A systems approach to biology

SB200

Lecture 2
18 September 2008

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I do not hold formal office hours. Please send me an e-mail if you have questions or would like to arrange a time to meet. My lab is in Goldenson 504 on the Harvard Medical School campus.

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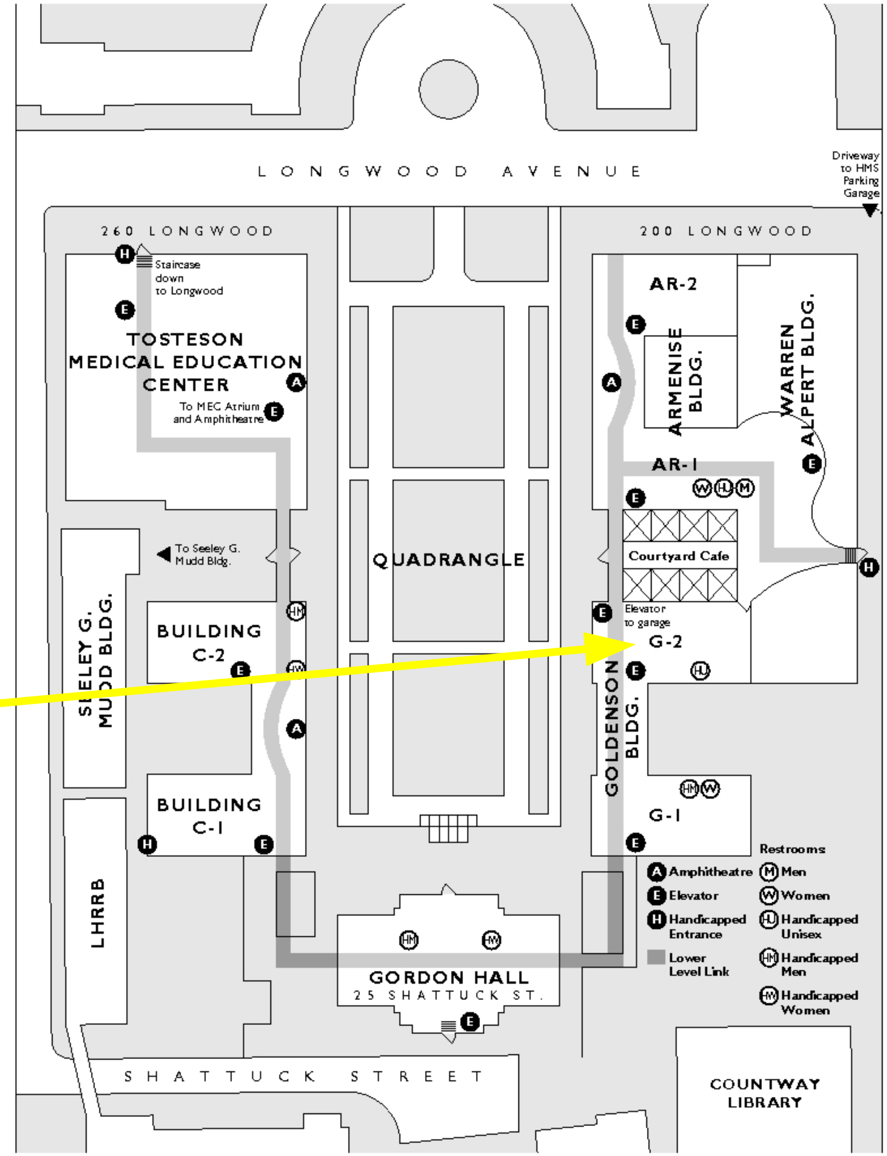
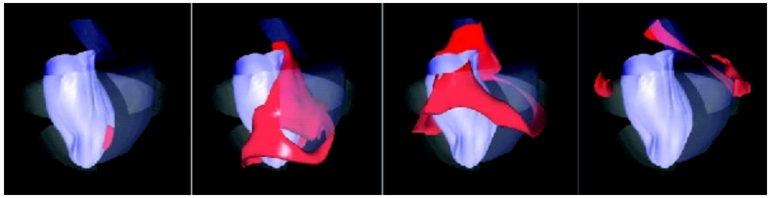


http://www.hms.harvard.edu/about/maps/quadmap.html

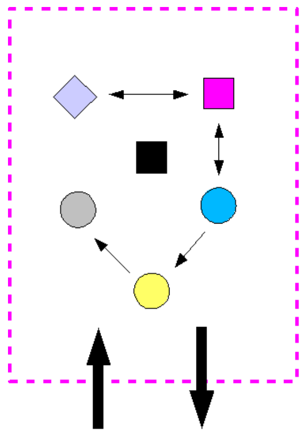
Recap of Lecture 1

role of mathematics

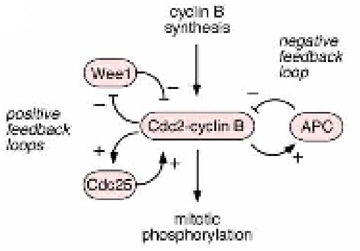
thick models



systems biology

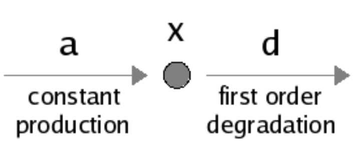


thin models – feedback control “ansatz”



