Imagine the Possibilities

Mathematical Biology
University of Utah

How Cells Make Measurements

J. P. Keener

Department of Mathematics
University of Utah

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

Imagine the Possibilities

Mathematical Biology
University of Utah

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide -

Imagine the Possibilities
Mathematical Biology
University of Utah

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - find the ratio of two numbers (Mathematician)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate -

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - find the slope of a function (Mathematician)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - change the function of a cell (Biologist)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - change the function of a cell (Biologist)
- a PDE -

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - change the function of a cell (Biologist)
- a PDE - Partial Differential Equation (Mathematician)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - change the function of a cell (Biologist)
- a PDE - Phosphodiesterase (Biologist)

A few words about words

A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.

Examples:

- to divide - replicate the contents of a cell and split into two (Biologist)
- to differentiate - change the function of a cell (Biologist)
- a PDE - Pennsylvania Department of Education

And so it goes with words like germs and fiber bundles (topologist or microbiologist), cells (numerical analyst or physiologist), complex (analysts or molecular biologists), domains (functional analysts or biochemists), and rings (algebraists or protein structure chemists).

The Challenge of Mathematical Biology

Basic challenges and goals:

- To discover general principles underlying biological complexity; to organize and describe the data in more comprehensible ways.
- To provide quantitative theories for how biological processes work.

Imagine the Possibilities
Mathematical Biology
University of Utah

The Problem

All living organisms make decisions (when to divide, when to differentiate, when to grow, when to die)

Basic questions:

- What information is available and how is it assessed?
- How is that information transduced into chemistry?

Outline: Two Examples

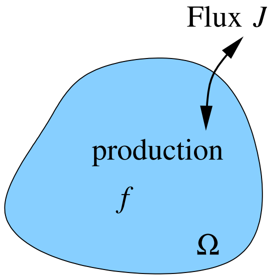
- Quorum sensing in P. aeruginosa
- Filament length regulation in Salmonella.

Quantitative Thinking

Biology is characterized by change. A major goal of mathematical modeling is to quantify how things change.

Fundamental Law:

rate of change of "stuff" in the region Ω =
rate of movement (flux J) + rate of production(f)



The questions to address are:

1. What is the "stuff" that matters?
2. How does it move?
3. How is it produced?

I - Quorum Sensing

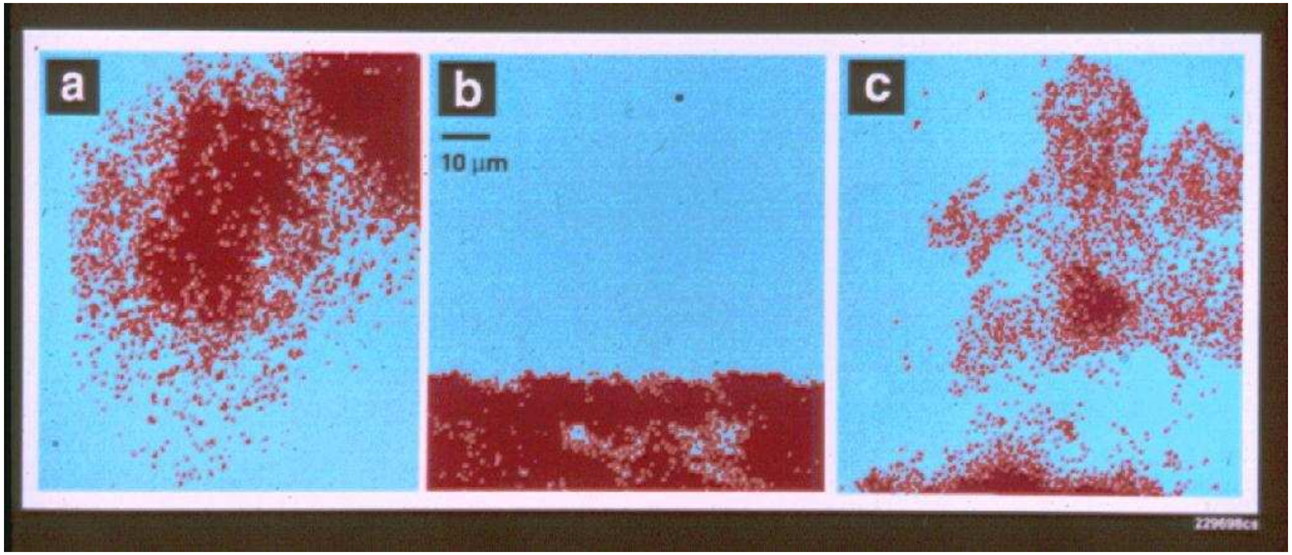
Quorum sensing: The ability of a bacterium to sense the size of its colony and to regulate its activity in response.
Examples:

- *Pseudomonas Aeruginosa*: Major cause of infection in hospitals and in Cystic Fibrosis patients. In planktonic form, they are readily cleared, but in biofilm they are well-protected by the polymer gel in which they reside. However, they do not form the gel until the colony is of sufficient size, i.e., quorum sensing.
- *Vibrio fisheri*: Populate the light organs of certain squids, and when the colony is large enough they become luminescent.

Question: How do bacteria measure the size of their colony?

Quorum Sensing

1: What stuff matters?



Wild Type Biofilm Mutant Mutant with autoinducer

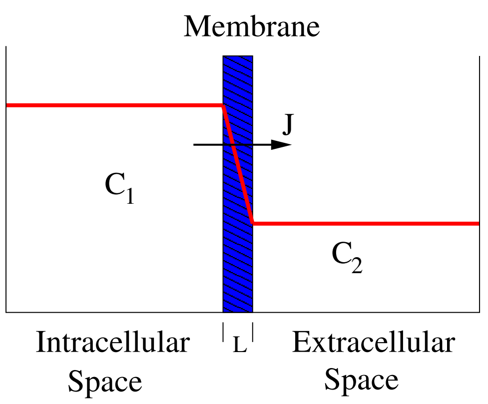
Autoinducer (HSL): a molecule that is made by the cell and can freely diffuse across the membrane of the cell.

Quorum Sensing

2: How does autoinducer move?

Small molecules undergo a random walk.
However, when there are a large number of molecules, their average motion is well-described by **Fick's Law**

$$J = \frac{AD}{L}(C_1 - C_2)$$



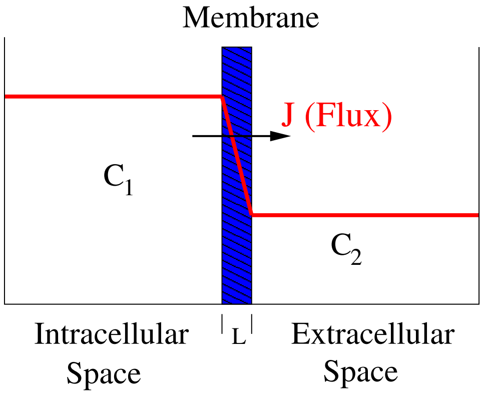
Quorum Sensing

2: How does autoinducer move?

Small molecules undergo a random walk.
However, when there are a large number of molecules, their average motion is well-described by **Fick's Law**

$$J = \frac{AD}{L}(C_1 - C_2)$$

Flux

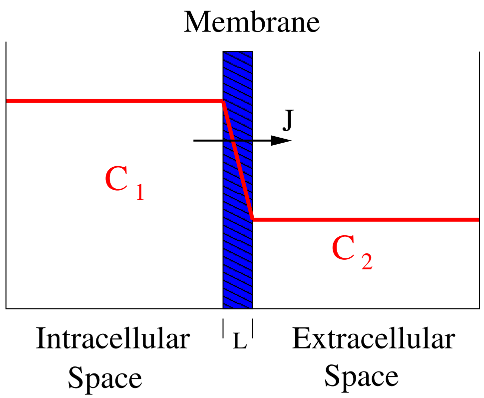


Quorum Sensing

2: How does autoinducer move?

Small molecules undergo a random walk.
However, when there are a large number of molecules, their average motion is well-described by **Fick's Law**

$$J = \frac{AD}{L}(C_1 - C_2)$$



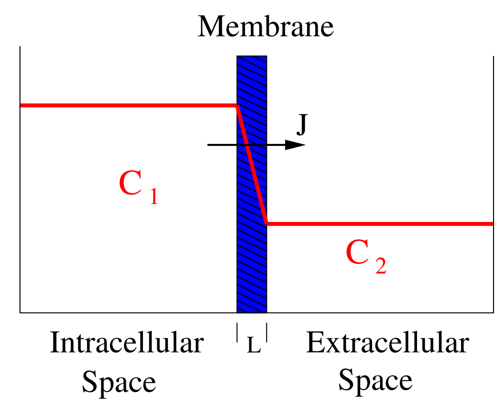
Flux is proportional to concentration difference.

Quorum Sensing

2: How does autoinducer move?

Small molecules undergo a random walk.
However, when there are a large number of molecules, their average motion is well-described by **Fick's Law**

$$J = \frac{AD}{L}(C_1 - C_2)$$

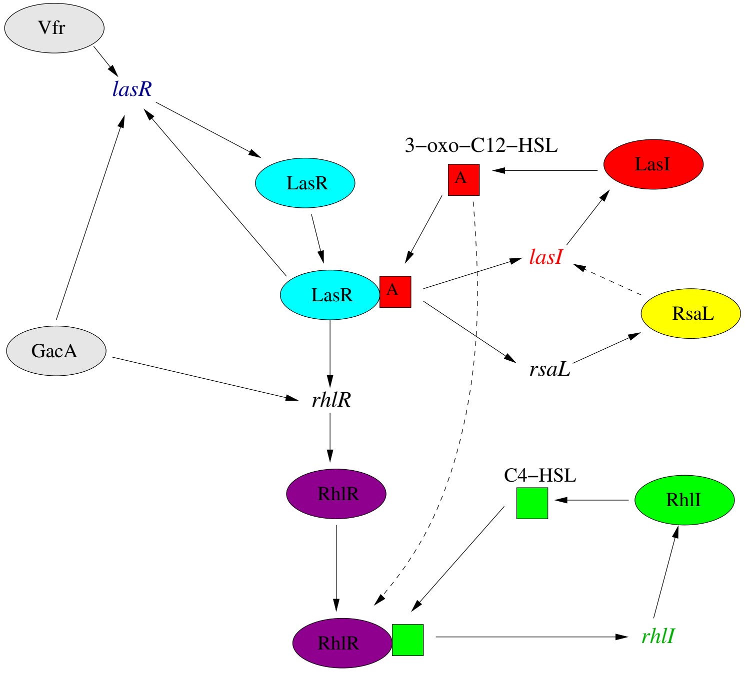


Flux is proportional to concentration difference.

Key Observation! Flux provides a quantitative measure of extracellular quantities.

