A systems approach to biology

SB200

Lecture 3
23 September 2008

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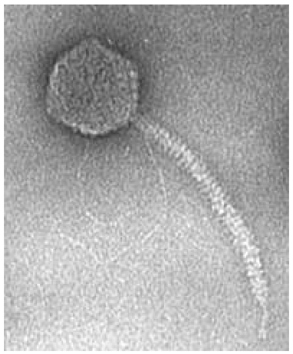
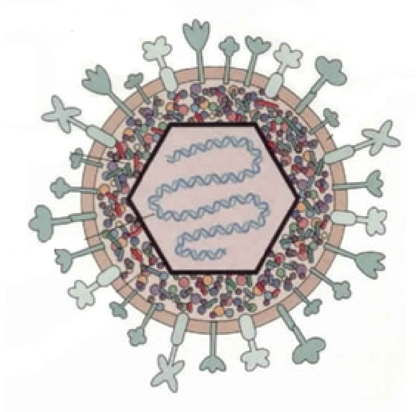
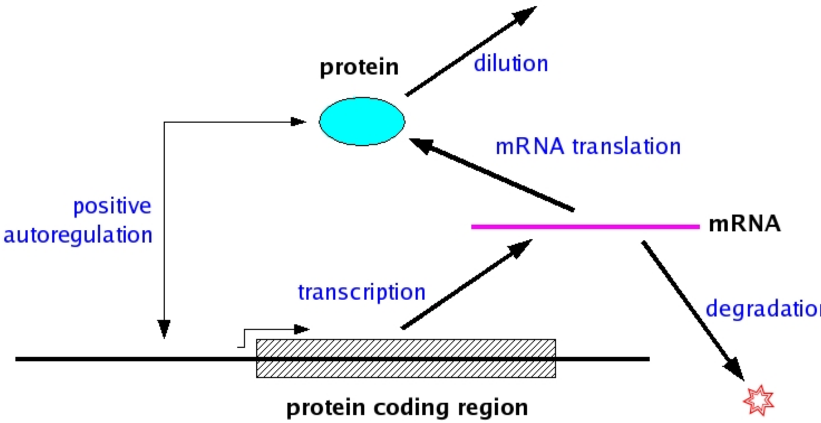
Recap of Lecture 2

decision making





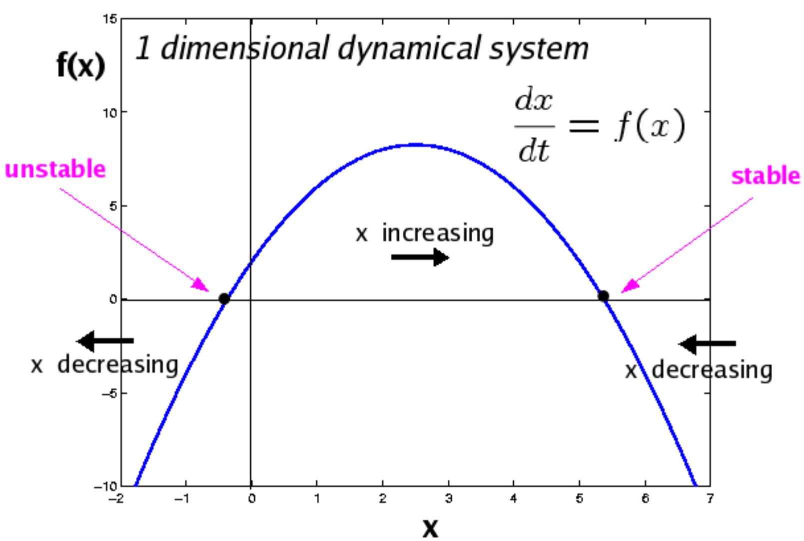


$$\frac{dx_1}{dt} = \lambda x_2 - a x_1$$

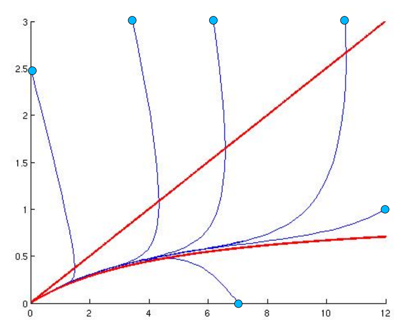
$$\frac{dx_2}{dt} = \frac{\alpha x_1}{k + x_1} - b x_2$$

