Lecture 9: A simple non-linear dynamical system

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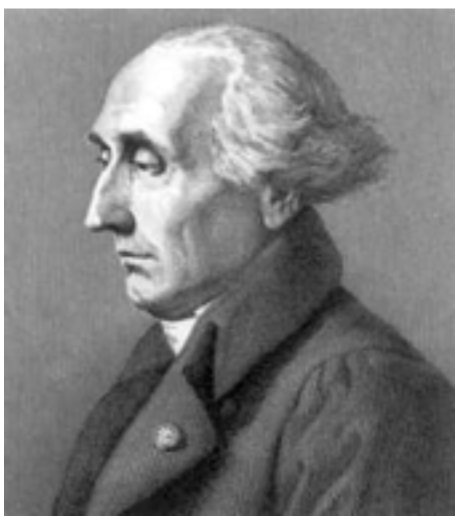
Making an irreversible all-or-nothing biological switch….a basic study of small non-linear system



Joseph-Louis LaGrange
1736 - 1813

Henri Poincare
1854 - 1912

;

Jim Ferrell
?

So, to make a direct contrast with our recent lecture, today we explore the non-trivial emergent properties of **non-linear dynamical systems**.

	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
Nonlinear	fixed points bifurcations, multi stability irreversible hysteresis overdamped oscillators	anharmonic oscillators relaxation oscillations predator-prey models van der Pol systems Chaotic systems	systems of non-linear oscillators non-equilibrium thermodynamics protein structure/ function neural networks the cell ecosystems	Nonlinear wave propagation Reaction-diffusion in dissipative systems Turbulent/chaotic flows

adapted from S. Strogatz

So, we will have several examples of **non-linear dynamical systems** in biology, small to large:

(1) the all-or-nothing, irreversible **MAPK switch** (Jim Ferrell, Stanford)
(2) the van der Pol oscillator and the **action potential** (Fitzhugh-Nagumo, NIH and ?)
(3) the **quantum bump** in invertebrate vision (RR, Alain Pumir, and Boris Shraiman, CNRS and UCSB)
(4) the problem of **proteins** (RR)

With that, let's look at a very simple **first-order non-linear differential equation** system…

Jim Ferrell

As you will see, this system exhibits **bistability** and **extreme hysteresis**…. properties that fundamentally emerge from the non-linearity.

But. first, what do these words mean?

First,….let's consider **monostability** in a biological setting

Most processes in cell signaling are reversible reactions and are largely monostable.

(1) $$A \underset{P}{\overset{S}{\rightleftharpoons}} A\text{-}P$$

A protein A is phosphorylated by kinase S and is de-phosphorylated by phosphatase P.

Monostability

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2. $$G_\alpha \cdot GDP \underset{GTPase}{\overset{receptor}{\rightleftharpoons}} G_\alpha \cdot GTP$$

   G-proteins are reversible.

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G-proteins are reversible.

(3) $$PIP_2 \longrightarrow IP_3 + DAG$$

Second messengers are ~~broken~~ created and broken down

(4)

Second messengers are released and re-sequestered

Monostability

Most processes in cell signaling are reversible reactions and are largely monostable.

5

synthesized $\longrightarrow$ A $\longrightarrow$ degraded

Even proteolysis is "reversible".

Now....**Bistability**

Most processes in cell signaling are reversible reactions and are largely monostable.

(5)

synthesized → A → degraded

Even proteolysis is "reversible".

But some processes are irreversible and some show bistability.

System progresses upon stimulation to a state that persists upon removal of stimulus

System has two stable states at rest.

Now....**Bistability**

(1) Differentiation :

$$\text{undifferentiated state} \xrightarrow{S} \text{differentiated state}$$

State is ~~stable~~ stable and persists for years after removal of S.

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② Cell cycle transitions :

$G2 \longrightarrow M$

Cells cannot go back through a cell cycle transition. This is despite the fact that the signaling machinery underlying the transition is reversible.

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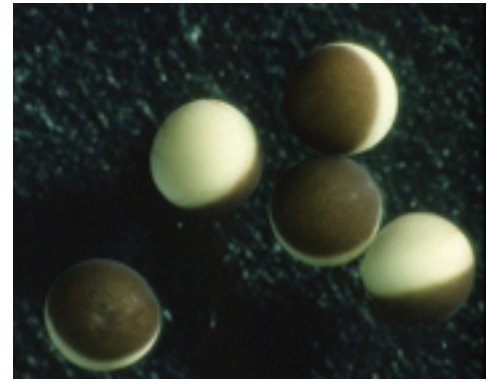
How do you build an irreversible, stable switch from reversible, graded reactions?

Xenopus oocyte maturation...our model system for today

Xenopus laevis...the south-african clawed frog



the oocytes...G2 phase arrested

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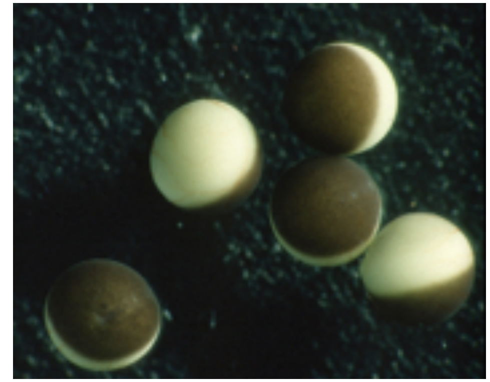

the oocytes...G2 phase arrested

oocytes are induced to mature to a ripe egg (ready for fertilization) by progesterone pulse. This is, at a molecular level, a G2-arrested cell entering meiosis I to ultimately arrest in metaphase to await fertilization.

J.E. Ferrell and E.M. Machleder, Science (1998), 280: 895-8

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G2 phase arrested

M-phase (of meiosis I) arrested.

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Phenomenological properties:

1. maturation is an all-or-nothing process. An oocyte either matures or does not mature. There is no intermediate state observable.

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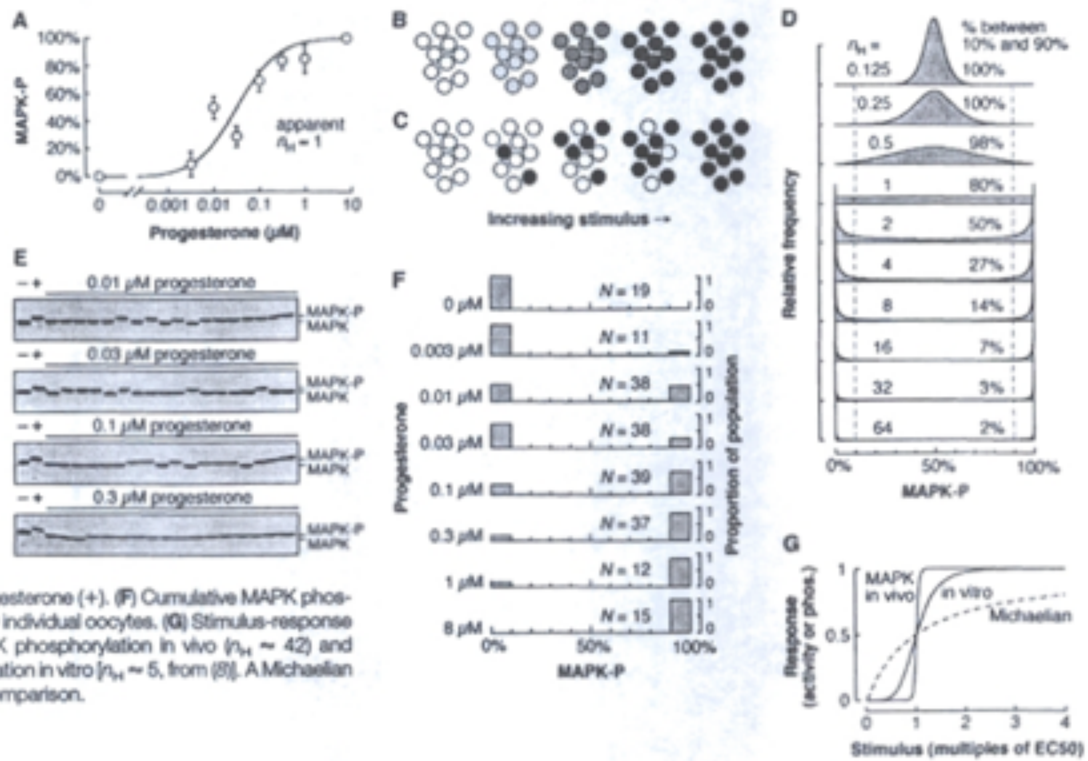

Fig. 1. Responses of oocytes to progesterone. **(A)** Overall responses. Each point represents a sample of 11 to 39 oocytes. Error bars denote two standard errors of the mean. MAPK-P, phosphorylated MAPK. **(B and C)** Two possible origins of a graded response. **(D)** Calculated distributions of oocytes incubated with a half-maximal stimulus for various assumed values of the Hill coefficient (n_H) for the individual oocytes' responses. The oocyte-to-oocyte variability was assumed here to correspond to an m = 1 curve (*15*). **(E)** MAPK immunoblots for individual oocytes treated with progesterone. The first two lanes of each blot represent oocytes treated with no progesterone (−) or 8 μM progesterone (+). **(F)** Cumulative MAPK phosphorylation data from N = 209 individual oocytes. **(G)** Stimulus-response curves inferred for p42 MAPK phosphorylation in vivo (n_H ~ 42) and measured for p42 MAPK activation in vitro [n_H ~ 5, from (*8*)]. A Michaelian (n_H = 1) curve is shown for comparison.

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Xenopus oocyte maturation...our model system for today

Phenomenological properties:

1. maturation is an all-or-nothing process. An oocyte either matures or does not mature. There is no intermediate state observable.

