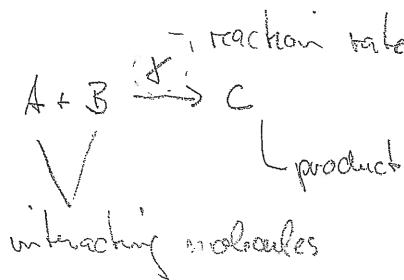


Biochemical reactions

- Molecular biologist, chemist, etc. use wrong diagrams to depict the reaction network



- Chemical reactions are intrinsically stochastic

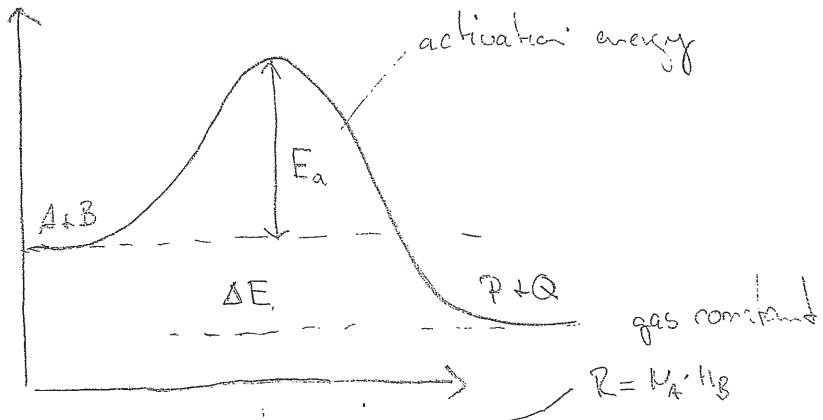
One can only give probabilities that a reaction occurs

- Both particles must come close to each other to react
- There is a certain activation energy barrier which must be overcome by the particles \rightarrow thermal energy \rightarrow temperature dependence of the reaction

- We will assume the following

- The probability that two particles meet is proportional to the concentration of the species \rightarrow true for large num. of particles
- The system is "well-stirred" i.e. no spatial variations of the components concentration
 - \rightarrow true if the typical diffusion time $\tau = \frac{R^2}{D}$ is small compared to the reaction time

Collision Theory



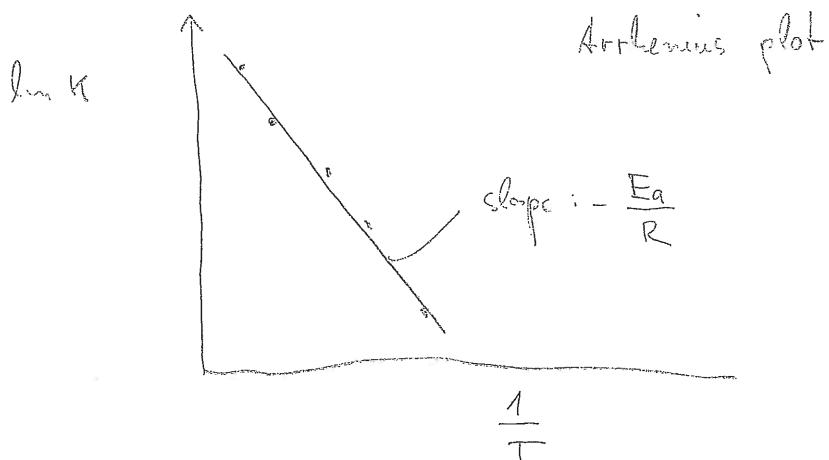
$$\left| \begin{array}{l} N_A = 6,022 \cdot 10^{23} \text{ mol}^{-1} \\ k_B = 1,38044 \cdot 10^{-23} \text{ J/K} \\ R = 8,31 \text{ J/(mol K)} \end{array} \right.$$

(reaction rate: $K = A e^{-E_a/RT}$)
 depends on the shape
 of the barrier

Arrhenius law (1889)
 was explained by Tammann
 using statistical physics (1940)

Arrhenius law is an approximation \rightarrow to improve this one has to consider quantum mechanics

- This shows that a simple reaction is actually quite complicated!



Homomolecular reactions

The simplest reaction is:



The meaning of the diagram:

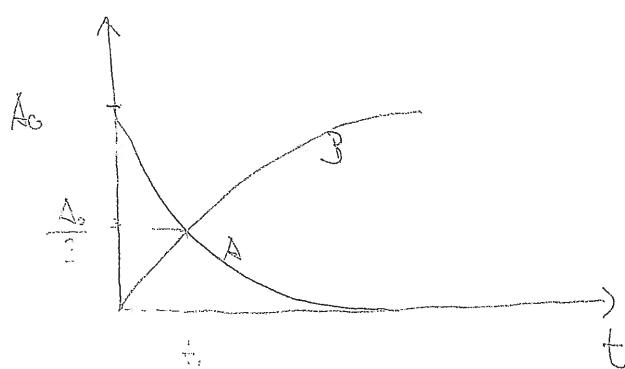
A is converted into B with rate γ .

The rate of change is proportional to the concentration of A.