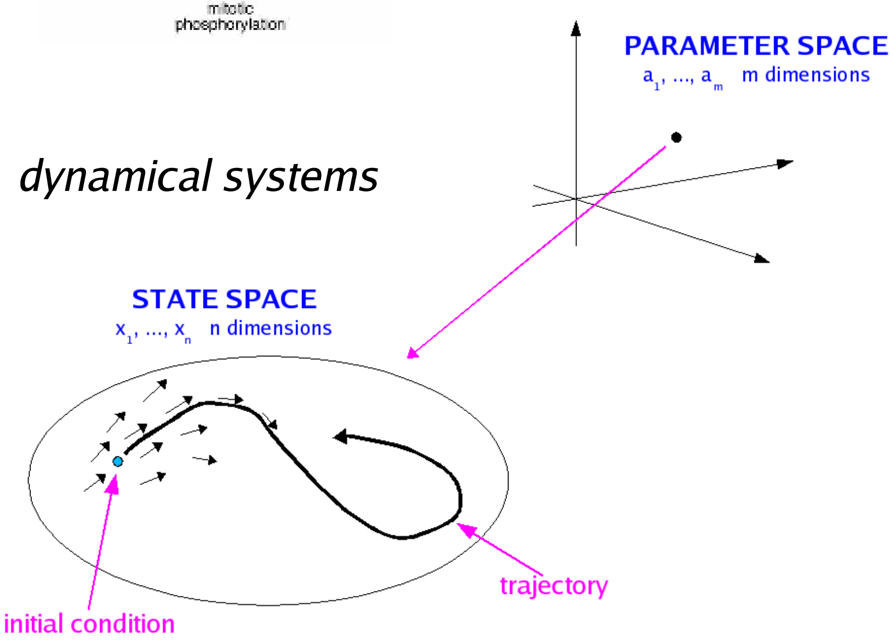
mathematical foundations

differential equations



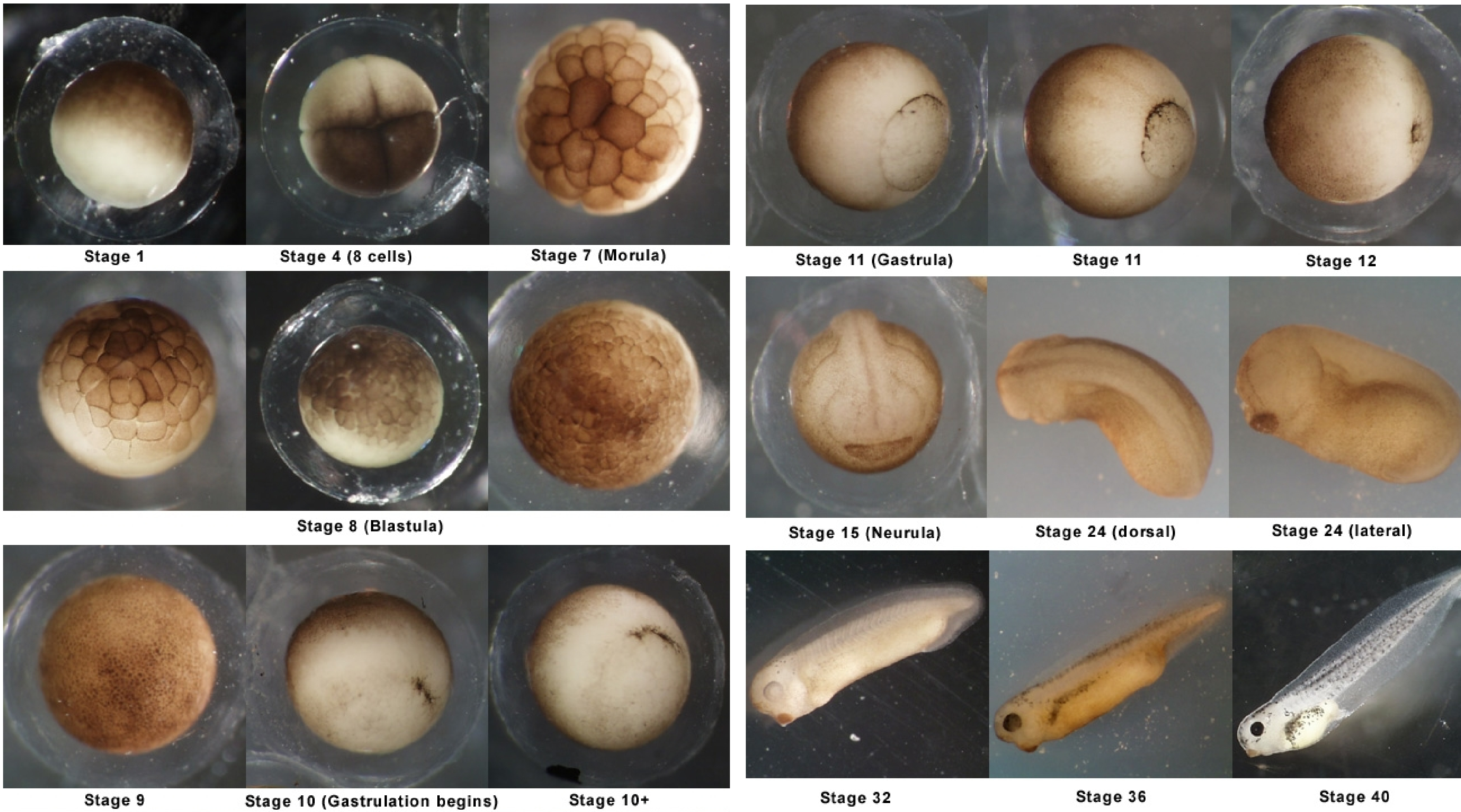
$$x_t = \frac{a}{d} + \left(x_0 - \frac{a}{d}\right)\exp(-dt)$$

dynamical systems



decision making

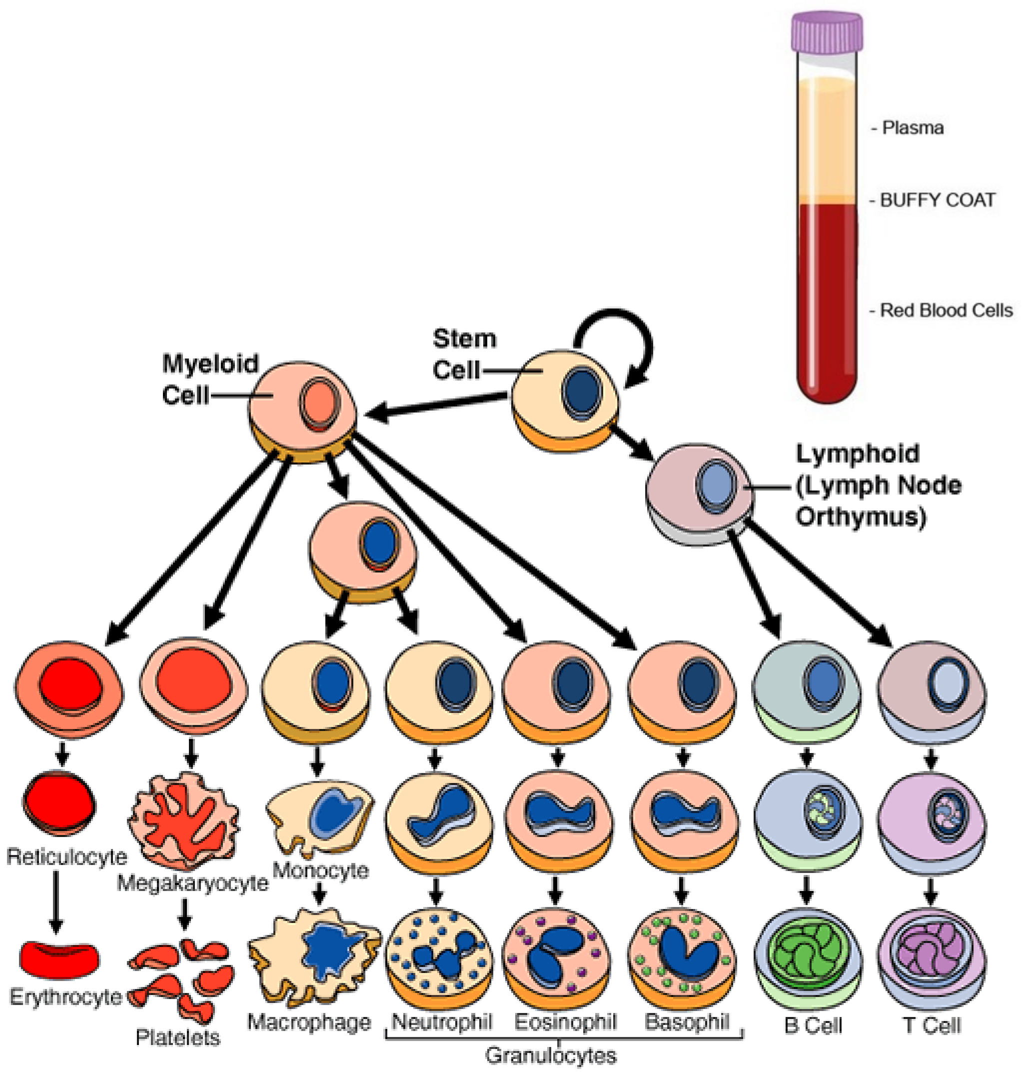
decisions, decisions, decisions – making the organism