positive feedback

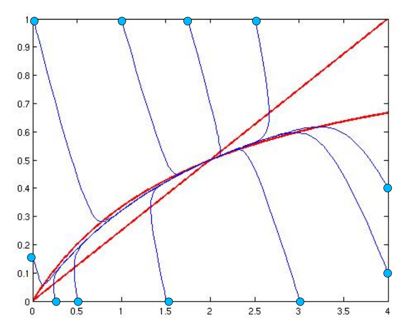
stable & unstable steady states



$k \geq \alpha\lambda/ab$



$k < \alpha\lambda/ab$



bifurcation

STABILITY THEOREM

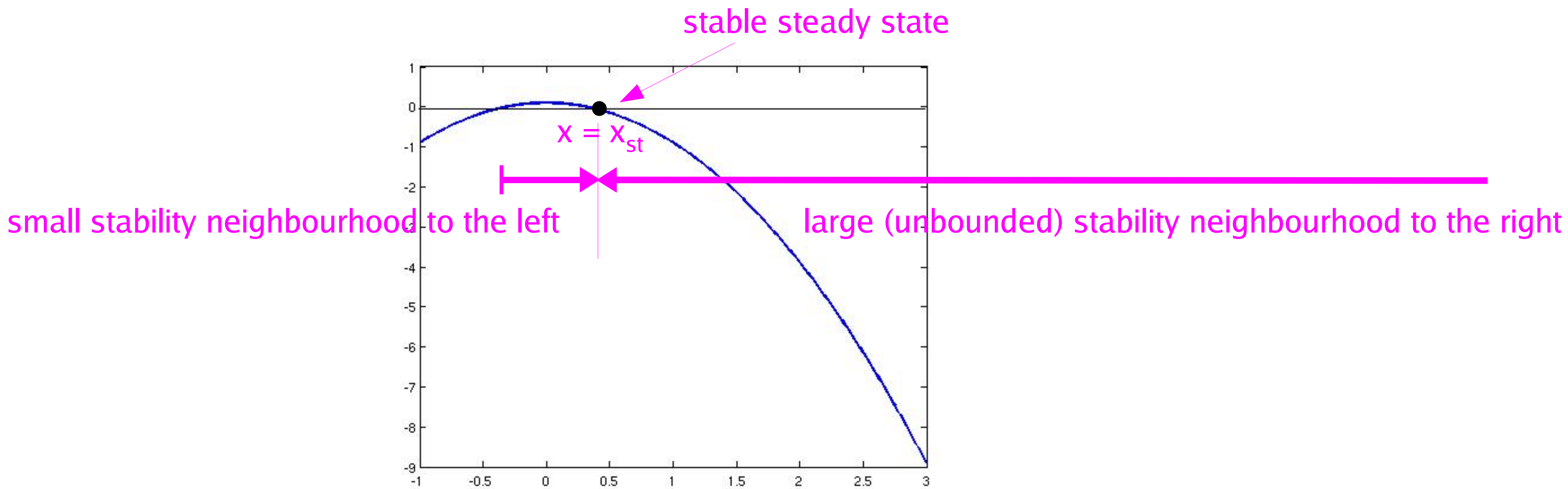
1 dimensional dynamical system $\frac{dx}{dt} = f(x)$

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

the sign of df/dx only tells us about **local** stability

ie: in some sufficiently small neighbourhood around the point $x = x_{st}$

these methods do not tell us how "small"



LINEARISATION THEOREM

the dynamics of

$$\frac{dx}{dt} = f(x)$$

is **qualitatively similar** to that of its linearisation

derivative of f at $x = x_{st}$

$$\frac{dx}{dt} = \left[\left(\frac{df}{dx} \right) \Big|_{x=x_{st}} \right] x$$

in the **local vicinity** of a steady state $x = x_{st}$

provided that

$$\left[\left(\frac{df}{dx} \right) \Big|_{x=x_{st}} \right] \neq 0$$

1 dimensional systems provide excellent intuition for n dimensional systems

The STABILITY and LINEARISATION THEOREMS hold in n dimensnions

but we need to understand

the **derivative** (in n dimensions)

what it means for an n-dimensional derivative to be “**negative**”

Jacobian matrix

eigenvalues

From this point we will need to use some matrix algebra. You will find everything needed for the lectures explained in the handouts