2. induction of maturation is irreversible. Transient exposure of oocytes to Progesterone leads to commitment of oocytes to maturation. Removal of stimulus does not cause de-maturation, no matter how long you wait.

3. Sub-threshold dose of progesterone will never cause oocyte maturation, no matter how long it is applied.

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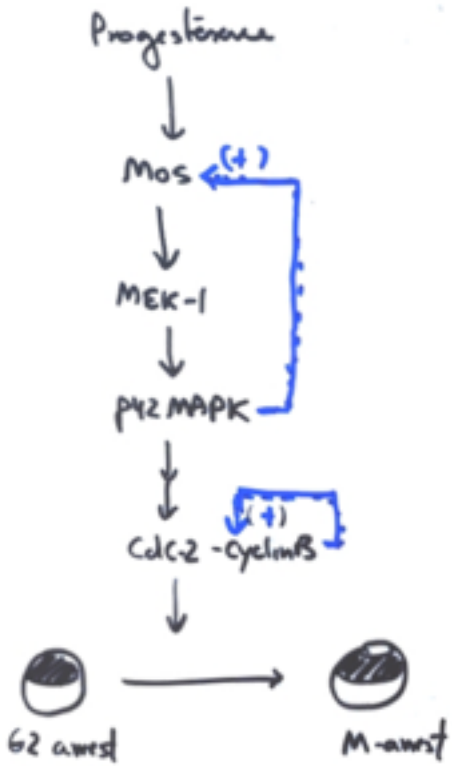
What does this imply?

There is a switch-like response to progesterone concentration, and once thrown, the switch leads to a stable on-state that persists.

$\boxed{\rightarrow \text{ switch with extreme hysteresis.}}$

J.E. Ferrell and E.M. Machleder, Science (1998), 280: 895-8

Ok, so what is the molecular biology underlying these phenomena?



① A signaling cascade with embedded (+) feedback loops.

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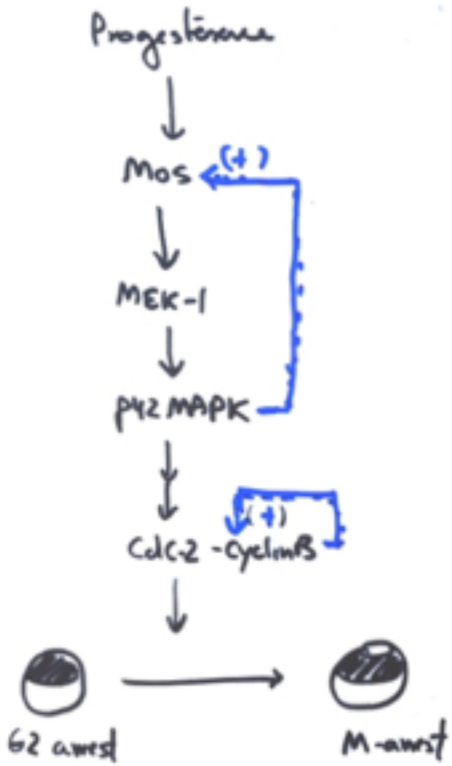

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② Cdc2 is a beautiful switch as a single molecule. Active state [T160-P, T14, T15 dephos] is 3×10^9 fold more active!

In principle, a single molecule of cdc2 could provide a switch-like response...

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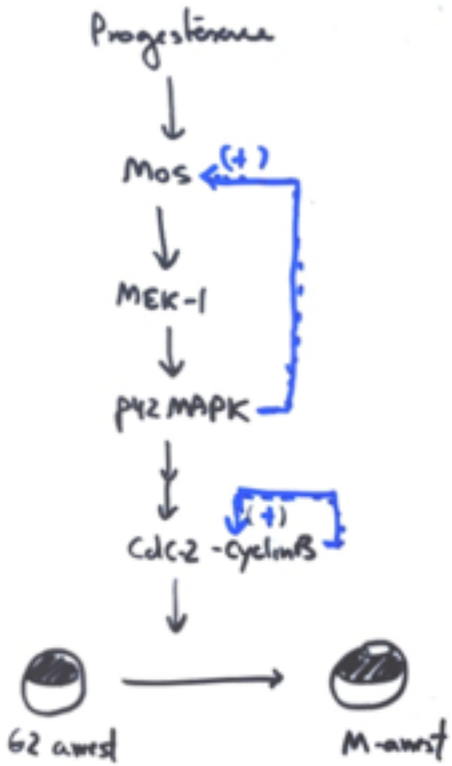

① A signaling cascade with embedded (+) feedback loops.

② Cdc2 is a beautiful switch as a single molecule. Active state [T160-P, T14, T15 dephos] is 3×10^7 fold more active!

③ But... an oocyte has $\sim 1 \times 10^{10}$ cdc2's, so output could be continuous.

④ Individual reactions are reversible too. p42MAPK is subject to -P by MEK1 and dephosphorylation by a phosphatase.

In principle, a single molecule of cdc2 could provide a switch-like response...but even if so, its not clear how irreversibility arises...

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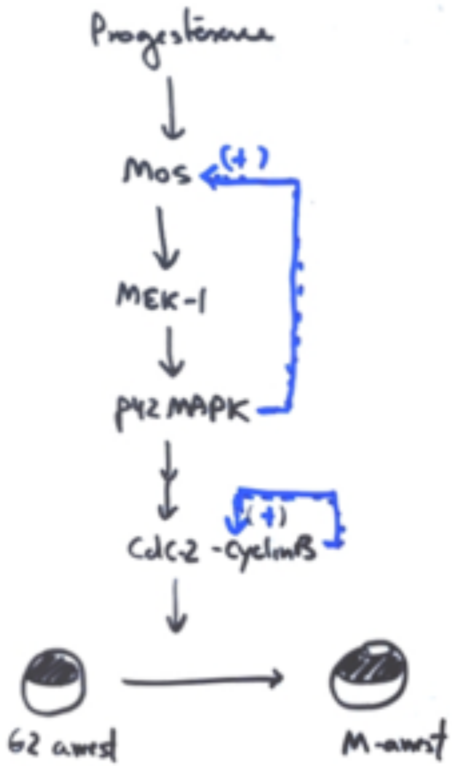

So.....

① How do you take a graded stimulus [progesterone] and continuously variable signaling proteins [p42MAPK, cdc2] and make an all-or-nothing biological response?

② How do you take a reversible stimulus, transduce it through reversible signaling proteins, and make an irreversible biological response?

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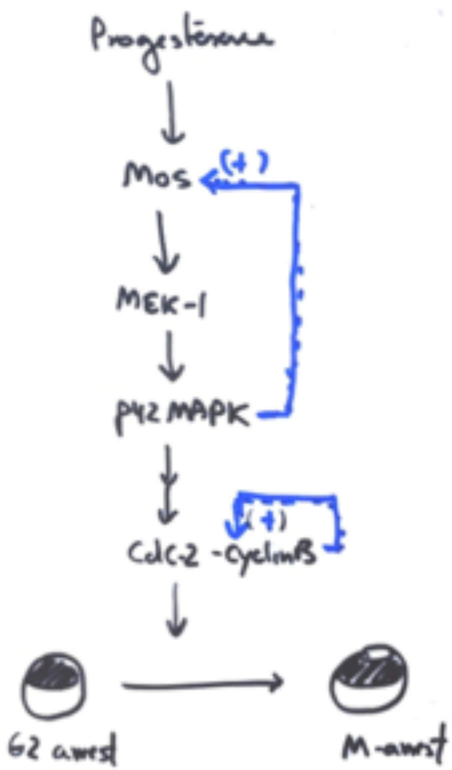

Well, this is an **emergent property** of the network of signaling reactions.....

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Analysis of the **Monocycle**

To see this and to develop the modeling, we begin with a simple reaction. [A monocycle].

(I) $A \underset{k_{-1} I}{\overset{k_1 S}{\rightleftharpoons}} A^*$; S could be a kinase, and $A \rightarrow A^*$ could be phosphorylation. I could be a phosphatase, and $A^* \rightarrow A$ could be

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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Let's say S & I are far from saturation. Then the forward reaction is:

$$\frac{dA^*}{dt} = k_1 S[A] = k_1 S[A_{tot} - A^*]$$

$$\boxed{= k_1 S[A_{tot}] - k_1 S[A^*]}$$

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Linear equations? or not?

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$$\boxed{\frac{dA}{dt} = k_{-1} I\,[A^*]}$$

At steady state, the forward & back reactions equal each other.

So...

$$k_1 S\,[A_{tot}] - k_1 S[A^*] = k_{-1} I\,[A^*]$$

or...

$$\frac{[A^*]}{[A_{tot}]} = \frac{S}{\frac{k_{-1} I}{k_1} + S}$$ [Michaelian response].

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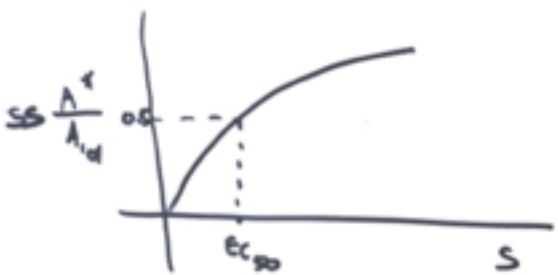
Analysis of the **Monocycle**

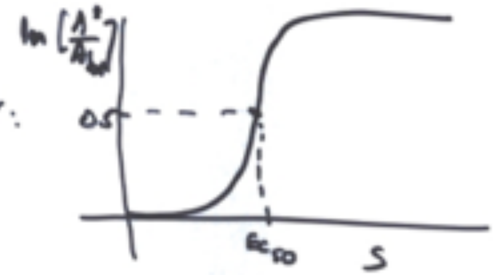
$$\frac{[A^*]}{[A_{tot}]} = \frac{S}{\frac{k_{-1}I}{k_1} + S}$$ [Michaelian response].