Autoinducer

3. How is autoinducer produced?

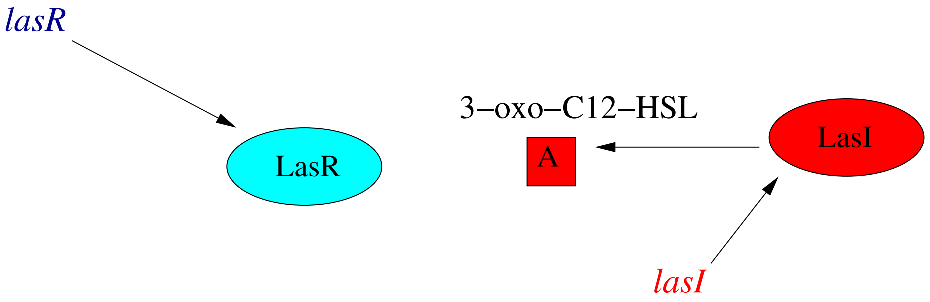


Biochemistry of Quorum Sensing

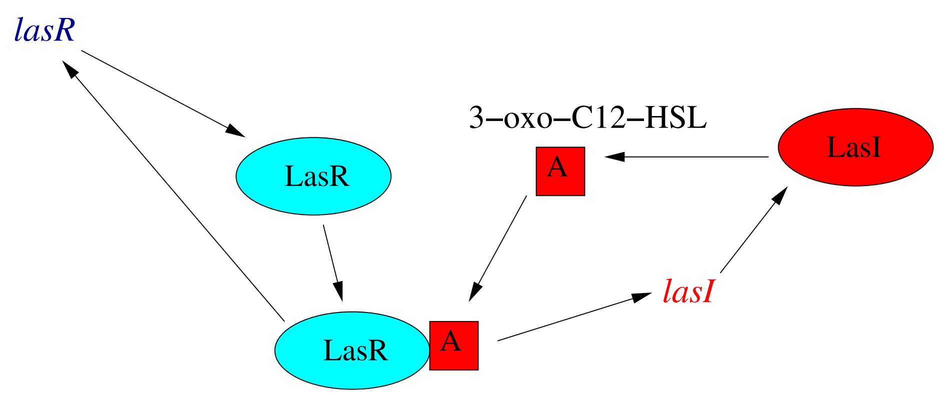
lasR

lasI

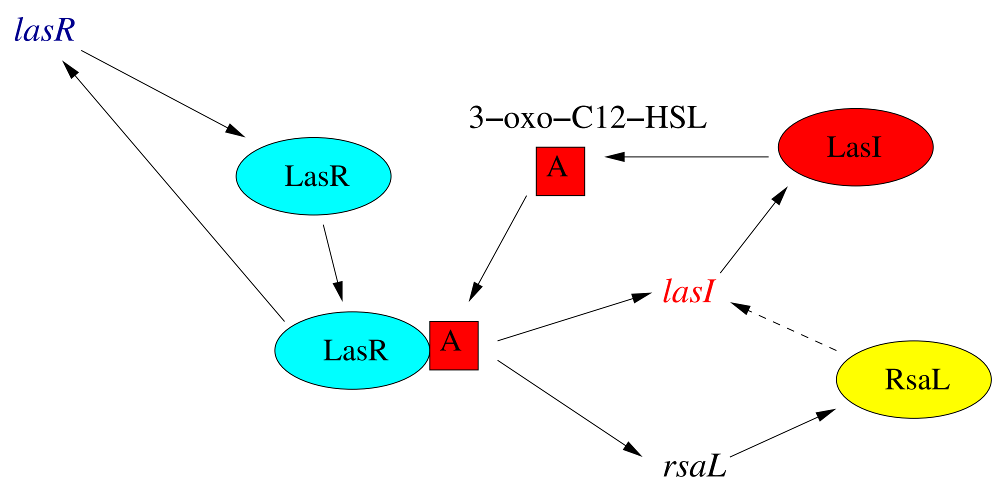
Biochemistry of Quorum Sensing



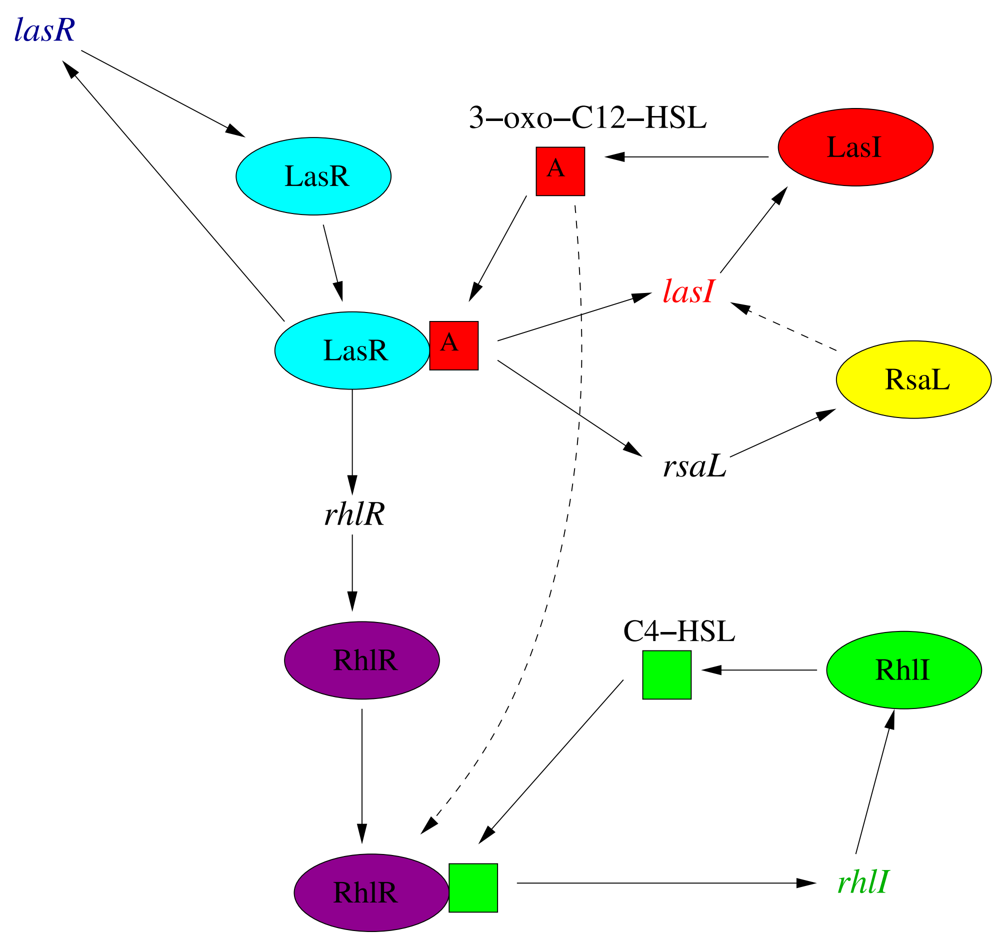
Biochemistry of Quorum Sensing



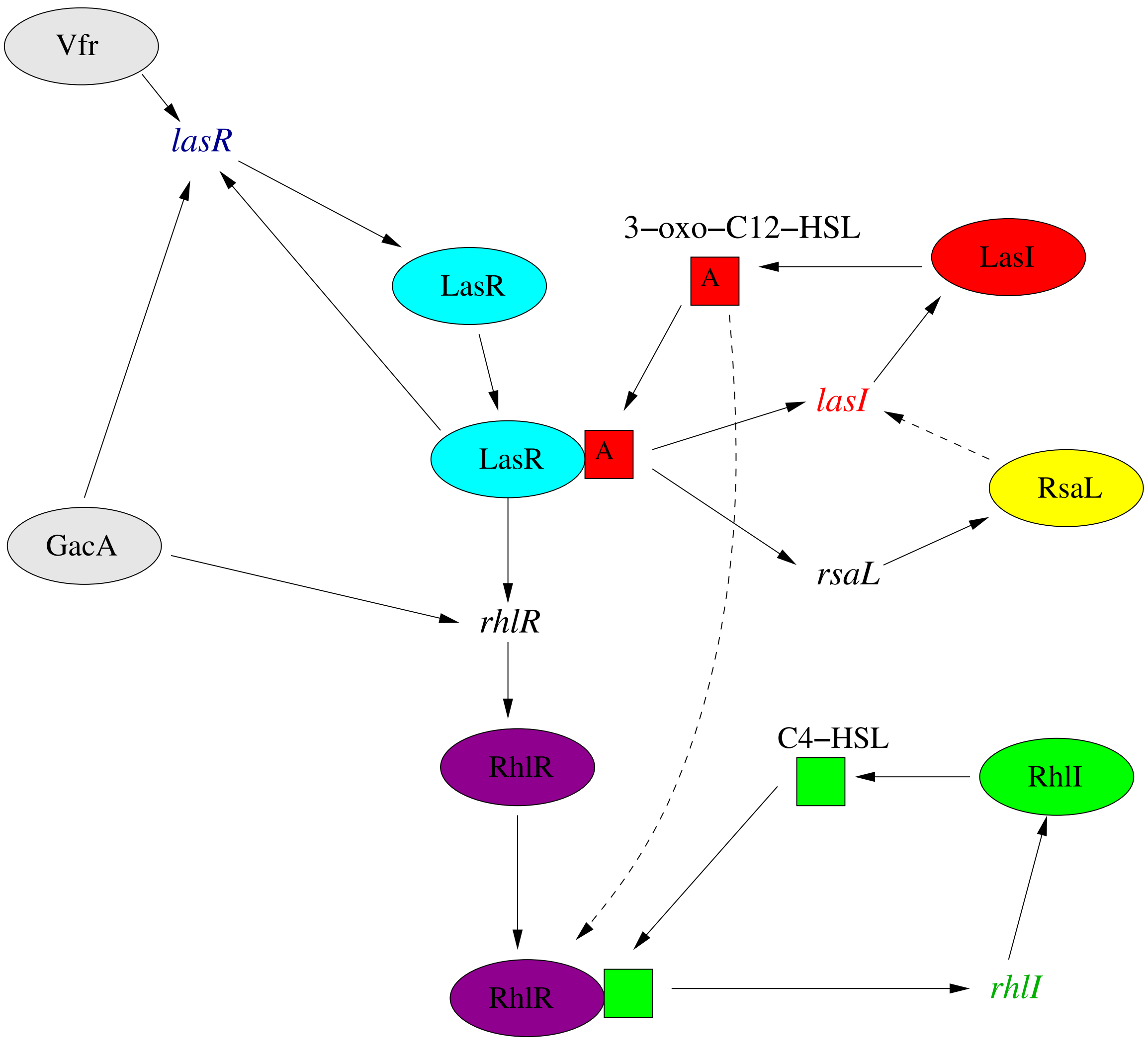
Biochemistry of Quorum Sensing



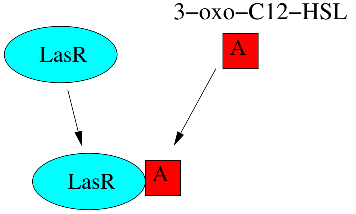
Biochemistry of Quorum Sensing



Biochemistry of Quorum Sensing



Modeling Biochemical Reactions

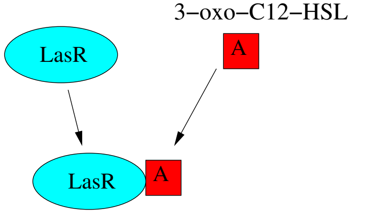


Bimolecular reaction $A + R \longleftrightarrow P$

$$\frac{dP}{dt} = k_+ AR - k_- P$$

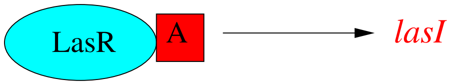
Modeling Biochemical Reactions

Bimolecular reaction $A + R \longleftrightarrow P$



$$\frac{dP}{dt} = k_+ AR - k_- P$$

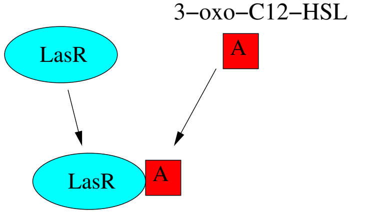
Production of mRNA $\xrightarrow{P} l$



$$\frac{dl}{dt} = \frac{V_{max} P}{K_l + P} - k_{-l} l$$

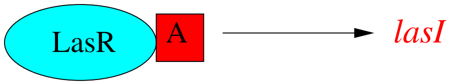
Modeling Biochemical Reactions

Bimolecular reaction $A + R \longleftrightarrow P$



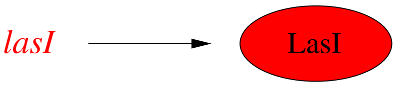
$$\frac{dP}{dt} = k_+ AR - k_- P$$

Production of mRNA $\xrightarrow{P} l$



$$\frac{dl}{dt} = \frac{V_{max} P}{K_l + P} - k_{-l} l$$

Enzyme production $l \rightarrow L$



$$\frac{dL}{dt} = k_l l - K_L L$$

Imagine the Possibilities
Mathematical Biology
University of Utah

Full system of ODE's

$$\frac{dP}{dt} = k_{RA}RA - k_P P$$

$$\frac{dR}{dt} = -k_{RA}RA + k_P P - k_R R + k_1 r,$$

$$\frac{dA}{dt} = -k_{RA}RA + k_P P + k_2 L - k_A A,$$

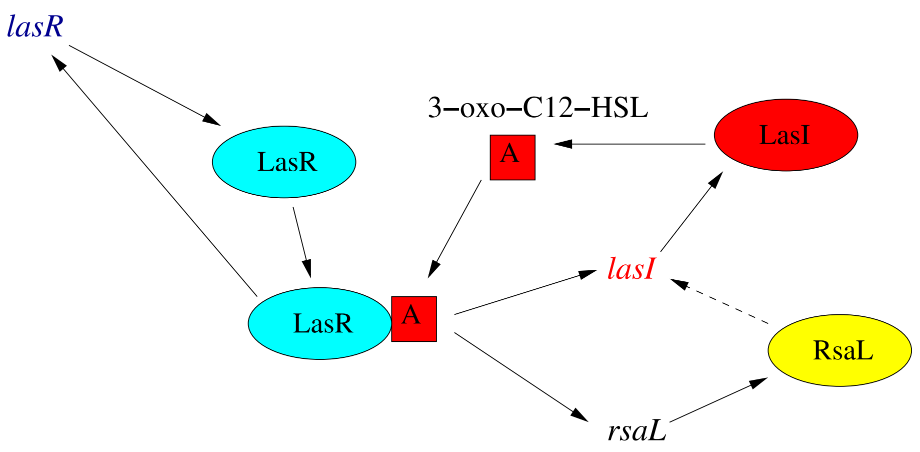
$$\frac{dL}{dt} = k_3 l - k_l L,$$

$$\frac{dS}{dt} = k_4 s - k_S S,$$

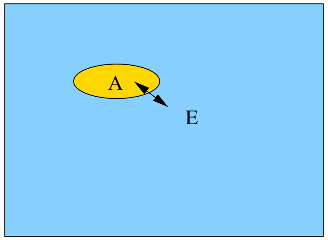
$$\frac{ds}{dt} = V_s \frac{P}{K_S + P} - k_s s,$$

$$\frac{dr}{dt} = V_r \frac{P}{K_r + P} - k_r r + r_0,$$

$$\frac{dl}{dt} = V_l \frac{P}{K_l + P} \frac{1}{K_S + S} - k_l l + l_0$$



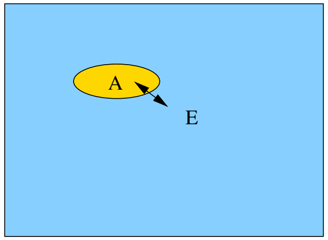
Diffusion