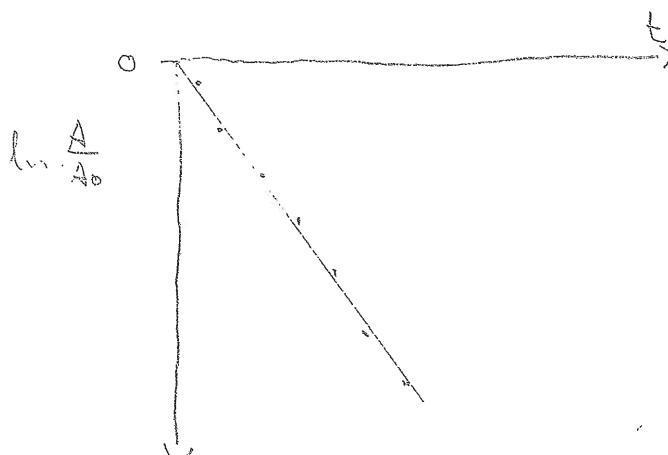
A: homogeneous differential equation

$$\frac{dA}{dt} = -\gamma A ; \quad \frac{dB}{dt} = \gamma A$$

$$\Rightarrow A(t) = A_0 e^{-\gamma t} ; \quad B = A_0 (1 - e^{-\gamma t})$$



Half life: $\frac{A(t)}{A_0} = \frac{1}{2} = e^{-\frac{t_{1/2}}{\gamma}} \quad (=) \quad t_{1/2} = \frac{\ln 2}{\gamma}$



$$\ln \frac{A}{A_0} = -\gamma t + \ln A_0$$

Increasing the rate coefficient γ

Bimolecular Reactions



Meaning of the diagram:

If A is close to B both species react with rate κ .

The probability that A and B come close together is proportional to the concentration of A and B

We obtain three equations:

$$\left. \begin{aligned} \frac{dA}{dt} &= -\kappa AB \\ \frac{dB}{dt} &= -\kappa AB \end{aligned} \right\} A = B$$

$$\frac{dC}{dt} = \kappa AB$$

Made the Ansatz: $A(t) = A_0 - f(t)$

we assume $B_0 > A_0$

$$B(t) = B_0 - f(t)$$

$$\Rightarrow \frac{df}{dt} = +\kappa [A_0 - f][B_0 - f]$$

$$(=) \frac{df}{(A_0 - f)(B_0 - f)} = +\kappa dt \quad \text{separation of variables}$$

$$(=) \frac{df}{(A_0 - B_0)} \left[\frac{1}{B_0 - f} - \frac{1}{A_0 - f} \right] = +\kappa t \quad \text{partial fractions}$$

Integration yields:

$$f(t) = \frac{B_0 - A_0 e^{-\tilde{\gamma}t - c}}{e^{-\tilde{\gamma}t - c} - 1} \quad \tilde{\gamma} = \gamma (A_0 - B_0)$$

c is determined by the initial condition

$$f(t=0) = 0 \quad (=) \quad B_0 = A_0 e^{-c} \quad \Rightarrow \quad c = -\ln \frac{B_0}{A_0}$$

$$f(t) = \frac{B_0 (e^{-\tilde{\gamma}t} - 1)}{\frac{B_0}{A_0} e^{-\tilde{\gamma}t} - 1} \quad ; \quad g(t) = \frac{B_0 \left[\frac{B_0}{A_0} - 1 \right] e^{\tilde{\gamma}t}}{\frac{B_0}{A_0} e^{\tilde{\gamma}t} - 1}$$

Two different cases

$$\Rightarrow A(t) = \frac{A_0 + B_0}{1 - \frac{B_0}{A_0} e^{\tilde{\gamma}t}} \quad ; \quad A_S = \lim_{t \rightarrow \infty} A(t) = 0 \quad B_0 > A_0$$

$\Leftrightarrow A_0 - B_0 \quad A_0 > B_0$

Unimolecular reaction of individual species

This is, of course, a special case of the previous section



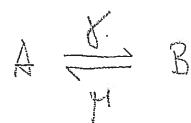
$$\frac{dA}{dt} = -\gamma A^2 \quad (=) \quad \frac{dA}{A^2} = -\gamma dt$$

Initial reaction speed $\Rightarrow A(t) = \frac{A_0}{1 + A_0 \gamma t}$

because in one step (collision)
the number is reduced by two

Lemma: This will be discussed in the tutorial again.

Reversible reaction:



$$\frac{dA}{dt} = -\gamma A + \mu B \quad \text{use } B_0 = 0; \quad A_0 = A + B \Rightarrow B = A_0 - A$$

$$\frac{dB}{dt} = \gamma A - \mu B$$

homogeneous differential equation

$$\therefore \frac{dA}{dt} = -(\gamma + \mu)A + \mu A_0 \quad (\because \frac{dB}{dt} = \gamma A - \mu B)$$

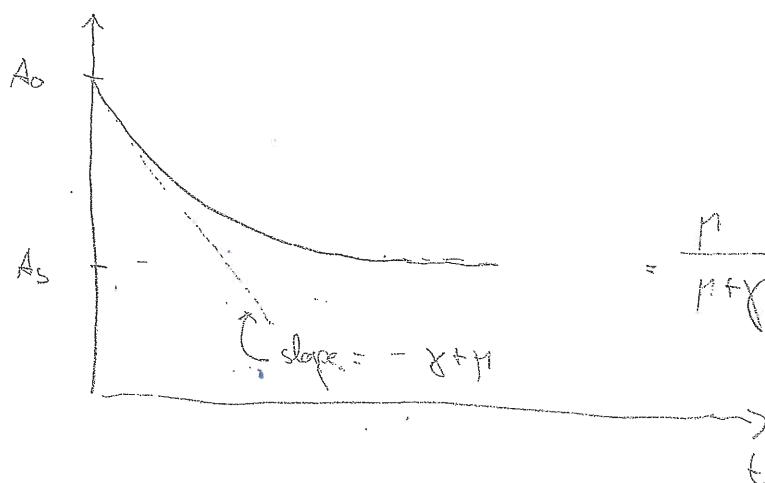
- What is the steady-state?