As all of you know, this is the old rectangular hyperbolic function:

$$\frac{[A^*]}{[A_{tot}]} = \frac{S}{EC_{50}+S}$$



or:



When S is small, $\frac{A^*}{A_{tot}}$ rises nearly linearly. But as S gets large, $\frac{A^*}{A_{tot}}$ levels off since there is less [A] around to convert to A^*. When $S = EC_{50}$, $\frac{A^*}{A_{tot}} = 0.5$.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

The **Rate-Balance Plot**...a clever graphical technique

$$A \underset{k_{-1} I}{\overset{k_1 S}{\rightleftharpoons}} A^*$$ ...and our forward and back rates

$$\frac{dA^*}{dt} = \boxed{k_1 S[A_{tot}] - k_1 S[A^*]}$$

$$\boxed{\frac{dA}{dt} = k_{-1} I [A^*]}$$

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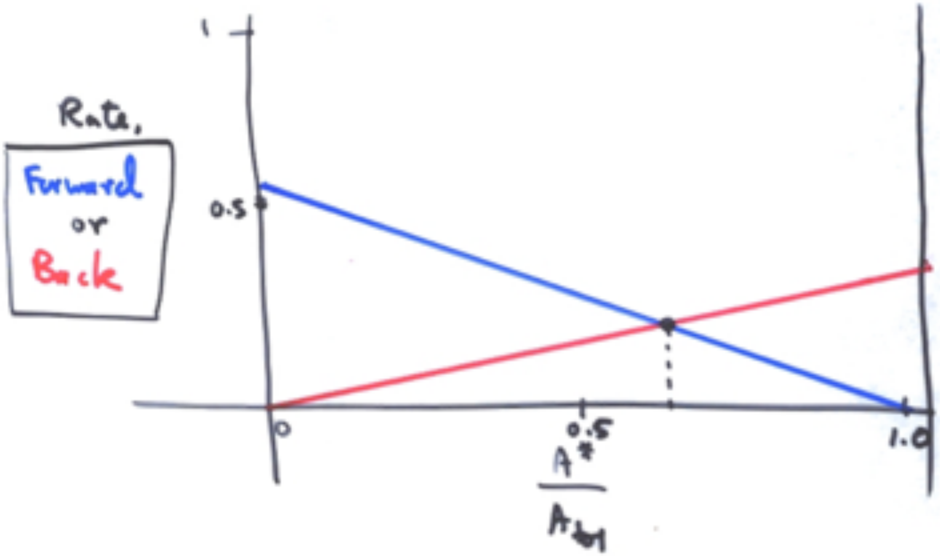
The Rate Balance Plot: A graphical way of seeing system behavior.



Forward rate $= k_1 S - k_1 S \frac{[A^*]}{[A_{tot}]}$

Back rate $= k_{-1} I \frac{[A^*]}{[A_{tot}]}$

Slope of forward reaction is dependent on [S].

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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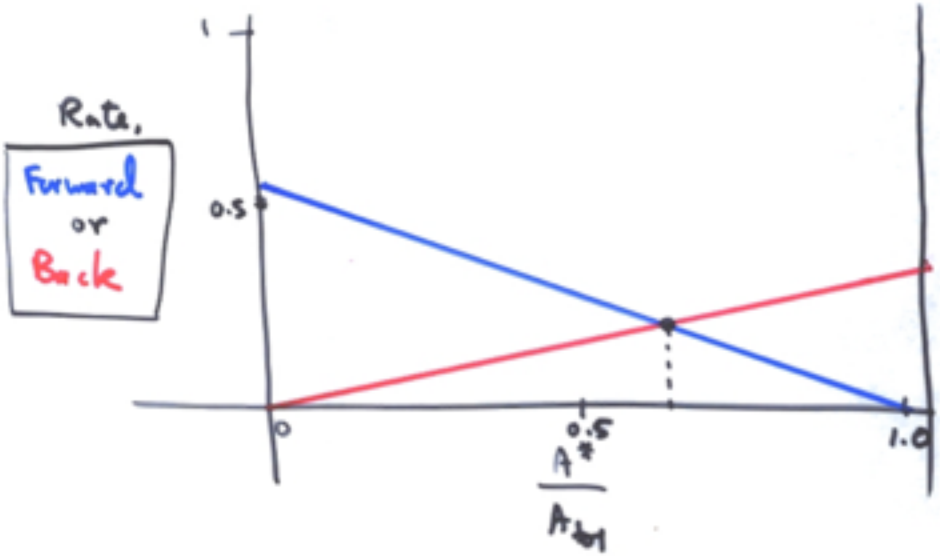


Forward rate $= k_1 S - k_1 S \frac{[A^*]}{[A_{tot}]}$

Back rate $= k_{-1} I \frac{[A^*]}{[A_{tot}]}$

Where is steady-state? That is where is a fixed-point of this system?

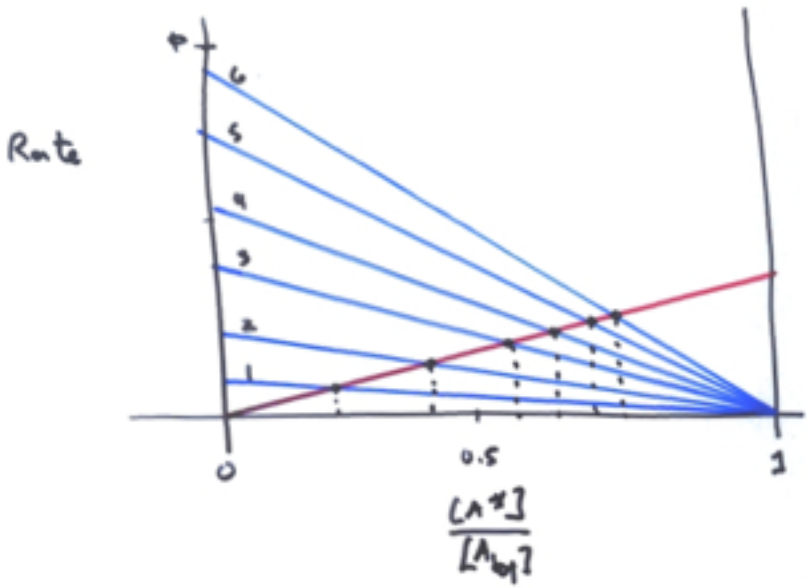
Slope of forward reaction is dependent on [S].

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

The **Rate-Balance Plot**...a clever graphical technique

Now vary the stimulus. [S]

$$A \underset{k_{-1}, I}{\overset{k_1, S}{\rightleftarrows}} A^*$$



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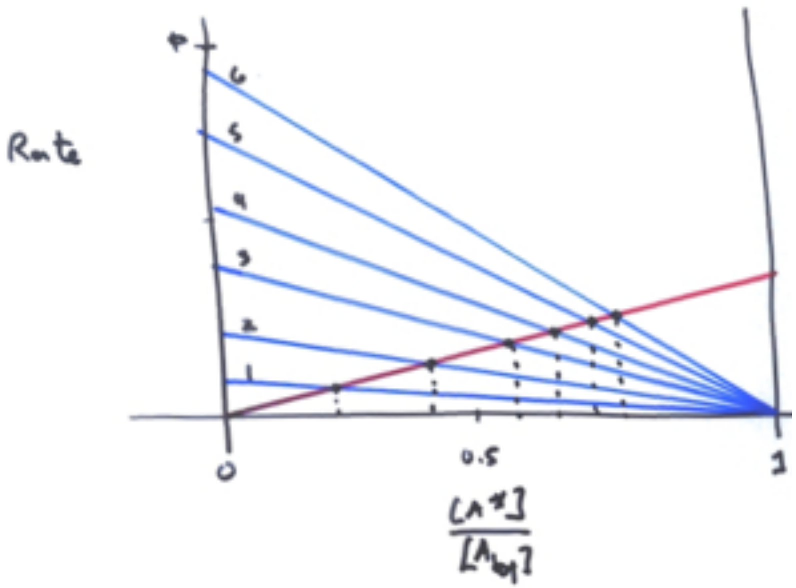
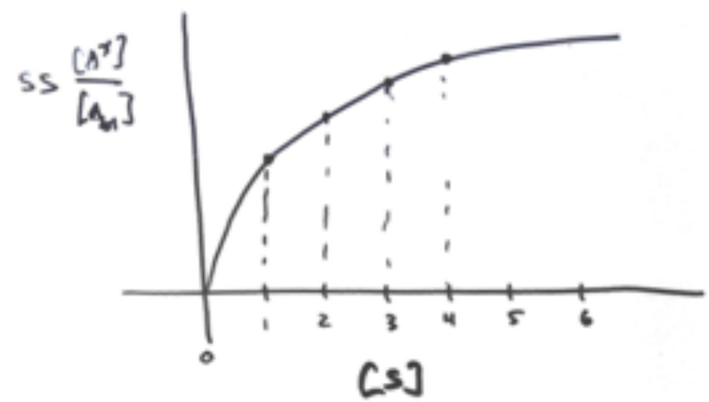


Now plot the steady state A^*/A_{tot} value against [S] :



The Michalean response with no calculations! A graphical way of "seeing" system behavior.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

The **Rate-Balance Plot**...a clever graphical technique

Now vary the stimulus. [S]