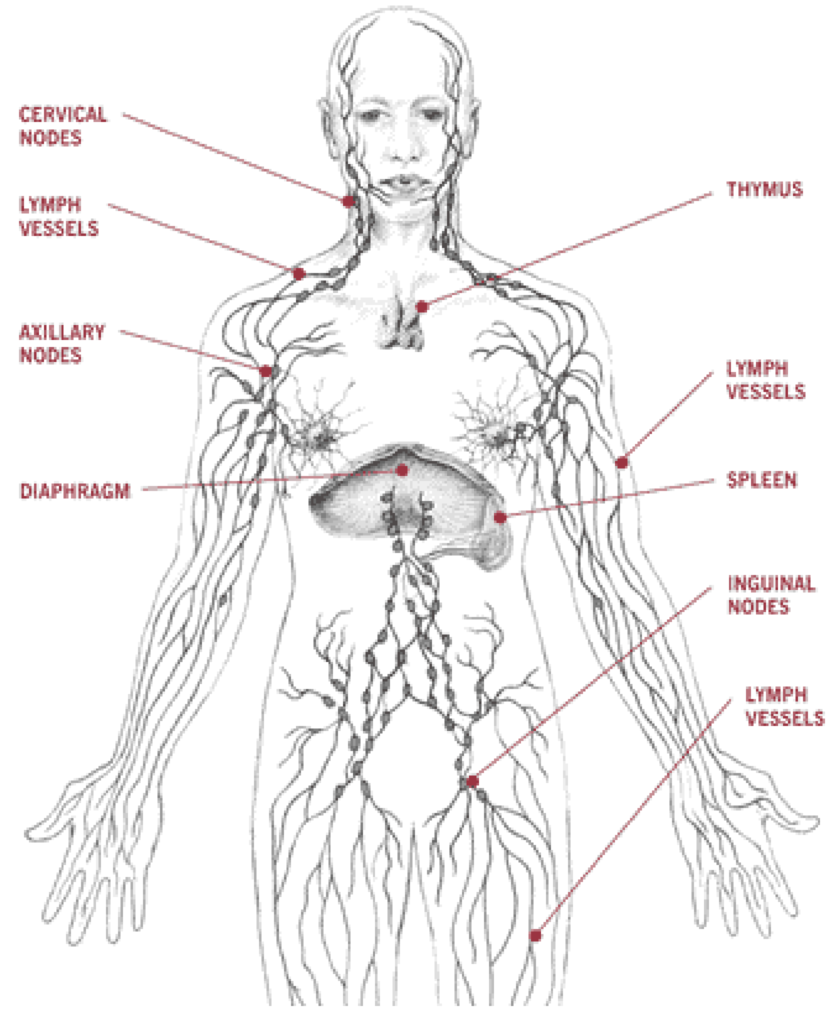
developmental stages in Xenopus laevis

www.xenbase.org , Manuel Thery & Michel Bornens, Institut Curie, Paris

decisions, decisions, decisions – running the organism

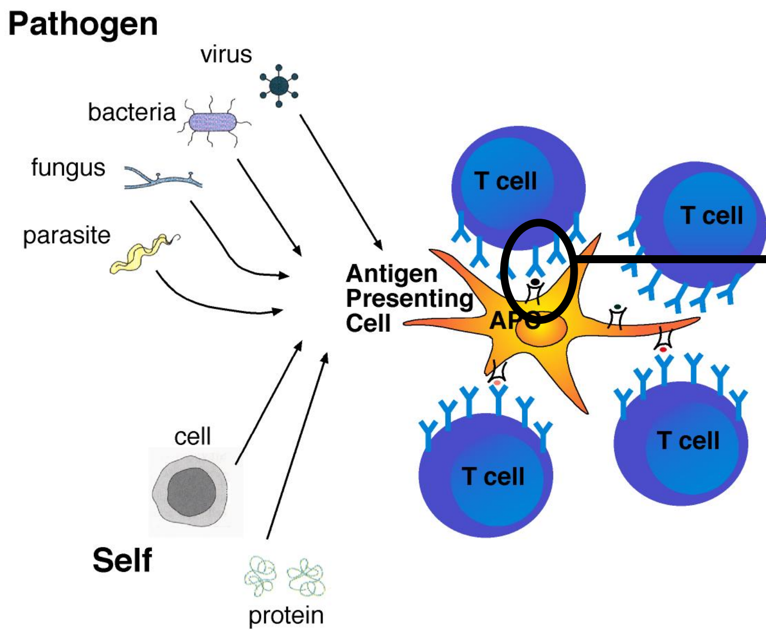


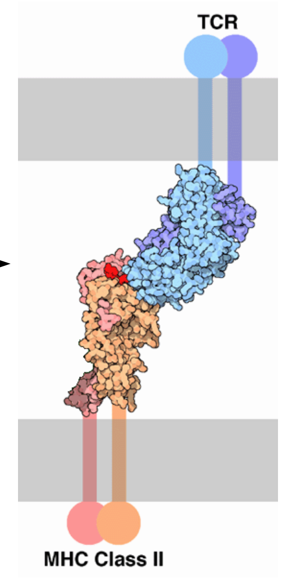
haematopoiesis

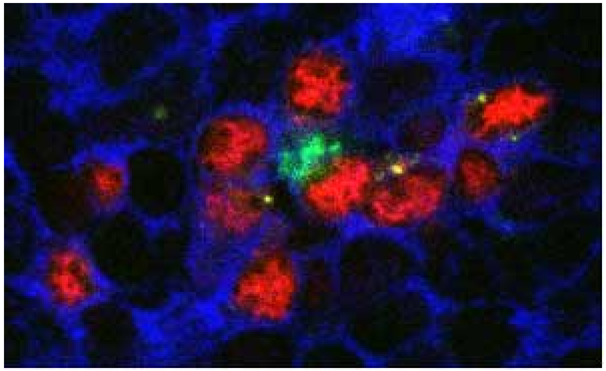


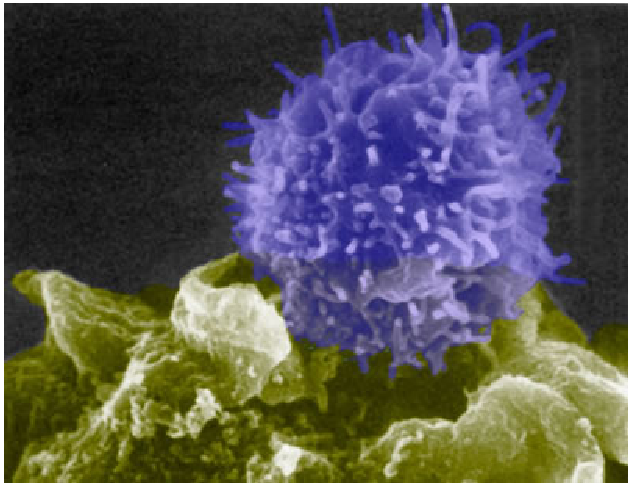
lymphatic system

decisions, decisions, decisions – protecting the organism









T cells interrogating antigen-presenting cells – friend or foe?

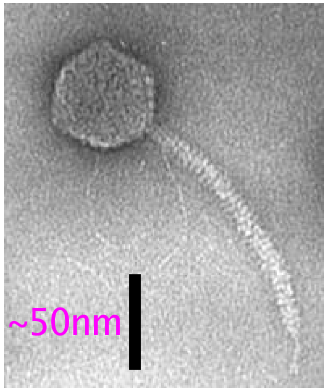
Mempel, Henrickson, von Andrian, "*T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases*", Nature **427**:154-9 2004 how do the molecular mechanisms (feedback control structures, etc) achieve

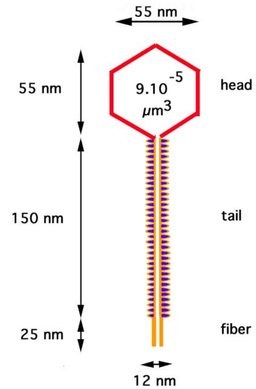
multiple states?
decisiveness?

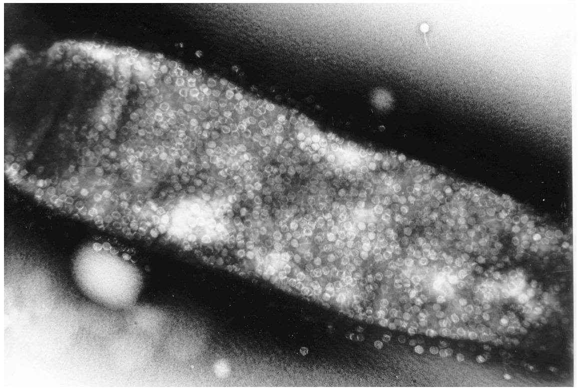
sensitivity?
resolution?
speed?

