"Cell Biology: Making Diffusion Your Friend"

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Introduction

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- To:
  Stochasticity, variation and variability are of fundamental importance to the operation of biological systems.

Facts of Death

Diffusion is Your Enemy

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- Diffusion is real; molecules move down their concentration gradient; nonuniformity is smoothed out.
- Structures deteriorate or dissipate - naturally. (Mountains erode, cars rust, computers fails, information is lost.) Randomness is the enemy of non-living things.

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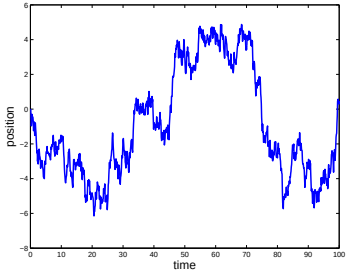
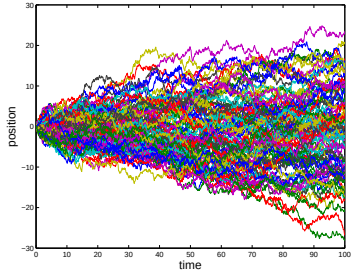
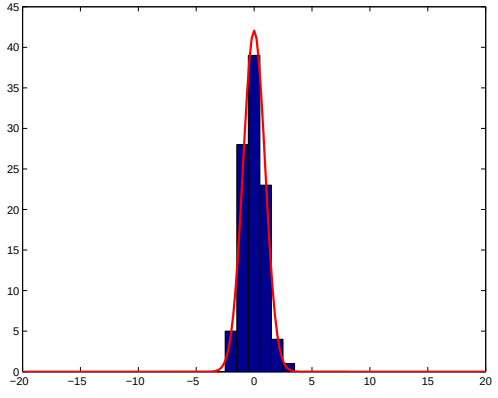
- Basic Question: How do they do this?
- Answer: Diffusion coupled with positive feedback enable living organisms to survive and flourish.

About Diffusion

Most molecules move by a random walk:



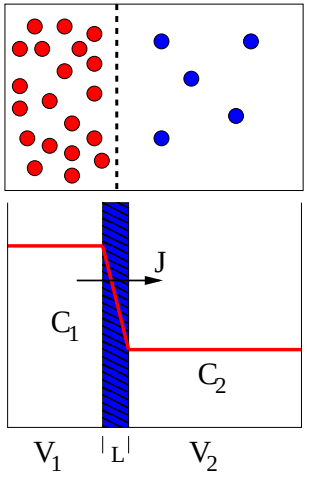




Diffusion across a Membrane

For diffusion across a membrane

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



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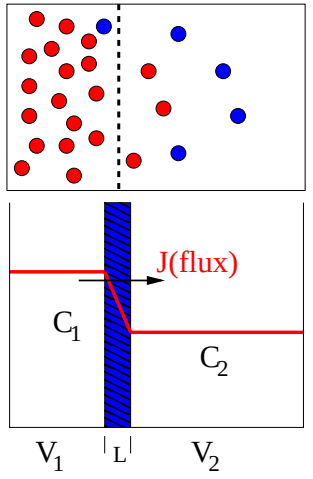
Flux



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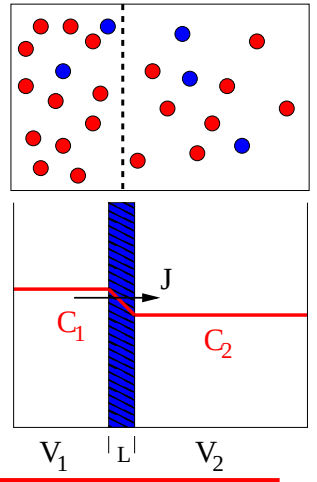

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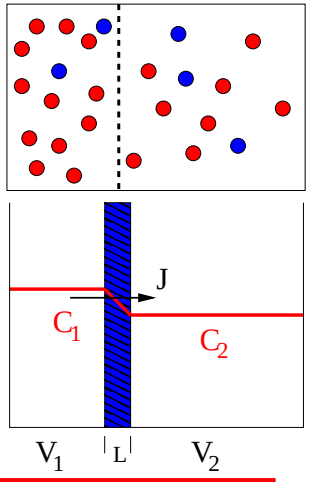

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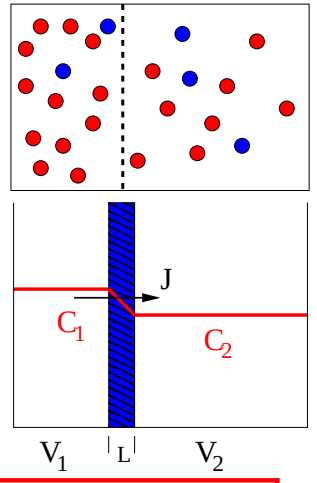

Flux is proportional to concentration difference, inversely proportional to Length.

- Flux is always from high to low concentrations;
- Flux is decreased when Length is large or concentration difference is small.

This fact presents both problems and opportunities.

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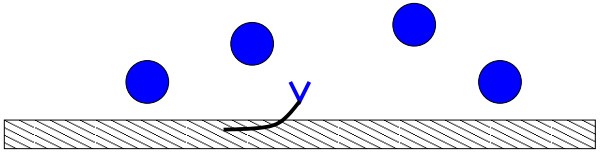
Carrier Mediated Diffusion

Problem: If glucose only diffuses down its gradient, there must always be more glucose in the blood than in cells, or else cells will lose their glucose.

Solution:

1) Use a transporter that binds and releases glucose;



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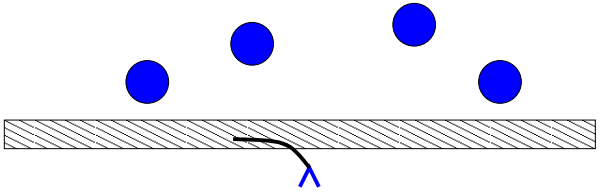

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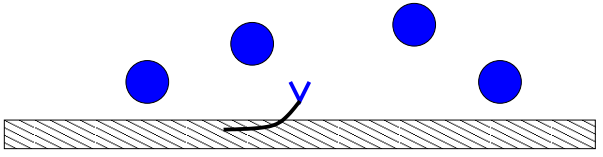

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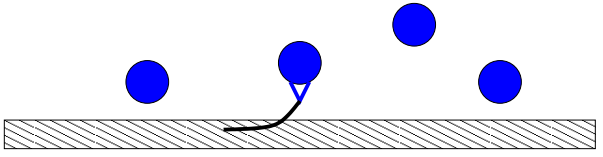

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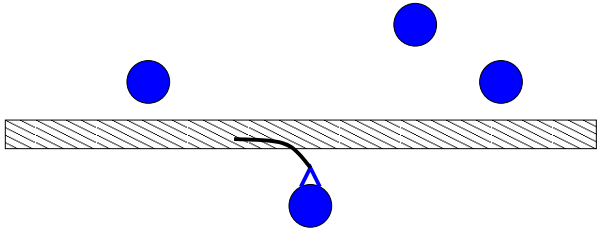

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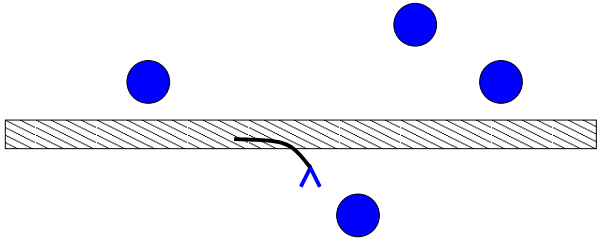

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$$J = J_{max} \frac{g_e - g_i}{(g_e + K)(\frac{g_i}{K} + 1)}$$

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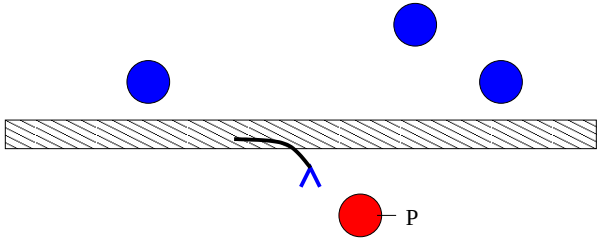

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2) Immediately phosphorylate internal glucose, setting $g_i = 0$ so that flux is always inward!

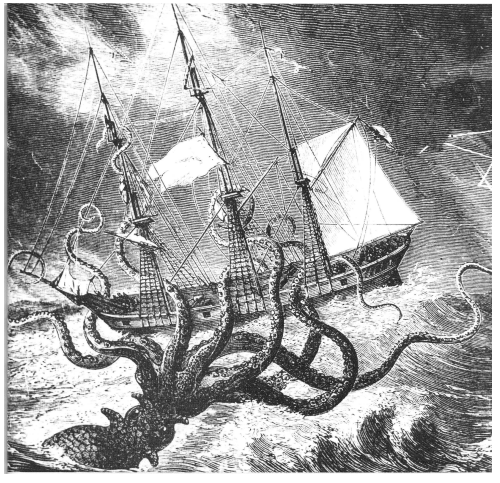
$$J = J_{max} \frac{g_e}{g_e + K}$$

Signalling - 1952

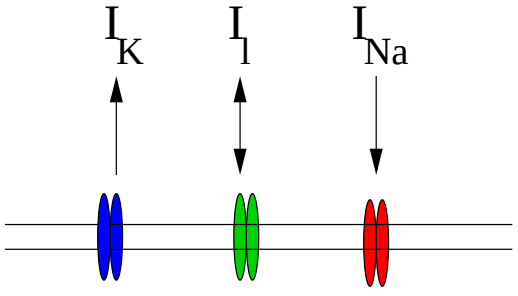
Lesson 1: Reaction/Diffusion systems describing excitable media can produce signals.

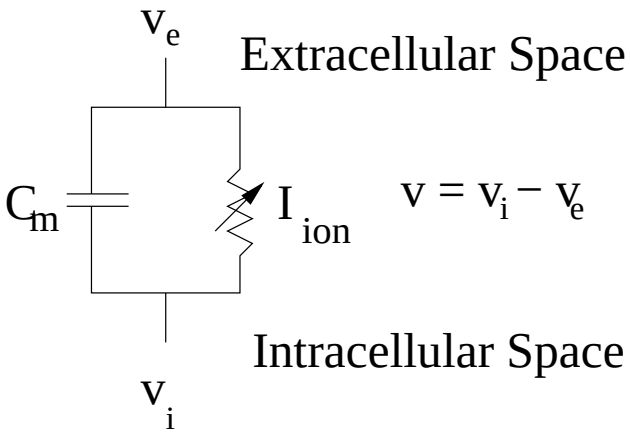
Alan Hodgkin 1914-1998, Andrew Huxley 1917-2012

HH worked on squid giant axon (*not* giant squid axons)



The Hodgkin-Huxley Equations





Tracking the ionic charge Q across a nerve cell membrane,

$$\frac{dQ}{dt} \equiv C_m \frac{dV}{dt} = - \ I_{\mathrm{Na}} \ - \ I_{\mathrm{K}} \ - \ I_{\mathrm{l}} \ ,$$

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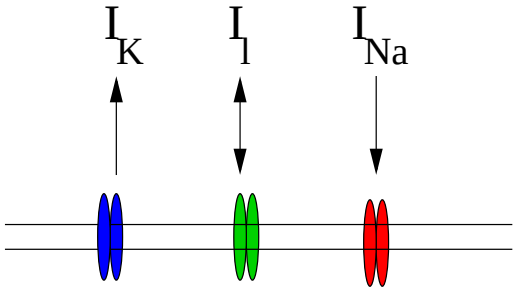

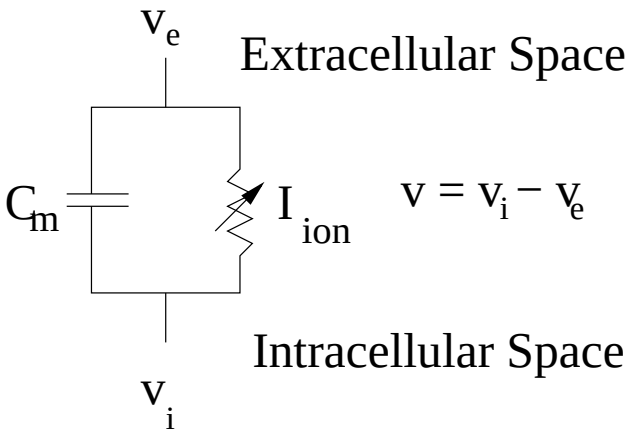

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with sodium current I_{Na},

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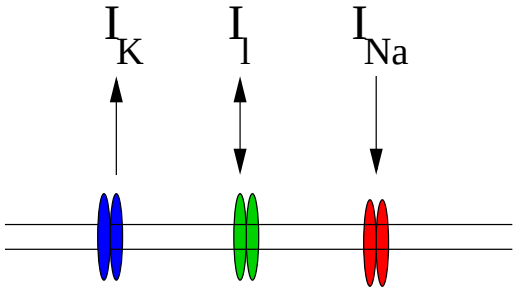

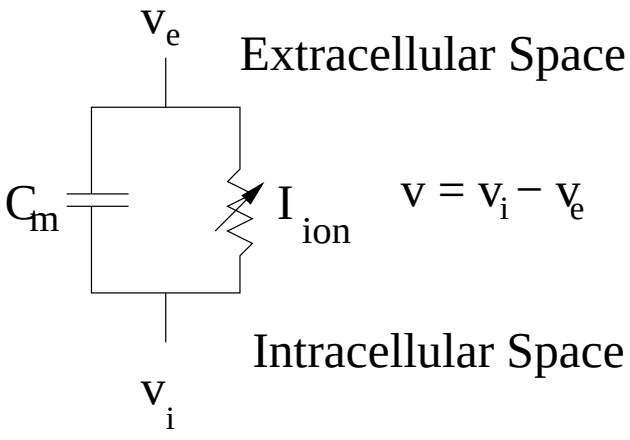

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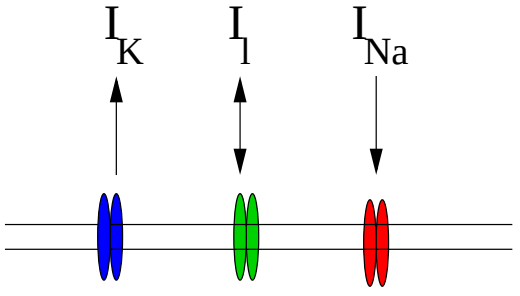