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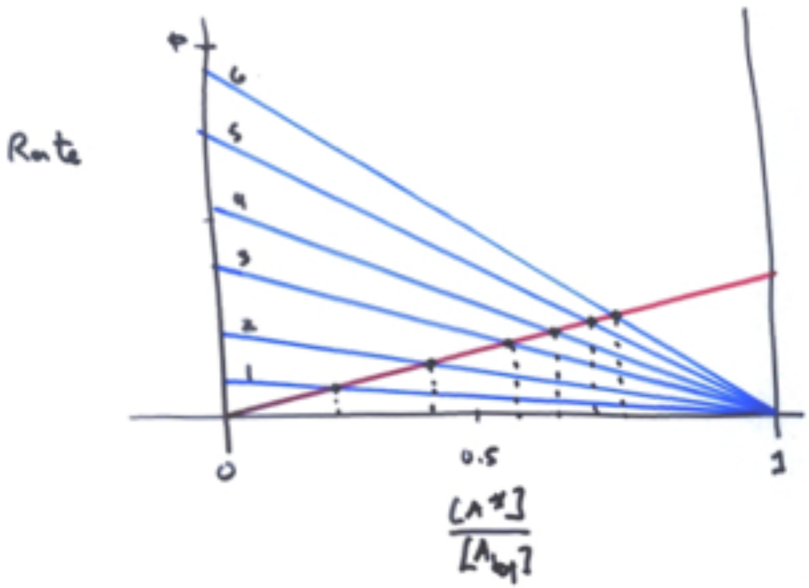
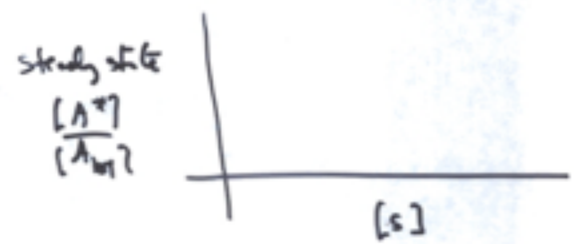


What can we learn from the rate balance plot?

1. where the forward and back rates meet, the system is in steady state.
2. when $[A^*]=0$, forward rate is maximal,
   when $[A^*]=[A_{tot}]$, forward rate is zero.
   Slope of line varies with [S]
3. Similar stuff for back rxn.
4. We can easily make a stimulus-response curve.

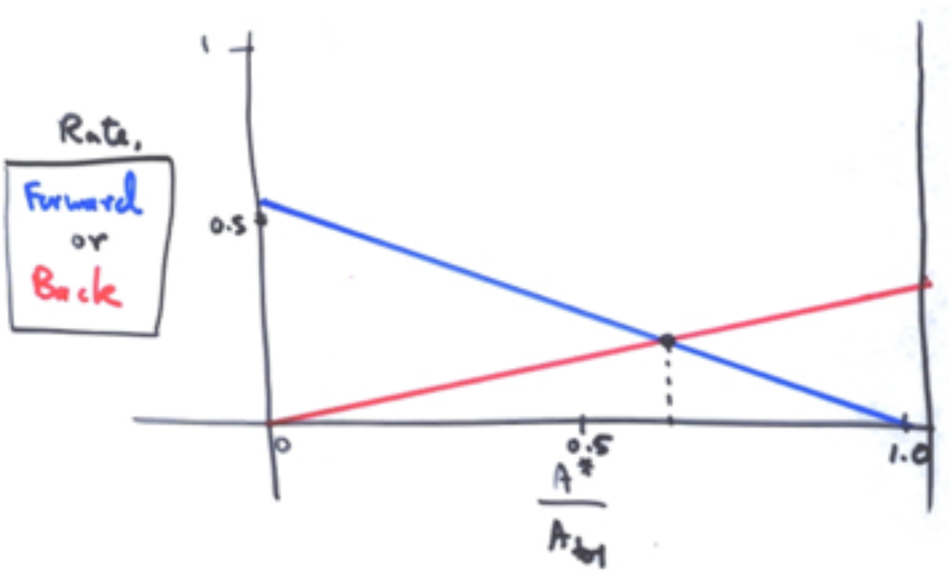


J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Analysis of the Michaelean response....

$$A \underset{k_{-1},I}{\overset{k_1,S}{\rightleftharpoons}} A^*$$

Stability of the Michaelian response



How do we test for stability of a steady-state?

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Analysis of the Michaelean response....

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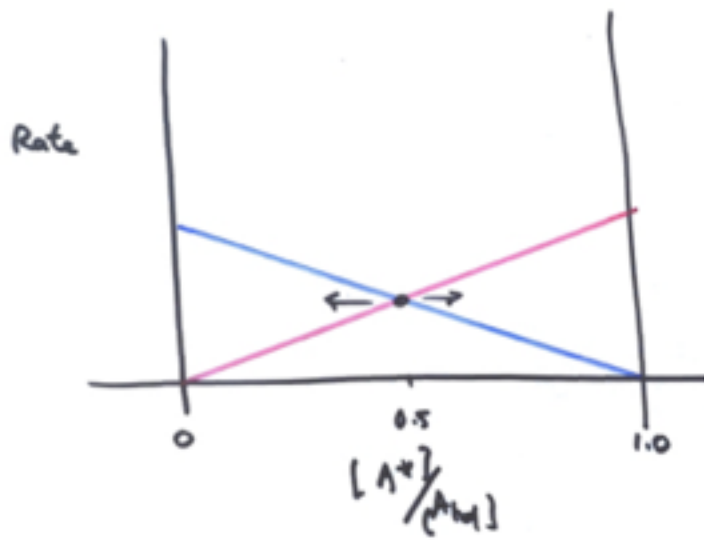
Stability of the Michaelian response

8

Start with the system at steady state, and perturb slightly: What happens?



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Stability of the Michaelian response 8

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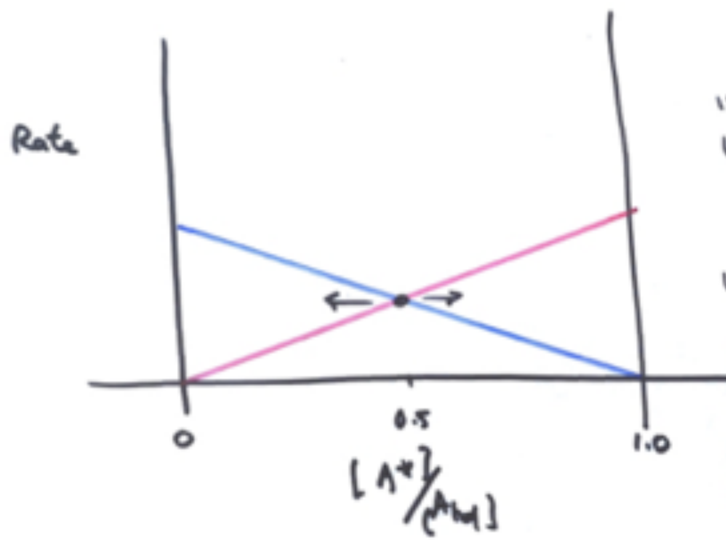

To the right, the back rxn is larger than the forward, and we return to SS.

To the left, the forward rxn wins, and we return to SS.

The SS is said to be **stable**

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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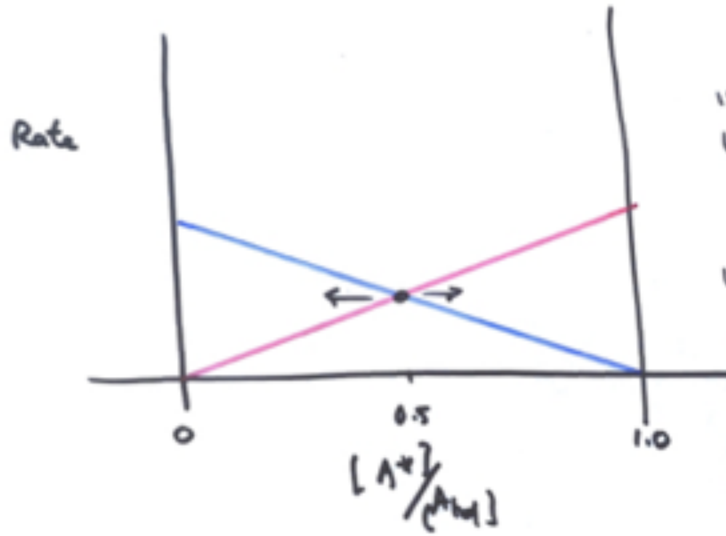

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Note that the Michaelian system is **monostable**. [one ss]

So, to get bistability, we need to add something....

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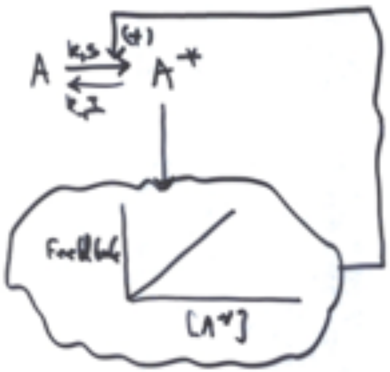
Now, **linear positive feedback**...

II. Add linear positive feedback.

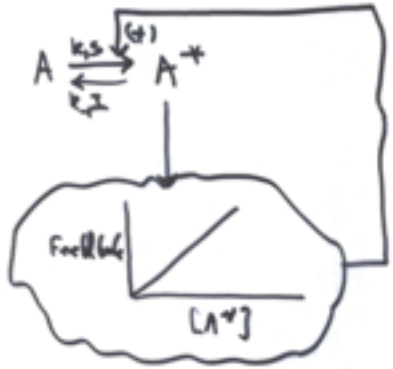


Molecularly, this could be A being phosphorylated by both S and [A*], or where A* increases the activity of S.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

II. Add linear positive feed



So now the forward rxn has two components:

$$\frac{d[A^*]}{dt} = \text{basal rate} + \text{feedback rate}$$

$$= k_1 S[A] + k_2[A^*][A]$$

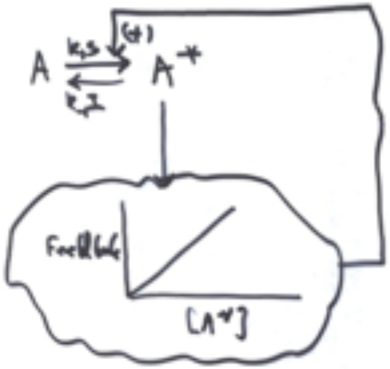
$$\boxed{= (k_1 S + k_2[A^*])([A_{tot}] - [A^*])}$$

And here is our non-linearity....