the lysis-lysogeny decision in viruses

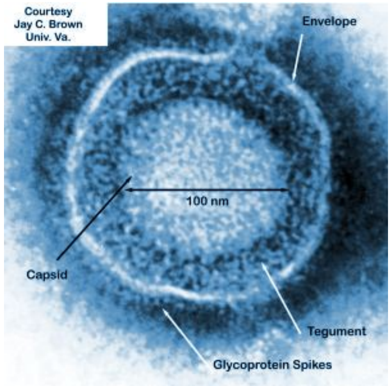
phage lambda

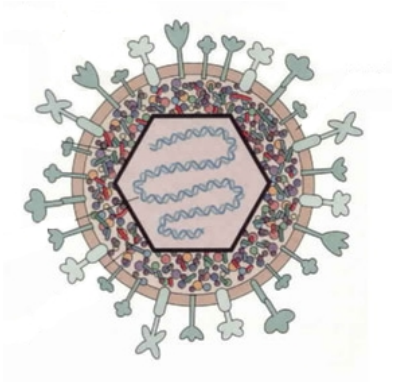


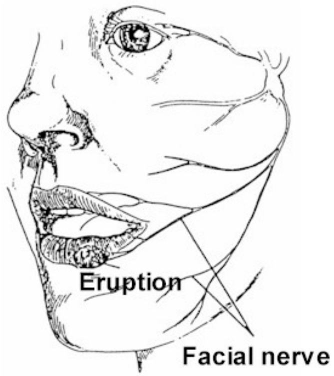




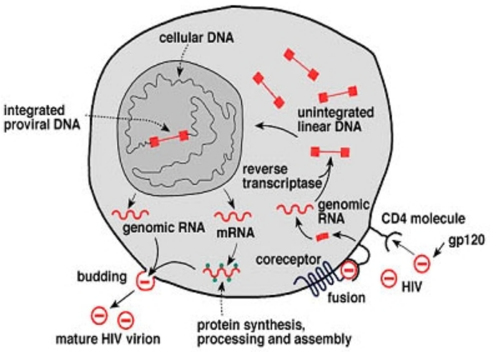
HSV 1

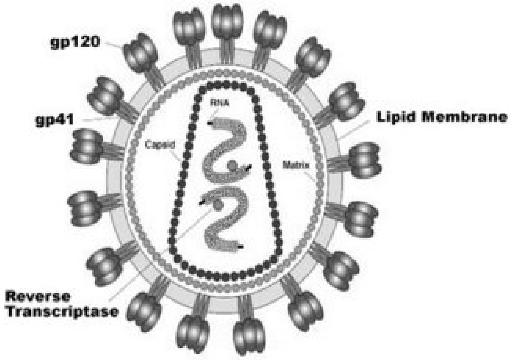


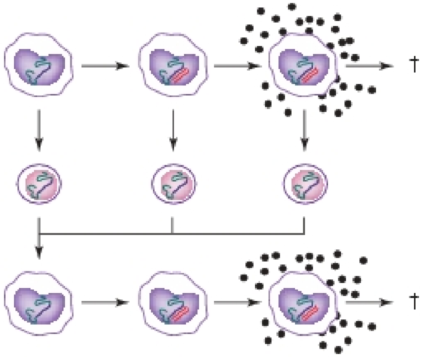




HIV

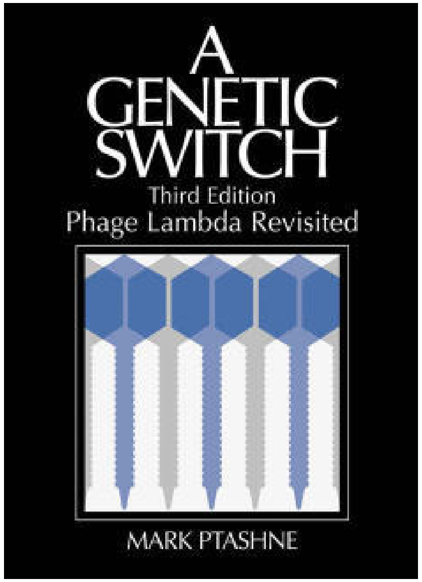




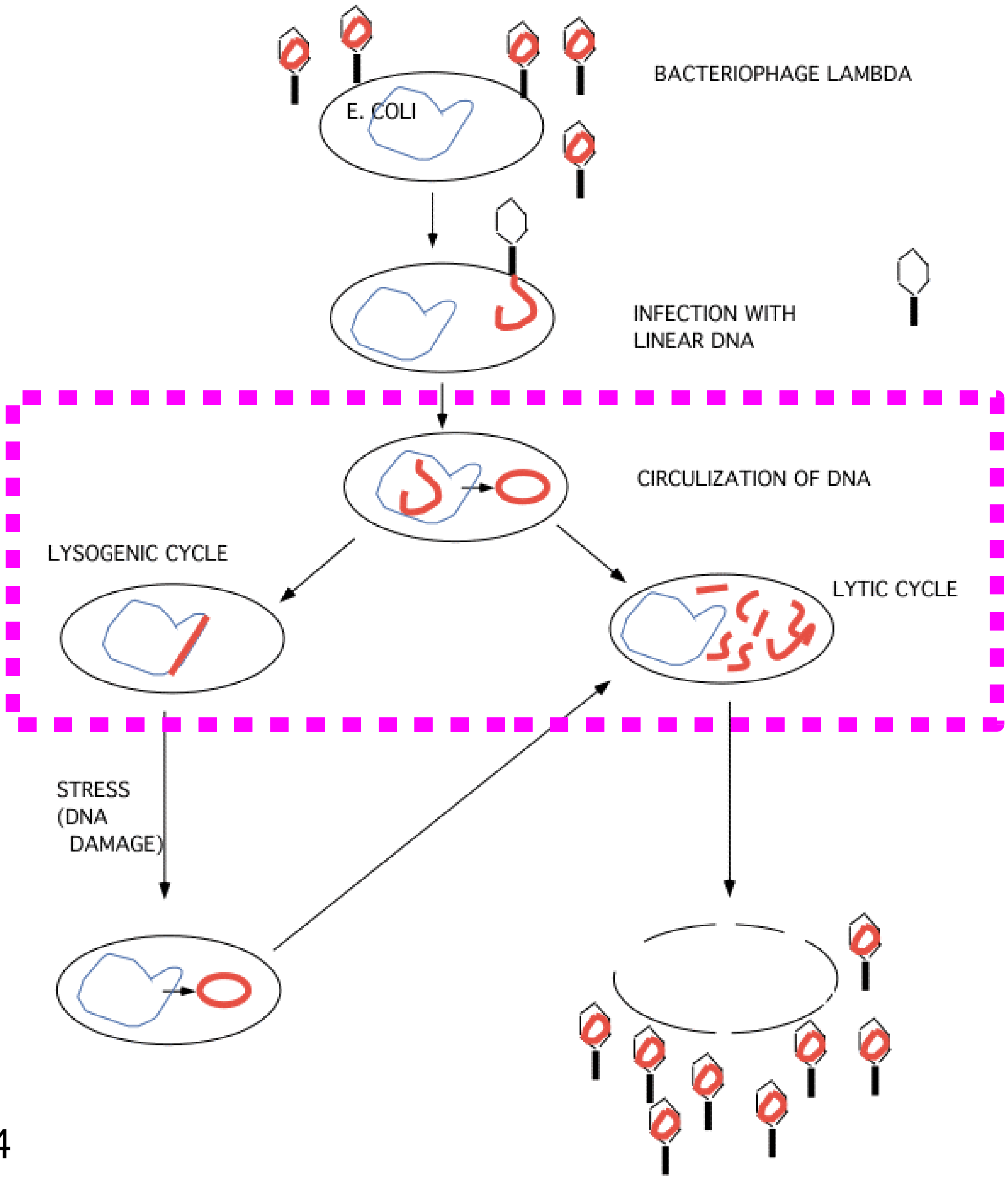


phage lambda

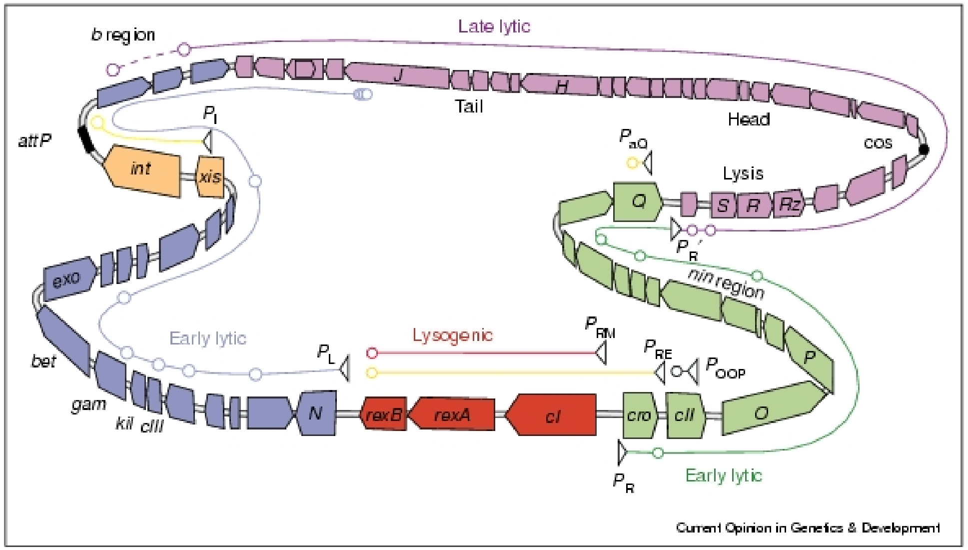
lysis-lysogeny decision

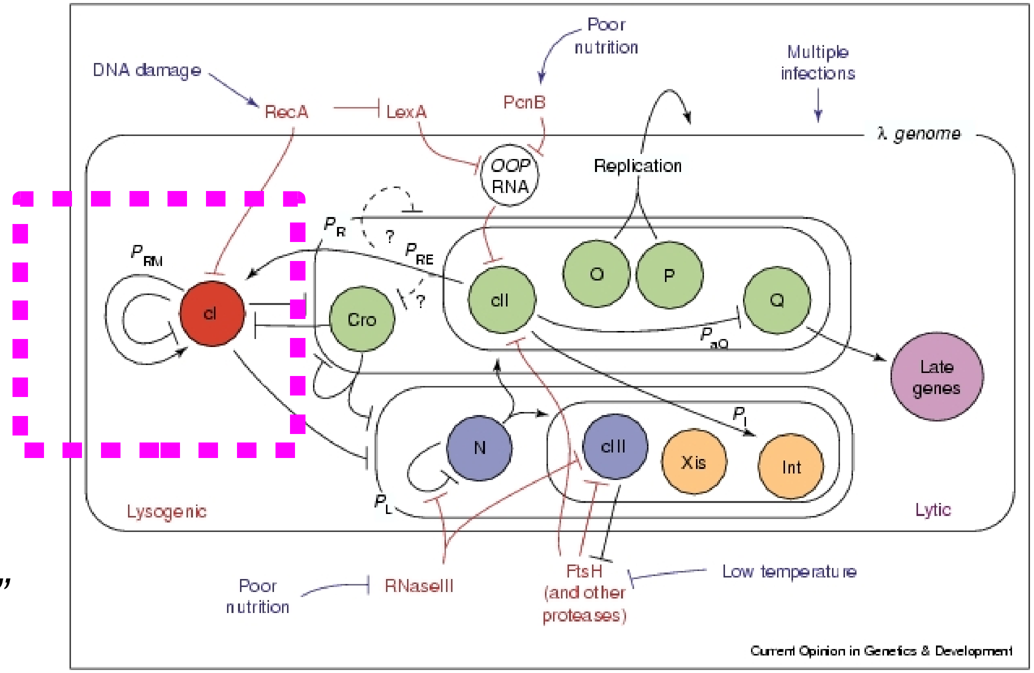