The steady state is determined by the equation $\frac{dA}{dt} = 0$

$$\Rightarrow 0 = -(\gamma + \mu)A_s + \mu A_0 \quad (\Leftarrow) \quad A_s = \frac{\mu}{\mu + \gamma} A_0$$

Full solution:

$$A(t) = A_0 e^{-(\gamma + \mu)t} + \frac{\mu}{\mu + \gamma} A_0 \left(1 - e^{-(\gamma + \mu)t}\right)$$



talk about
measuring the rates

General formula

(Present this after page 17)

$$S_1^1 X_1 + S_2^1 X_2 + \dots + S_n^1 X_n \xrightarrow[\mu_1]{\kappa_1} \Gamma_1^1 X_1 + \Gamma_2^1 X_2 + \dots + \Gamma_n^1 X_n \quad 1, \text{ reaction}$$

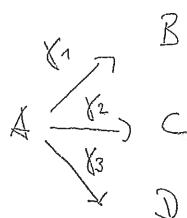
⋮

$$S_1^m X_1 + S_2^m X_2 + \dots + S_n^m X_n \xrightarrow[\mu_m]{\kappa_m} \Gamma_1^m X_1 + \Gamma_2^m X_2 + \dots + \Gamma_n^m X_n \quad m, \text{ reaction}$$

We obtain the system of ODE's:

$$\frac{dx_i}{dt} = \sum_{p=1}^m \left\{ \kappa_p (\Gamma_i^p - S_i^p) \prod_{j=1}^n x_j^{S_j^p} - \mu_p (\Gamma_i^p - S_i^p) \prod_{j=1}^n x_j^{\Gamma_j^p} \right\}$$

Parallel Reactions



(Talk about initial conditions)

$$\frac{dA}{dt} = -(\kappa_1 + \kappa_2 + \kappa_3) A \quad | \quad A + B + C + D = A_0$$

$$A(t) = A_0 e^{-(\kappa_1 + \kappa_2 + \kappa_3)t}$$

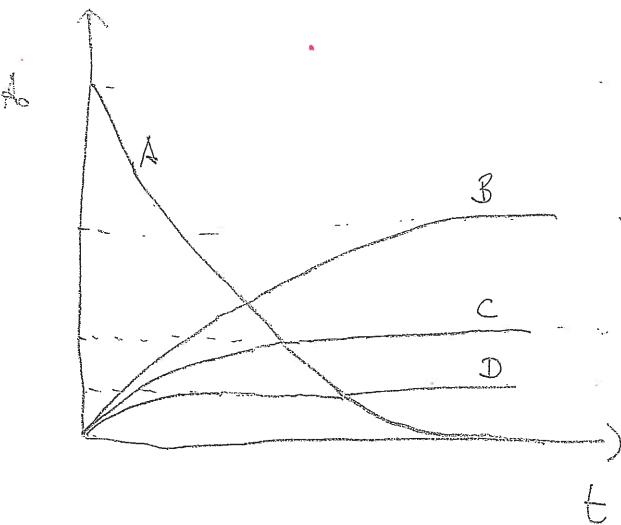
$$B(t) = \frac{\kappa_1 A_0}{\kappa_1 + \kappa_2 + \kappa_3} \left(1 - e^{-(\kappa_1 + \kappa_2 + \kappa_3)t} \right)$$

$$\frac{dC}{dt} = \kappa_2 A$$

$$C(t) = \frac{\kappa_2 A_0}{\kappa_1 + \kappa_2 + \kappa_3} \left(1 - e^{-(\kappa_1 + \kappa_2 + \kappa_3)t} \right)$$