$$\frac{dA}{dt} = F(A, R, P) + \delta(E - A)$$

$$\frac{dE}{dt} = -k_E E + \delta(A - E)$$

Diffusion

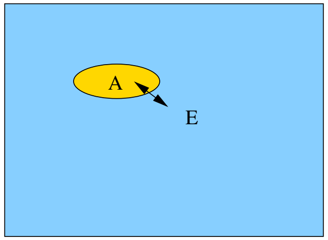


$$\boxed{\frac{dA}{dt}} = F(A, R, P) + \delta(E - A)$$

$$\boxed{\frac{dE}{dt}} = -k_E E + \delta(A - E)$$

rate of change,

Diffusion

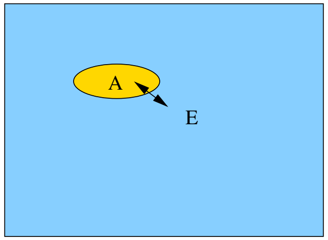


$$\frac{dA}{dt} = \boxed{F(A,R,P)} + \delta(E - A)$$

$$\frac{dE}{dt} = -\boxed{k_E E} + \delta(A - E)$$

rate of change, production or degradation rate,

Diffusion

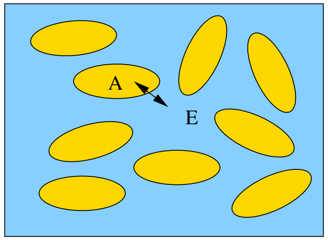


$$\frac{dA}{dt} = F(A,R,P) + \boxed{\delta(E-A)}$$

$$\frac{dE}{dt} = -\,k_E E + \boxed{\delta(A-E)}$$

rate of change, production or degradation rate, diffusive exchange,

Diffusion



$$\frac{dA}{dt} = F(A,R,P) + \delta(E-A)$$

$$\boxed{(1-\rho)}\left(\frac{dE}{dt} + K_E E\right) = \boxed{\rho}\,\delta(A-E)$$

rate of change, production or degradation rate, diffusive exchange, density dependence.

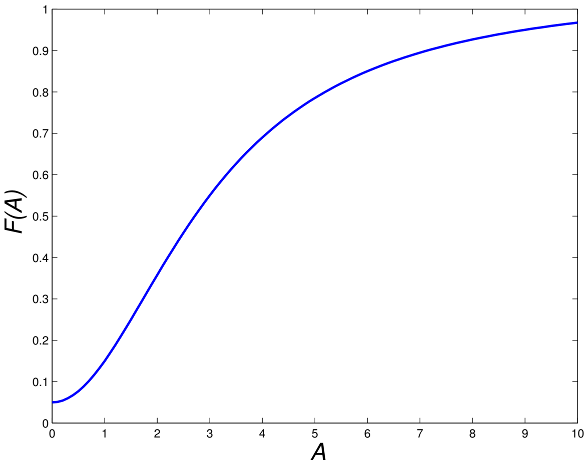
Main point reiterated!!! Flux of A out of the cell is related to the amount of E in the extracellular space.

Simplified Model

$$\frac{dA}{dt} = F(A) + \delta(E - A),$$

$$(1-\rho)\left(\frac{dE}{dt} + k_E E\right) = \rho\delta(A - E),$$

where $F(A) = F_0 + \frac{VA^2}{K_A^2 + A^2}$.



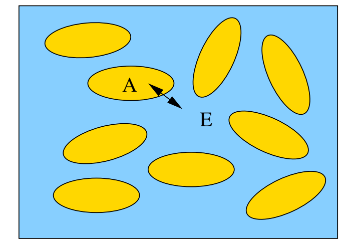
Two Variable Phase Portrait

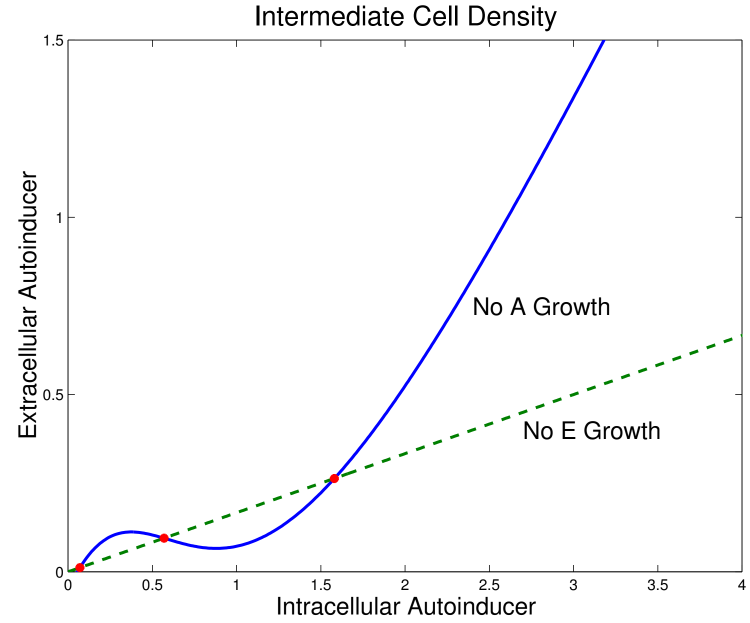
$$\frac{dA}{dt} = F(A) + \delta(E - A),$$

$$(1-\rho)\left(\frac{dE}{dt} + k_E E\right) = \rho\delta(A - E),$$

Nullclines:

- $\frac{dA}{dt} = 0 : \quad E = A - \frac{1}{\delta}F(A)$
- $\frac{dE}{dt} = 0 : \quad A = \left(\frac{1-\rho}{\rho\delta}k_E + 1\right)E$





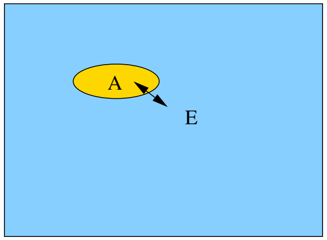
Two Variable Phase Portrait

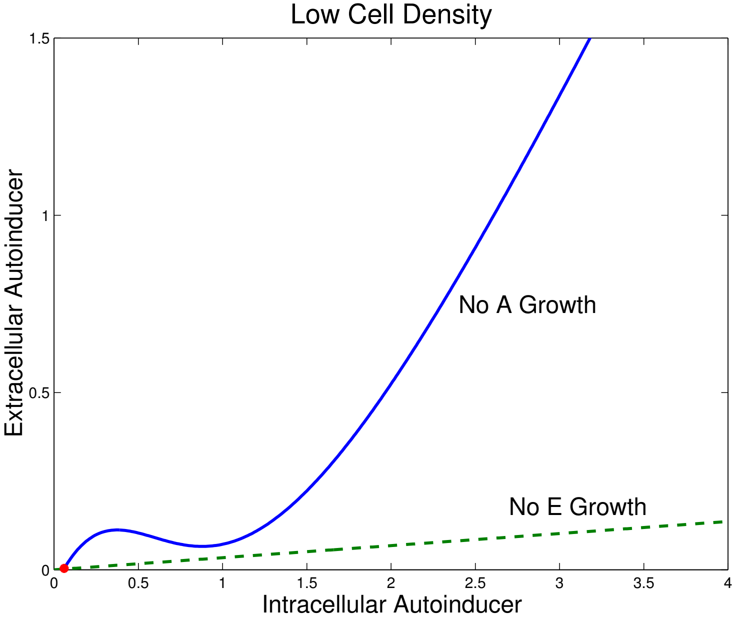
$$\frac{dA}{dt} = F(A) + \delta(E - A),$$

$$(1-\rho)(\frac{dE}{dt} + k_E E) = \rho\delta(A - E),$$

Nullclines:

- $\frac{dA}{dt} = 0: \quad E = A - \frac{1}{\delta}F(A)$
- $\frac{dE}{dt} = 0: \quad A = (\frac{1-\rho}{\rho\delta}k_E + 1)E$