"Matrix algebra for beginners, Parts I, II and III"

Matrix algebra for beginners, Part I
matrices, determinants, inverses

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24 September 2007

Contents

STABILITY THEOREM

n dimensional dynamical system $\frac{dx}{dt} = f(x)$ ***x is a vector !!!***

1. find a steady state x = x_{st}, so that $\left.\left(\frac{dx}{dt}\right)\right|_{x=x_{st}} = f(x_{st}) = 0$

2. calculate the **Jacobian matrix** at the steady state $A = (Df)|_{x=x_{st}}$

3. if all the eigenvalues of A have **negative real part** then x_{st} is **stable**

4. if none of the eigenvalues of A are **zero** and at least one of the eigenvalues has **positive real part** then x_{st} is **unstable**

5. if at least one of the eigenvalues of A is **zero** then x_{st} can be either **stable or unstable**

Jacobian matrix

Df = ($\partial f_i / \partial x_j$) n x n matrix

$$f_1(x_1, x_2) = \lambda x_2 - a x_1$$

$$f_2(x_1, x_2) = \frac{\alpha x_1}{k + x_1} - b x_2$$

$$\mathrm{Df} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{pmatrix} = \begin{pmatrix} -a & \lambda \\ \frac{\alpha k}{(k+x_1)^2} & -b \end{pmatrix}$$

Jacobian matrix

Eigenvalues

eigenvalue – a number (scalar)

$$Ax = ux \qquad x \neq 0$$

n x n matrix

eigenvector
n x 1 “column” vector

The eigenvalues satisfy the **characteristic equation** of the matrix A

$$\det(A - uI) = 0$$

This is a polynomial equation in u, of degree n.

By the Fundamental Theorem of Algebra, this equation has n solutions
but some of them may be complex numbers (of the form *a + i b*)

An n x n matrix always has n (possibly complex) eigenvalues

Matrices are like numbers –
they can be added and multiplied together

except that multiplication is not commutative
and not all non-zero matrices have an inverse

for any n x n matrix A

A is invertible – A^{-1} *exists – if and only if det* $\neq 0$

det A = product *of the eigenvalues of A*

Tr A = sum *of the eigenvalues of A*

det AB = (det A)(det B)

At the steady state $(x_1, x_2) = (0,0)$

$$\det \begin{pmatrix} -a-u & \lambda \\ \frac{\alpha}{k} & -b-u \end{pmatrix} = (a+u)(b+u) - \frac{\lambda\alpha}{k}$$