Ptashne
A Genetic Switch: Phage Lambda Revisited
3rd Edition
Cold Spring Harbor Laboratories Press 2004



phage lambda

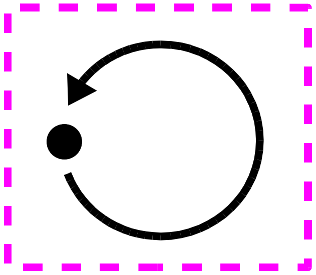




Friedman & Court, *“Bacteriophage λ: alive and well and still doing its thing,”* Curr Op Microbiology **4**:201-7 2001

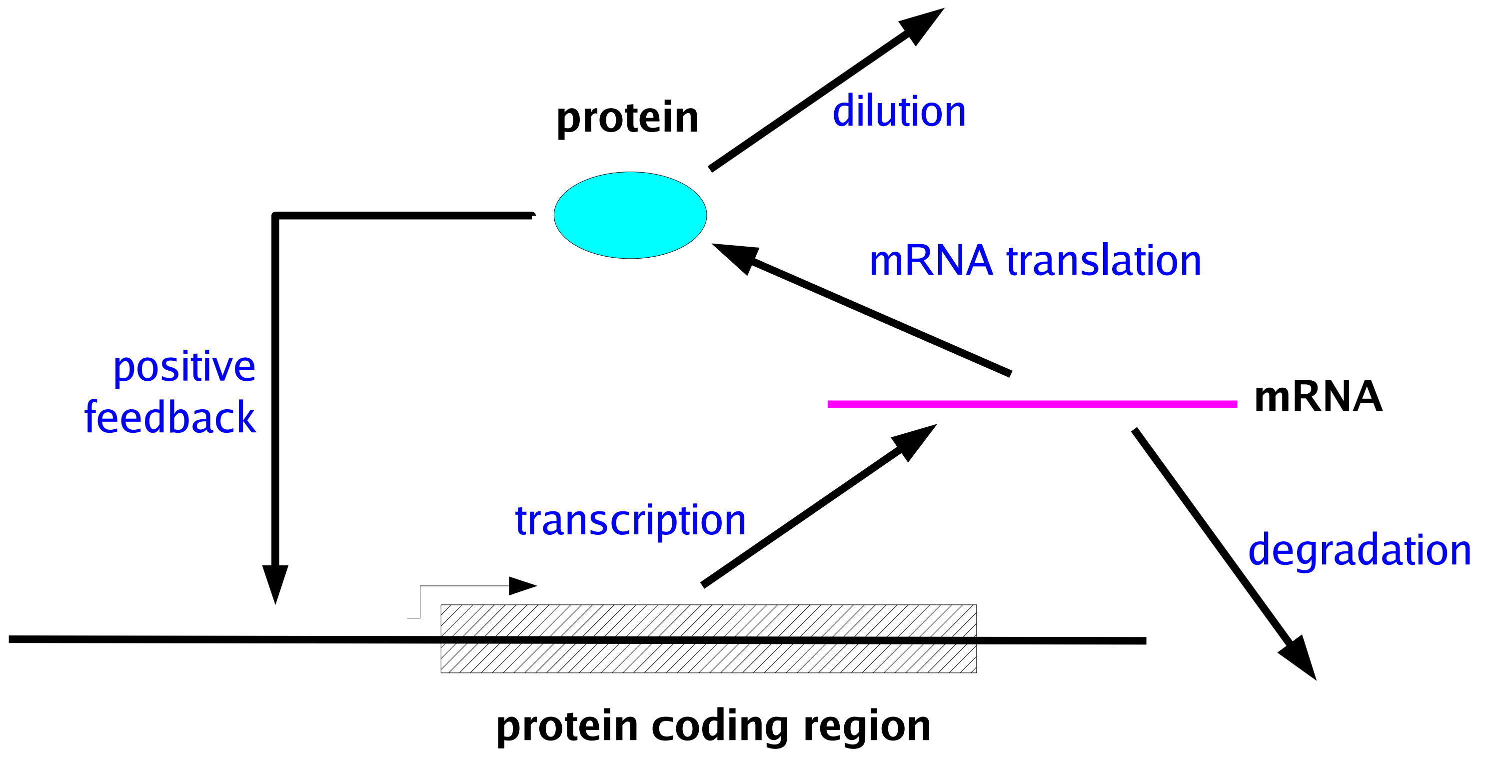
Dodd, Shearwin & Egan
“Revisted gene regulation in bacteriophage λ”
Curr Op Gen Dev **15**:145-52 2005

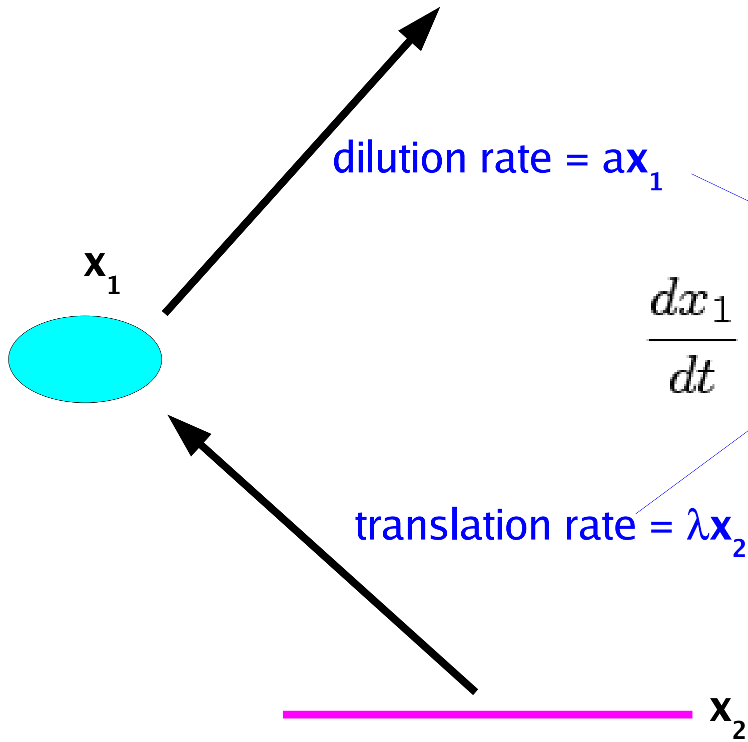
positive feedback control structure that exhibits decision making