$$\frac{dD}{dt} = \kappa_3 A$$





End of 2. lecture

Consecutive Reactions

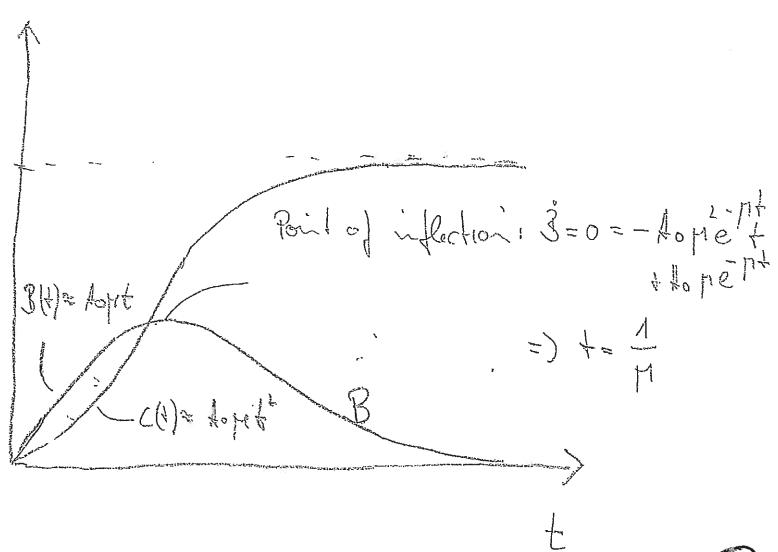


$$\left. \begin{array}{l} \frac{dA}{dt} = -\kappa A \\ \frac{dB}{dt} = \kappa A - \mu B \\ \frac{dC}{dt} = \mu B \end{array} \right\} \Rightarrow \begin{aligned} A(t) &= A_0 e^{-\kappa t} \\ B(t) &= A_0 \frac{\kappa}{\mu - \kappa} \left[e^{-\kappa t} - e^{-\mu t} \right] \\ C(t) &= \frac{A_0 \mu}{\mu - \kappa} \left[1 - e^{-\kappa t} - \frac{\kappa}{\mu} \left(1 - e^{-\mu t} \right) \right] \end{aligned}$$

Consider the case $\kappa \rightarrow \mu$

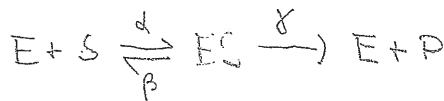
$$C(t) = A_0 \left[1 - e^{-\mu t} - \mu t e^{-\mu t} \right]$$

$$B(t) = A_0 \mu e^{-\mu t} t$$



<u>Order of reaction</u>	<u>rate of change</u>	<u>example</u>
Zero	$\frac{dx}{dt} \sim \text{constant}$	Synthesis $\emptyset \rightarrow x$
First	$\frac{dx}{dt} \sim x$	degradation $x \rightarrow \emptyset$
Second	$\frac{dx}{dt} \sim x \cdot y \text{ or } x^2$	$x + y \rightarrow \emptyset; 2x \rightarrow \emptyset$
Third	$\frac{dx}{dt} \sim x^2y$	$2x + y \rightarrow z$

Michaelis-Menten equation



Variables: $e = [E]$ $c = [ES]$
 $s = [S]$ $p = [P]$
 (concentrations)

If differential equations:

$$\frac{de}{dt} = -\alpha e \cdot s + \beta c + \gamma c \quad (1)$$

$$\frac{ds}{dt} = -\alpha e \cdot s + \beta c \quad (2)$$

$$\frac{dc}{dt} = \alpha e \cdot s - \beta c - \gamma c \quad (3)$$

$$\frac{dp}{dt} = \gamma c \quad (4)$$

The enzyme is not conserved $\Rightarrow e(t) + c(t) = e_0$

Follows also from adding eq. (1) and (3): $\frac{d}{dt}(e+c) = 0$

Michaelis and Menten 1913

Leonor Michaelis (1875 - 1949)
 (Born in Berlin)

Maud Menten (1879 - 1960)
 (Born in Ontario)

was one of the first Canadian women
 to receive a medical doctorate

Initial conditions:

$$e_0 = e(0); \quad c_0 = c(0); \quad e(0) = 0; \quad p(0) = 0$$

$$\frac{ds}{dt} = -\alpha e_0 s + (\beta s + \gamma) c \quad (5)$$

$$\frac{dc}{dt} = \alpha e_0 s - (\beta s + \gamma + \beta) c \quad (6)$$

If one now assumes that complex formation is fast, so that it is essentially a steady state, i.e. $\frac{dc}{dt} \approx 0$

points to talk about steady state and equilibrium
(Gleichgewicht)

Setting eq. (6) to zero leads to:

$$c = \frac{c_0 s}{K_m + s} \quad \text{with } K_m = \frac{\beta + \gamma}{\alpha} \quad \text{Michaelis-Menten constant}$$

using this we arrive at:

$$\frac{ds}{dt} = -\frac{K_m c_0 s}{K_m + s} \quad (\text{closed equation for } s)$$

This approximation is known as the quasi-steady state approximation

$$\text{it follows: } s(t) + K_m k_m s(t) = \overbrace{s_0 + K_m k_m s_0}^c - K_m c_0 (t - t_0) ; \quad t > t_0$$

$$\Rightarrow s(t) = K_m W \left[\frac{s_0}{K_m} e^{-\frac{K_m c_0 (t - t_0)}{K_m}} + \frac{s_0}{K_m} \right]$$

But: $c(t=0) = \frac{c_0 s_0}{K_m + s_0} \neq 0$ it does not fulfill the initial condition

What is wrong?