Characteristic equation is

– Tr A

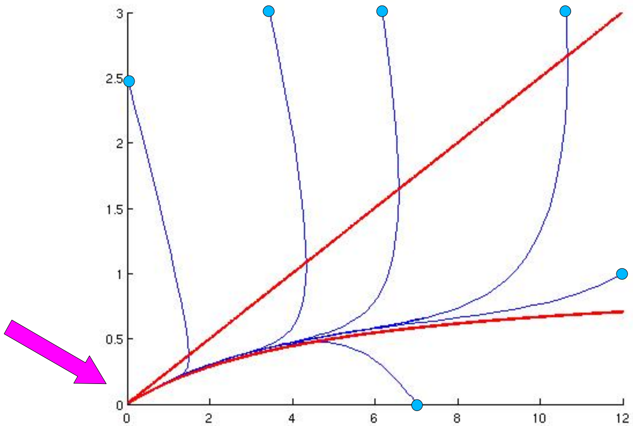
det A

$$u^2 + (a+b)u + \left(ab - \frac{\lambda\alpha}{k}\right) = 0$$

Eigenvalues are

disc A = (Tr A)^2 -4 de t A

$$u = \frac{-(a+b) \pm [(a+b)^2 - 4(ab - \frac{\lambda\alpha}{k})]^{1/2}}{2}$$

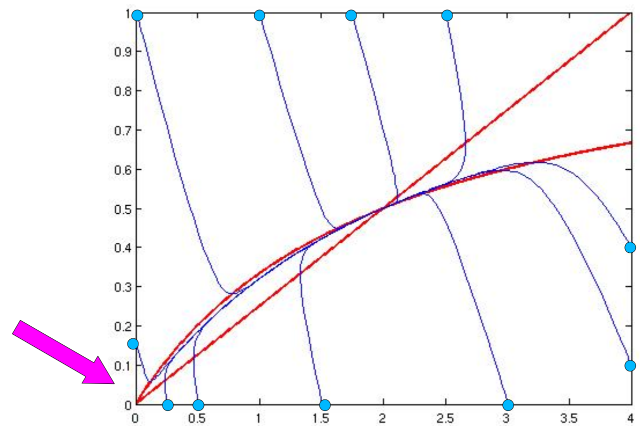


λ	0.08	$(sec)^{-1}$
a	0.02	$(sec)^{-1}$
b	0.1	$(sec)^{-1}$
α	0.1	$(\mu M)(sec)^{-1}$
k	5	(μM)

$$u^2 + 0.12u + 0.0014 = 0$$

$u = -0.12 \pm 0.094$

u = -0.214
u = -0.026



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

$$u^2 + 0.12u - 0.002 = 0$$

$u = -0.12 \pm 0.1497$

u = -0.2697
u = +0.0297

A simple theorem about stability and instability in feedback loops.

Details in the handout.

Stability of steady states for a general autoregulatory loop

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24 September 2007

This is a handout for SB200, *"A systems approach to biology"*. It provides details of the theorem proved in the lectures, which gives a graphical method for determining the stability of a steady state for a general autoregulatory loop. If you have any comments or questions, and especially if you notice any misprints or errors, please send me a message at jeremy@hms.harvard.edu.

The autoregulatory loop is shown schematically in Figure 1, where x_1 and x_2 are the concentrations of protein and mRNA, respectively. This scheme allows for first-order degradation of mRNA and protein, with (positive) rate constants b and a, respectively, but the rate of mRNA translation can be an arbitrarily function, $f(x_2)$, of mRNA concentration and the rate of gene expression can be an arbitrary function, $g(x_1)$, of protein concentration. This translates into the following system of differential equations

$$\begin{aligned} dx_1/dt &= f(x_2) - ax_1 \\ dx_2/dt &= g(x_1) - bx_2\,, \end{aligned} \tag{1}$$

which defines a two-dimensional dynamical system. We assume throughout that $a, b > 0$.

We want to work out the stability of a steady state of this system. As we discussed in Lectures 2 and 3, the stability a steady state depends on the eigenvalues of the Jacobian matrix at that steady state. Since this is a two-dimensional system, we can work out the stability more quickly by calculating the determinant and the trace of the Jacobian (as summarised in the Determinant/Trace diagram for two-dimensional dynamical systems). It is easy to work out the Jacobian matrix at any state $x = (x_1, x_2)$. Let us call this $J(x)$. Calculating the partial derivatives, we find that

$$J(x) = \begin{pmatrix} -a & \dfrac{df}{dx_2} \\ \dfrac{dg}{dx_1} & -b \end{pmatrix}. \tag{2}$$

Note that the partial derivatives in the Jacobian can be replaced by ordinary derivatives because f and g are each functions of only a single state variable. We see from (2) that $\mathrm{Tr}\,J(x) = -(a+b) < 0$, independently of x. It follows that the stability of any steady state will depend soley on the sign of

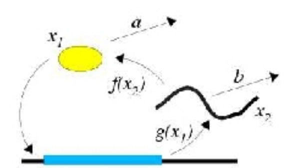
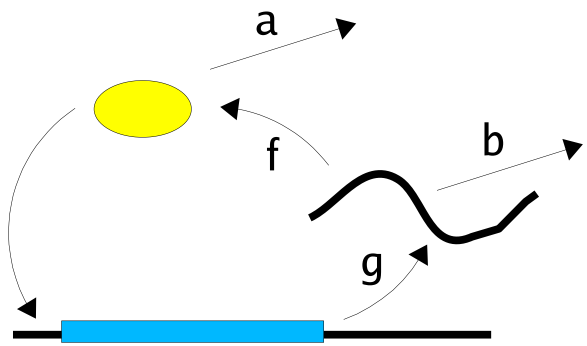


Figure 1: The general autoregulatory loop. A single gene is transcribed into mRNA which is translated into protein which feeds back on its own expression. Both mRNA and protein are degraded.