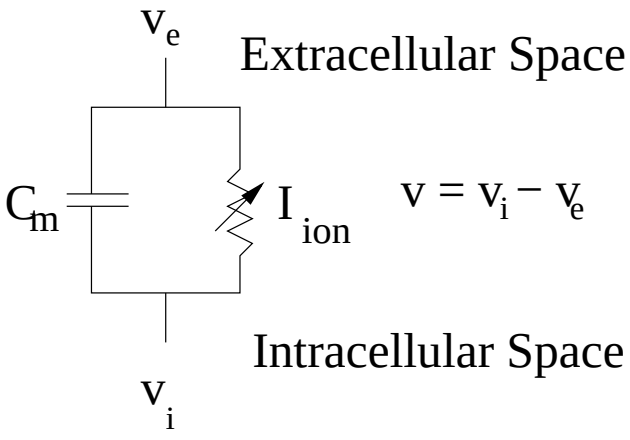

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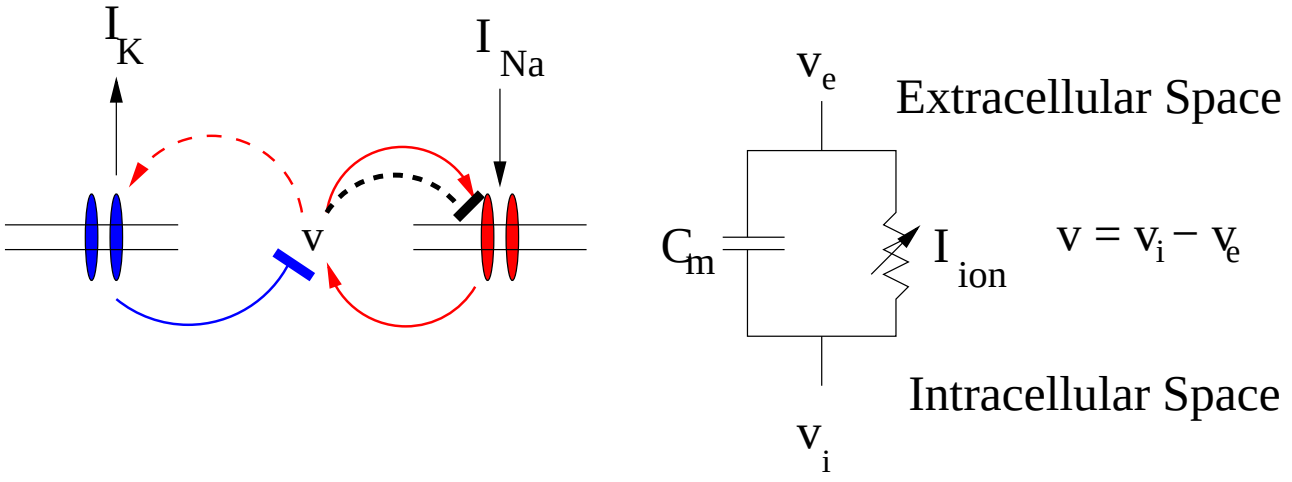
with sodium current I_{Na}, potassium current I_{K}, and leak current I_{l}.

Modeling Membrane Electrical Activity

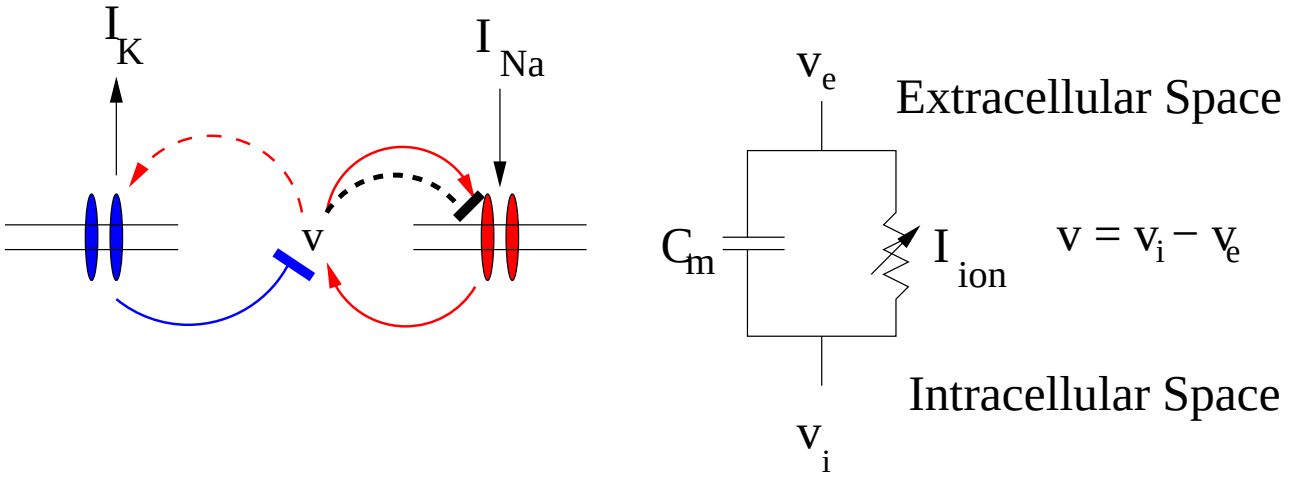


Ionic currents are regulated by voltage in time dependent fashion

$$C_m \frac{dv}{dt} + I_{ion}(v, w) = I_{in} \quad \text{where } \frac{dw}{dt} = g(v, w), \qquad w \in R^3$$

w (m, n, and h in HH parlance) are called gating variables.

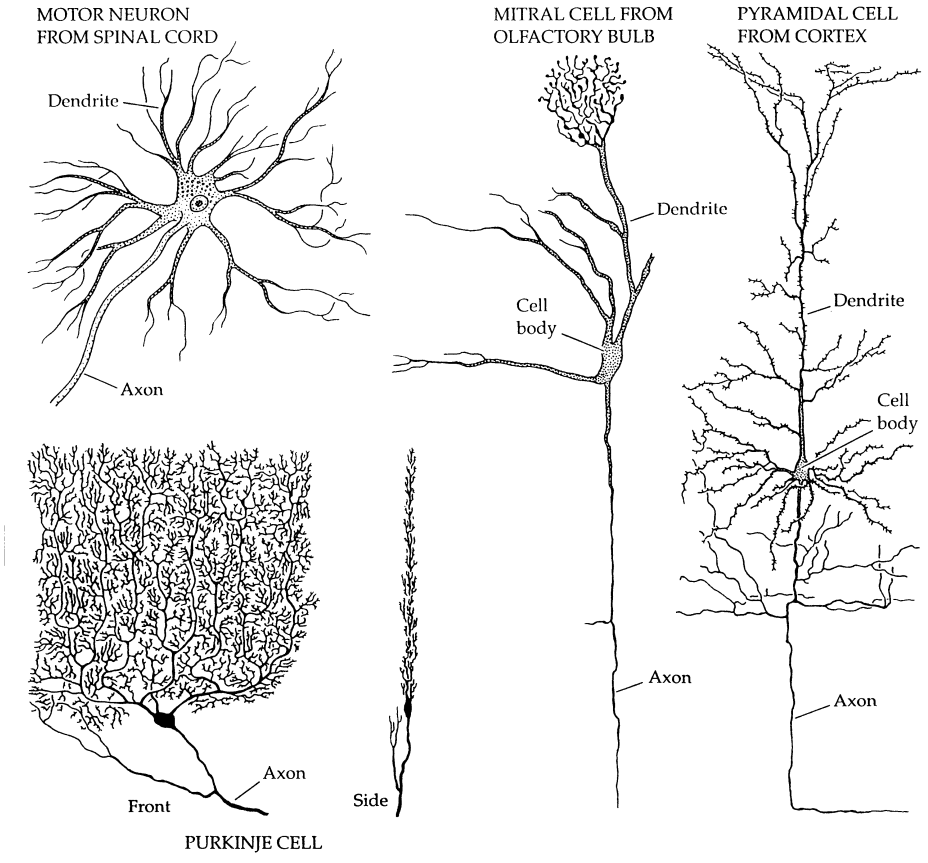
Sodium Ion Channel kinetics



Important observations:

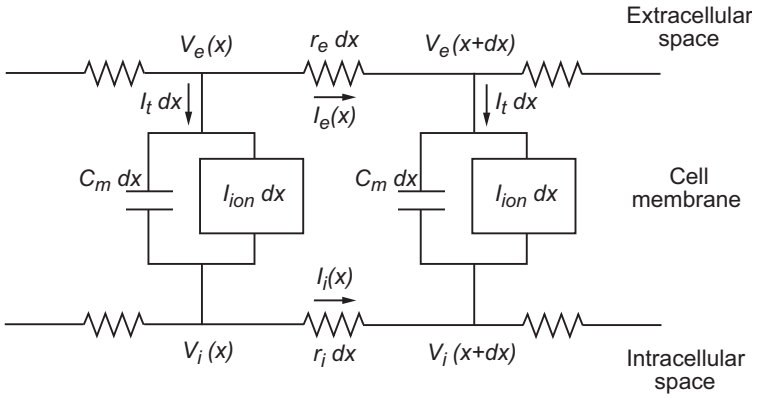
- Currents are driven by concentration differences (via Nernst-Planck equation);
- Currents are regulated via positive (for sodium) and negative (for potassium) feedbacks.

Spatially Extended Excitable Media



Neurons and axons

The Cable Equation



$$C_m \frac{\partial v}{\partial t} + I_{ion}(v,w) = \frac{\partial}{\partial x}\left(\frac{1}{r_c}\frac{\partial v}{\partial x}\right) \qquad \text{where } \frac{dw}{dt} = g(v,w), \qquad w \in R^3$$

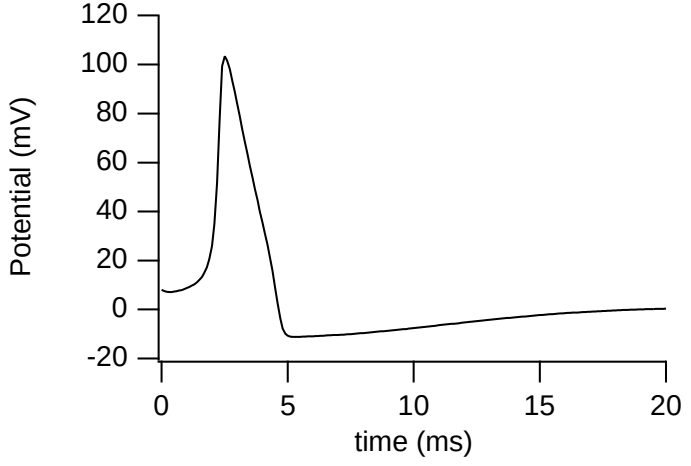
This equation is referred to as the cable equation, and is a diffusion-reaction equation.

Excitable Wave Behavior

HH calculated that their equations had propagating pulse solutions (travelling waves), a breakthrough discovery!

This is now known to be the fundamental mechanism underlying signalling in

- neurons
- cardiac tissue
- calcium signalling
- Dictyostelium cAMP signalling



Problem 2: Patterns and Development - 1952

Reaction/Diffusion in activator-inhibitor systems can produce patterns.