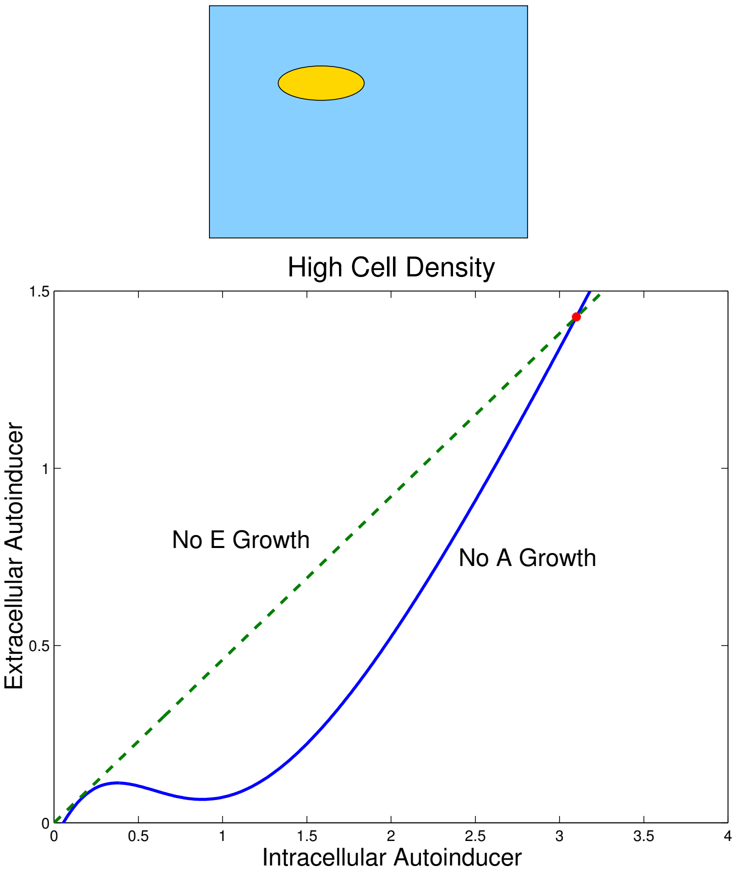
Two Variable Phase Portrait

$$\frac{dA}{dt} = F(A) + \delta(E - A),$$

$$(1-\rho)\left(\frac{dE}{dt} + k_E E\right) = \rho\delta(A - E),$$

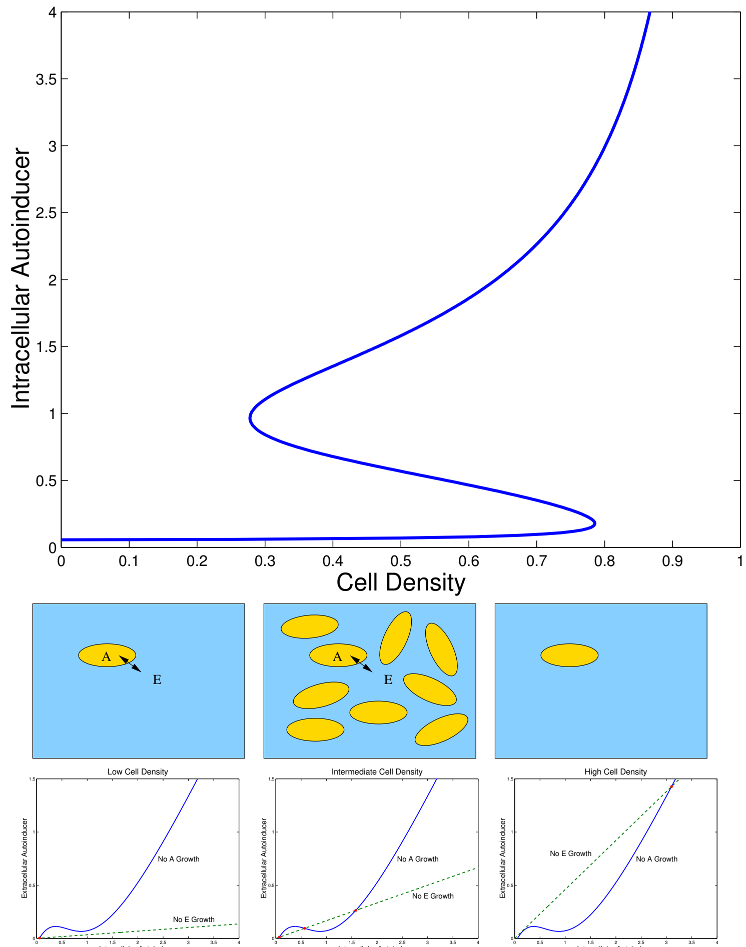
Nullclines:

- $\frac{dA}{dt} = 0: \quad E = A - \frac{1}{\delta}F(A)$
- $\frac{dE}{dt} = 0: \quad A = \left(\frac{1-\rho}{\rho\delta}k_E + 1\right)E$



Result

A density dependent switch (like a thermostat).

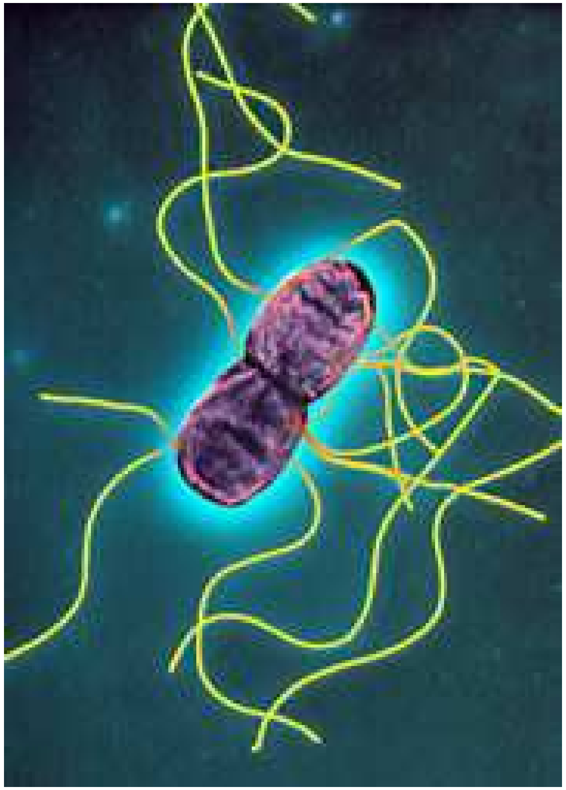


Summary: Part I

- Rate at which something can be dumped is an indicator of the size of the space into which it is being dumped.
- Diffusion coupled with positive feedback enables hysteretic switches.
- This generic behavior remains the same, even with much more complicated (PDE) models.

II - Length Detection

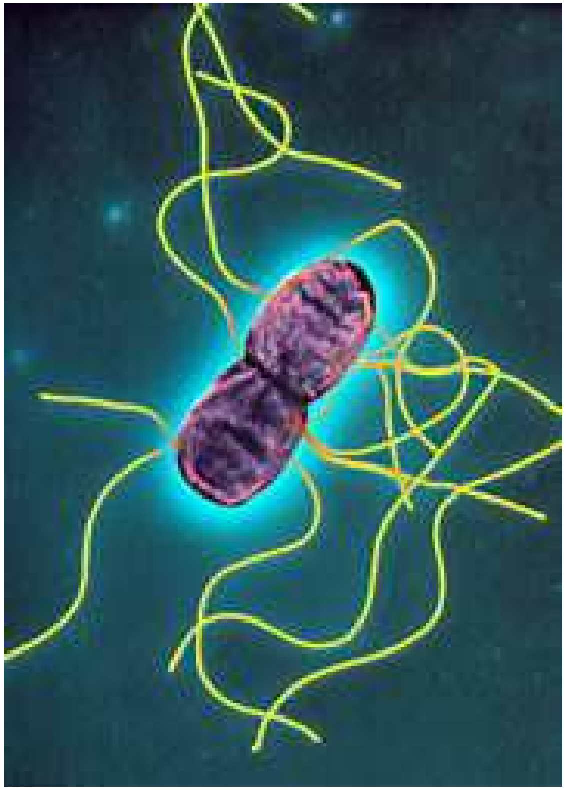
Salmonella: The "critters" that cause food poisoning.



II - Length Detection

Salmonella: The "critters" that cause food poisoning.

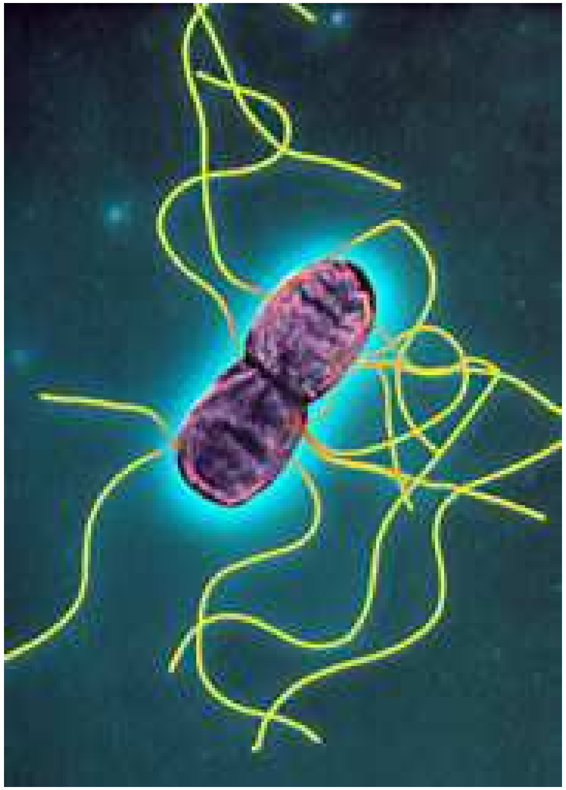
- Flagella grow at a velocity that decreases as they get longer.



II - Length Detection

Salmonella: The "critters" that cause food poisoning.

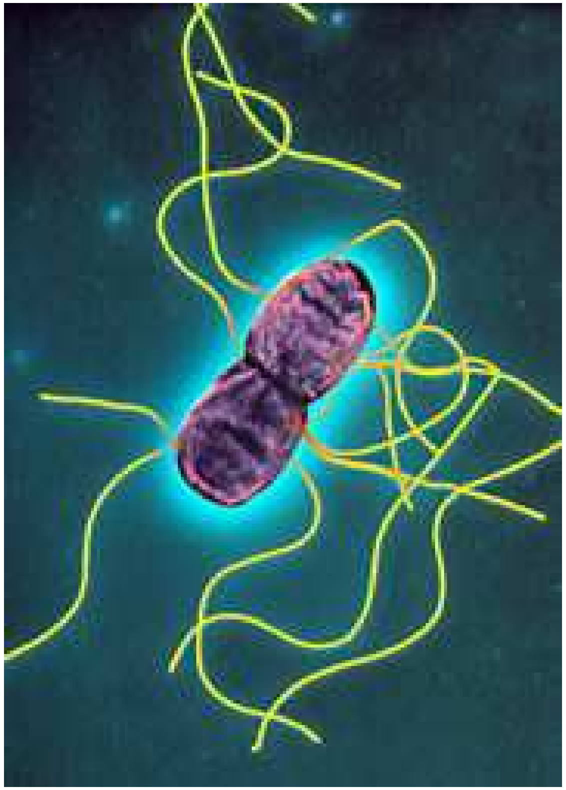
- Flagella grow at a velocity that decreases as they get longer.
- If a flagellum is broken off, it will regrow at the same velocity as when it first grew.