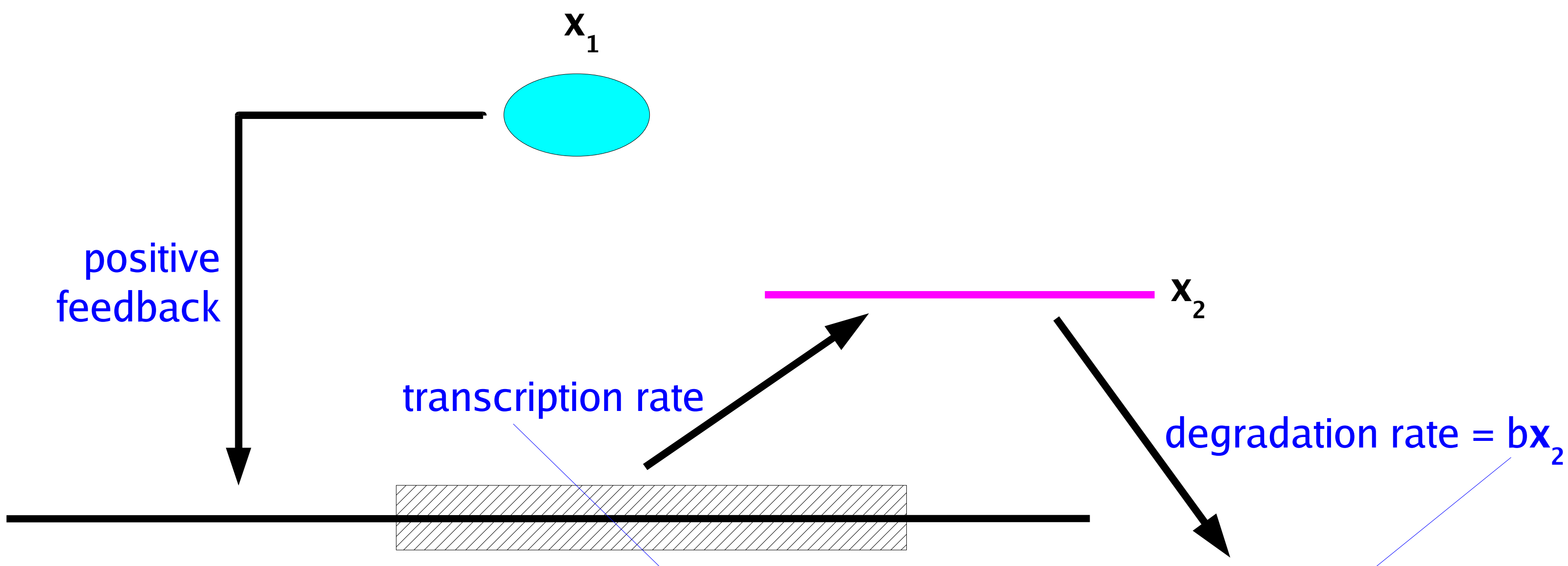
synthetically engineered –

Isaacs et al, "*Prediction and measurement of an autoregulatory genetic module*", PNAS **100**:7714-9 2003


protein
dilution
mRNA translation
positive
feedback
mRNA
transcription
degradation
protein coding region



$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$



$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - bx_2$$

x_1 = protein concentration

x_2 = mRNA concentration

state space

$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2$$

dynamical equations

λ	mRNA translation rate	$(sec)^{-1}$
a	protein degradation rate	$(sec)^{-1}$
b	mRNA degradation rate	$(sec)^{-1}$
α	maximal gene expression rate	$(M)(sec)^{-1}$
k	"Michaelis-Menten" constant	(M)

parameters

the first question to ask is -

are there any steady states?