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

II. Add linear positive feed



So now the forward rxn has two components:

$$\frac{d[A^*]}{dt} = \text{basal rate} + \text{feedback rate}$$

$$= k_1 S[A] + k_2[A^*][A]$$

$$\boxed{= (k_1 S + k_2[A^*])([A_{tot}] - [A^*])}$$

And here is our non-linearity....

The back reaction is the same $\boxed{(k_{-1} I [A^*])}$.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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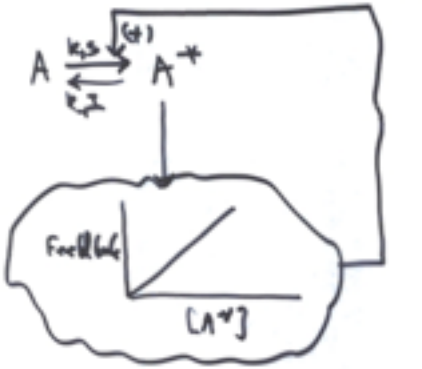
I. Add linear positive feed



Let's consider the shape of the forward and back rates...

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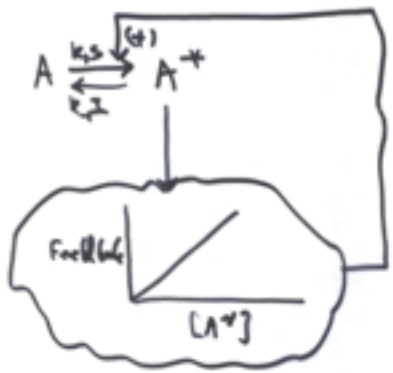

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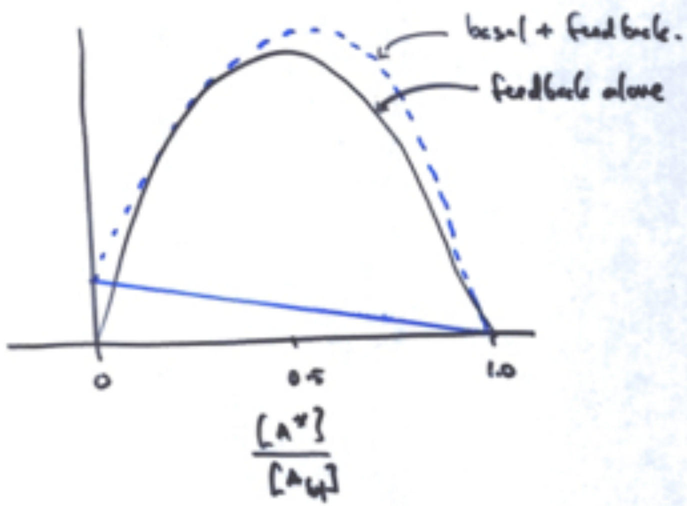
Plot the forward rate as a function of $\frac{[A^*]}{[A_{tot}]}$:



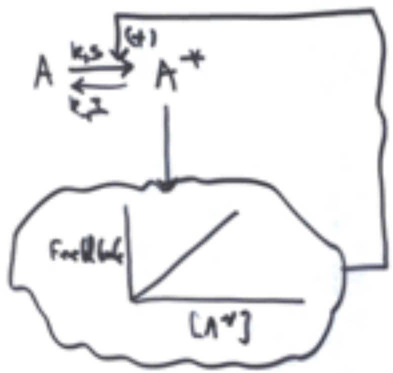
$(k_2[A^*]([A_{tot}] - [A^*]))$

The feedback rate is in the form of a parabola, the basal forward rate tilts it, and the back rate is still linear

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

II. Add linear positive feedb



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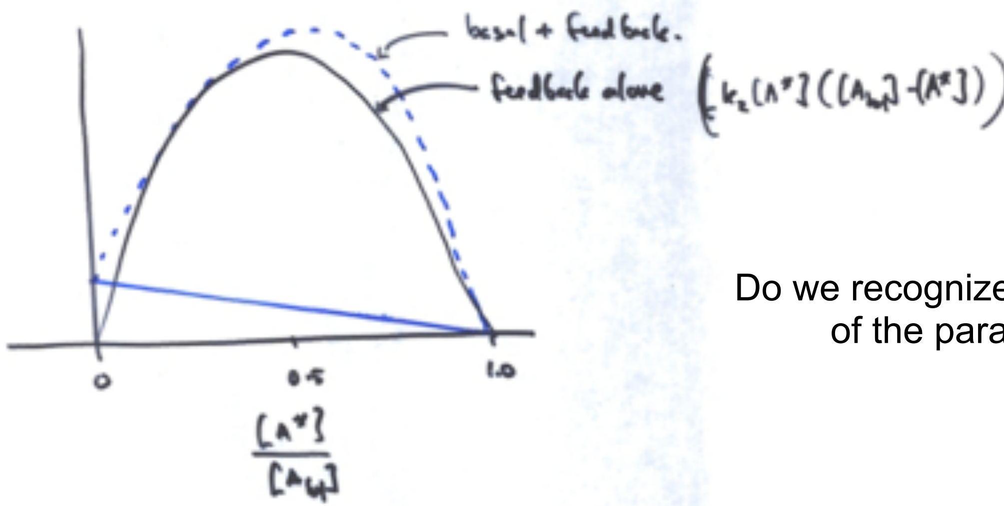
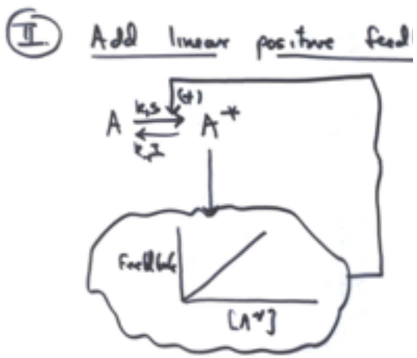


Do we recognize the equation? And what set's the height of the parabola?

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...



So, how does this linear positive feedback make the system behave? Let's forget the basal rate for now (i.e. [S] = 0), and just look at the feedback rate...

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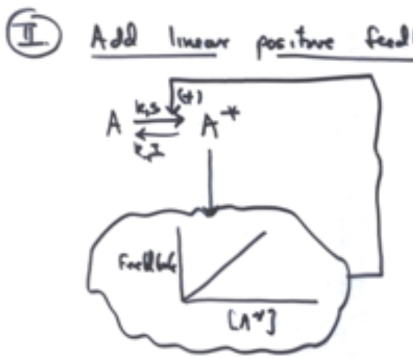
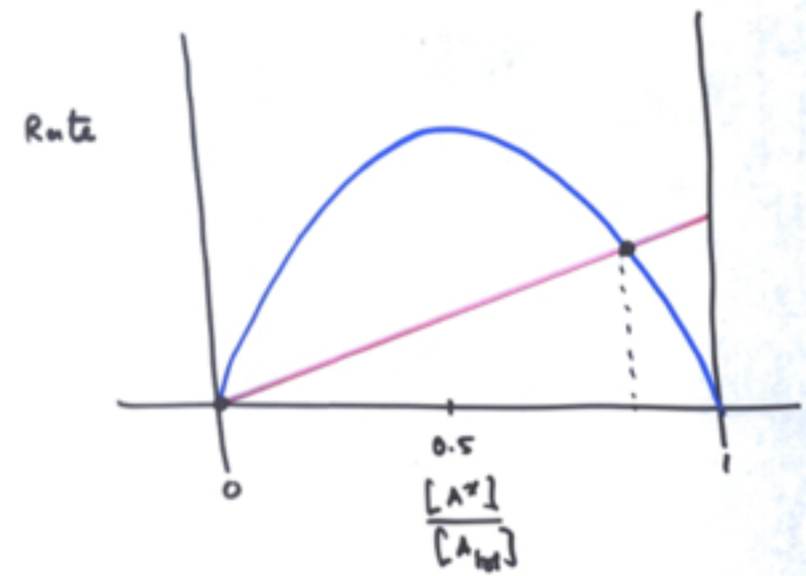
Now, **linear positive feedback**...





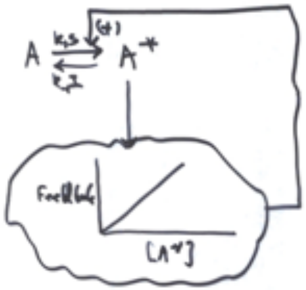
What can we say? Well . . .