II - Length Detection

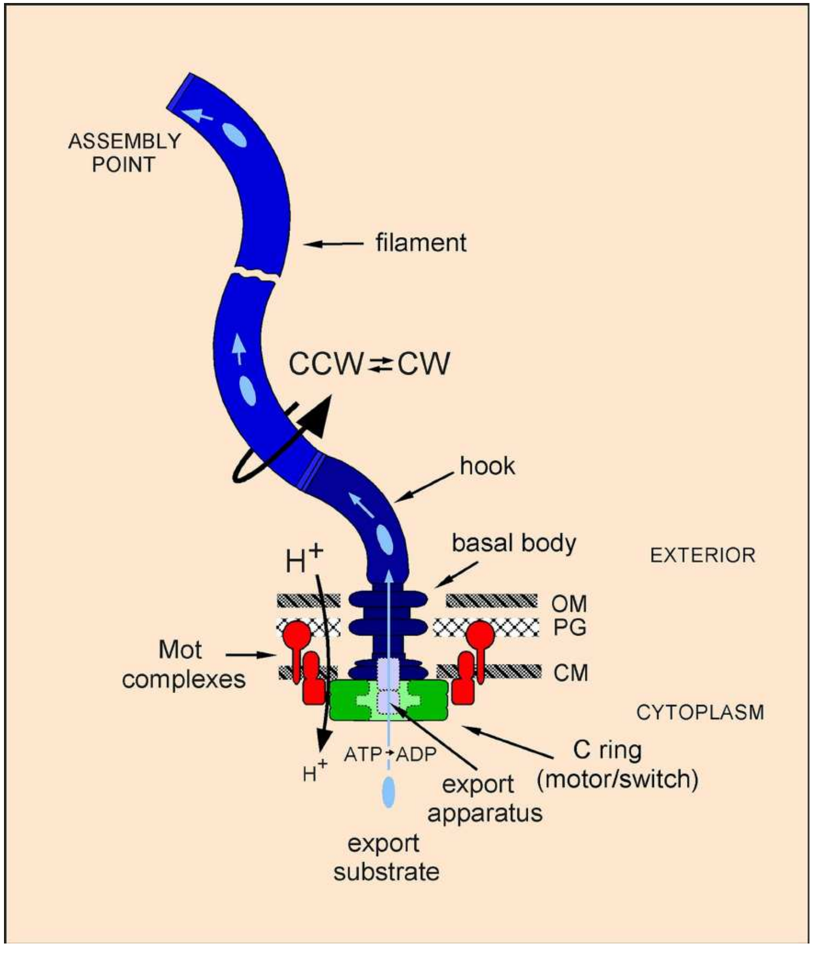
Salmonella: The "critters" that cause food poisoning.

- Flagella grow at a velocity that decreases as they get longer.
- If a flagellum is broken off, it will regrow at the same velocity as when it first grew.



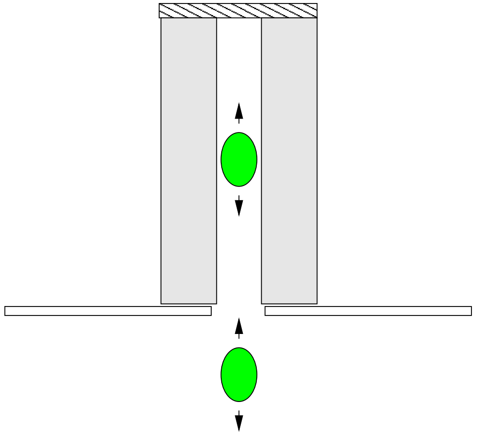
Question: How does the bacterium measure flagellar length?

Rotary Flagellar Motors



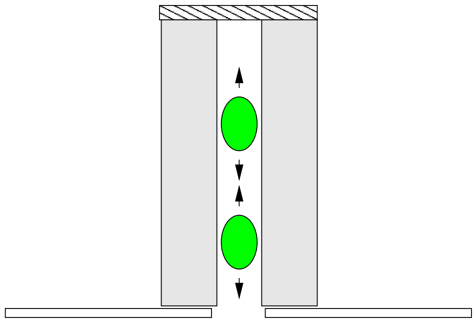
How Do Flagella Grow?

- Step 1: Secretion
- Step 2: Diffusion
- Step 3: Polymerization



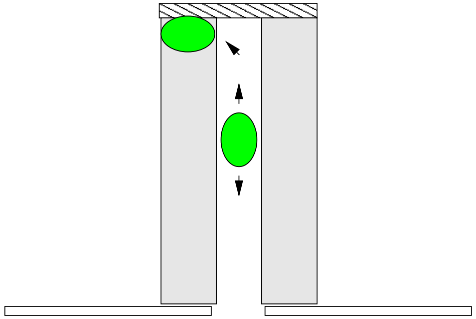
How Do Flagella Grow?

- Step 1: Secretion
- Step 2: Diffusion
- Step 3: Polymerization



How Do Flagella Grow?

- Step 1: Secretion
- Step 2: Diffusion
- Step 3: Polymerization



Modelling Flagellar Growth

Step 2: Diffusion

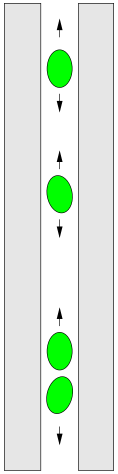
Important Fact: Filament is a hollow tube, so movement (diffusion) is single file.

Let $p(x,t)$ be the probability that a molecule is at position x at time t. Then,

$$\frac{\partial p}{\partial t} + \frac{\partial J}{\partial x} = 0$$

where

$$J = -D\frac{\partial p}{\partial x}.$$



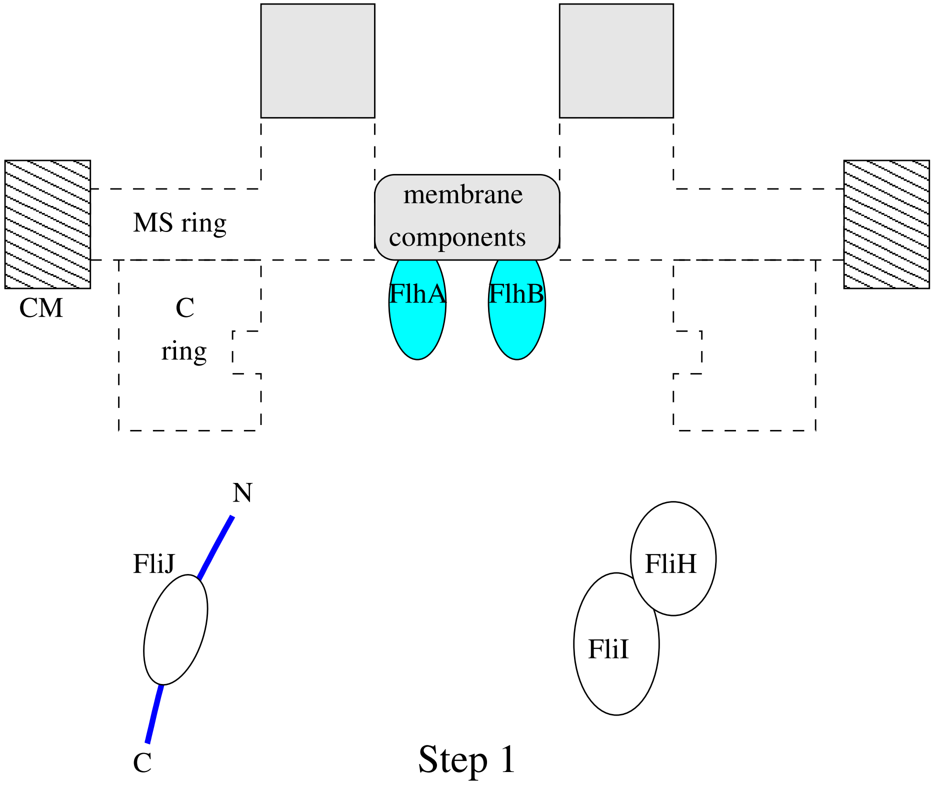
Remark: $\frac{J}{l}$ = flux in molecules per unit time.

