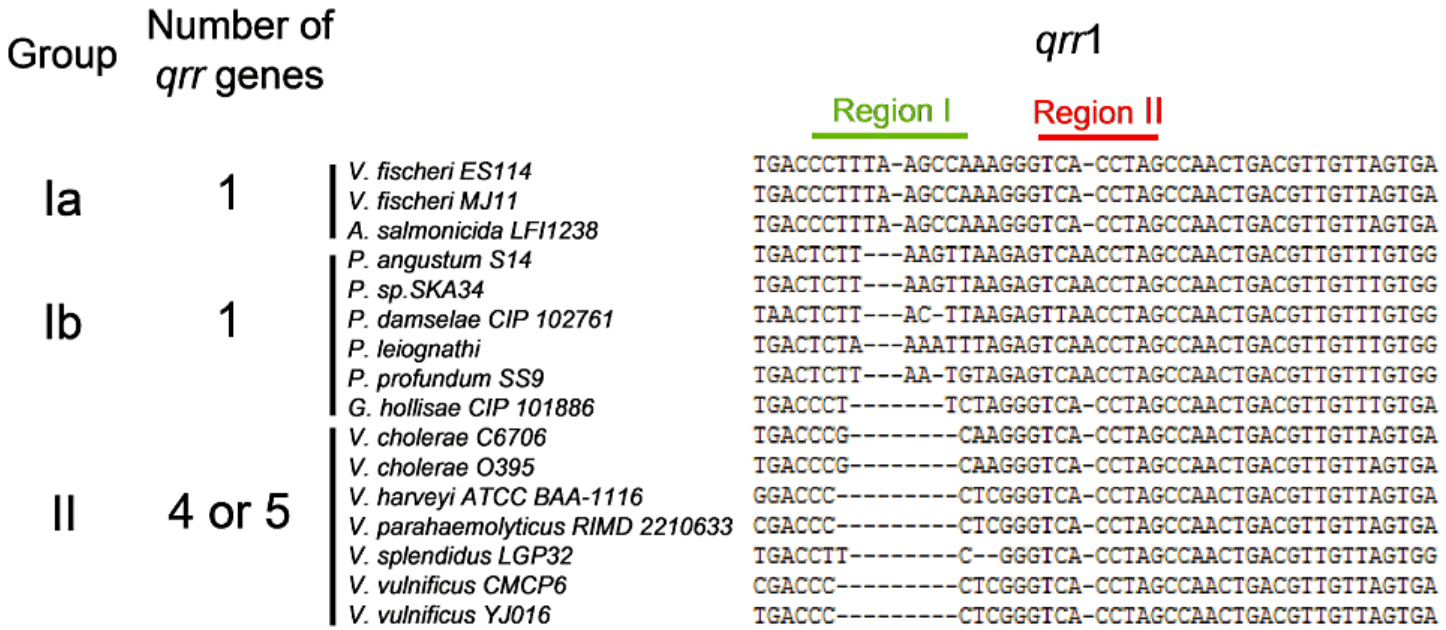
time

Network design accelerates HCD➔LCD response:

- Multiple Qrrs
- LuxR co-activation of Qrrs
- Qrr repression of LuxO
- Cap on total LuxR
- Negative feedback via AphA limits Qrr accumulation

AphA regulation correlates with multiplication of Qrrs

A

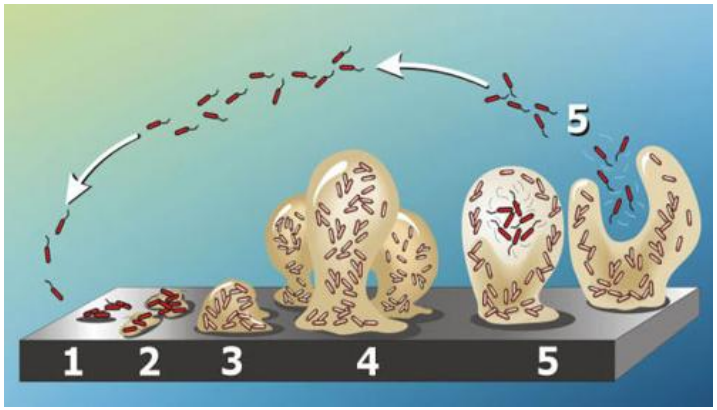


B

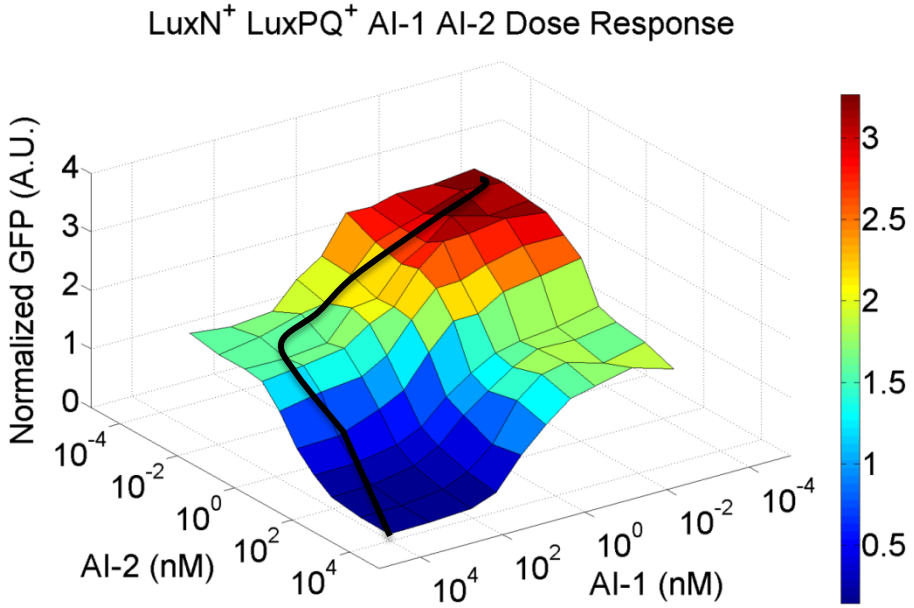
Shao & Bassler *Mol Micro* (2012)

So why is the QS network so complex?

Lifecycle of bacteria in a biofilm



Courtesy of Davis Lab at Binghamton Univ.



- **Multiple autoinducers and feedbacks may allow multi-stage developmental program.**
- **Feedbacks can help cells focus on most relevant signal and respond quickly to HCD ➔LCD transitions.**

Summary

- AphA/LuxR are the LCD/HCD master regulators in the Vibrio quorum-sensing network.
- Complex network architecture allows:
  - Increased information on cell density
  - “Attention” to specific signals
  - Fast response to HCD ➔LCD transition
- Interspecies comparison helps track network evolution.

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