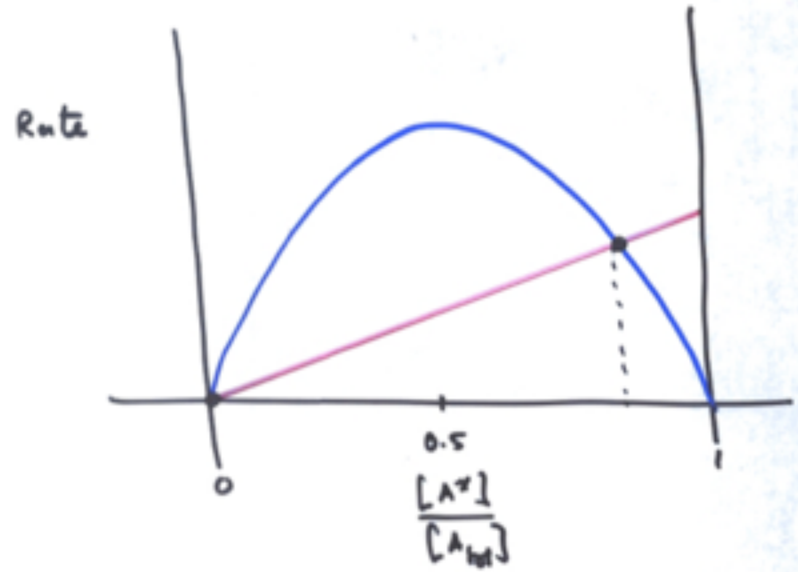
How many steady states are there now?

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

II. Add linear positive feedback





What can we say? Well ...

1. There are two steady state values possible. It is a two state system.
2. But one of the states is unstable! Which one?

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

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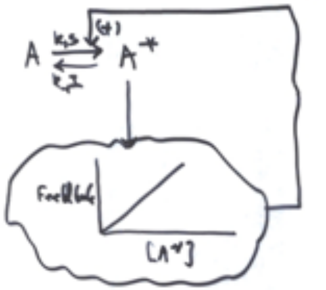
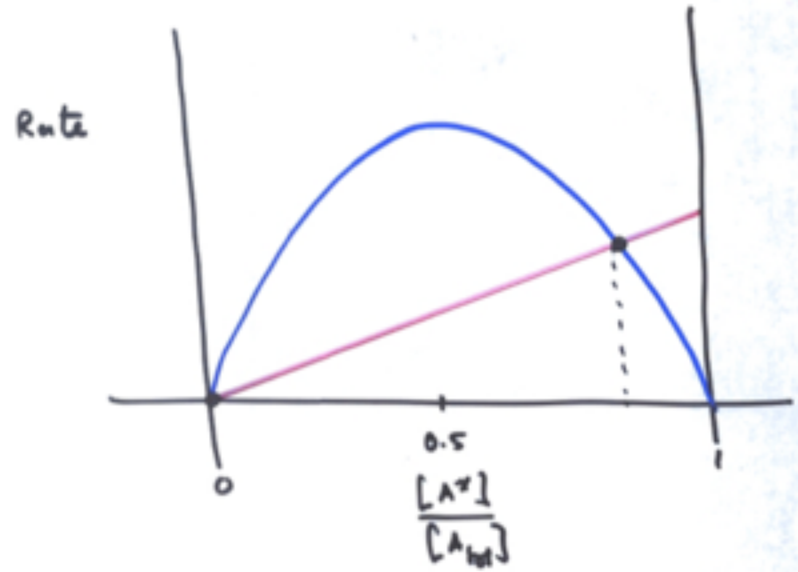




What can we say? Well ...

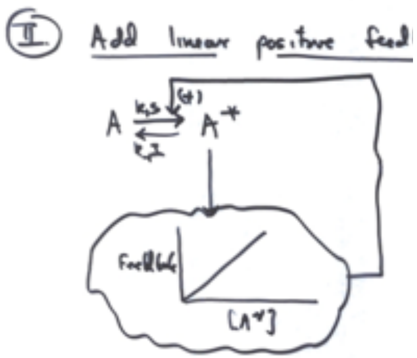
(1) There are two steady state values possible. It is a two state system.

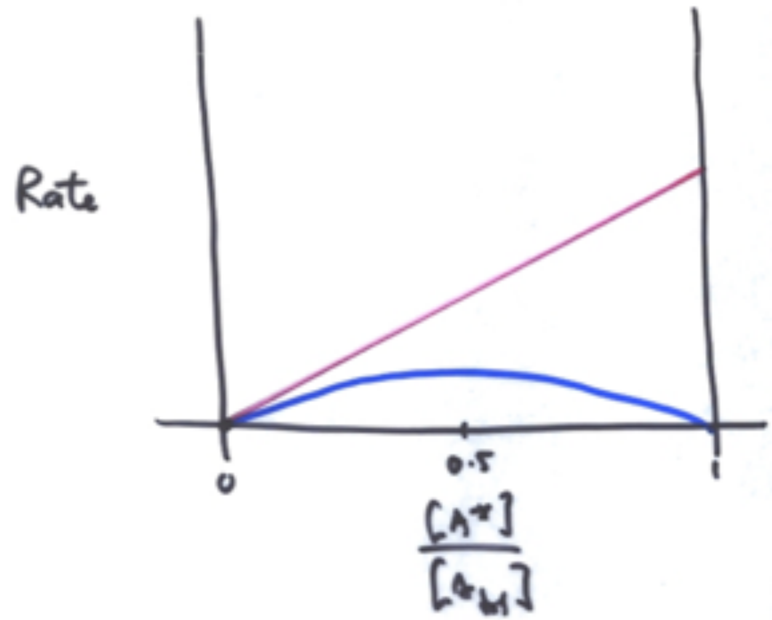
(2) But one of the states is unstable! Which one?

How can we "fix" the instability of the off-state? Well....

J.E. Ferrell and W. Xiong, <u>Chaos</u> (2001), 11: 227-236

Now, **linear positive feedback**...

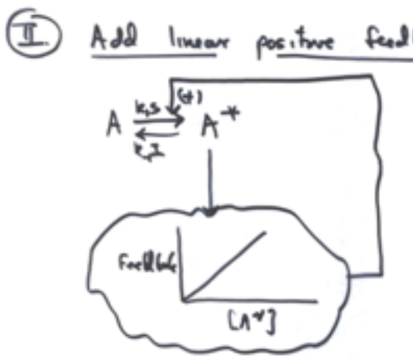


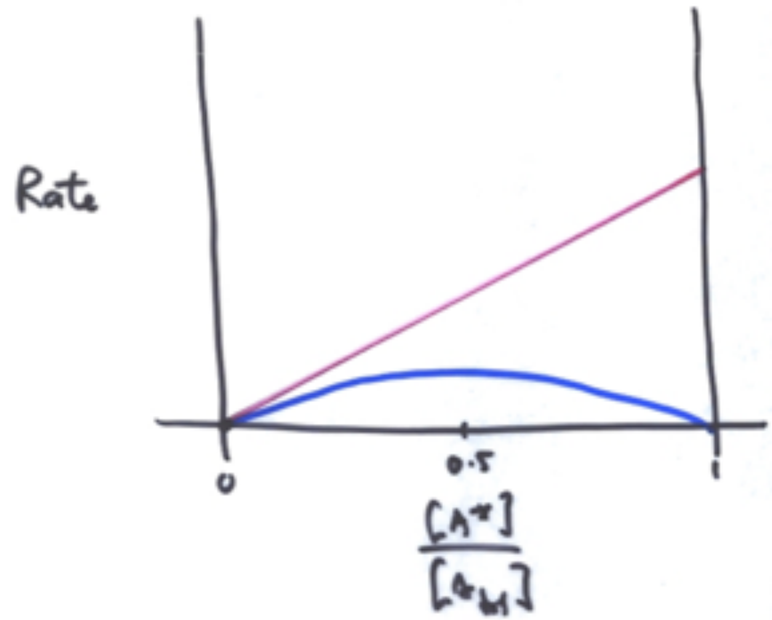


We can lower the feedback rate constant k_2 ...

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...





We can lower the feedback rate constant k_2 ...but what happened? The on-state disappeared!

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Now, **linear positive feedback**...

So... + feedback alone is insufficient to make a bistable system with switch-like character.

There are two (at least) ways of making ~~the~~ both the off- and on-states stable.

1. Nonlinear (ultrasensitive) feedback instead of linear feedback.

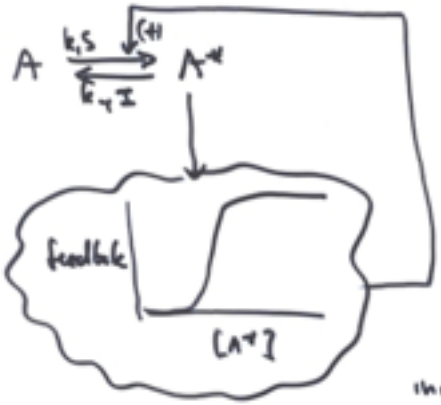
2. Saturation of the back reaction.

Lets see this one at a time...

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Ultrasensitive positive feedback...

① Ultrasensitive feedback [cooperativity in feedback system]



The flat part of the feedback at initial [A*] makes it so that thermal [unstimulated] conversion of A → A* will not destabilize the off-state.

Is that obvious?

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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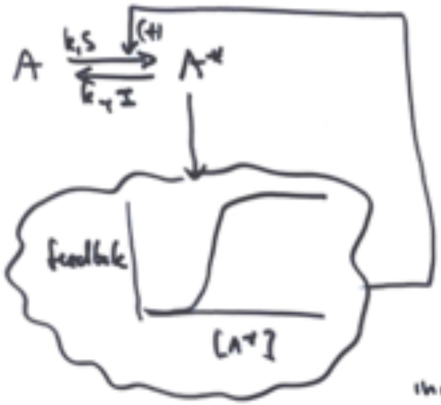

The flat part of the feedback at initial [A*] makes it so that thermal [unstimulated] conversion of $A \rightarrow A^*$ will not destabilize the off-state.

Is that obvious?

By the way, how can one make ultrasensitive feedback, molecularly?