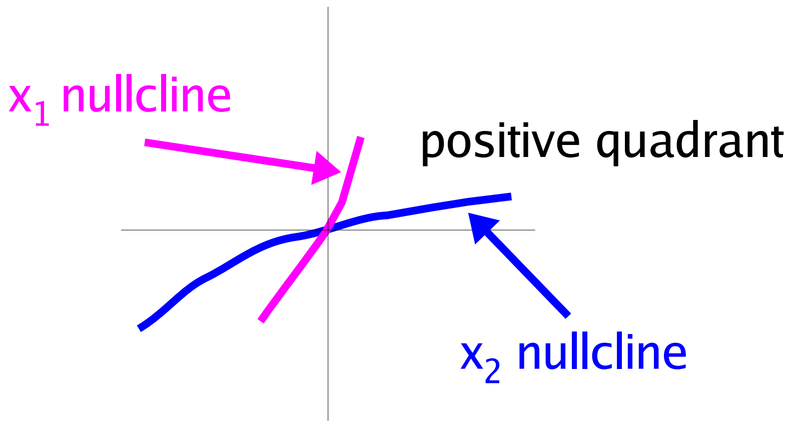
arbitrary functions

- $$\frac{dx_1}{dt} = f(x_2) - ax_1$$

- $$\frac{dx_2}{dt} = g(x_1) - bx_2$$

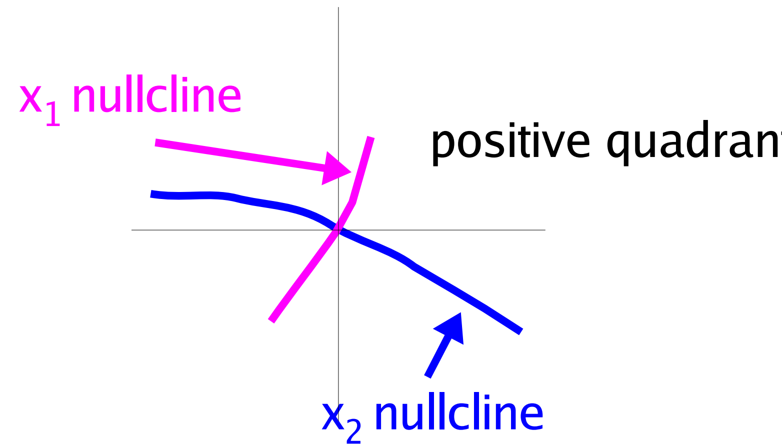
a, b > 0

x_1 nullcline lies above x_2 nullcline,
both in the positive quadrant



OR

x_1 nullcline in positive quadrant
x_2 nullcline in fourth quadrant



STABLE

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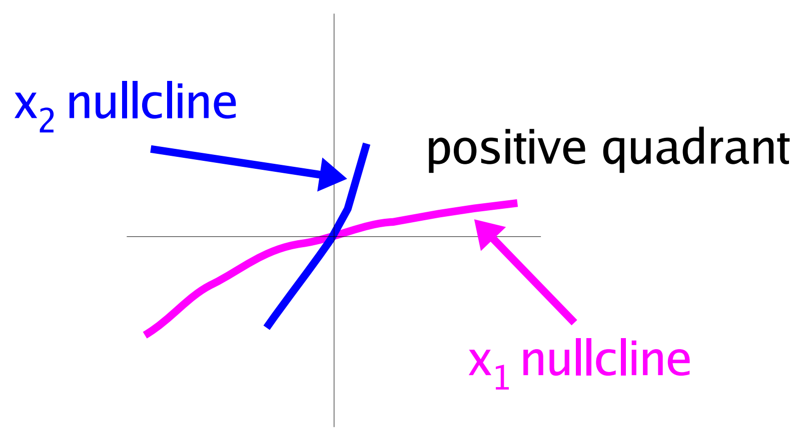
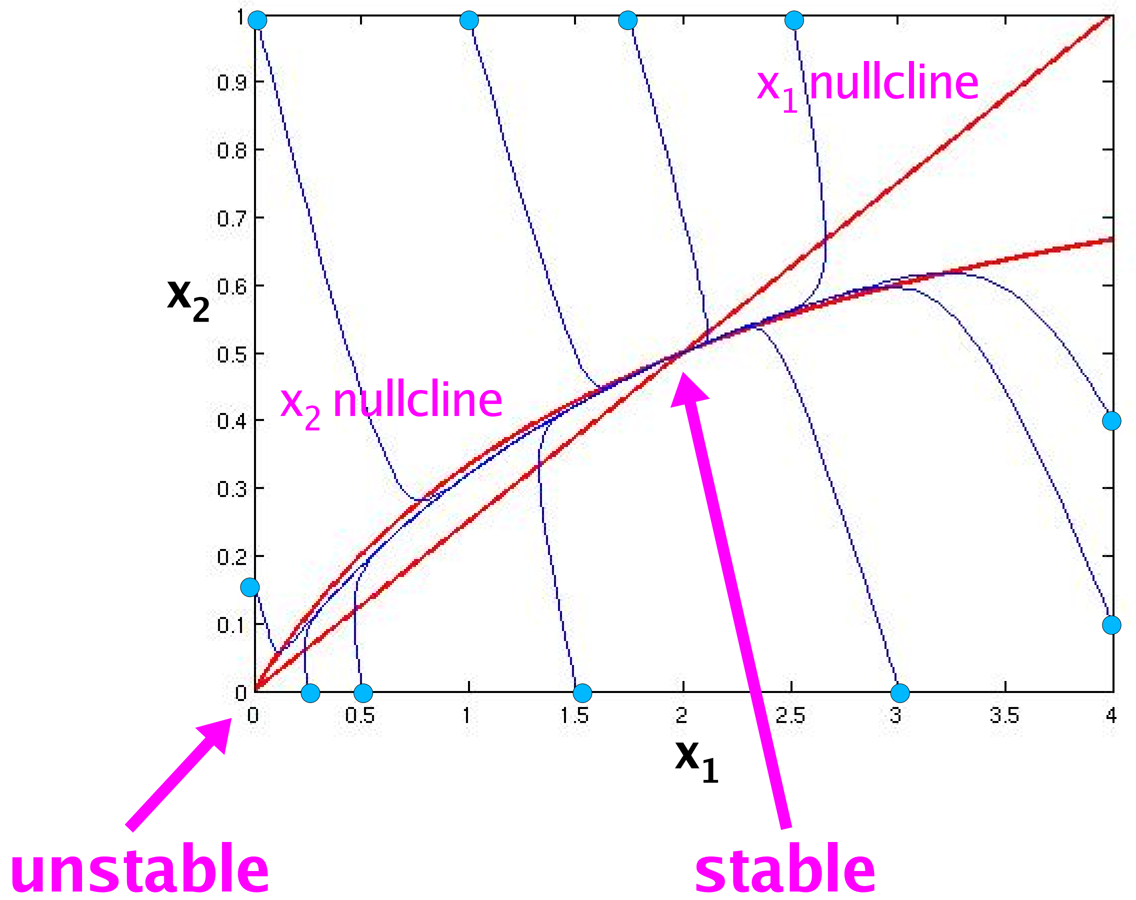
x_2 nullcline lies above x_1 nullcline
both in the positive quadrant



UNSTABLE



x1 nullcline
x2 nullcline
x2
x1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
0.5
1
1.5
2
2.5
3
3.5
4
unstable
stable

LINEARISATION THEOREM

in n dimensions the dynamics of

$$\frac{dx}{dt} = f(x)$$

is **qualitatively similar** to that of its linearisation

Jacobian of f at $x = x_{st}$

$$\frac{dx}{dt} = \left[(Df)|_{x=x_{st}} \right] x$$

in the **local vicinity** of a steady state $x = x_{st}$

provided that none of the eigenvalues of the Jacobian matrix

$$\left[(Df)|_{x=x_{st}} \right]$$

are 0

$$\frac{dx}{dt} = f(x)$$ with steady state at $x = x_{st}$

1 dimensional	n > 1 dimensional
$a = \left(\frac{df}{dx}\right)\Big\vert_{x=x_{st}}$	$A = (Df)\vert_{x=x_{st}}$
$dx/dt = ax$	$dx/dt = Ax$
$x(t) = \exp(at)x_0$	$x(t) = \exp(At)x_0$
$\exp(a) = 1 + a + a^2/2 + a^3/3! + \ldots$ exponential	$\exp(A) = I + A + A^2/2 + A^3/3! + \ldots$ matrix exponential
$\exp(a+b) = \exp(a)\exp(b)$	$\exp(A+B) = \exp(A).\exp(B)$ **provided AB = BA**