Discussion of the M-M reaction term

$$\frac{ds}{dt} = -\frac{V e_0 s}{K_M + s} \rightarrow \dot{s} = -\frac{Vs}{K_M + s}$$

$V := V e_0$

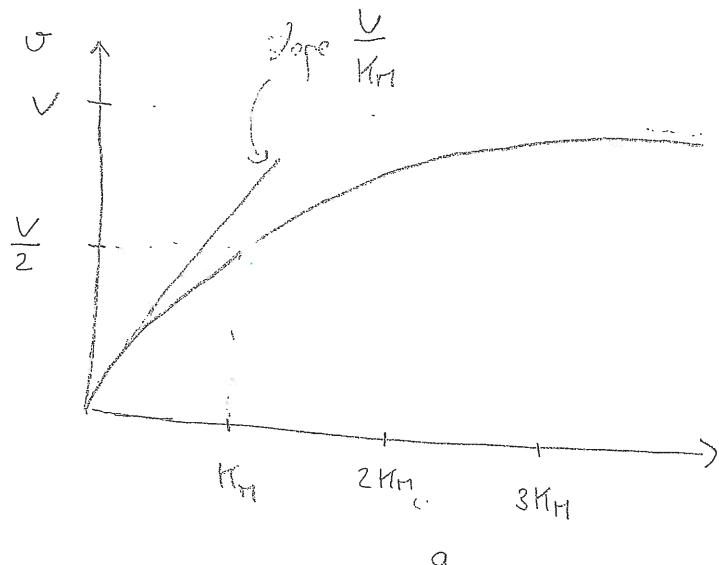
$K_M := \frac{B + \gamma}{\alpha}$

\dot{s} is the rate of change of the substrate

Often \dot{s} is named σ

$$\Rightarrow \sigma = +\frac{Vs}{K_M + s}$$

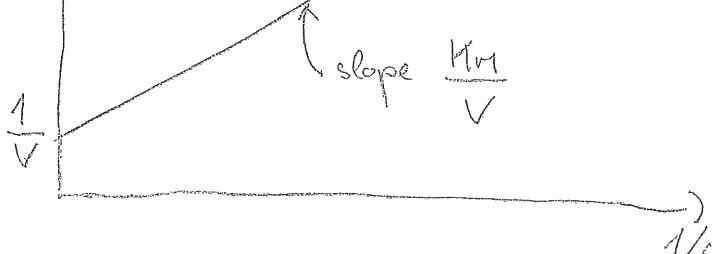
$$\sigma(s = K_M) = \frac{VK_M}{2K_M} = \frac{V}{2}$$



Lineweaver-Burk plot



$$\frac{1}{\sigma} = \frac{1}{V} + \frac{K_M}{V} \frac{1}{s}$$



19

Nonlinear Dynamics

History

(1643-1727)

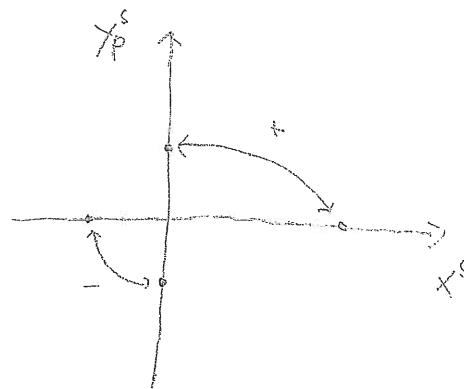
- Newton initiated the field of dynamics; he studied the motion of the earth around the sun
- In most cases physicists and mathematicians studied linear equations. There was no way to solve non-linear systems (such as the three-body problem) analytically.
- Poincaré (1854-1912) introduced a new viewpoint by focusing on qualitative rather than quantitative questions (stability, geometric optics, etc.)
- Non-linear oscillations were extensively studied (radio, radar...)
- The invention of the computer made numerical experiments possible.
- In 1963 Lorenz discovered chaotic behavior by studying convection rolls in the atmosphere. He noticed that even small changes in the initial conditions results in a totally different behavior. However, the solution never settled down to an equilibrium or regular oscillation. It continued to oscillate in an aperiodic fashion.

Consider the steady state:

$$x^s = \frac{1}{2} \frac{K_1}{K_2} \frac{s}{\gamma} + \sqrt{\frac{K_1 s}{K_3}} \frac{\Gamma}{2 K_2 \gamma}$$

$$\Gamma := \sqrt{K_1 K_3 + 4 K_2 K_4 \gamma}$$

$$\gamma_p^s = - \frac{K_1 K_2 s}{2 K_2 K_4} + \frac{\sqrt{K_1 K_3 s}}{2 K_2 K_4} \Gamma.$$



Final: 2.3.1. more solutions

i. biologically meaningful

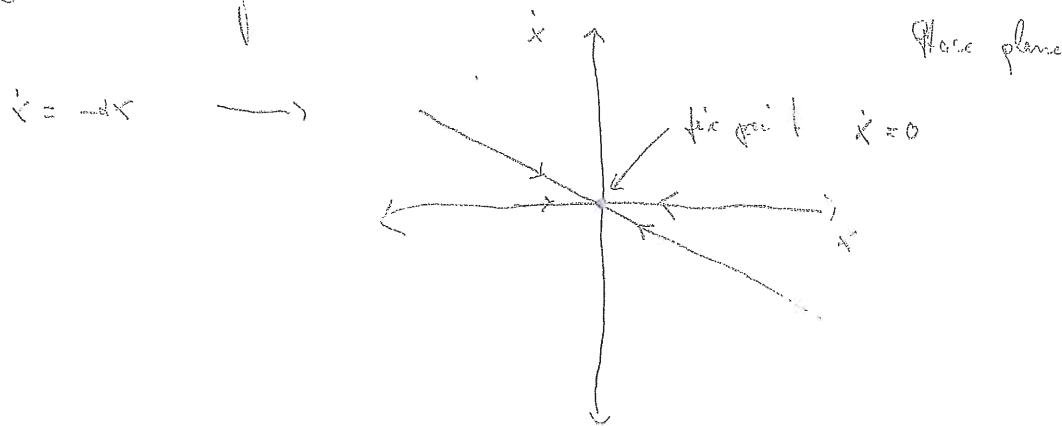
The question: What solution will be obtained?