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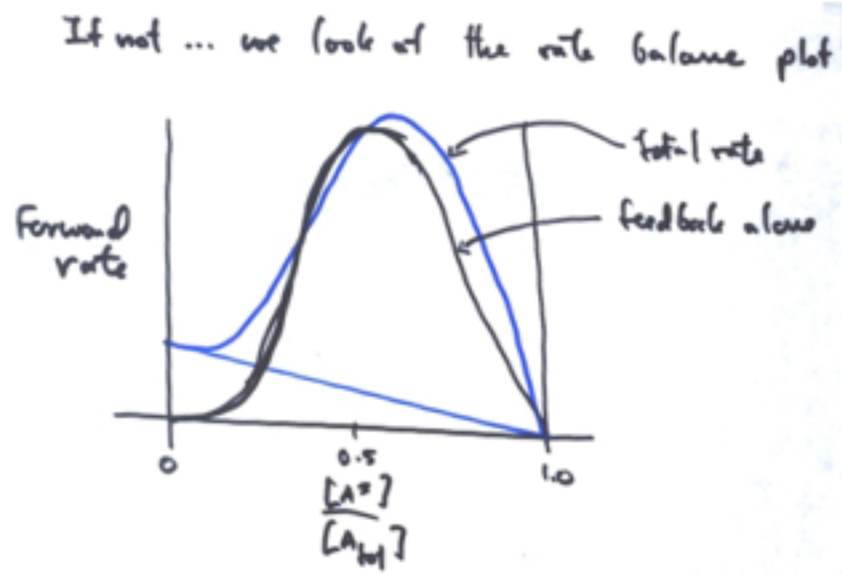
Ultrasensitive positive feedback...



And...again we look at the system with no stimulus (i.e. [S] = 0)...

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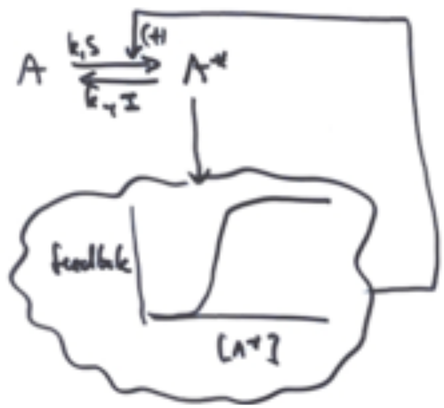
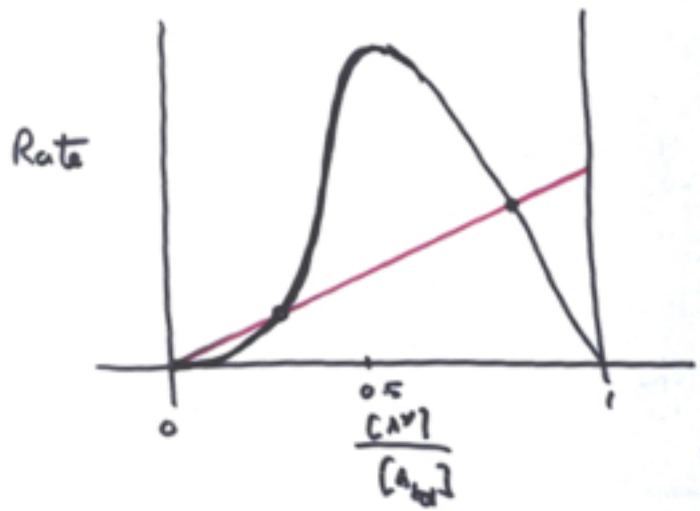
Ultrasensitive positive feedback...

① Ultrasensitive feedback





What does this show?

How many steady states?

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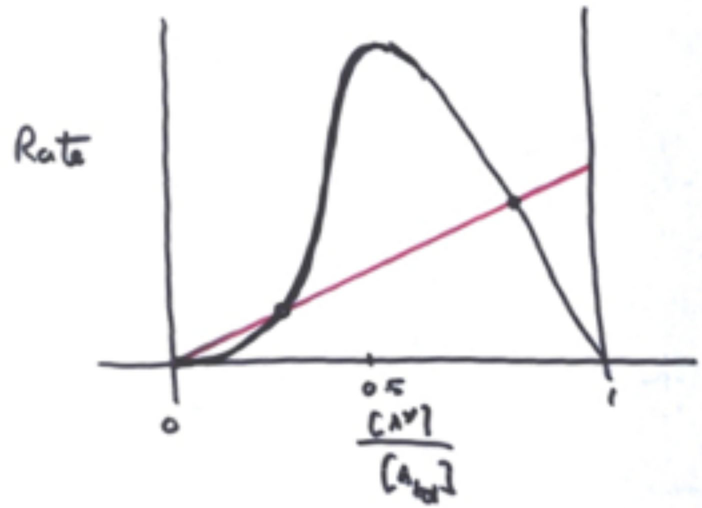
Ultrasensitive positive feedback...

① Ultrasensitive feedback



What does this show?

① There are now three ~~st~~ steady states possible.

② Two are stable, one isn't. Which is which?

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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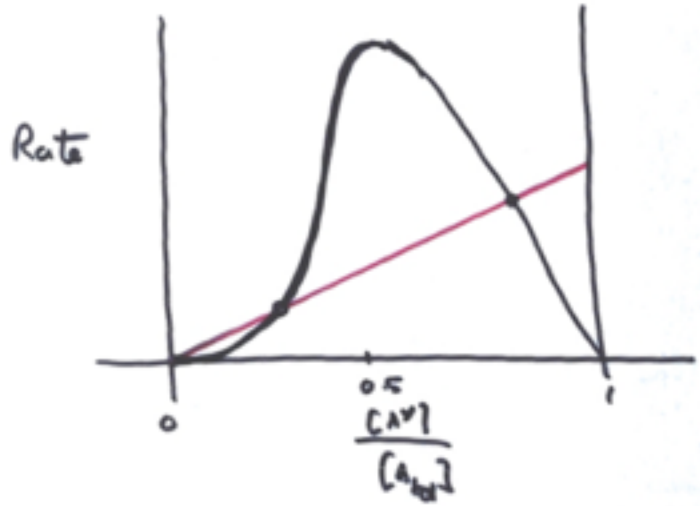

What does this show?

① There are now three ~~st~~ steady states possible.

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③ The middle state is a threshold. Start the system to the left of it, and it goes off. Start it to the right, and it goes on.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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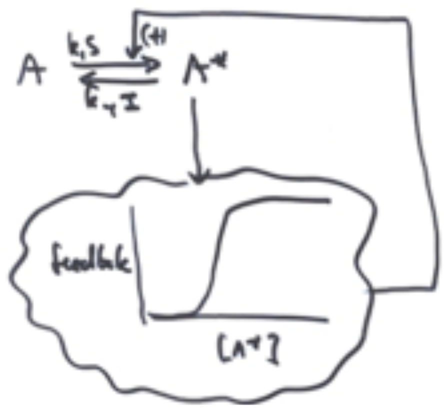

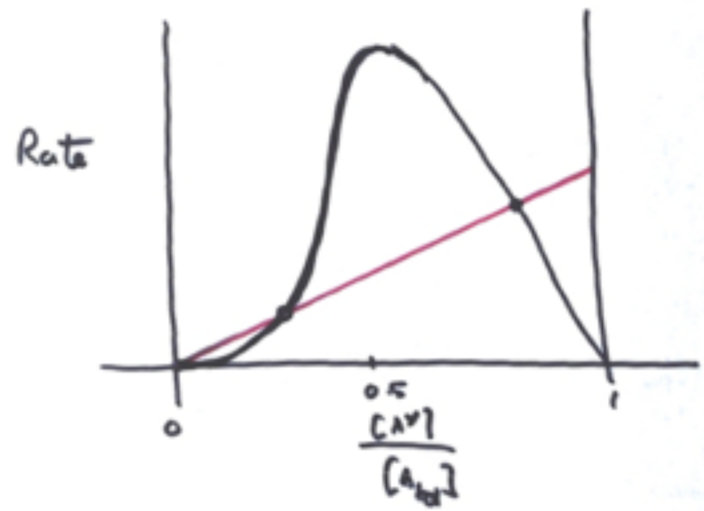

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② Two are stable, one isn't. Which is which?

③ The middle state is a threshold. Start the system to the left of it, and it goes off. Start it to the right, and it goes on.

④ The bistability only holds over certain ranges of parameters. If basal activity of S is high.... If activity of I is too high....

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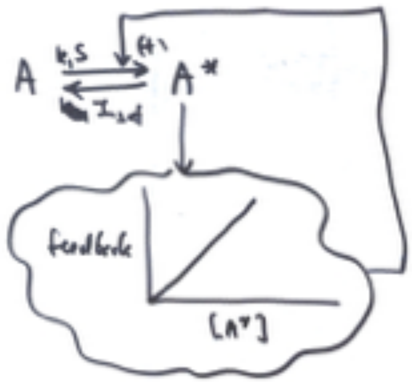
Ultrasensitive positive feedback...

(2) Back reaction saturation:



so... linear positive feedback, but where the back rxn saturates quickly with A*:

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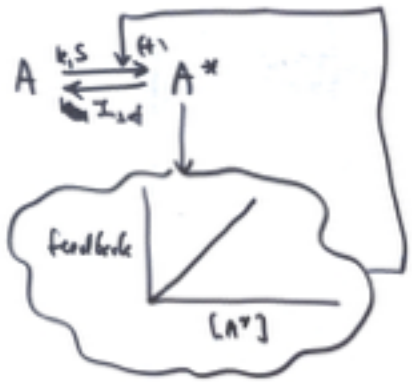
Ultrasensitive positive feedback...