in two dimensions, the way to work this out is to determine the

NULLCLINES

$$dx_1/dt = 0 \qquad dx_2/dt = 0$$

$$x_2 = \left(\frac{a}{\lambda}\right) x_1$$

$$x_2 = \left(\frac{\alpha}{b}\right) \frac{x_1}{k + x_1}$$

steady states occur at the intersections of the nullclines

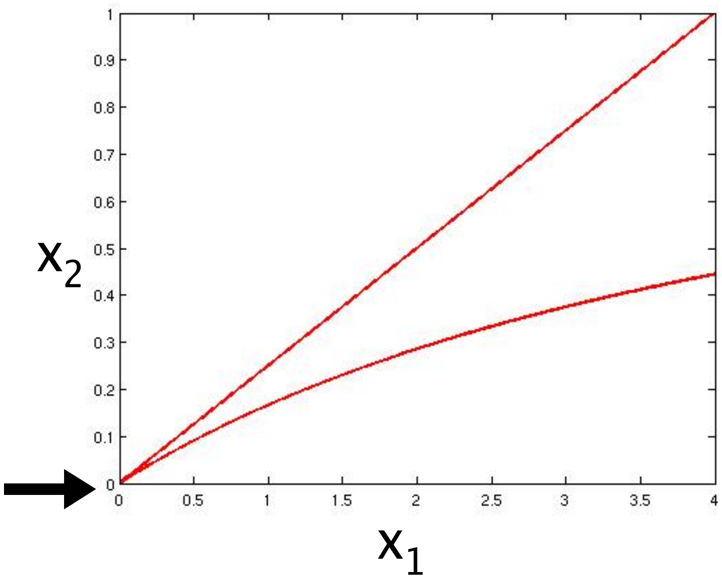
Two cases to consider

$k \geq \alpha\lambda/ab$ parameters $k < \alpha\lambda/ab$

Michaelis-Menten constant for transcription

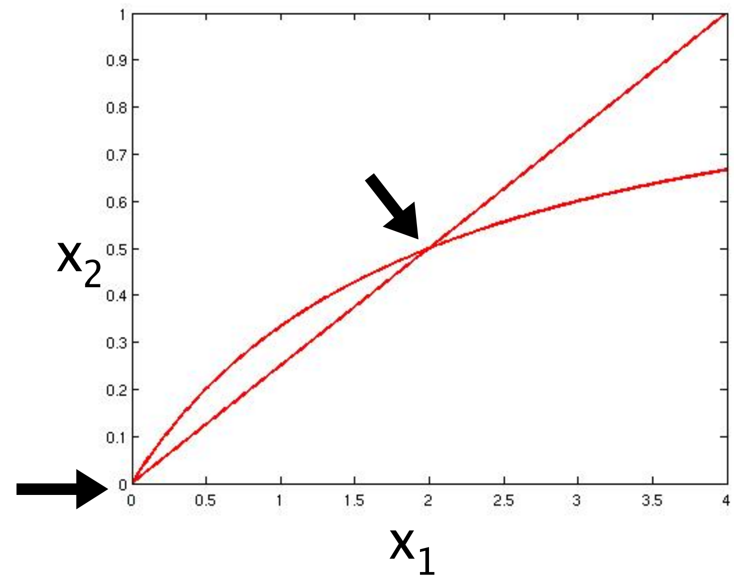
ratio of synthesis to degradation

STATE SPACE



one steady state

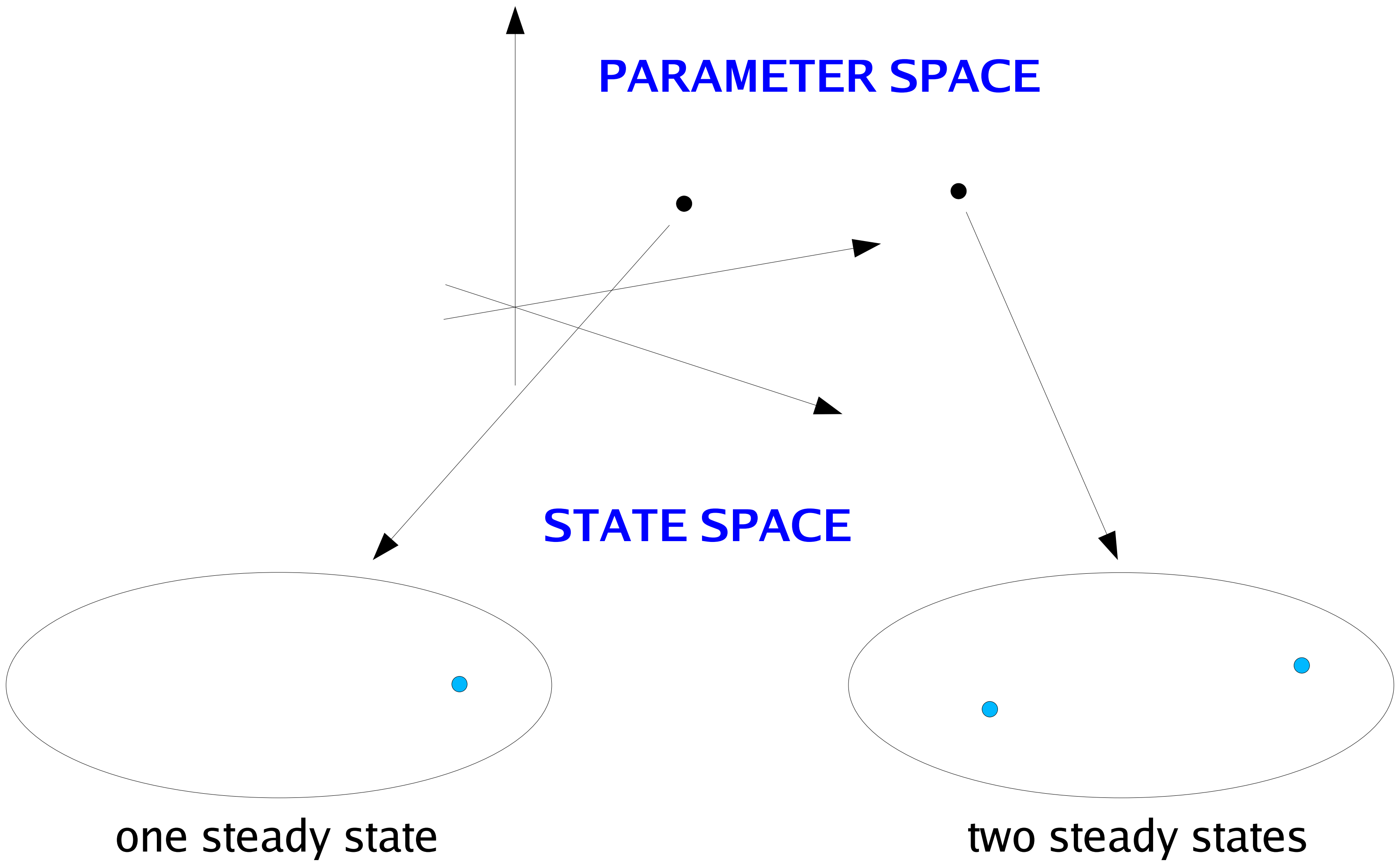
STATE SPACE



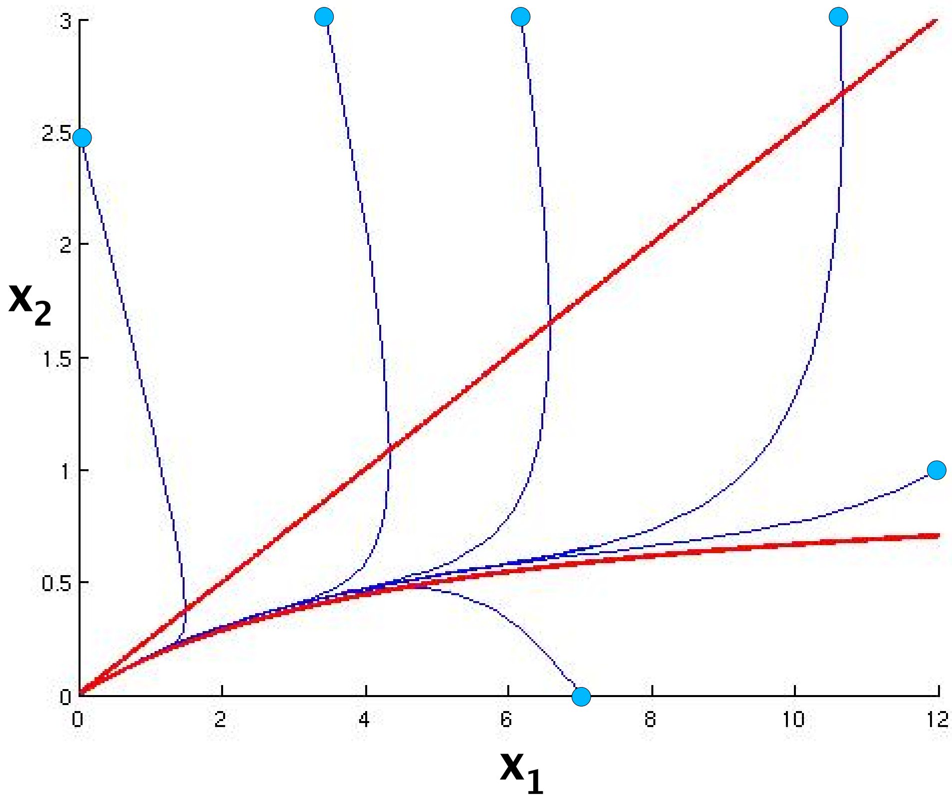
two steady states

BIFURCATION

a qualitative change in dynamics due to variation of parameters



$k \geq \alpha\lambda/ab$

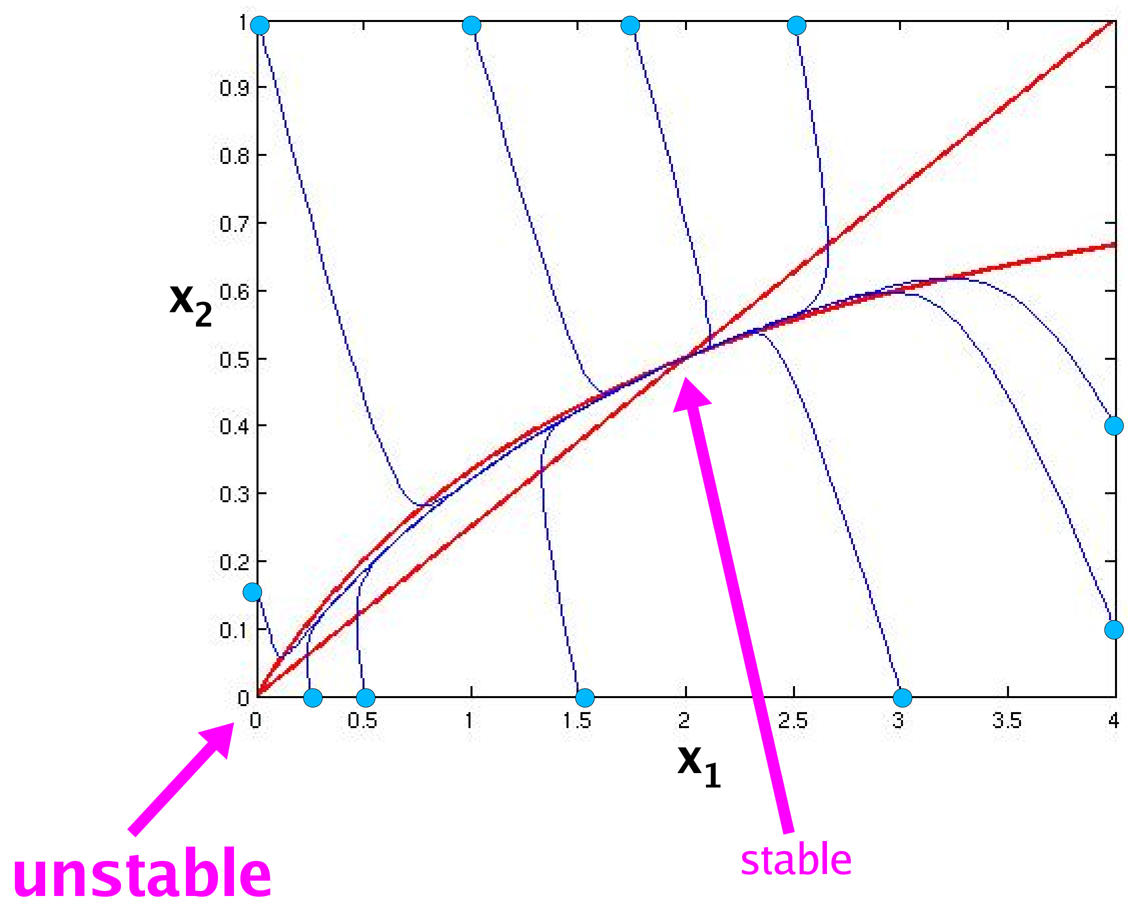


λ	0.08	$(\text{sec})^{-1}$
a	0.02	$(\text{sec})^{-1}$
b	0.1	$(\text{sec})^{-1}$
α	0.1	$(\mu\text{M})(\text{sec})^{-1}$
k	5	(μM)

$\alpha\lambda/ab = 4$

$k = 5$

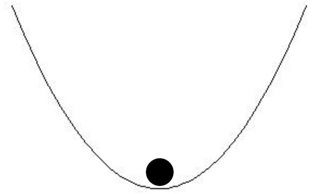
k < αλ/ab



λ	0.08	$(\text{sec})^{-1}$
a	0.02	$(\text{sec})^{-1}$
b	0.1	$(\text{sec})^{-1}$
α	0.1	$(\mu M)(\text{sec})^{-1}$
k	2	(μM)