↳ The next topic is Non-linear dynamics

End of 3H. Lecture

Non-linear Dynamics: Fixpoints, Stability and Bifurcations

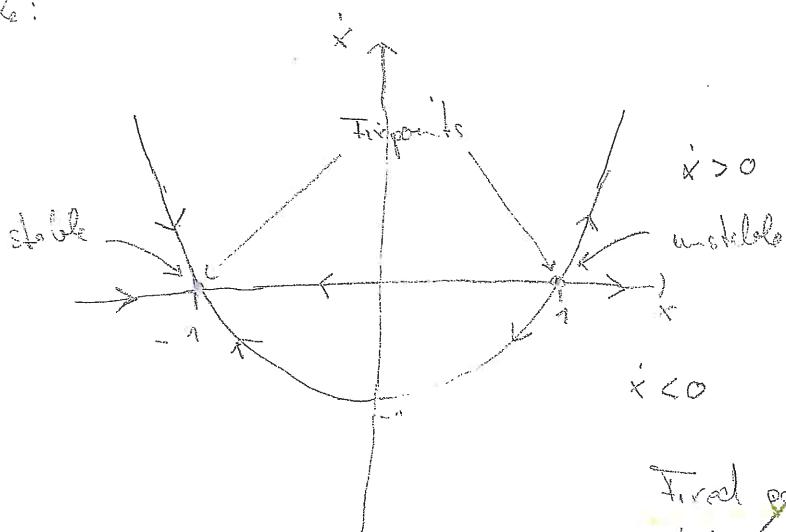
geometric way to consider ODEs:



The ODE represents a vector field on a line

Other Example:

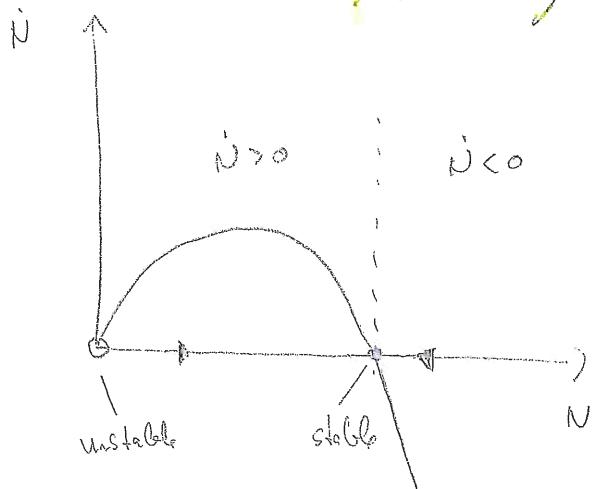
$$\boxed{\dot{x} = x^2 - 1}$$



Fixed points:
 - stable if $\dot{x} < 0$; attractors
 - unstable if $\dot{x} > 0$; repellers

Population Growth

$$\dot{N} = rN \left(1 - \frac{N}{K}\right)$$



So far we used graphical methods.

Analytical tool to analyze the stability of fix points

Linear stability analysis

| see page 51a before

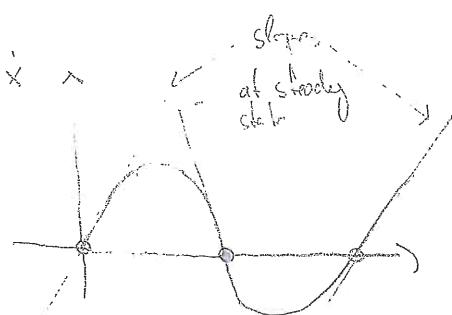
Main idea: $\dot{x} = f(x)$ $f(x_s) = 0$; set $x = x_s + s$ s is the deviation from the steady state

$$\rightarrow \dot{s} = f(x_s + s) \approx f(x_s) + f'(x_s)s$$

$$\dot{s} = f'(x_s)s$$

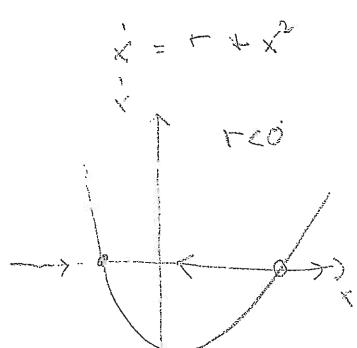
slope at the steady state

$$\Rightarrow s(t) = s_0 e^{f'(x_s)t}$$

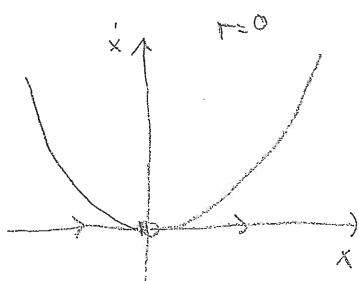


Example:

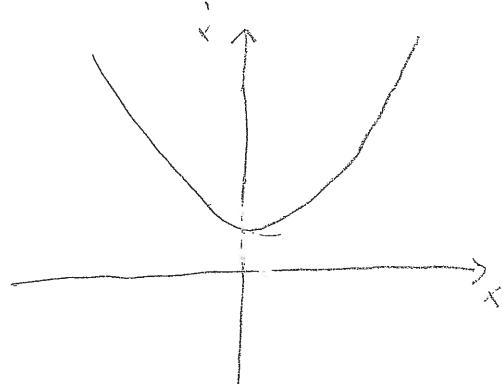
(Saddle-Node Bifurcation)



two fixpoints

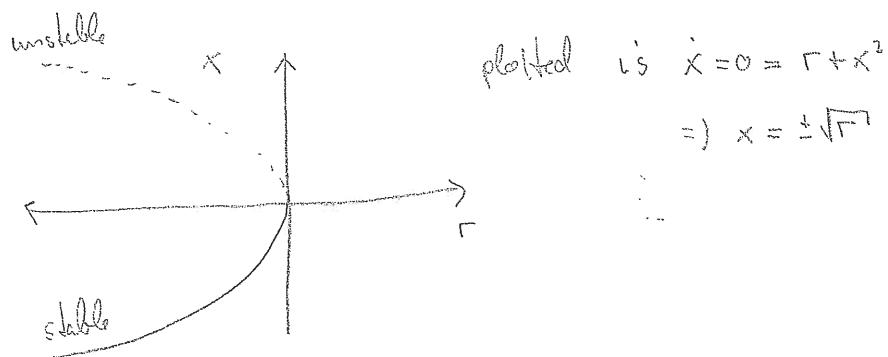


one fixpoint
stable



no fixpoint

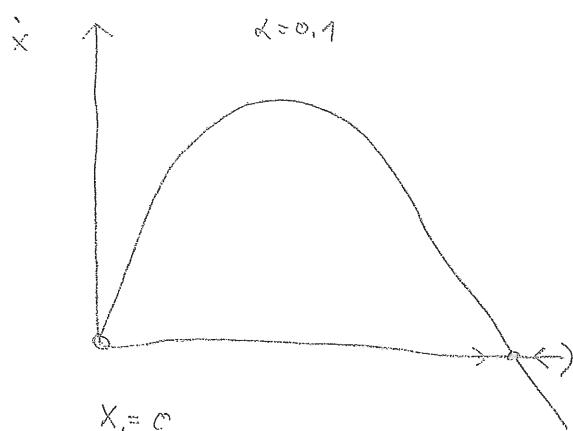
Another way to depict the mechanism: Bifurcation diagram



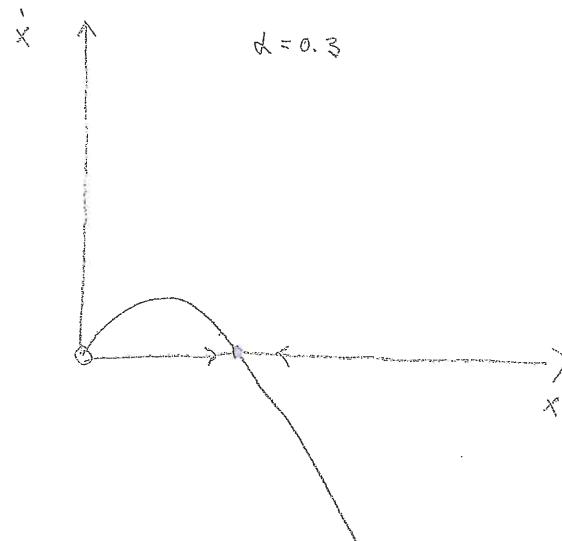
$$\text{plotted is } \dot{x} = 0 = r + x^2 \\ \Rightarrow x = \pm \sqrt{r}$$

Non-linear production - linear degradation

$$\dot{x} = \frac{x}{1+x} - \kappa x$$



$$x_2 = +\frac{1-d}{d}$$



Example: Population Growth

$$\dot{N} = rN \left(1 - \frac{N}{K}\right) ; N_s = K ; N = K + s$$

$$\dot{s} = r(K+s)\left(1 - \frac{K+s}{K}\right) = -r(K+s)\frac{s}{K}$$

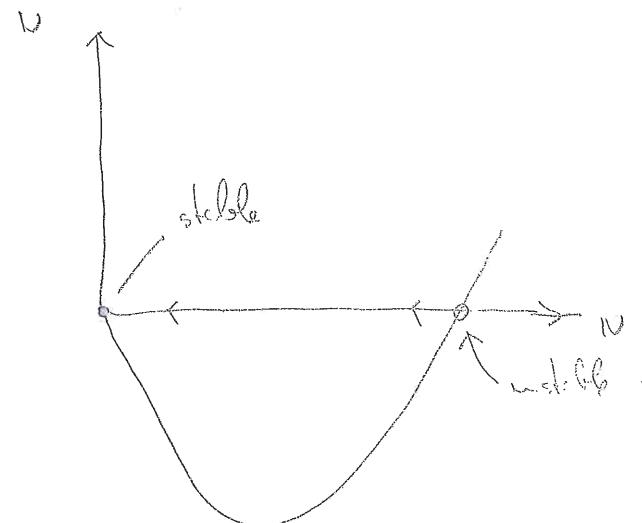
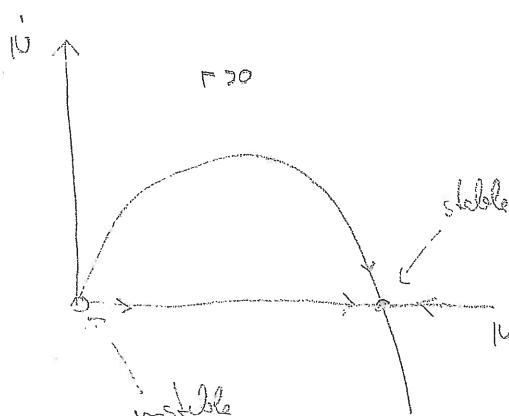
$\dot{s} = -rs \Rightarrow$ for $r > 0$ the fix point $N_s = K$ is stable.