② Back reaction saturation:



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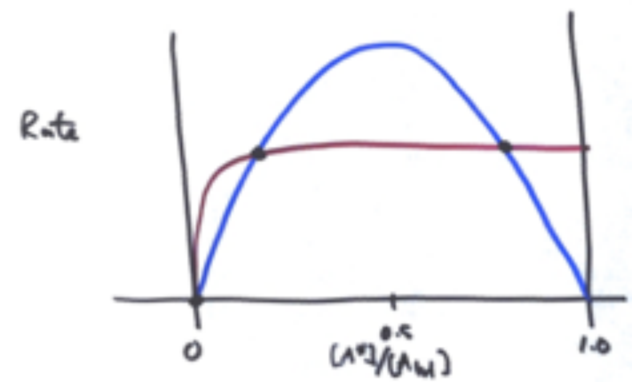
so... linear positive feedback, but where the back rxn saturates quickly with A*:

Rate balance plot:



so... again, three steady state values of $\frac{A^*}{A_{tot}}$, two stable and one unstable.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Getting over the threshold....

Ok, so we have built a bistable system with a threshold separating the two states, but ... how do we get over the threshold?

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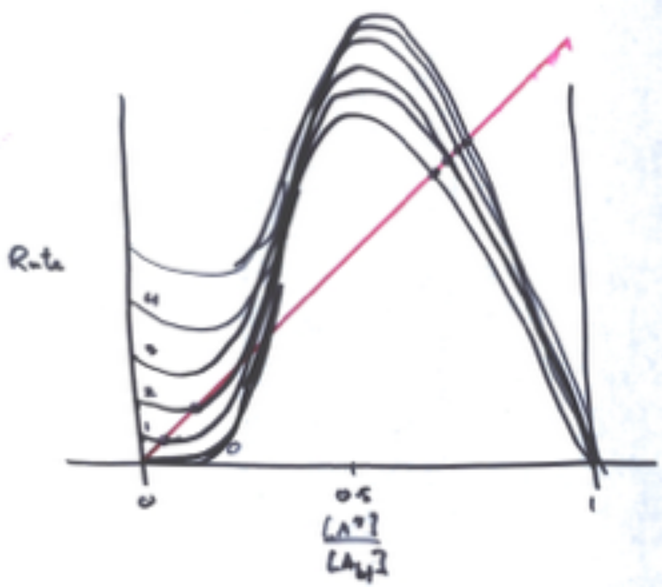
Consider the case of ultrasensitive feedback with varying stimulus concentration :



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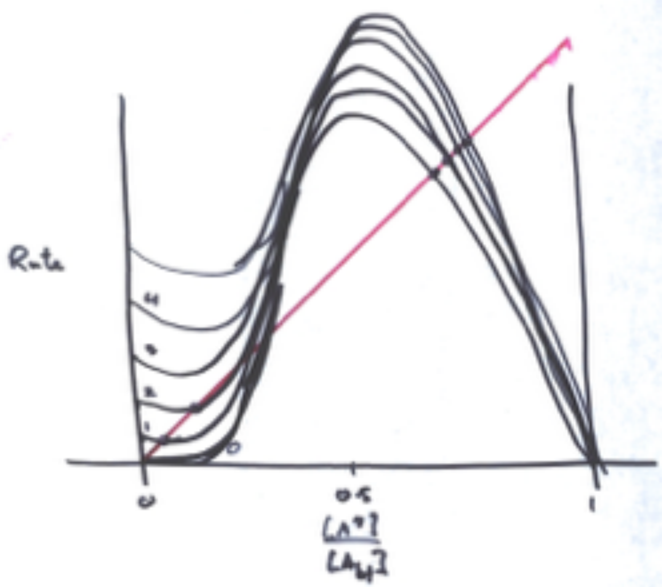

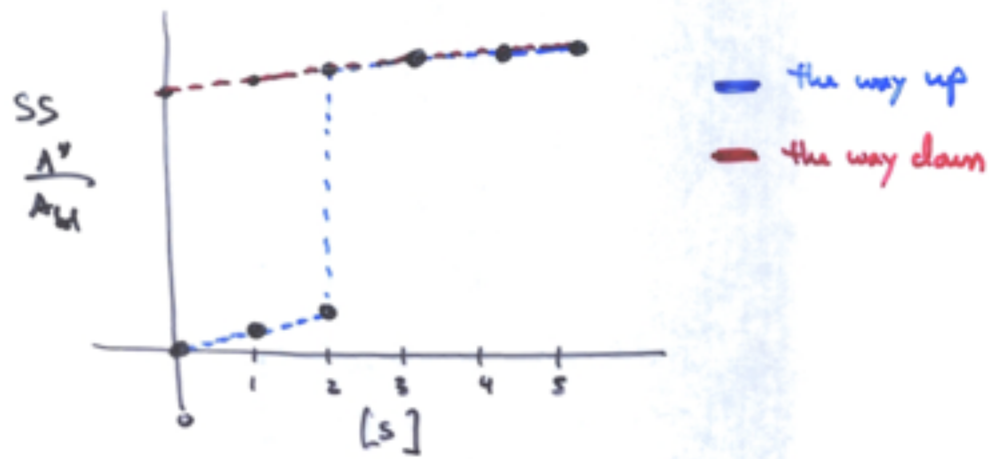

And now, we have an irreversible, bistable switch...

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

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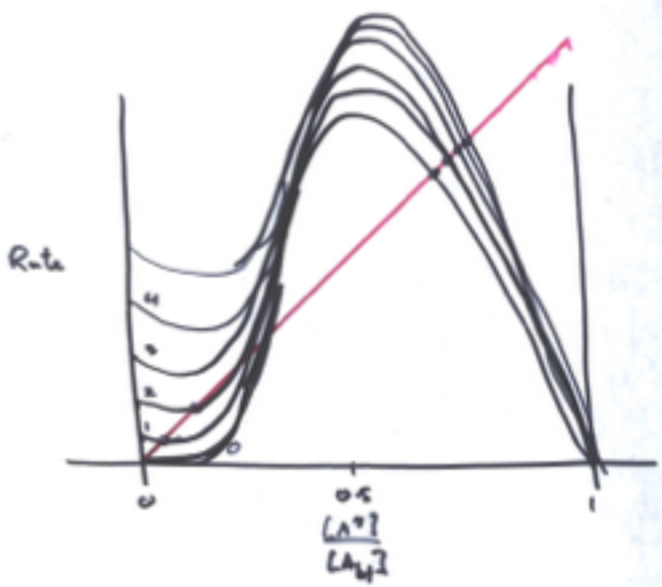
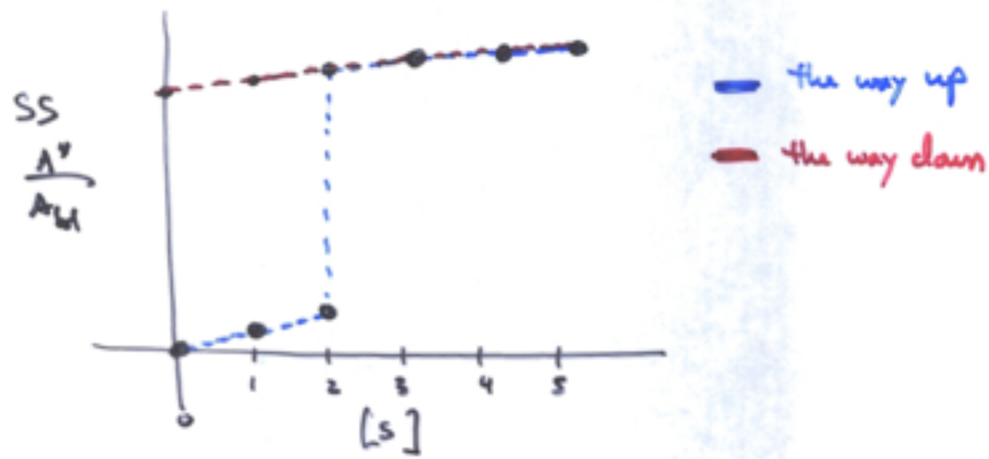


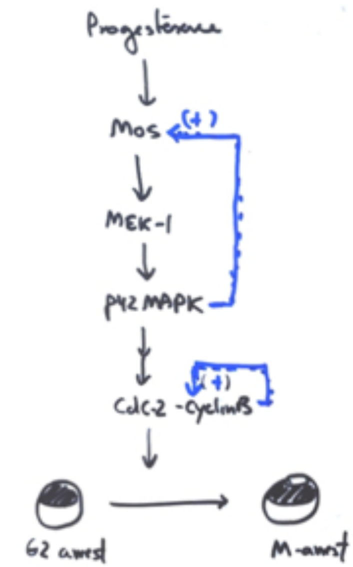


Hysteresis is interesting...it's a way of the cell "remembering" some history of events.

J.E. Ferrell and W. Xiong, Chaos (2001), 11: 227-236

Xenopus oocyte maturation...so this is now it works in fact

Oocytes are induced to mature to a ripe egg (ready for fertilization) by progesterone pulse. This is, at a molecular level, a G2-arrested cell entering meiosis I to ultimately arrest in metaphase to await fertilization.



An ultrasensitive positive feedback in the MAP-kinase cascade underlies the all-or-nothing, irreversible, switch-like characteristics of oocyte maturation.

Fundamentally due to the non-linearity introduced by the feedback system.

Next, we will consider the **van der Pol oscillator** and the **FitzHugh-Nagumo model** for the action potential in detail.

	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
Nonlinear	fixed points bifurcations, multi stability irreversible hysteresis overdamped oscillators	anharmonic oscillators relaxation oscillations predator-prey models van der Pol systems Chaotic systems	systems of non-linear oscillators non-equilibrium thermodynamics protein structure/ function neural networks the cell ecosystems	Nonlinear wave propagation Reaction-diffusion in dissipative systems Turbulent/chaotic flows

adapted from S. Strogatz