Alan Turing
1912-1954

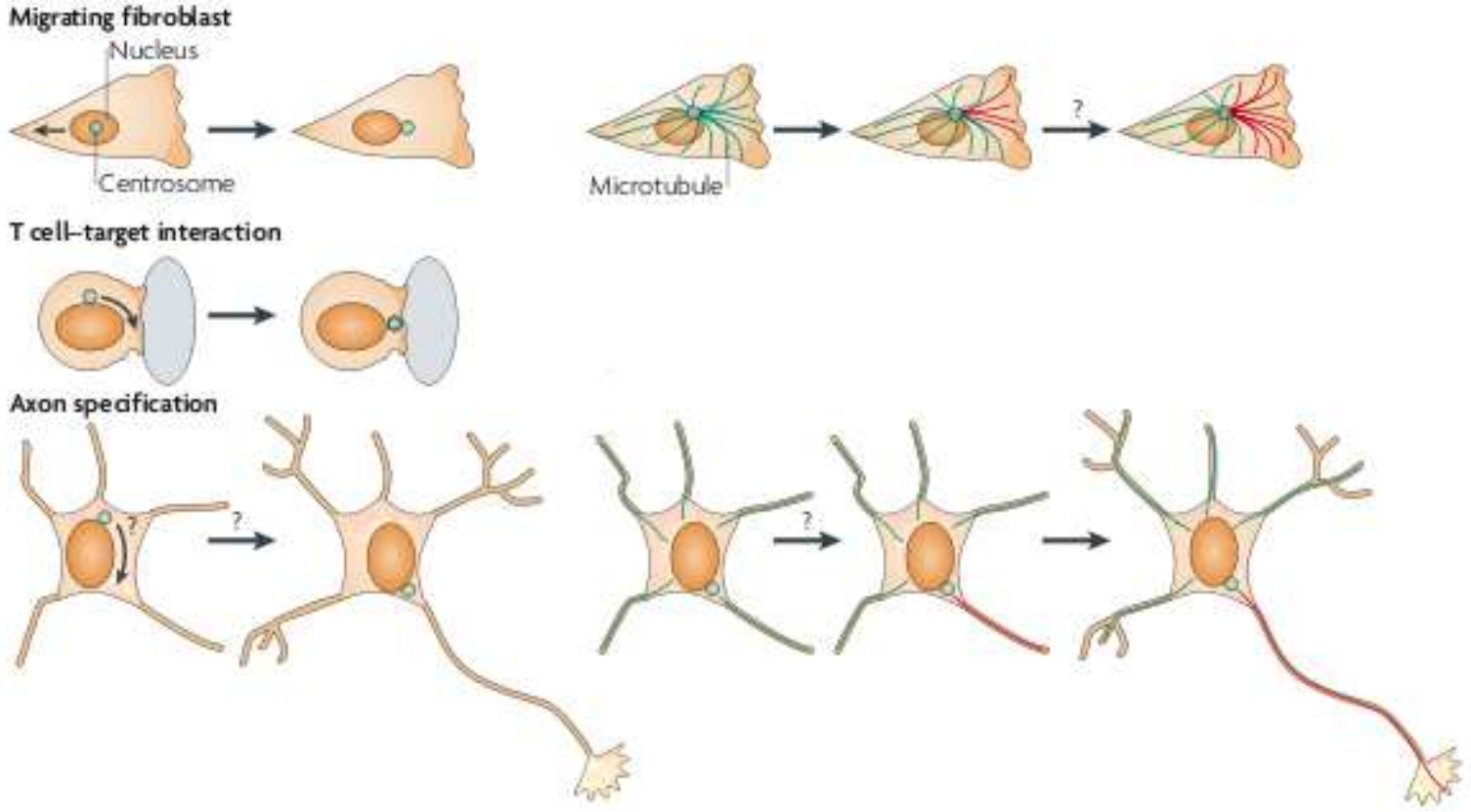
Zebra fish

Zebra stripes

Shell patterns

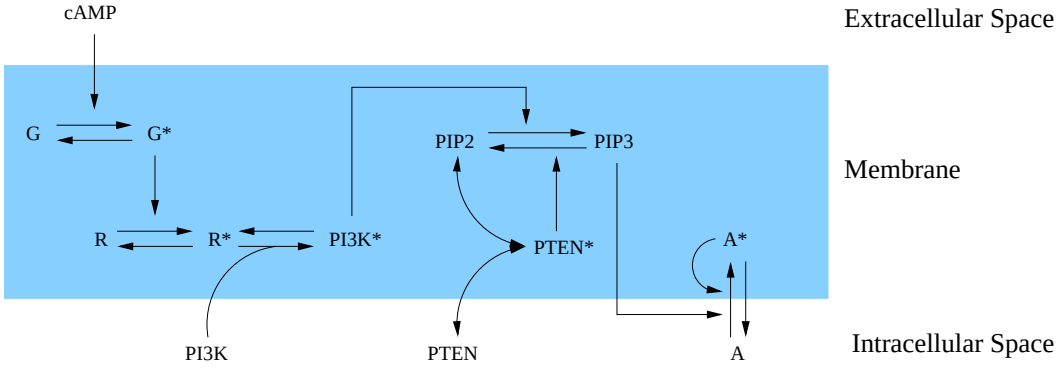
Cell Polarization

Question: How do cells determine their front or back? How do they go where they “want" to go?



(Click on Figure to see movie)

Biology of Cell Polarization



Small GTPases, denoted A (e.g., Cdc42, Rac and Rho) are regulators of actin nucleation and growth in eukaryotic cells.

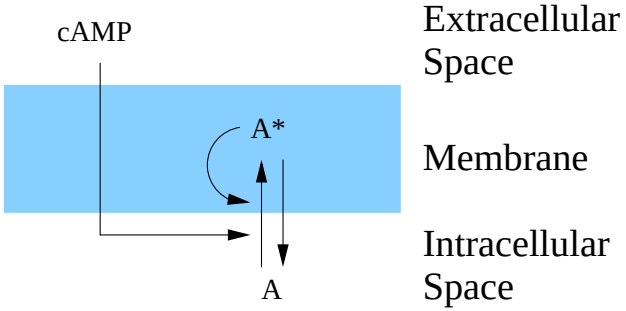
- Is activated by a signalling cascade;
- In active form (A^*) is membrane bound, diffuses slowly, and regulates actin polymerization;
- In inactive form (A) is in cytosol, and diffuses freely.
- The active form acts to activate the inactive form (positive feedback).

Cell Polarization

Build a model with $u = [A^*]$, $v = [A]$,

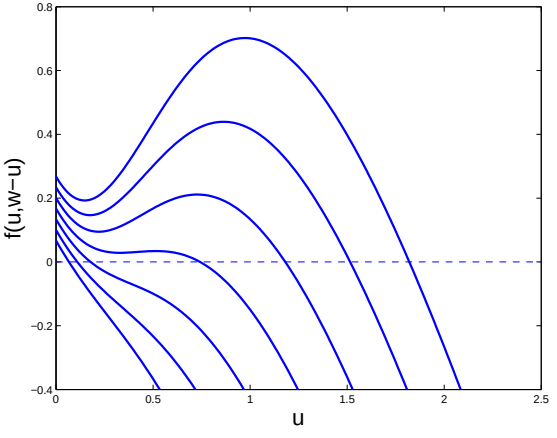
$$\frac{\partial u}{\partial t} = \frac{D_u}{R^2}\frac{\partial^2 u}{\partial \theta^2} + f(u,v)$$

$$\frac{\partial v}{\partial t} = \frac{D_v}{R^2}\frac{\partial^2 v}{\partial \theta^2} - f(u,v)$$



where

$$f(u,v) = (S(\theta,t) + \frac{\gamma u^2}{K^2+u^2})v - \delta u$$



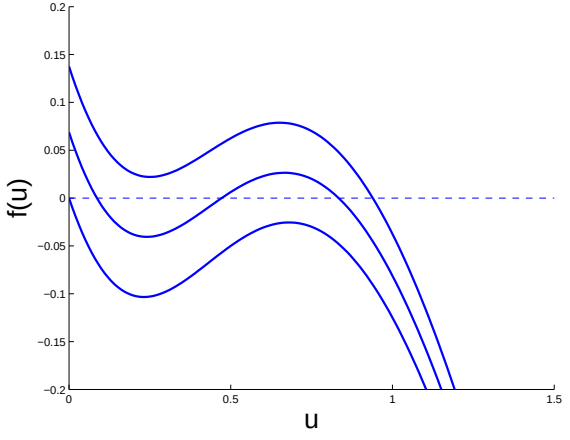
and θ is the angular variable, $D_u \ll D_v$, and periodic boundary conditions.

(This model adapted from work of Edelstein-Keshet, Jilkine, Holmes, et al.)

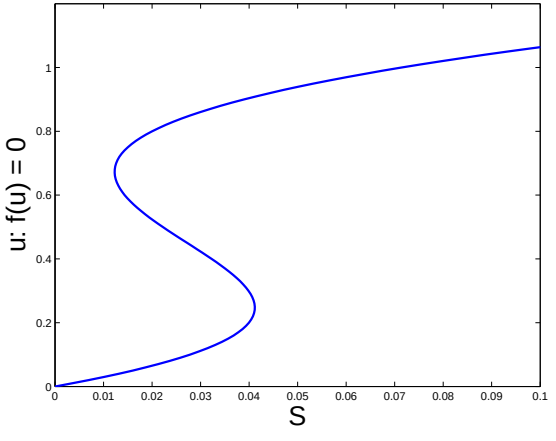
The ODE System ...

The ODE system is bistable,

$$u + v = W_T$$



$$\frac{du}{dt} = (S + \frac{\gamma u^2}{K^2 + u^2})(W_T - u) - \delta u$$



exhibits hysteretic response to Stimuli.

The PDE System...

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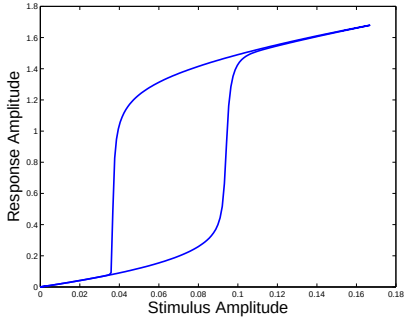
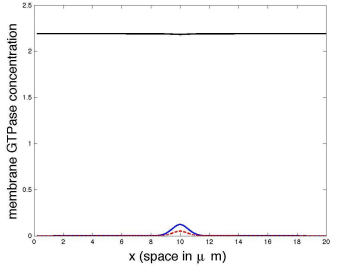


can follow a moving Stimulus:



Lesson 2: Differences in rates of diffusion coupled with appropriate reactions can be used to make stimulus-response decisions.

Problem 3: Quorum Sensing

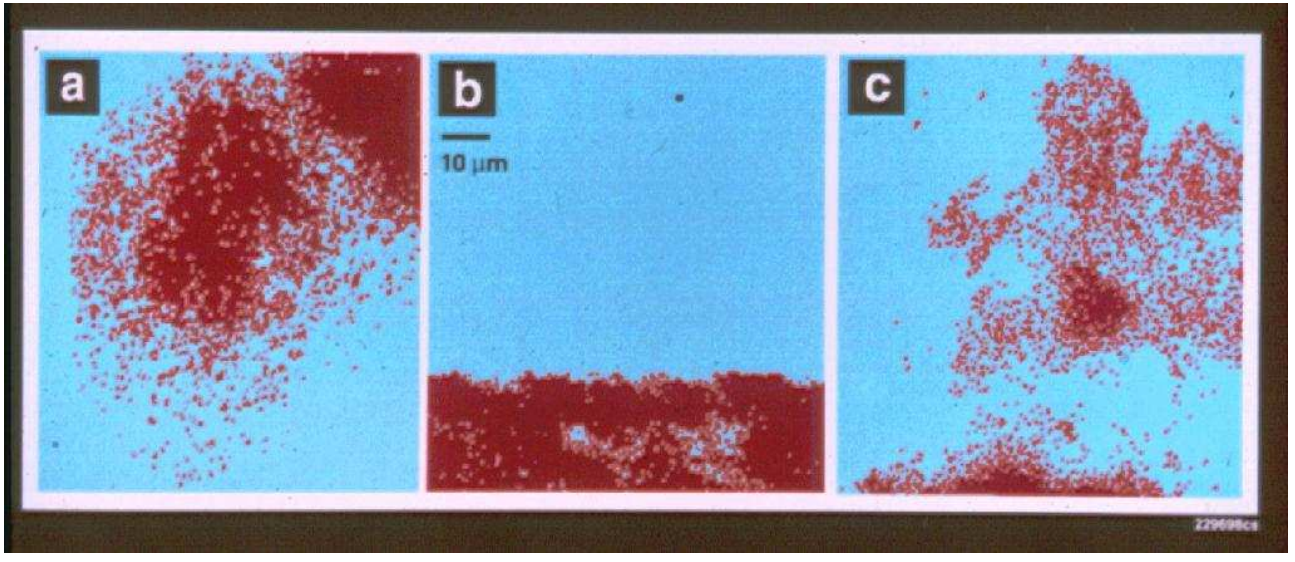
Quorum sensing: The ability of a bacterium to sense the size of its colony and to regulate its activity in response.

Examples:

- *Vibrio fischeri* live in the photophores (light organs) of Hawaiian Bobtail squid and luminesce when colony size is sufficiently large.
- *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.

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

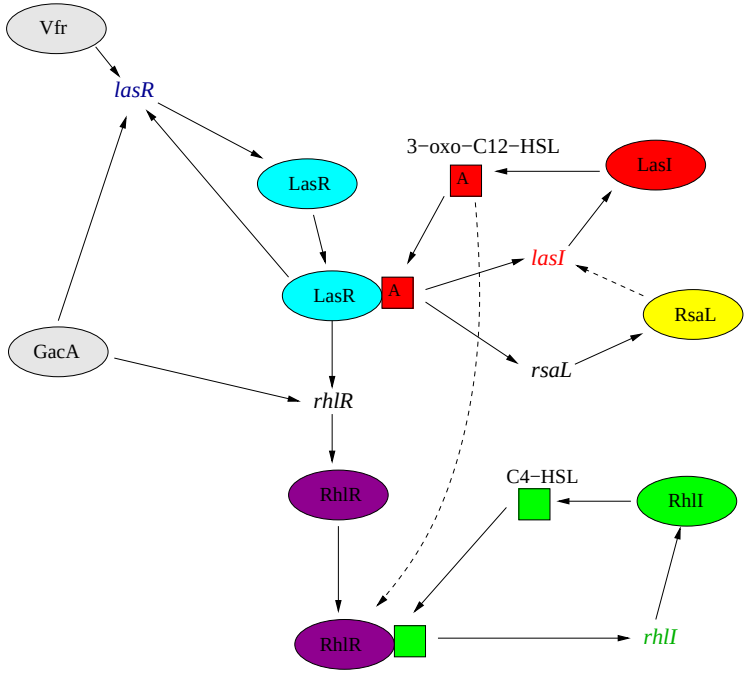
What Stuff Matters?



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.

How Is Autoinducer Produced?