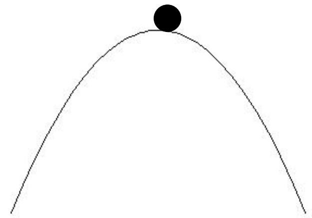
αλ/ab = 4
k = 2

stable steady state



any sufficiently small perturbation returns back to the steady state

unstable steady state



not stable - some perturbations do not return

You can prove instability by simulation but you can never prove stability

changing parameter values can cause a **bifurcation**

steady states can be **stable** or **unstable**

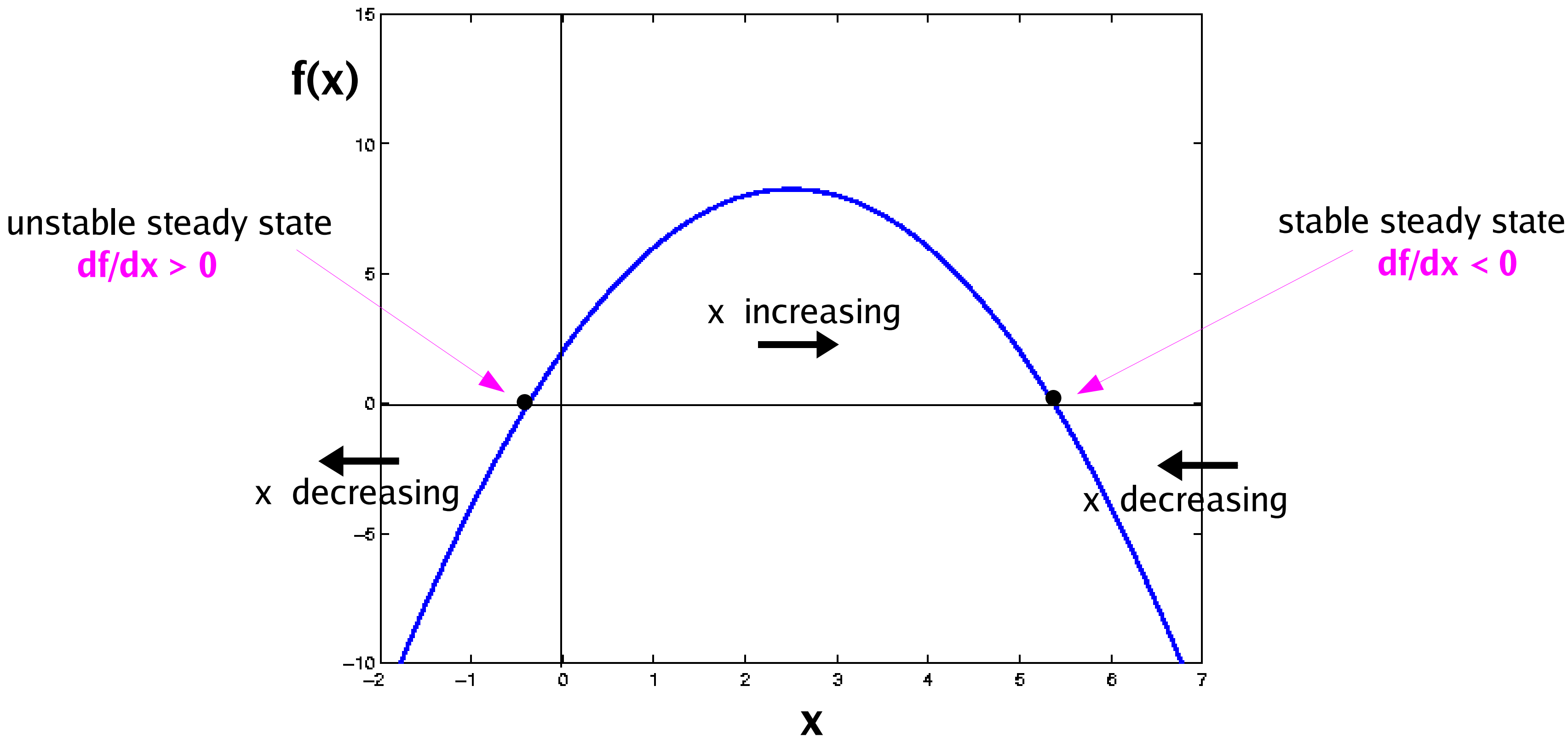
how can we tell the difference without simulation?

this feedback loop has only one stable steady state:

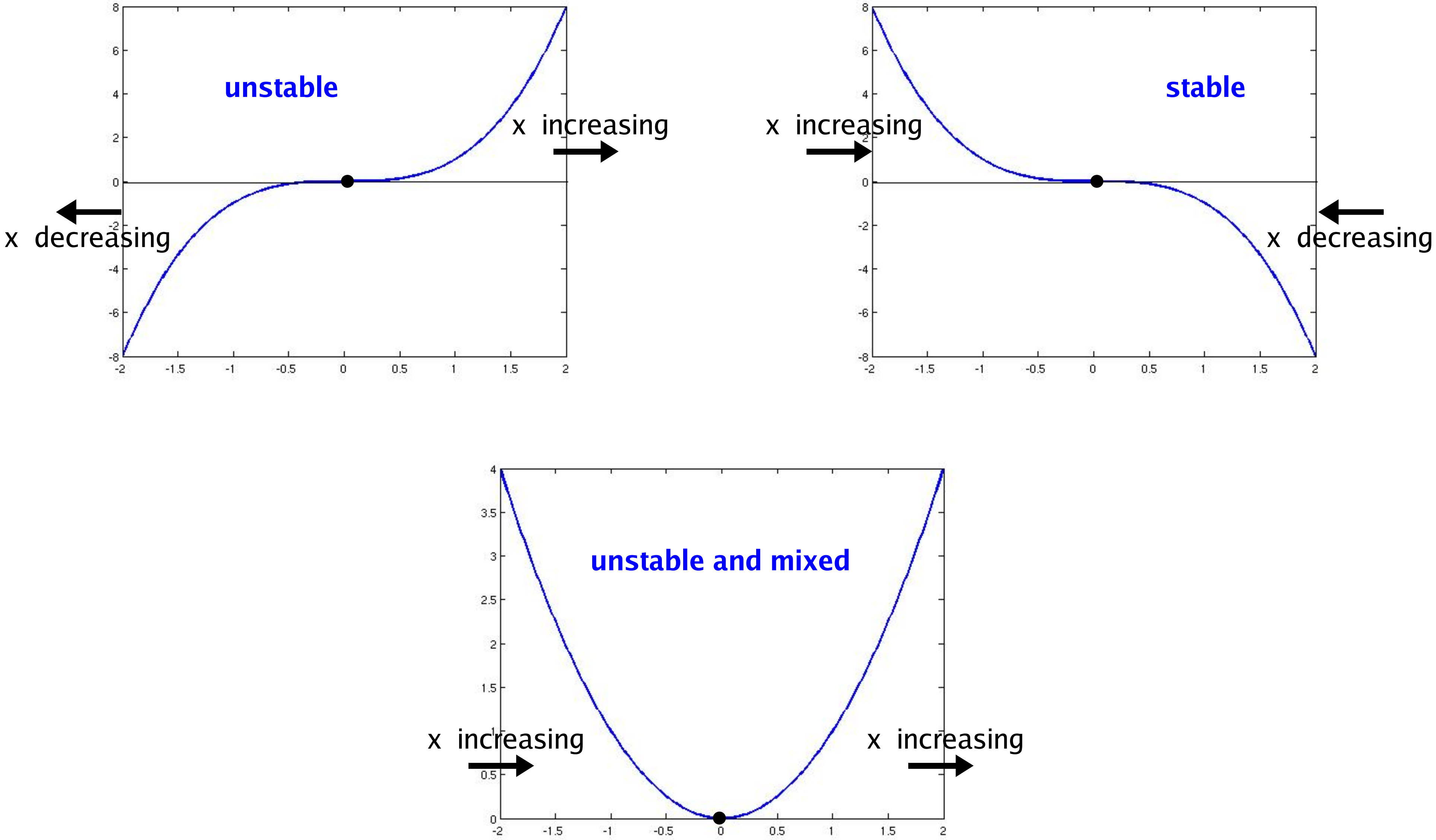
the “off” state is unstable.

how does phage lambda create a stable “off” state?

1 dimensional dynamical system $\frac{dx}{dt} = f(x)$



df/dx = 0


unstable
x increasing
x decreasing
stable
x increasing
x decreasing
unstable and mixed
x increasing
x increasing

1 dimensional dynamical system $\frac{dx}{dt} = f(x)$

1. find a steady state $x = x_{st}$, so that $\left(\frac{dx}{dt}\right)\Big|_{x=x_{st}} = f(x_{st}) = 0$
2. calculate the derivative of f at the steady state $\left(\frac{df}{dx}\right)\Big|_{x=x_{st}}$
3. if the derivative is negative then x_{st} is stable
4. if the derivative is positive then x_{st} is unstable
5. if the derivative is zero then x_{st} can be stable or unstable