Imagine the Possibilities

Mathematical Biology
University of Utah

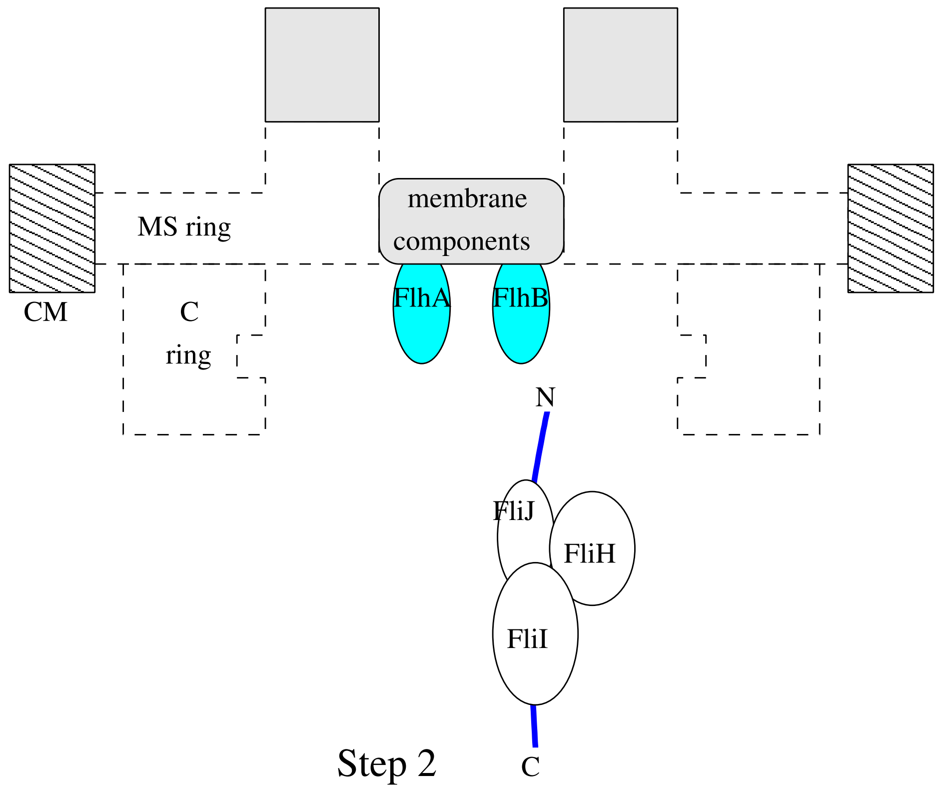
Modelling Flagellar Growth

Step 1: Secretion



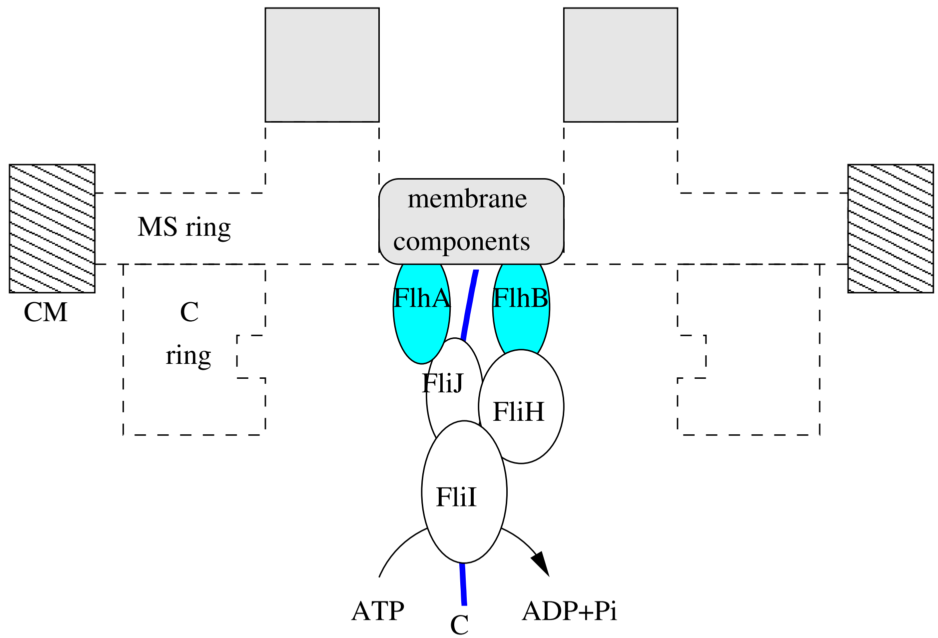
Modelling Flagellar Growth

Step 1: Secretion



Modelling Flagellar Growth

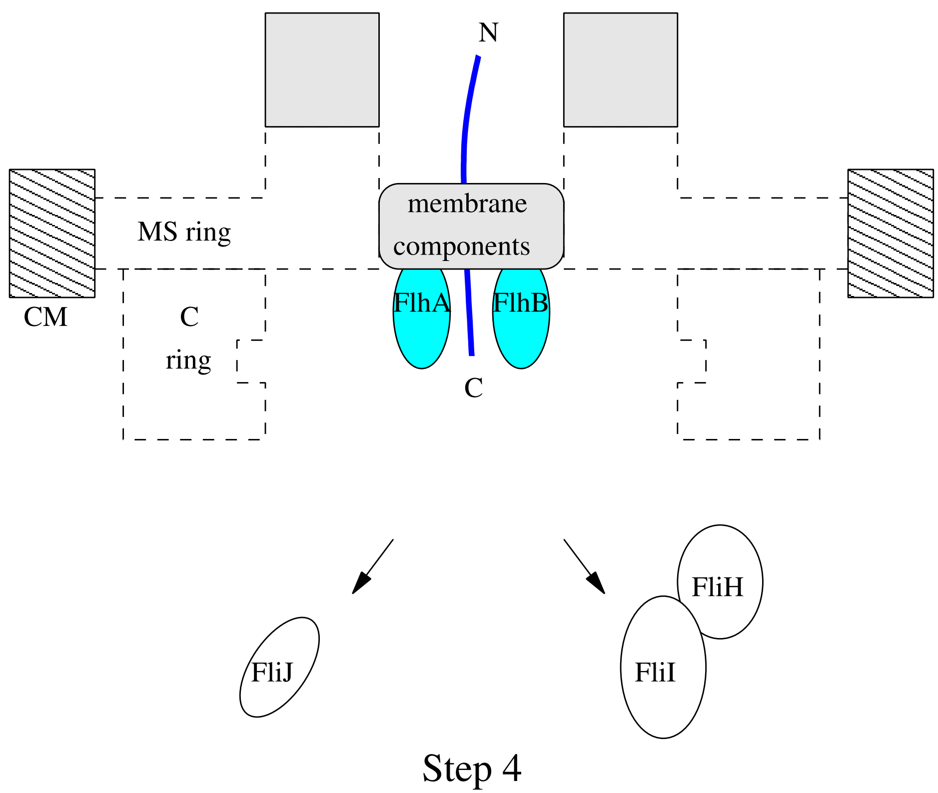
Step 1: Secretion



Step 3

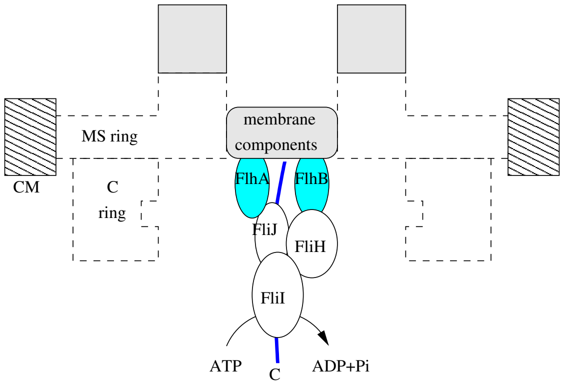
Modelling Flagellar Growth

Step 1: Secretion



Rate of Secretion

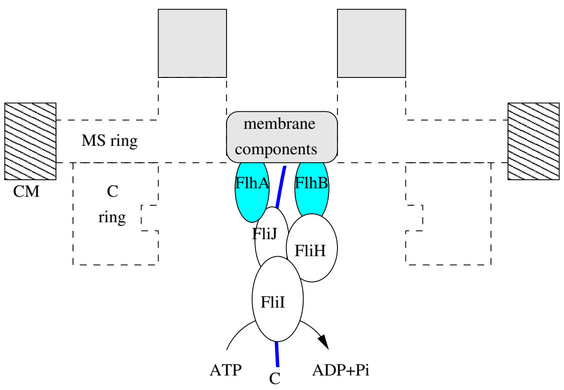
Let $P(t)$ be the probability that ATP-ase is bound



Step 3

Rate of Secretion

Let $P(t)$ be the probability that ATP-ase is bound

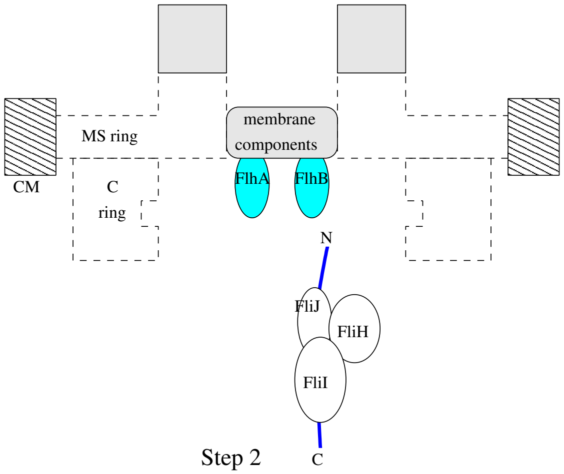


Step 3

$$\frac{dP}{dt} =$$

Rate of Secretion

Let $P(t)$ be the probability that ATP-ase is bound

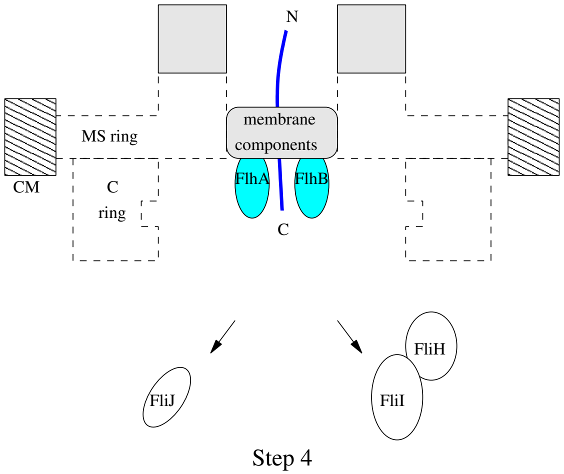


$$\frac{dP}{dt} = \boxed{K_{on}(1 - P)}$$

on rate,

Rate of Secretion

Let $P(t)$ be the probability that ATP-ase is bound

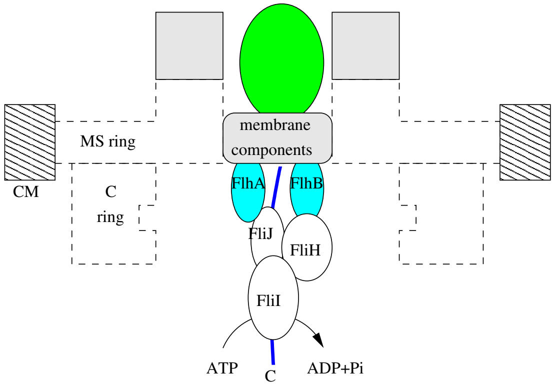


$$\frac{dP}{dt} = K_{on}(1-P) \;\; - \boxed{k_{off}P}$$

on rate, off rate,

Rate of Secretion

Let $P(t)$ be the probability that ATP-ase is bound



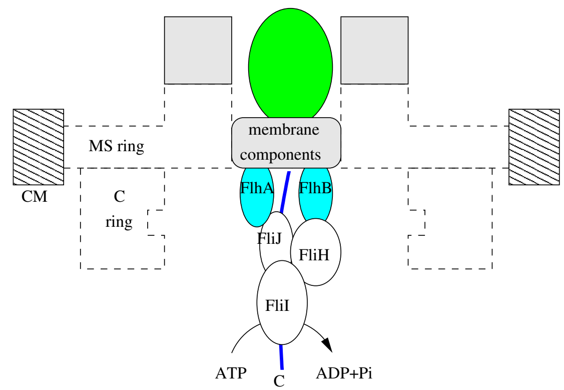
Step 4 Blocked

$$\frac{dP}{dt} = K_{on}(1-P) - k_{off}(1-p(0,t))P$$

on rate, off rate, restricted if blocked by another molecule in the tube.

Rate of Secretion

Let $P(t)$ be the probability that ATP-ase is bound



Step 4 Blocked

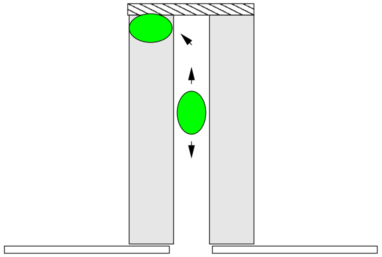
$$\frac{dP}{dt} = K_{on}(1-P) \;-\; \boxed{k_{off}(1-p(0,t))P}$$

on rate, off rate, restricted if blocked by another molecule in the tube. Thus,

$\frac{J}{l} = \boxed{k_{off}(1-p(0,t))P}$ at $x = 0$ (A Robin boundary condition).

Rate of Polymerization

Stage 3: Polymerization



$$\frac{J}{l} = k_p p$$

at the polymerizing end $x = L$.

Then, the growth velocity is

$$\frac{dL}{dt} = \beta \frac{J}{l} \equiv V$$

where $\beta =$length of filament per monomer (0.5nm/monomer)

$\cdots$ a moving boundary problem.

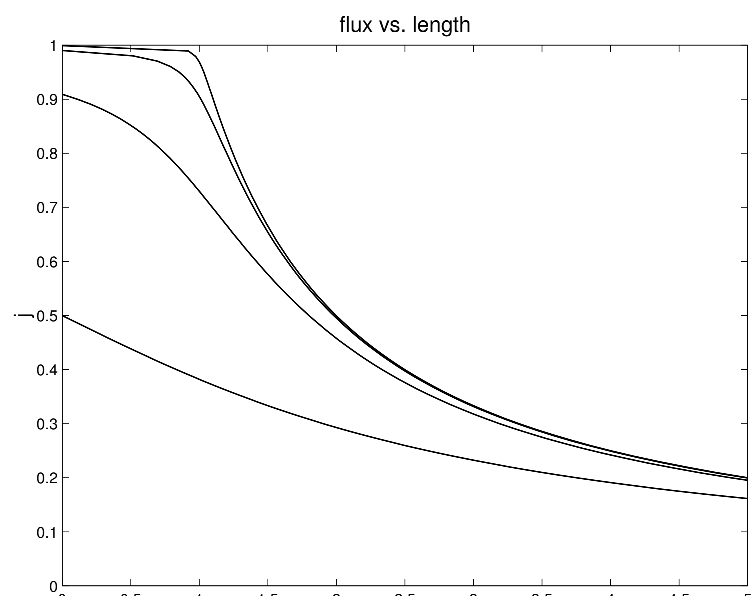
Diffusion Model

After some work, it can be shown that

$$\lambda = \frac{1}{j} - \frac{K_a}{1-j} - K_b$$

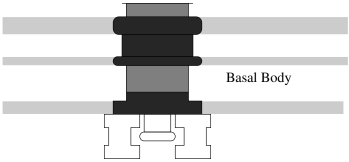
where $j = \frac{J}{lK_{on}}$, $\lambda = \frac{lLK_{on}}{D}$, $K_a = \frac{K_{on}}{k_{off}}$, $K_b = \frac{K_{on}}{k_p}$.