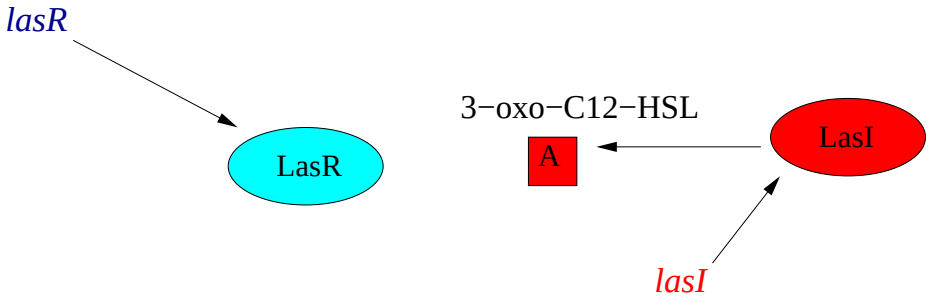


Biochemistry of Quorum Sensing

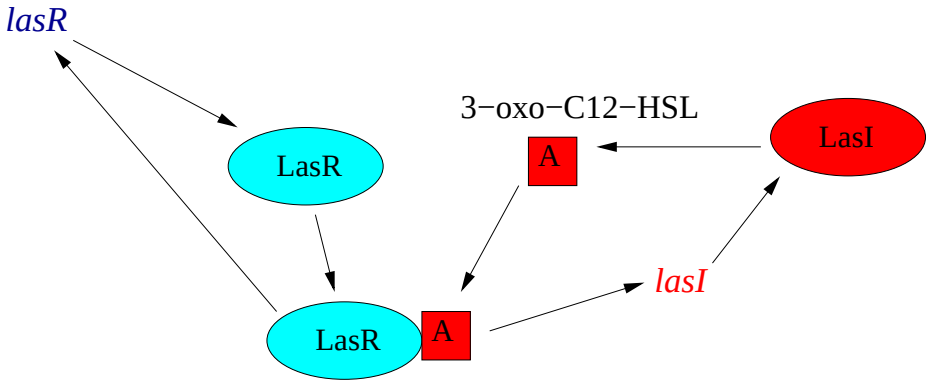
lasR

lasI

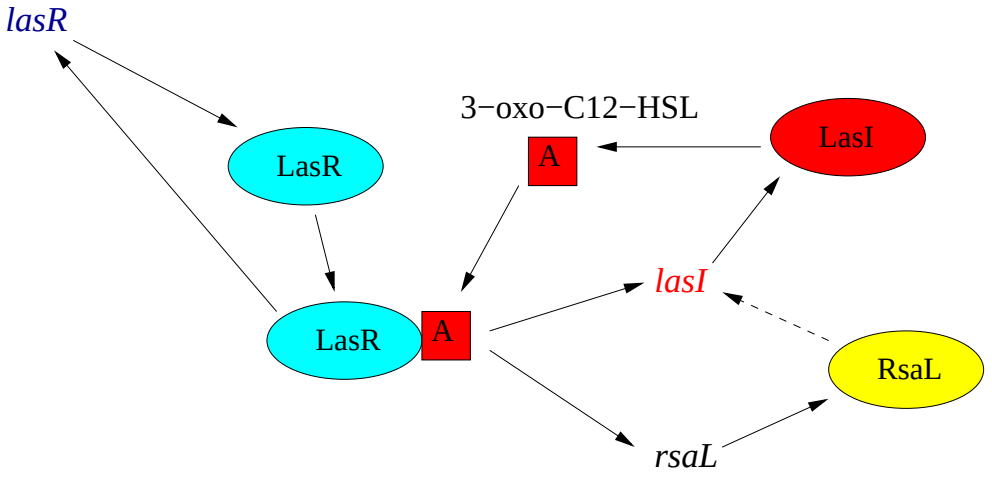
Biochemistry of Quorum Sensing



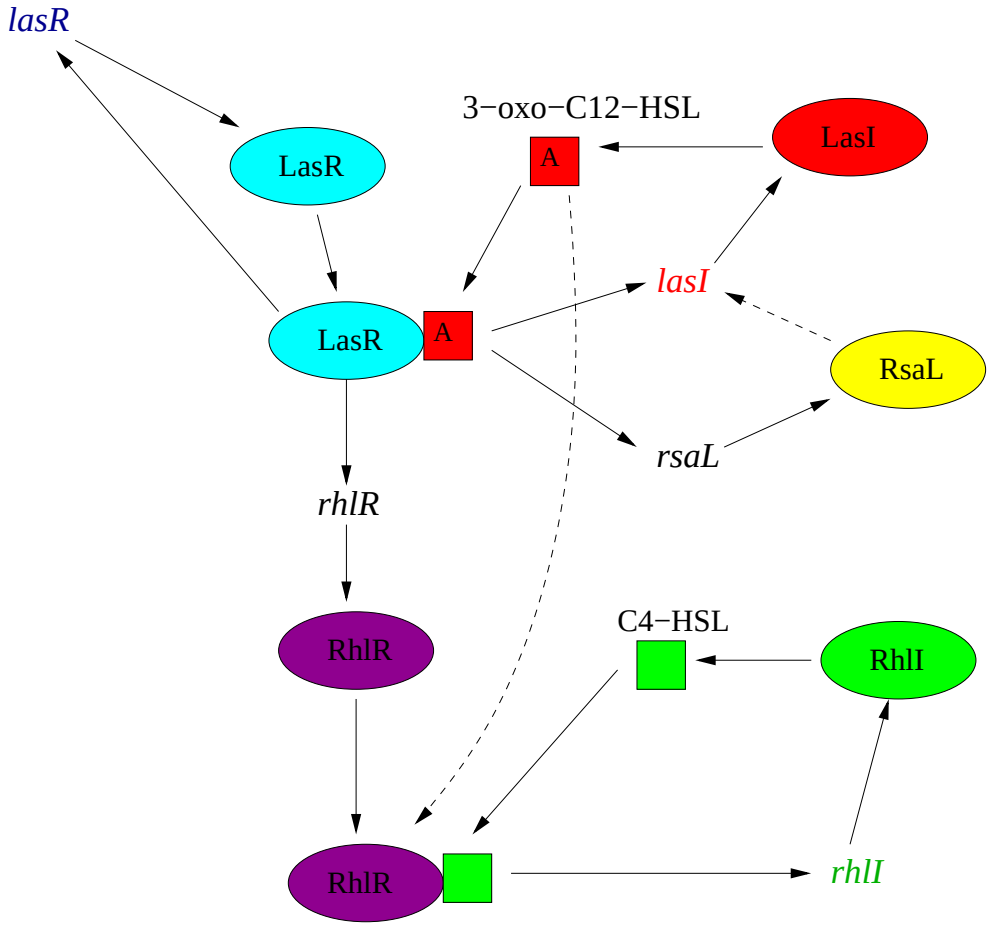
Biochemistry of Quorum Sensing



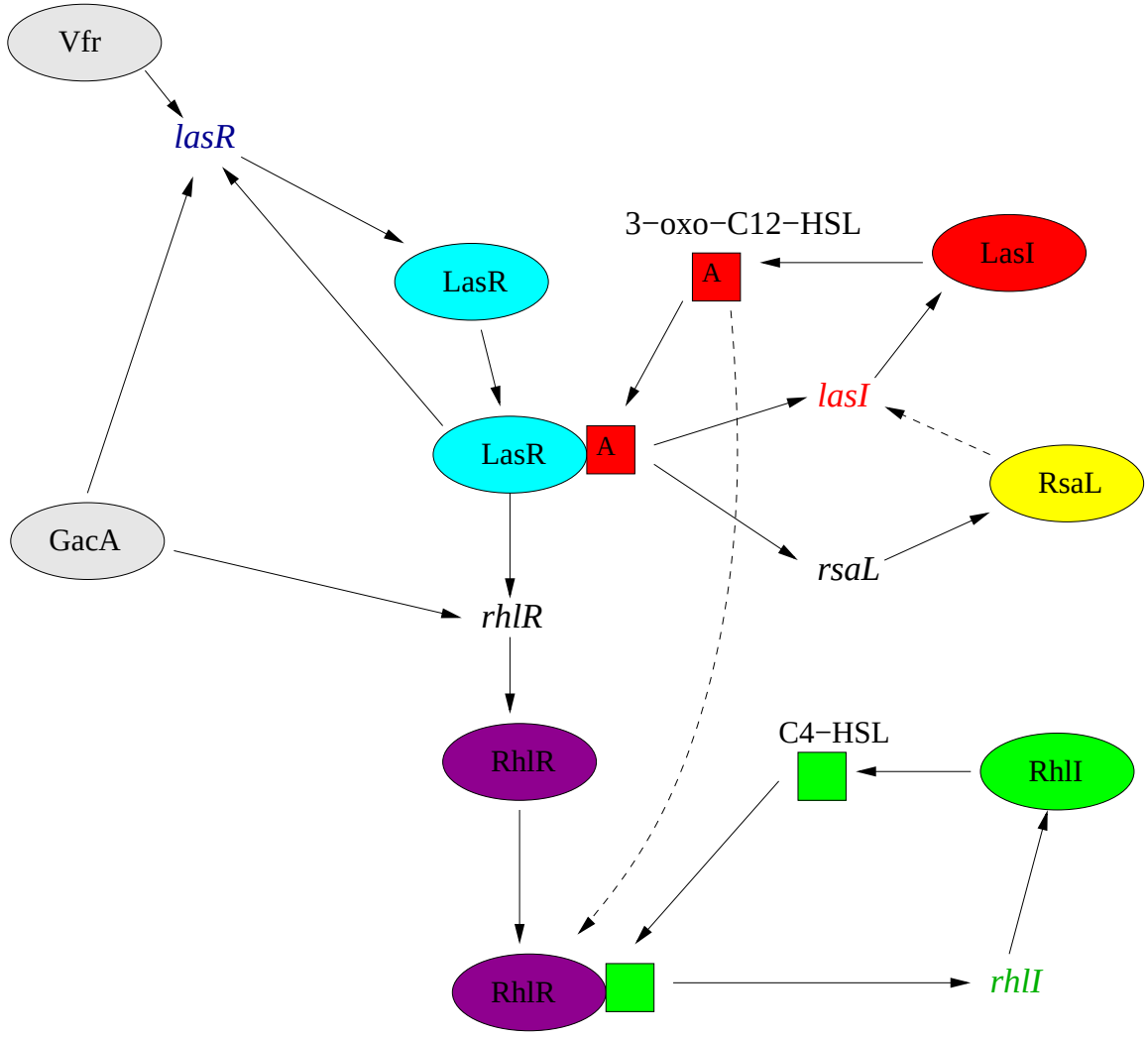
Biochemistry of Quorum Sensing



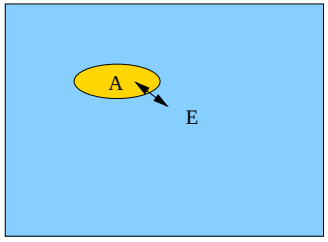
Biochemistry of Quorum Sensing



Biochemistry of Quorum Sensing



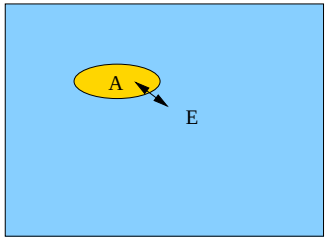
Autoinducer Kinetics



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

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

Autoinducer Kinetics

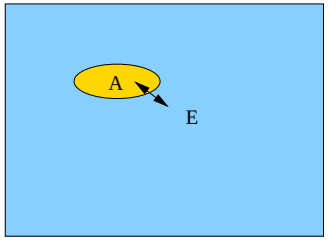


$$\boxed{\frac{dA}{dt}} = F(A,R,P) + \delta(E-A)$$

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

rate of change,

Autoinducer Kinetics

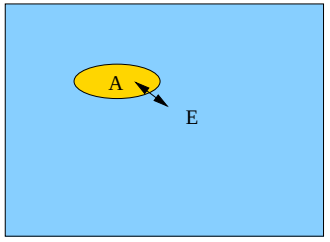


$$\frac{dA}{dt} = \boxed{F(A,R,P)} + \delta(E-A)$$

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

rate of change, production or degradation rate,

Autoinducer Kinetics

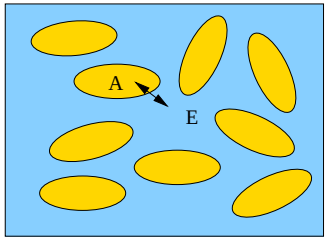


$$\frac{dA}{dt} = F(A,R,P) + \boxed{\delta(E-A)}$$

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

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

Autoinducer Kinetics



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

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

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

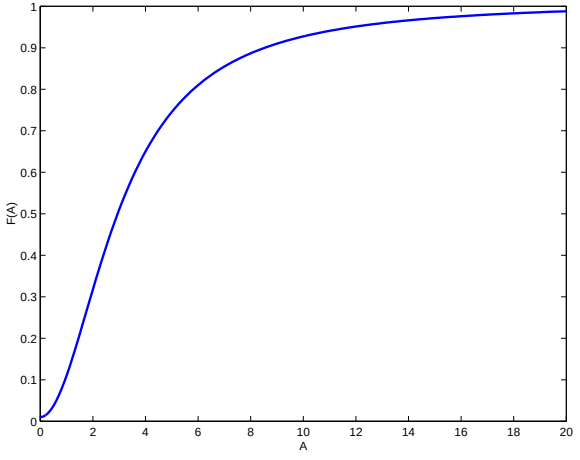
Main point reiterated!!! Flux of A out of the cell is related to the amount of E in the extracellular space.

Simplified Model

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

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

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



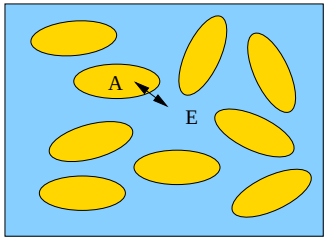
Two Variable Phase Portrait

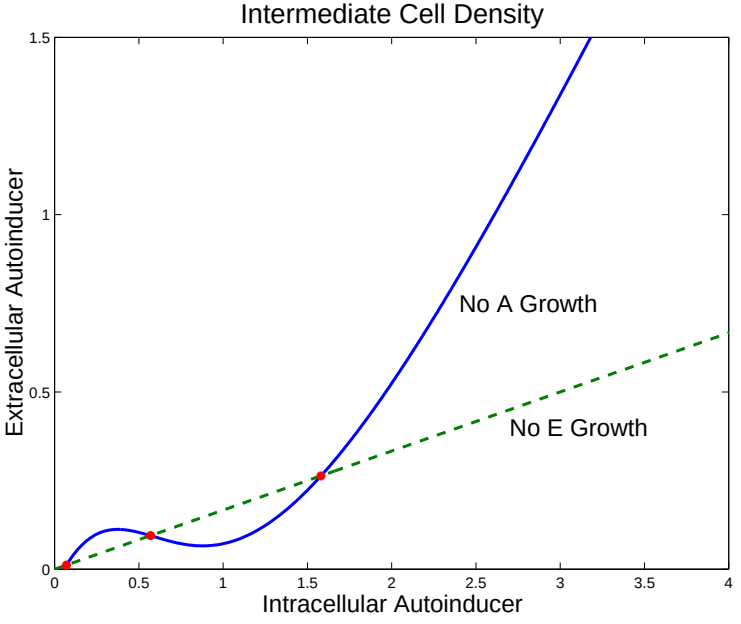
$$\frac{dA}{dt} = F(A) + \delta(E - A),$$

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

Nullclines:

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





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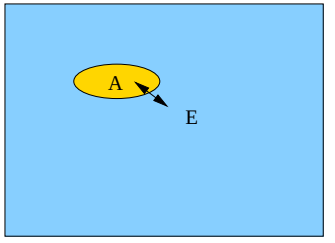
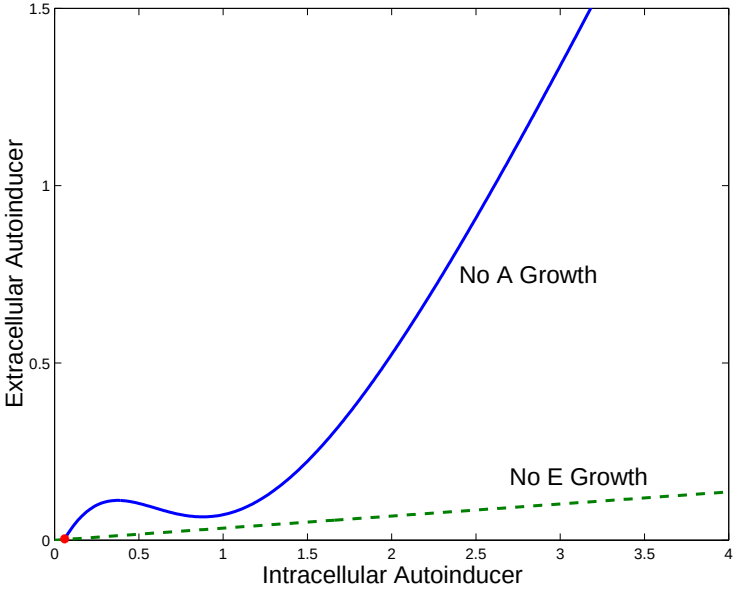


Low Cell Density



Two Variable Phase Portrait

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

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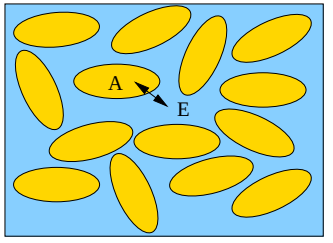
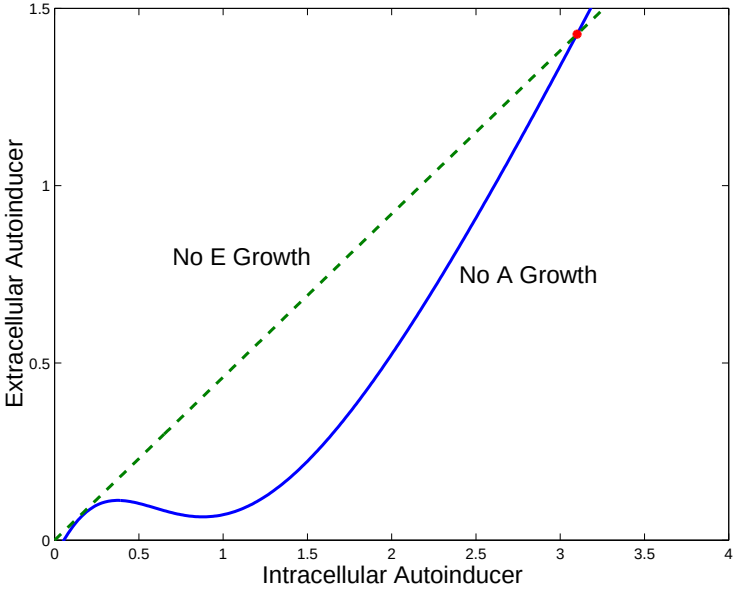
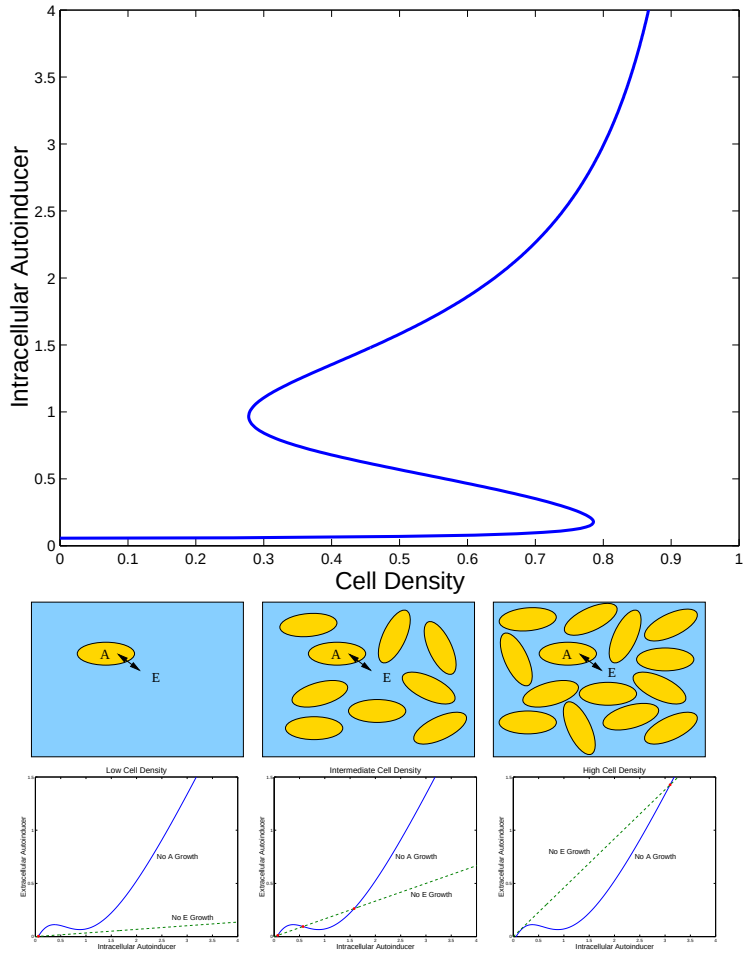


High Cell Density



Result

A density dependent switch (like a thermostat).

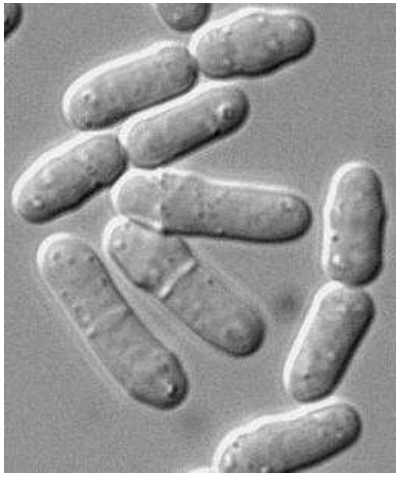


Summary: Quorum Sensing

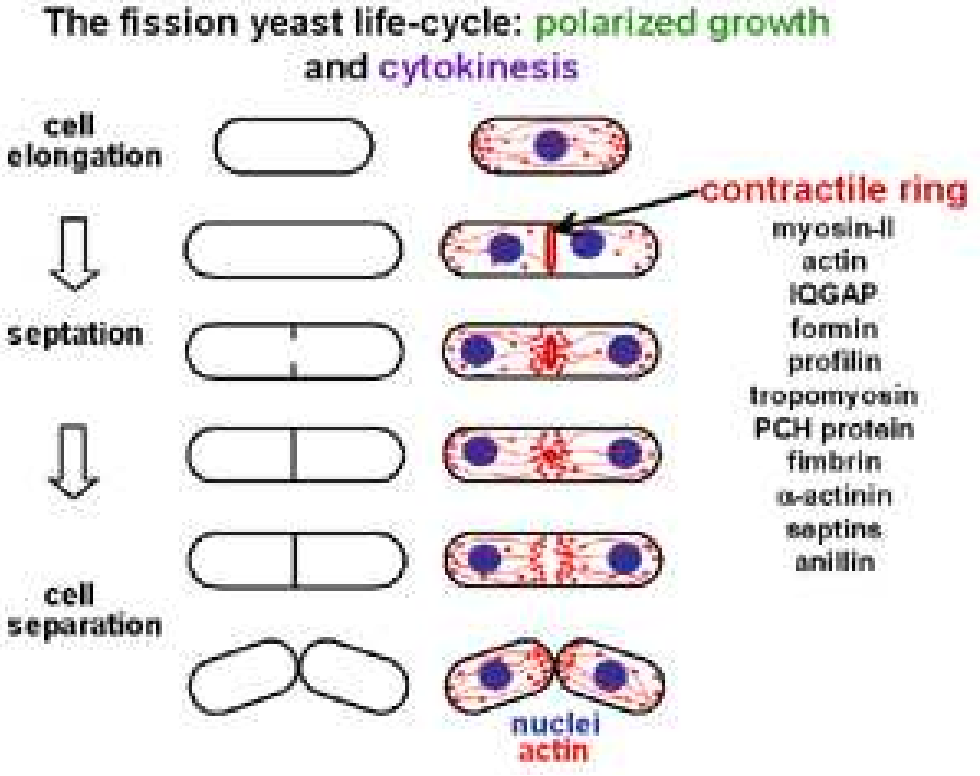
Lesson 3:

- 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,
- which enable an organism to make decisions based on a measurement.

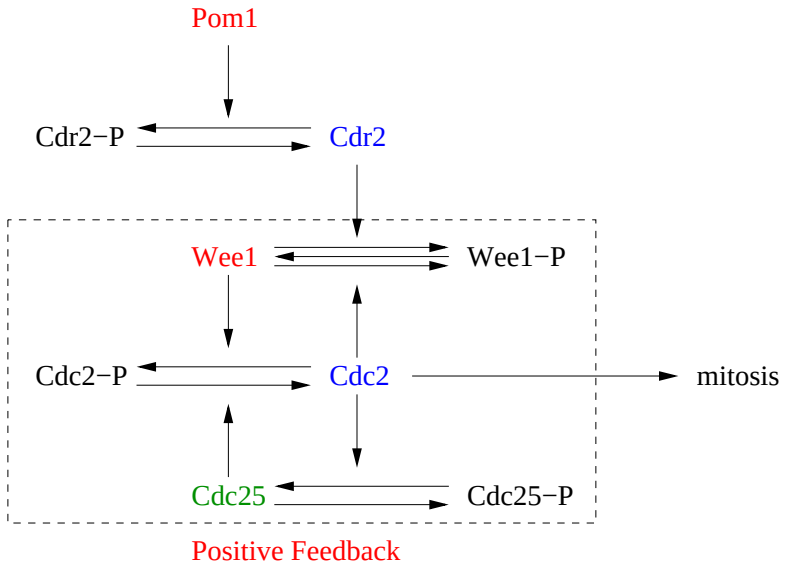
Problem 4: Cell Size Measurement



Fission Yeast *S. pombe*

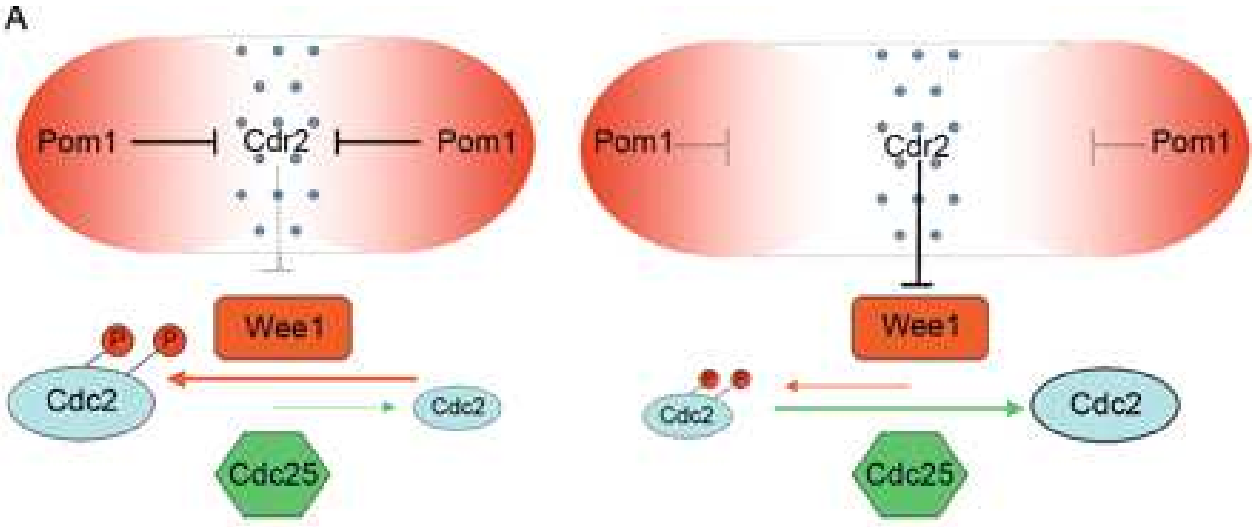


Cell Cycle Chemistry



- Pom1, which inhibits Cdr2 activity, is localized to the cell membrane, at the pole.
- Cdr2, which inhibits Wee1 activity, diffuses freely in the cell
- Cdc2, which activates mitosis via a positive feedback network, is localized to the cell center (the nucleus).