A good approximation $J \approx \frac{1}{K_J + \frac{L}{D}} \approx \frac{D}{L}$ for large L



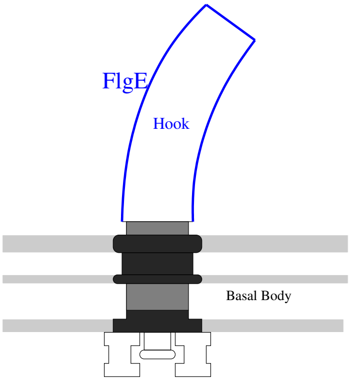
Control of Flagellar Growth

- Step 1: Basal Body
- Step 2: Hook (FlgE secretion)
- Step 3: Filament (FliC secretion)



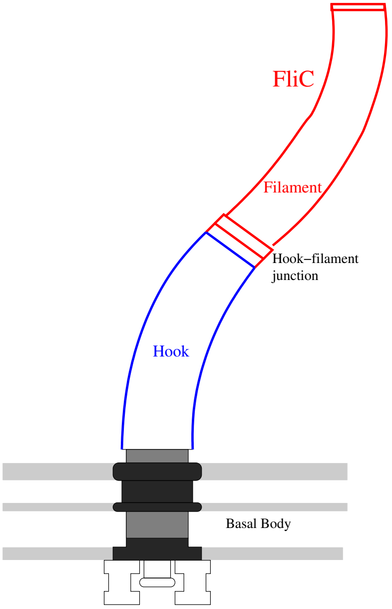
Control of Flagellar Growth

- Step 1: Basal Body
- Step 2: Hook (FlgE secretion)
- Step 3: Filament (FliC secretion)



Control of Flagellar Growth

- Step 1: Basal Body
- Step 2: Hook (FlgE secretion)
- Step 3: Filament (FliC secretion)



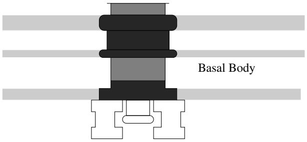
Filament Length Control

Introducing FlgM and σ^{28}:

Filament Length Control

Introducing FlgM and σ^{28}:

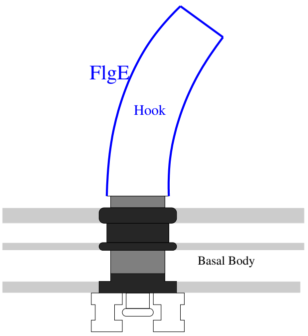
Class 1



Filament Length Control

Introducing FlgM and σ^{28}:

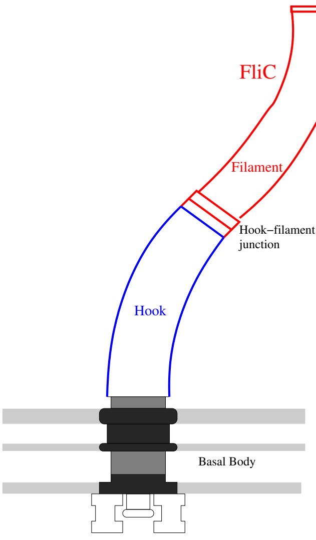
$$\text{Class 1} \rightarrow \text{Class 2} \left\{ \begin{array}{c} \sigma^{28} \\ \text{FlgE} \\ \text{FlgKL} \\ \text{FlgM} \\ \text{FliK} \end{array} \right\}$$



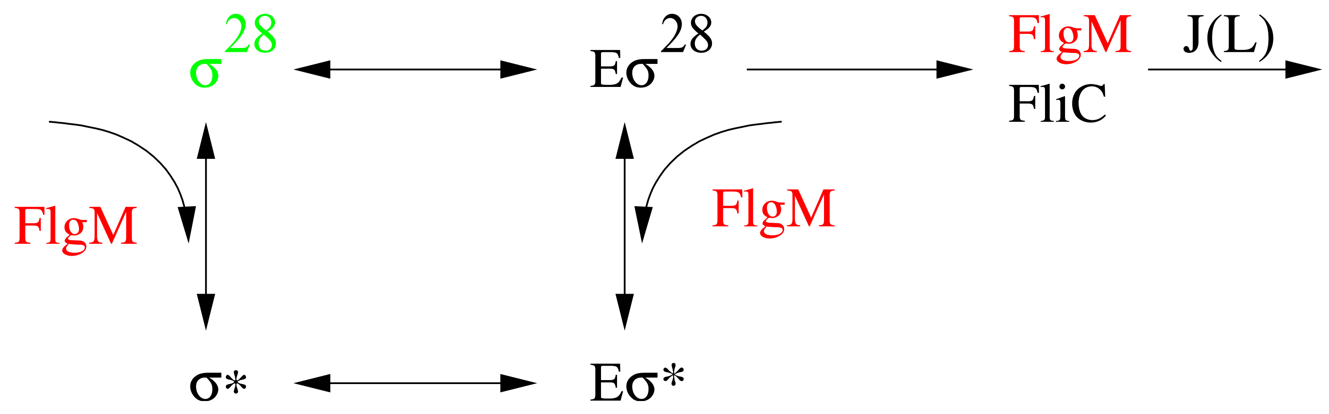
Filament Length Control

Introducing FlgM and σ^{28}:

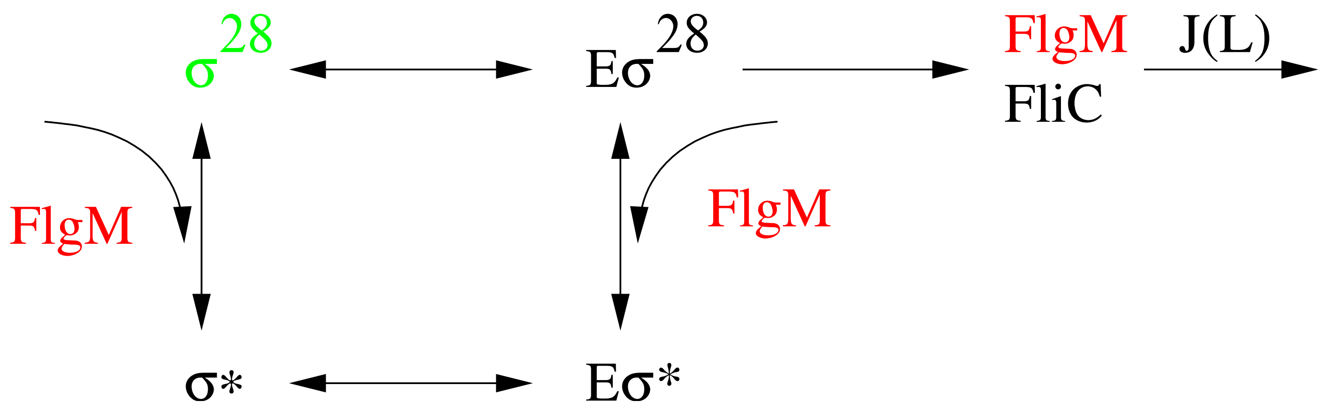
$$\text{Class 1} \rightarrow \text{Class 2} \left\{ \begin{array}{c} \sigma^{28} \\ \text{FlgE} \\ \text{FlgKL} \\ \text{FlgM} \\ \text{FliK} \end{array} \right\} \xrightarrow{E\sigma^{28}} \text{Class 3} \left\{ \begin{array}{c} \text{FliC} \\ \text{FliD} \\ \text{FlgM} \end{array} \right\}$$



FlgM-σ^{28} Chemistry

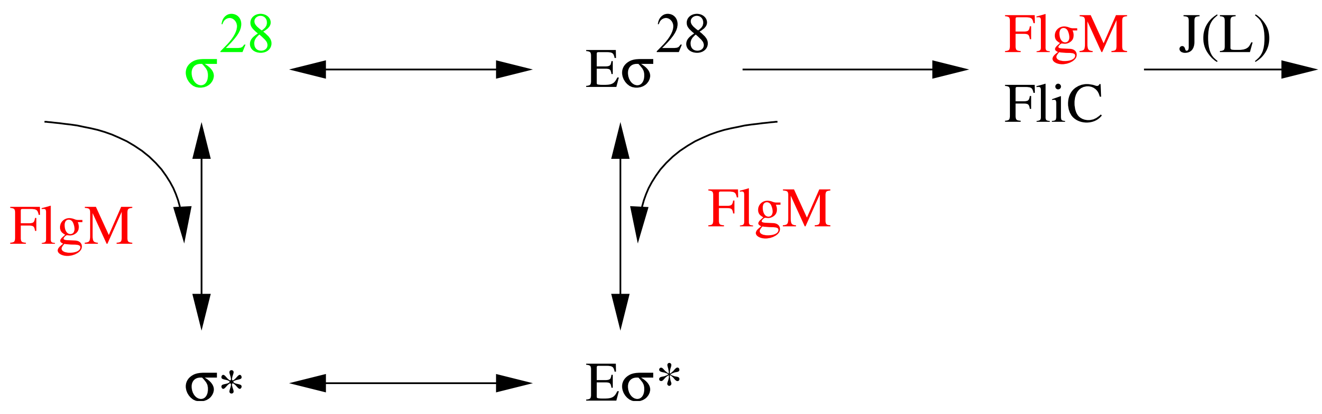


FlgM-σ^{28} Chemistry



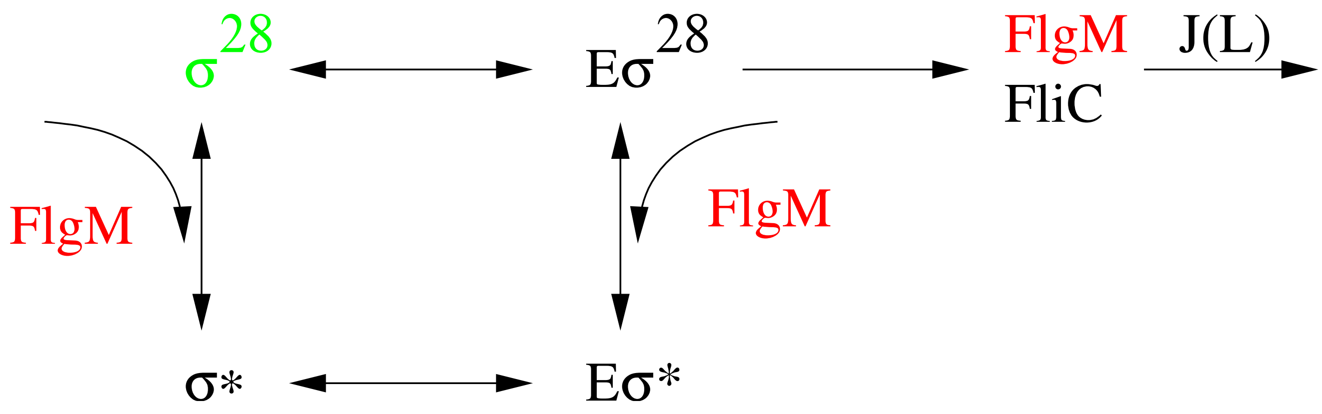
- FlgM inhibits σ^{28} activity, by binding σ^{28} and by destabilizing $E\sigma^{28}$;