Cell Size Measurements



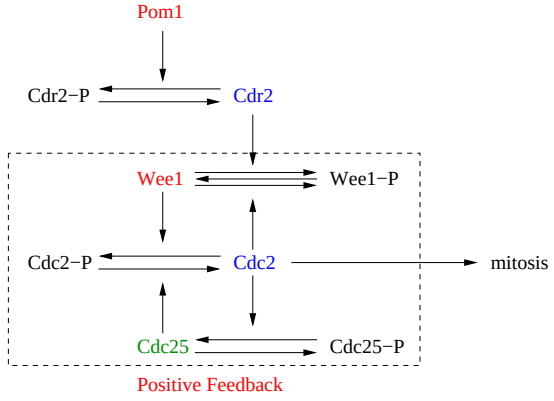
Track the amount of [Cdr2] in the cell:

$$\frac{\partial r}{\partial t} = D\frac{\partial^2 r}{\partial x^2} + \frac{k_{r_P} r_P}{K_{r_P} + r_P}, \qquad r = [\mathrm{Cdr2}], \qquad r_P = [\mathrm{Cdr2P}],$$

with boundary conditions $D\frac{\partial r}{\partial x} = -\boxed{\frac{k_r r}{K_r + r}}$ at $x = L$ and $D\frac{\partial r}{\partial x} = 0$ at $x = 0$, with Pom 1 activity at the boundary

Cell Size Measurements

The remaining entities are localized to $x = 0$ and are governed by ordinary differential equations



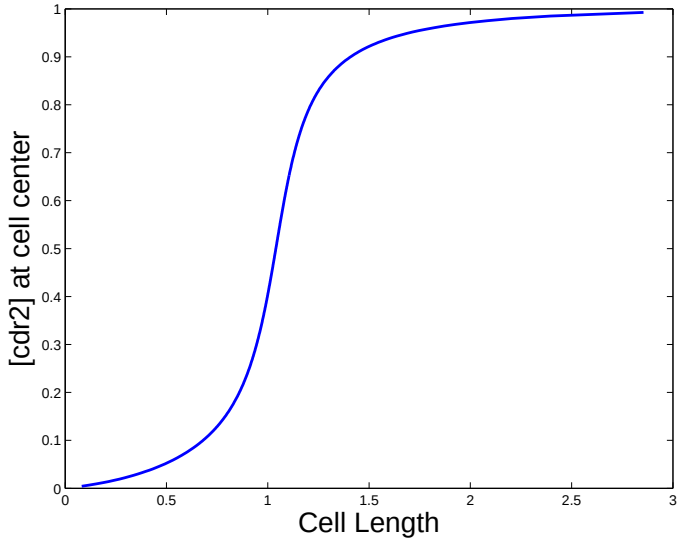
$$\frac{dw}{dt} = -\frac{k_w^1 m w}{K_w^1 + w} - \frac{k_w^2 r(0) w}{K_w^2 + w} + \frac{k_{w_P} w_P}{K_{wp} + wP},$$

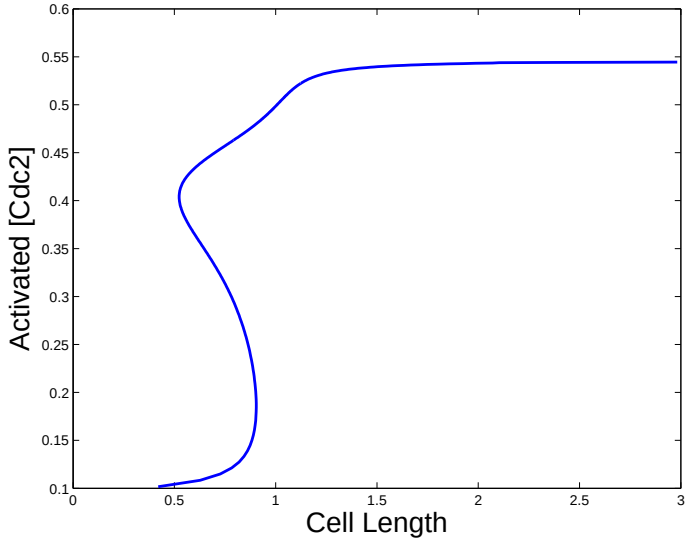
$$\frac{dm}{dt} = \frac{k_m c m_P}{K_m + m_P} - \frac{k_{m_P} w m}{K_{m_P} + m},$$

$$\frac{dc}{dt} = \frac{k_c c_P}{K_c + c_P} - \frac{k_{c_P} m c}{K_{c_P} + c}.$$

with $w =$[Wee1], $m =$[Cdc2], $c =$[Cdc25].

Cell Size Measurements

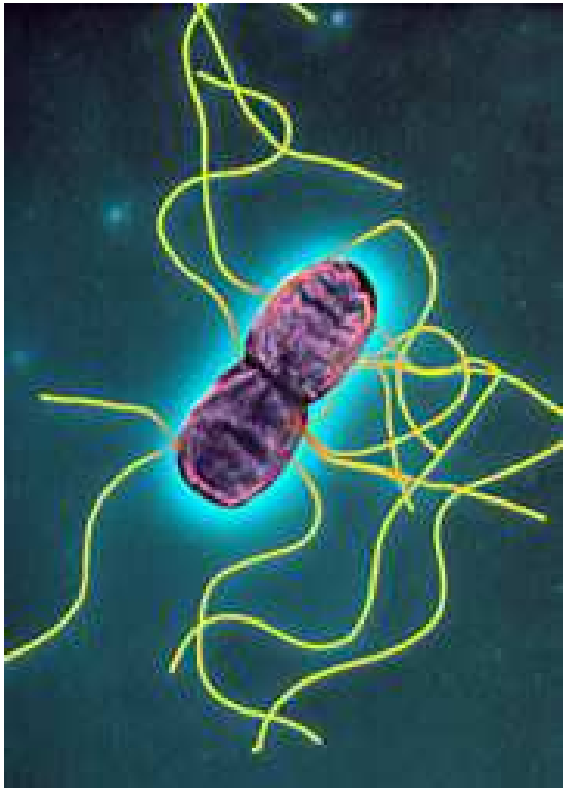




- There is ultrasensitive (i.e., sharp sigmoidal) dependance of [Cdr2] at the cell center on cell length.
- The concentration of [Cdr2] at the cell center triggers a switch in Cdc2 activity,
- leading to (Lesson 4:) a length dependent, hysteretic, transition to mitosis.

II - Flagellar Length Detection

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



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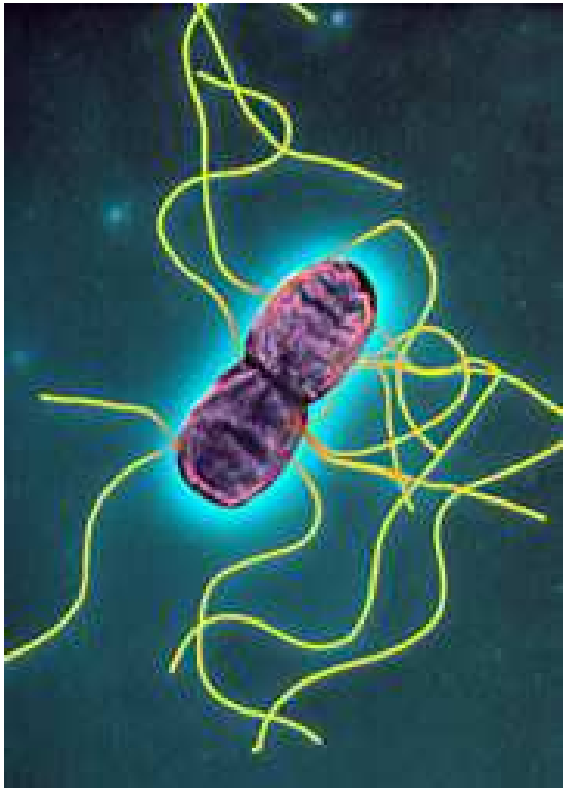
- Flagella grow at a velocity that decreases as they get longer.
- If a flagellum is broken off, it will regrow at the same velocity as when it first grew.



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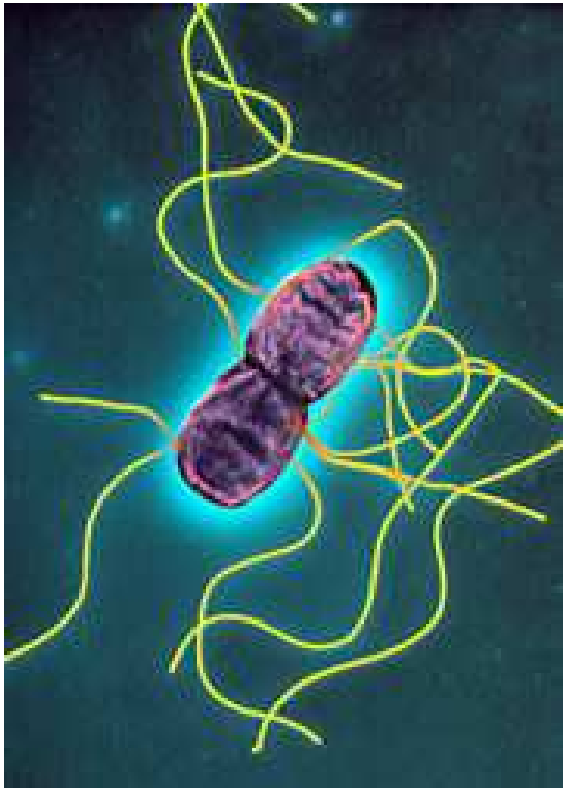
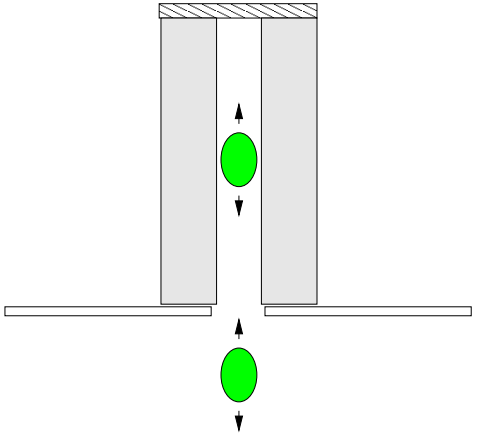


Question: How does the bacterium measure flagellar length?

How Do Flagella Grow?

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



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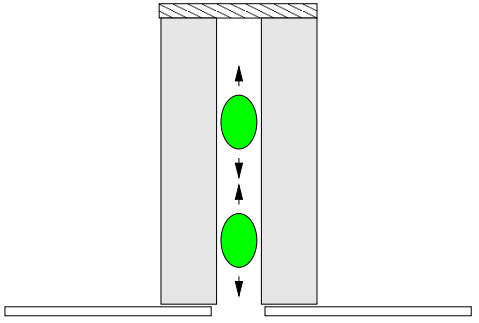

How Do Flagella Grow?

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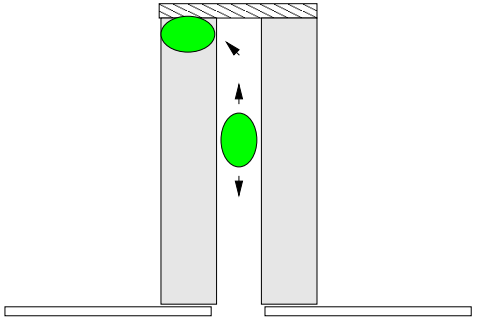


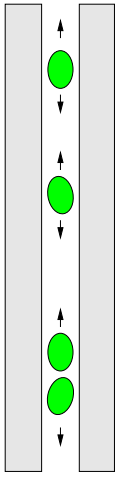
Modelling Flagellar Growth

Step 2: Diffusion

Important Fact: Filament is a narrow 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

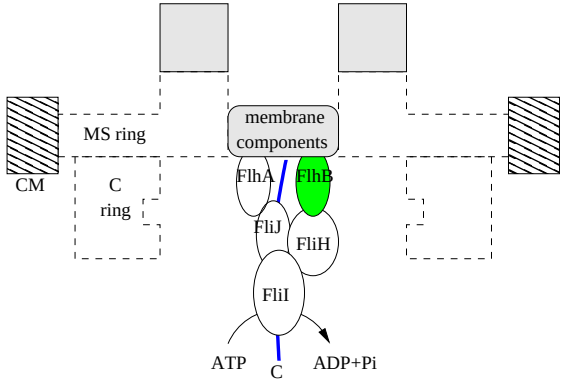
$$J = -D\frac{\partial p}{\partial x}.$$

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

Rate of Secretion

Step 1: Secretion

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

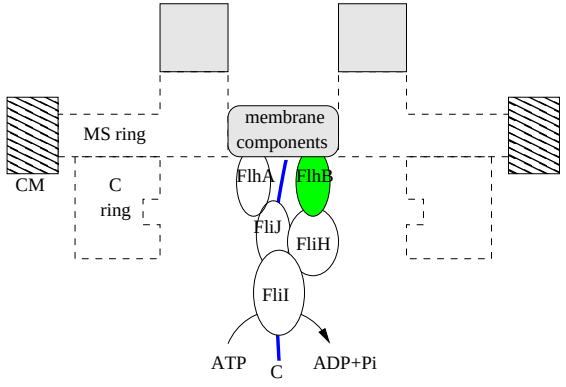


Step 3

Rate of Secretion

Step 1: Secretion

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



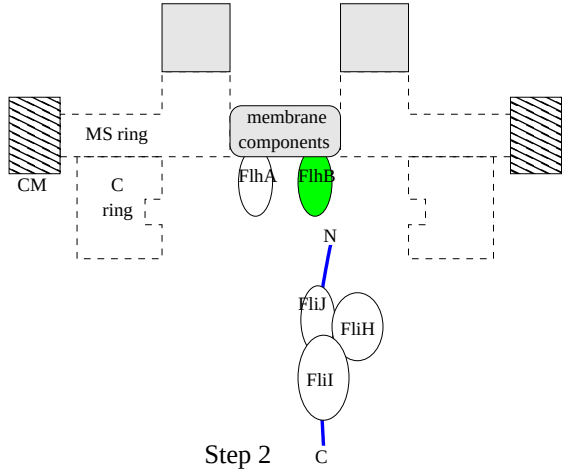
Step 3

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

Rate of Secretion

Step 1: Secretion

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



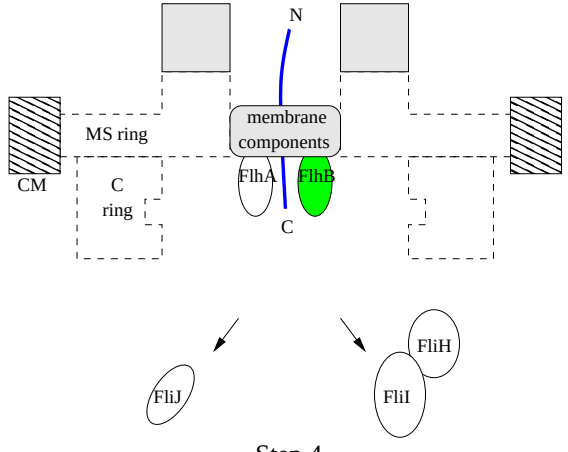
$$\frac{dP}{dt} = \boxed{K_{on}(1-P)}$$

on rate,

Rate of Secretion

Step 1: Secretion

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



Step 4

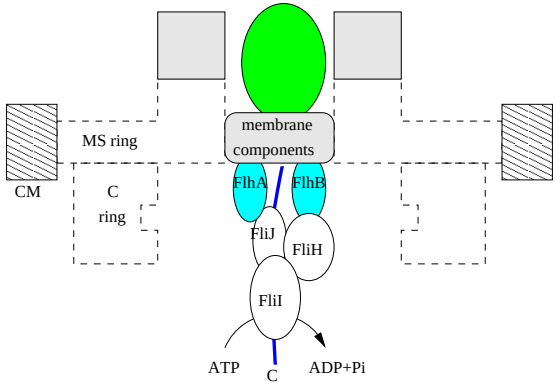
$$\frac{dP}{dt} = K_{on}(1-P) - \boxed{k_{off}P}$$

on rate, off rate,

Rate of Secretion

Step 1: Secretion

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



Step 4 Blocked

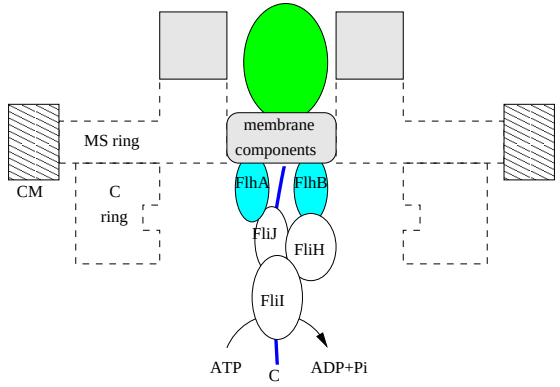
$$\frac{dP}{dt} = K_{on}(1-P) - k_{off}(1-p(0,t))P$$

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

Rate of Secretion

Step 1: Secretion

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



Step 4 Blocked

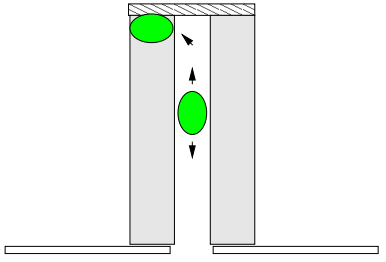
$$\frac{dP}{dt} = K_{on}(1-P) \; - \boxed{k_{off}(1-p(0,t))P}$$

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.

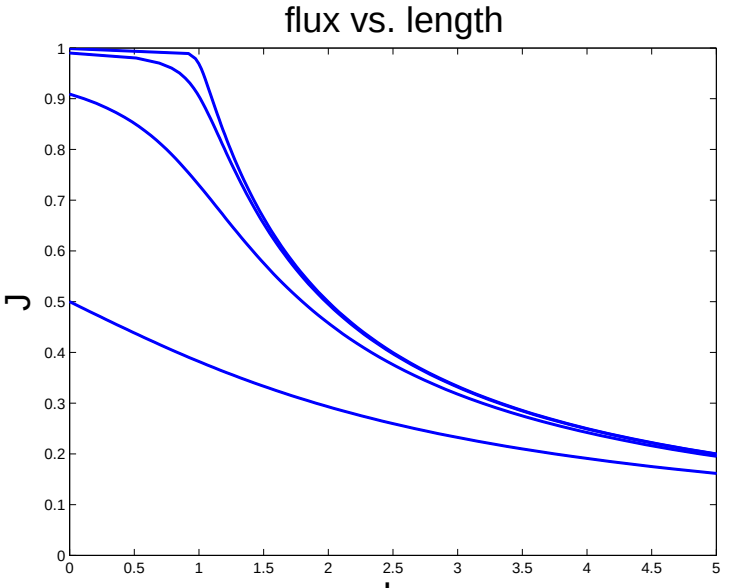
Diffusion Model

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



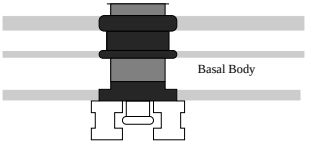
Filament Length Control

Introducing FlgM and σ^{28}:

Filament Length Control

Introducing FlgM and σ^{28}:

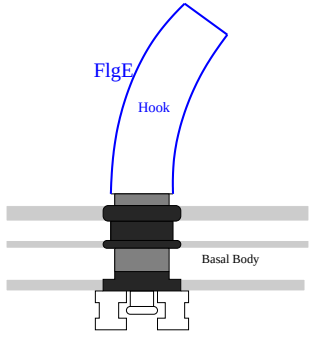
Class 1



Filament Length Control

Introducing FlgM and σ^{28}:

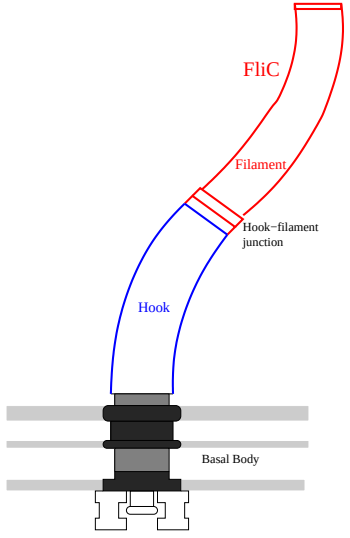
Class 1 $\rightarrow$ Class 2 $\left\{ \begin{array}{c} \sigma^{28} \\ \text{FlgE} \\ \text{FlgKL} \\ \text{FlgM} \\ \text{FliK} \end{array} \right\}$



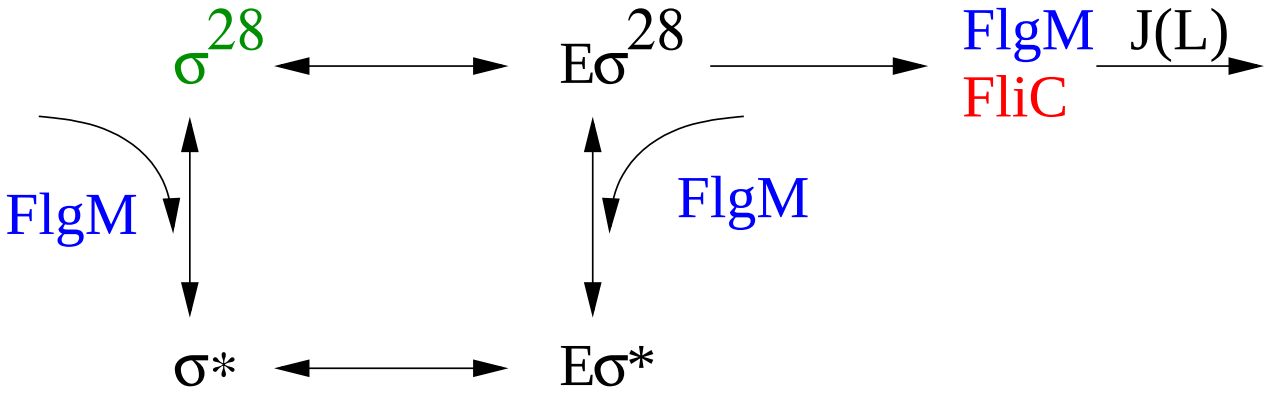
Filament Length Control

Introducing FlgM and σ^{28}:

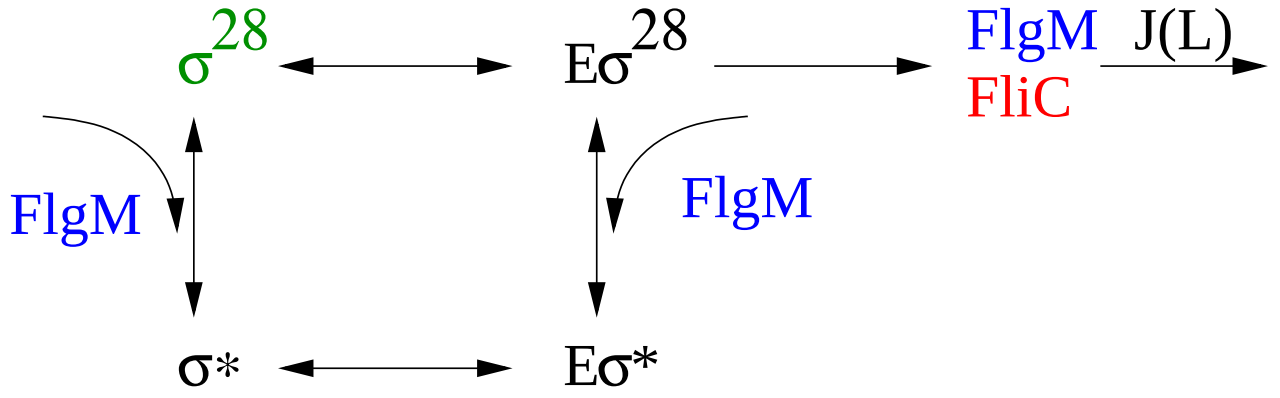
$$\text{Class 1} \rightarrow \text{Class 2} \left\{ \begin{array}{c} \sigma^{28} \\ \text{FlgE} \\ \text{FlgKL} \\ \text{FlgM} \\ \text{FliK} \end{array} \right\} \overset{E\sigma^{28}}{\rightarrow} \text{Class 3} \left\{ \begin{array}{c} \text{FliC} \\ \text{FliD} \\ \text{FlgM} \end{array} \right\}$$



FlgM-σ^{28} Chemistry

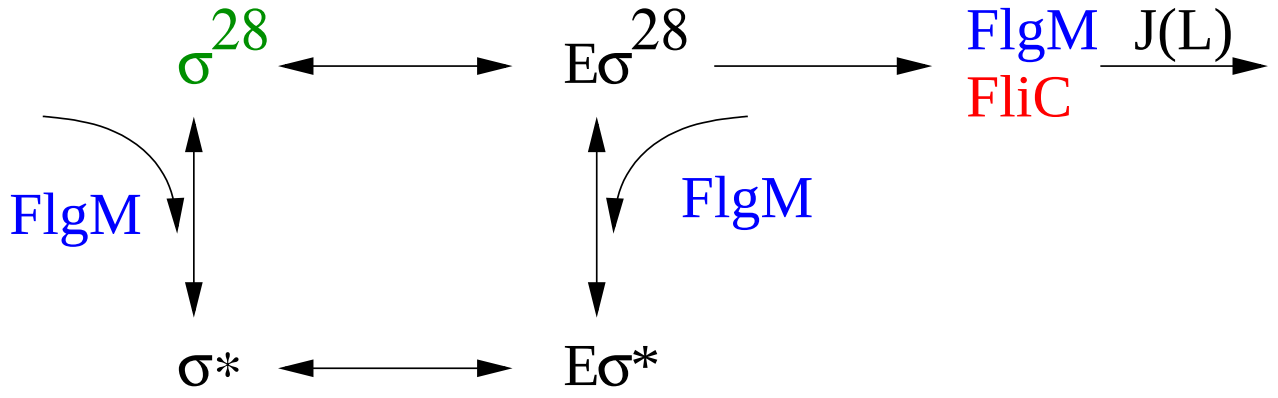


FlgM-σ^{28} Chemistry



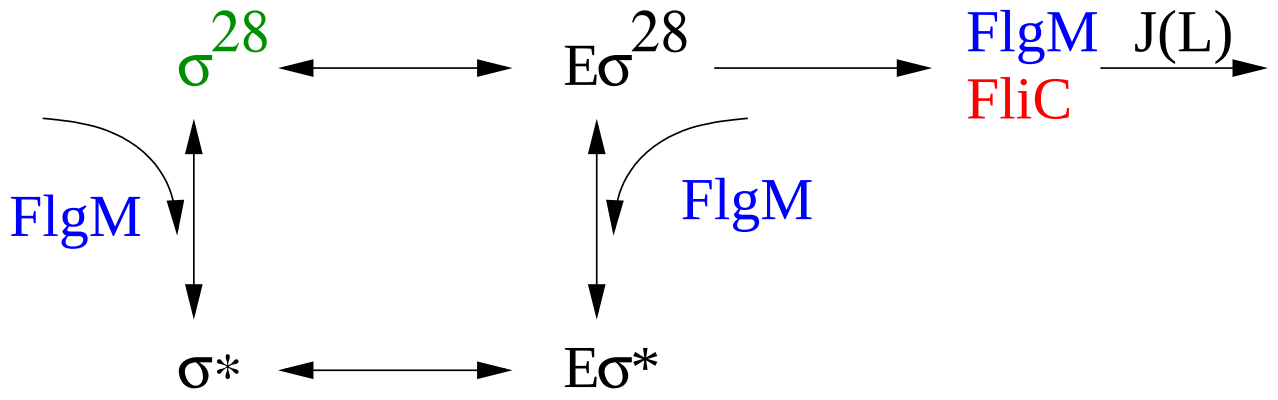
- FlgM inhibits σ^{28} activity;

FlgM-σ^{28} Chemistry



- FlgM inhibits σ^{28} activity;
- Therefore, during stage 3, FlgM inhibits its own production (negative feedback);

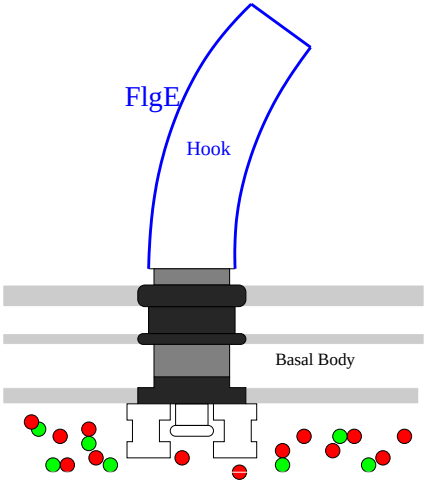
FlgM-σ^{28} Chemistry



- FlgM inhibits σ^{28} activity;
- Therefore, during stage 3, FlgM inhibits its own production (negative feedback);
- And, FlgM inhibits the production of Flagellin (FliC).