FlgM-σ^{28} Chemistry



- FlgM inhibits σ^{28} activity, by binding σ^{28} and by destabilizing $E\sigma^{28}$;
- Therefore, during stage 3, FlgM inhibits its own production (negative feedback);

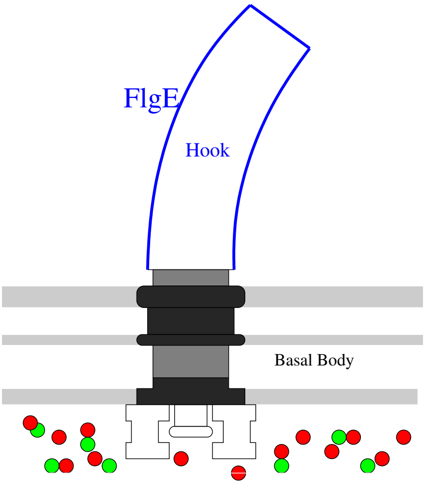
FlgM-σ^{28} Chemistry



- FlgM inhibits σ^{28} activity, by binding σ^{28} and by destabilizing $E\sigma^{28}$;
- Therefore, during stage 3, FlgM inhibits its own production (negative feedback);
- And, FlgM inhibits the production of Flagellin (FliC).

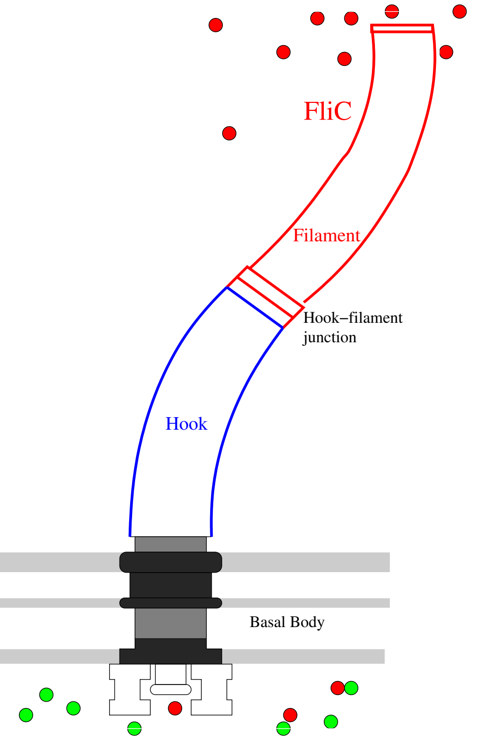
FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth.



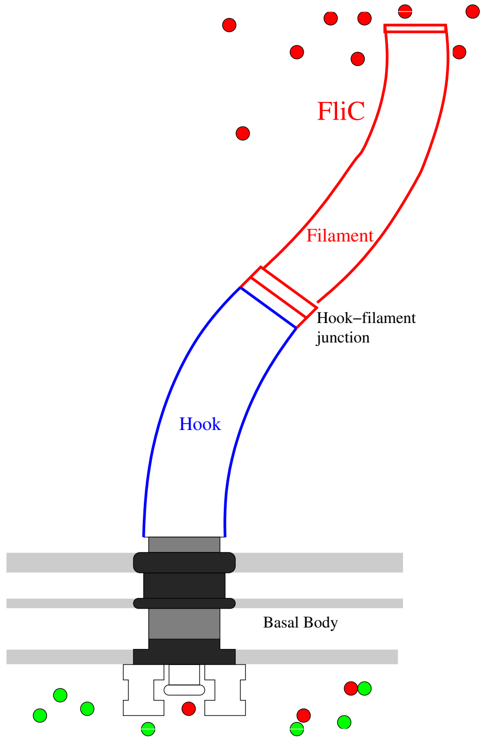
FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth.
- FlgM **is** secreted during filament growth.



FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth.
- FlgM **is** secreted during filament growth.



So, how fast is FlgM secreted, and why does it matter?

Tracking Concentrations

FlgM (M):

$$\frac{dM}{dt} = \text{rate of production} - \text{rate of secretion}$$

Flagellin (FliC) (F):

$$\frac{dF}{dt} = \text{rate of production} - \text{rate of secretion}$$

Filament Length (L):

$$\frac{dL}{dt} = \beta * \text{rate of FliC secretion}$$

Tracking Concentrations

FlgM (M):

$$\frac{dM}{dt} = \frac{K_*}{K_M + M} - \alpha \frac{M}{F + M} J$$

Flagellin (FliC) (F):

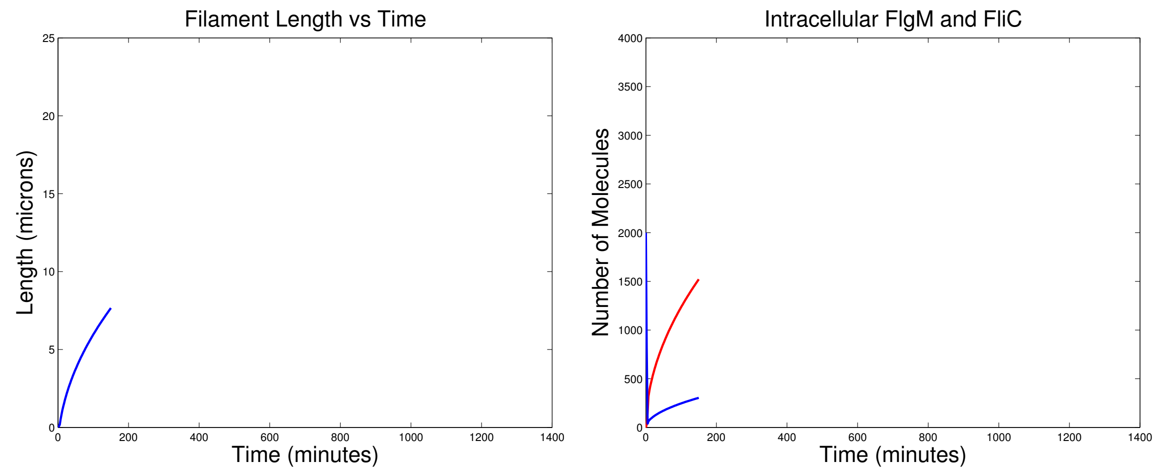
$$\frac{dF}{dt} = \frac{K_*}{K_M + M} - \alpha \frac{F}{F + M} J$$

Filament Length (L):

$$\frac{dL}{dt} = \beta \frac{F}{M + F} J$$

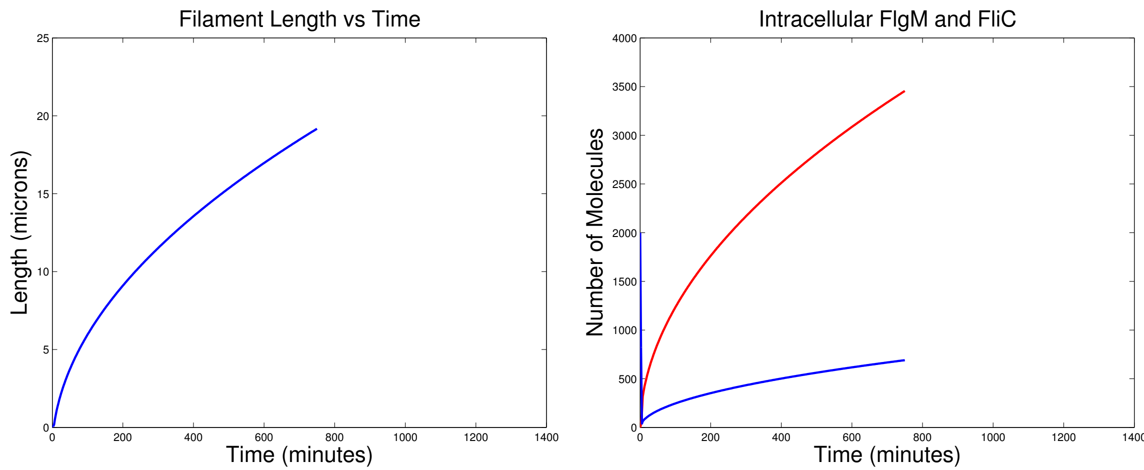
with (remember the main point!) $J = \frac{1}{K_J + \frac{L}{D}}$.

Filament Growth



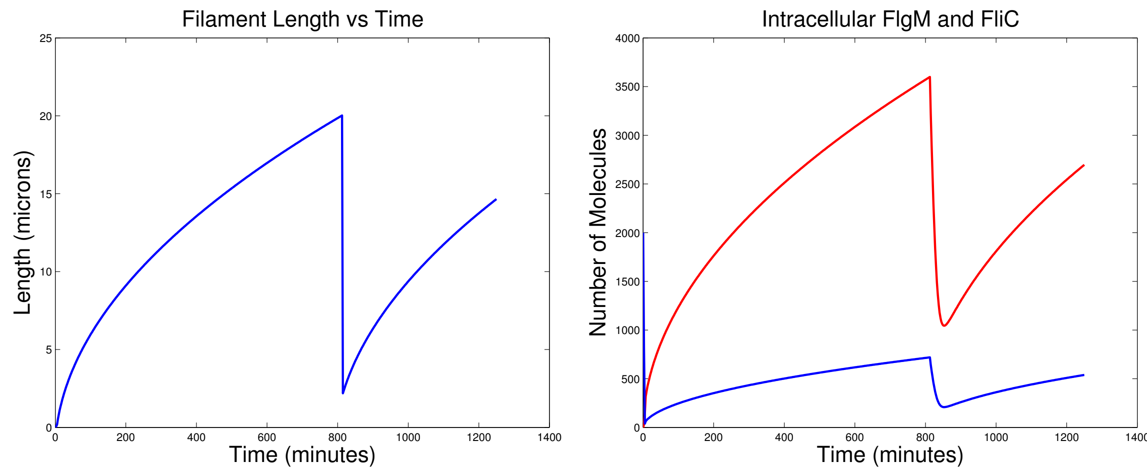
- FlgM concentration is initially large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.

Filament Growth



- FlgM concentration is initially large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.
- As filament length grows, secretion slows, FlgM concentration increases, shutting off FliC and FlgM production.

Filament Growth



- FlgM concentration is initially large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.
- As filament length grows, secretion slows, FlgM concentration increases, shutting off FliC and FlgM production.
- If filament is suddenly shortened, secretion suddenly increases, reinitiating the growth phase.

Imagine the Possibilities
Mathematical Biology
University of Utah

Summary

- The rate of diffusion contains quantifiable information.
- When coupled with positive feedback, environmental decisions are possible (as in quorum sensing);
- When coupled with negative feedback, regulation of mechanical structures is possible (as with length of flagella).

The list of places where these mechanisms are used is probably vast, but they are just beginning to be uncovered.

Acknowledgments

Collaborators

- Jack Dockery, Montana State University (quorum sensing)

Notes

- Funding for research provided by a grant from the NSF.
- No computers were harmed by Microsoft products during the production of this talk.

The End