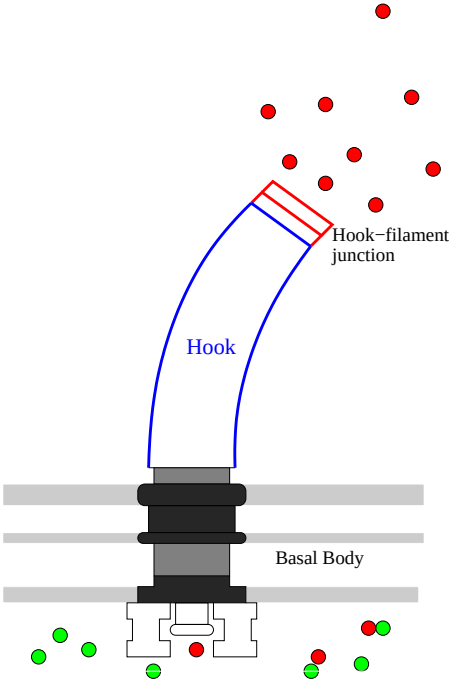
FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth; σ^{28} inactivated.



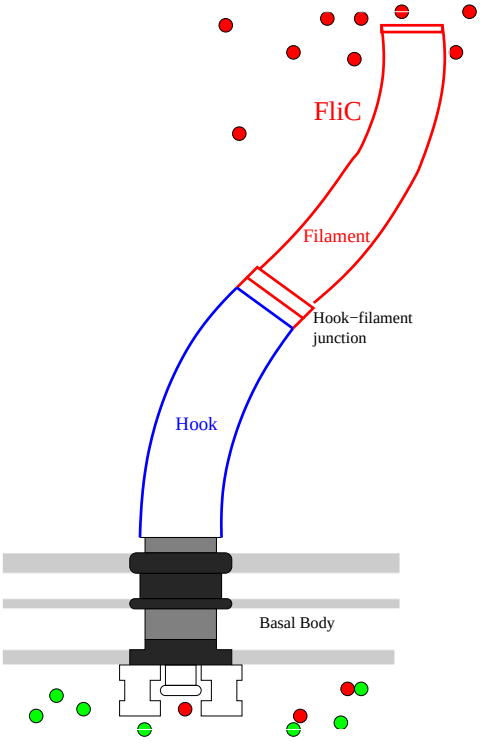
FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth; σ^{28} inactivated.
- When hook growth is terminated, FlgM secretion begins, initiating FliC production.



FlgM-σ^{28} Secretion Dynamics

- FlgM **is not** secreted during hook growth; σ^{28} inactivated.
- When hook growth is terminated, FlgM secretion begins, initiating FliC production.
- FlgM **is** secreted during filament growth.



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):

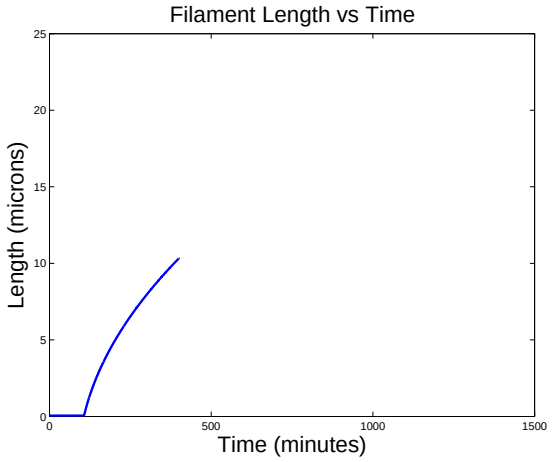
$$\frac{dF}{dt} = \frac{K_*}{K_M + M} - \alpha \frac{F}{F + M} J$$

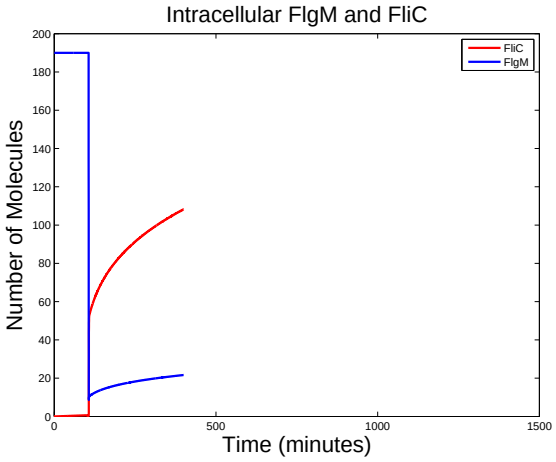
Filament Length (L):

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

with $J = \frac{1}{K_J + \frac{L}{D}}$ (which is length dependent!) .

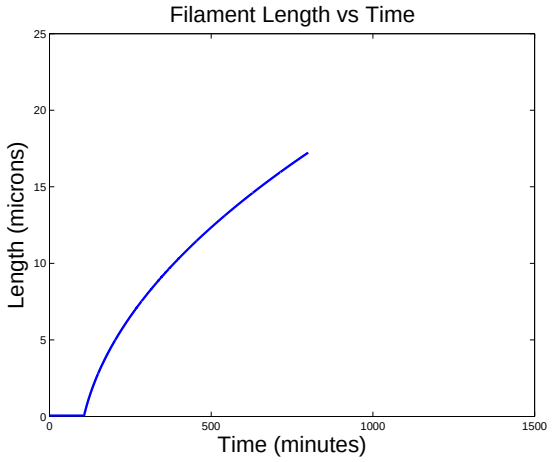
Filament Growth

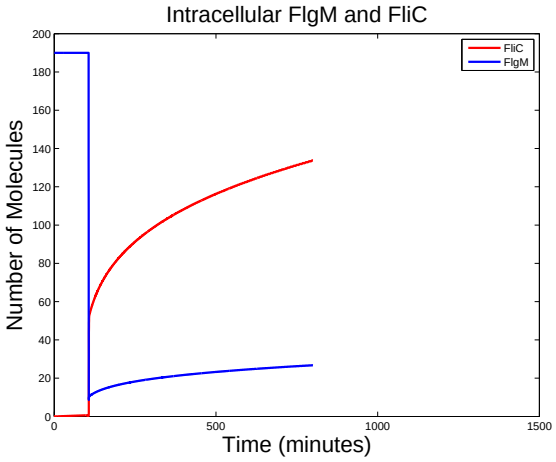




- Before secretion begins FlgM concentration is large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.

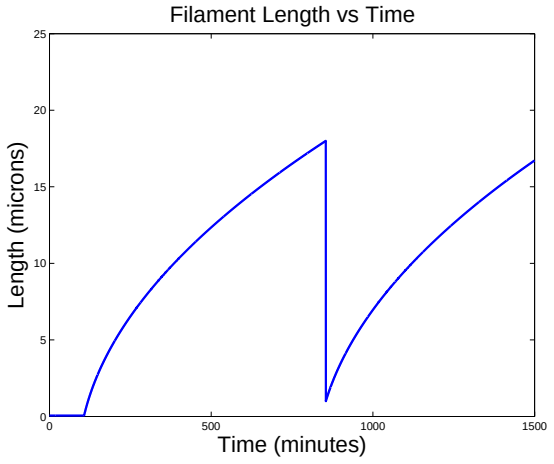
Filament Growth

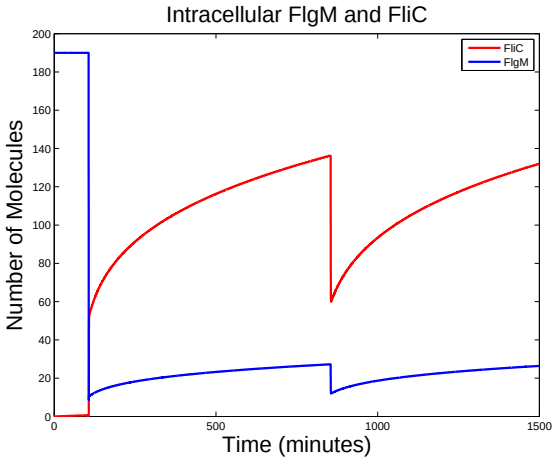




- Before secretion begins FlgM concentration is large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.
- As the filament grows, secretion slows, FlgM concentration increases, shutting off FliC and FlgM production.

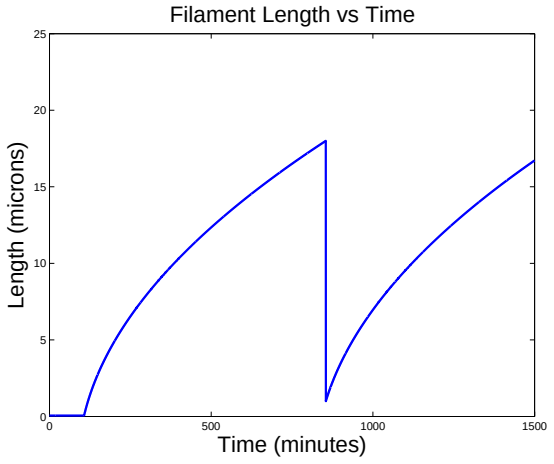
Filament Growth

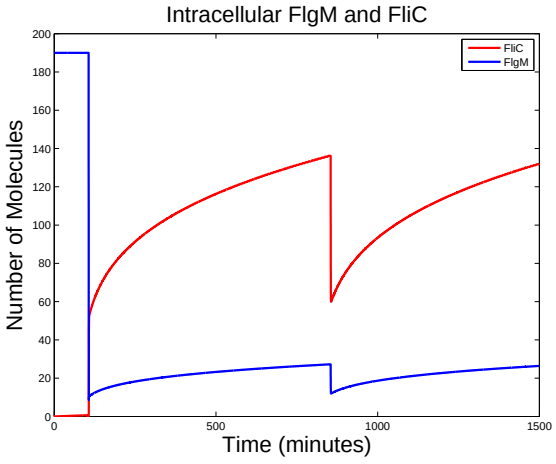




- Before secretion begins FlgM concentration is large. When secretion begins, FlgM concentration drops, producing FliC and more FlgM.
- As the filament grows, secretion slows, FlgM concentration increases, shutting off FliC and FlgM production.
- If filament is suddenly shortened, secretion suddenly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

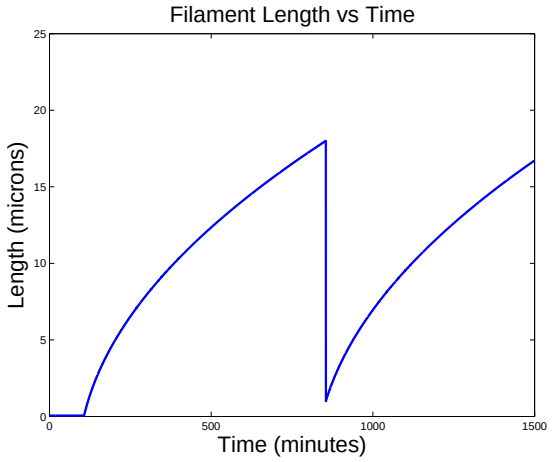
Observations

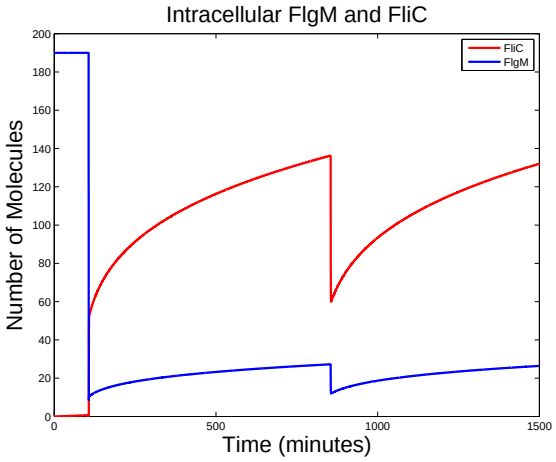




- Because the flux is inversely proportional to length, the amount of FlgM in the cell is a direct measure of the length of the filament.

Observations





- Because the flux is inversely proportional to length, the amount of FlgM in the cell is a direct measure of the length of the filament.
- Lesson 5: Because of negative feedback, the cell "knows" to produce FliC only when it is needed.

And So it Goes...

What have we seen?

- The combination of diffusion with reactions involving positive and negative feedbacks enables cells to communicate, respond to stimuli, and make measurements and decisions.
- Other examples are foraging decisions by ants, size regulation of cilia by chlamydomonas, size regulation of mitotic spindle by centrosomes, ...
- The mathematical description of these processes has much in common (i.e., transferable principles) even though the biological details are vastly different, with the result that
- Mathematics has told us something about how biology works.

Thanks!

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- Jack Dockery (Montana State)
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- Megan Gorringe-Dixon (Utah)
- Geoffrey Hunter (Toronto)
- NSF

National Science Foundation
WHERE DISCOVERIES BEGIN

- and YOU for listening!