Test the fix point at $N=0 \Rightarrow N = s$

$$\dot{s} = rs\left(1 - \frac{s}{K}\right) \quad \text{keep only linear terms}$$

$\dot{s} = rs \Rightarrow$ for $r > 0$ the fix point $N_s = 0$ is unstable

But: New happens something at $r = 0$!

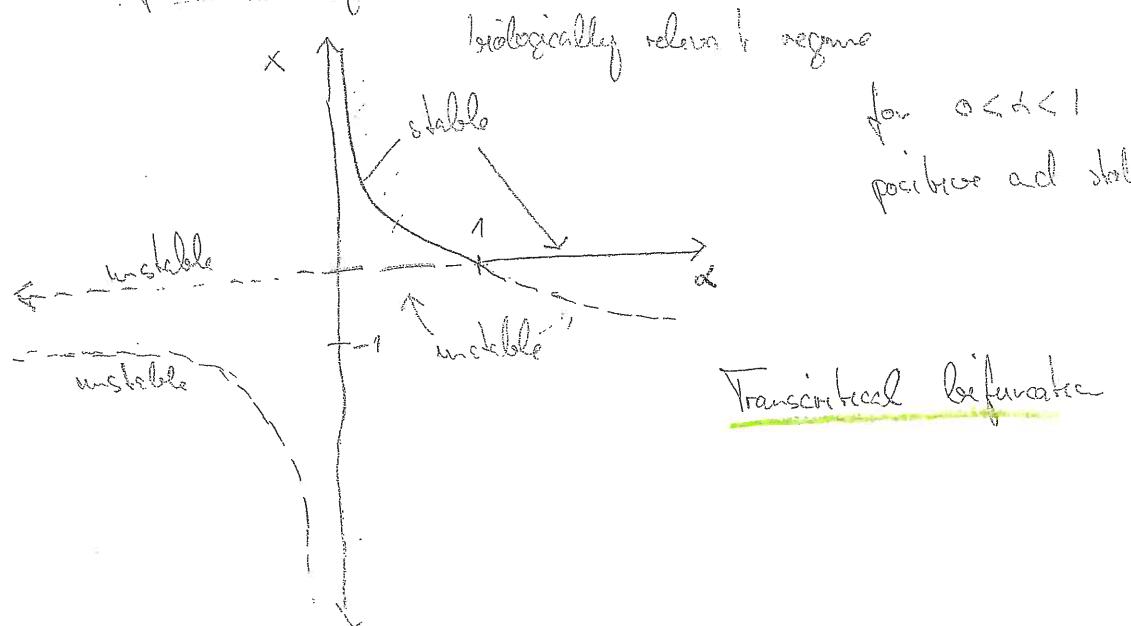


The qualitative structure of the flow changes as the parameter r is varied.

Fixpoints can be created, destroyed as their stability can change.

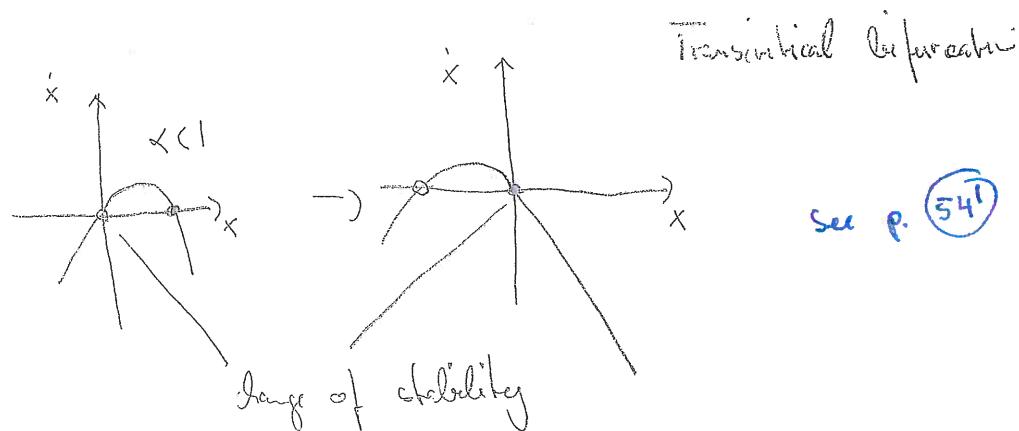
This qualitative changes in the dynamics are called Bifurcations.

Bifurcation diagram

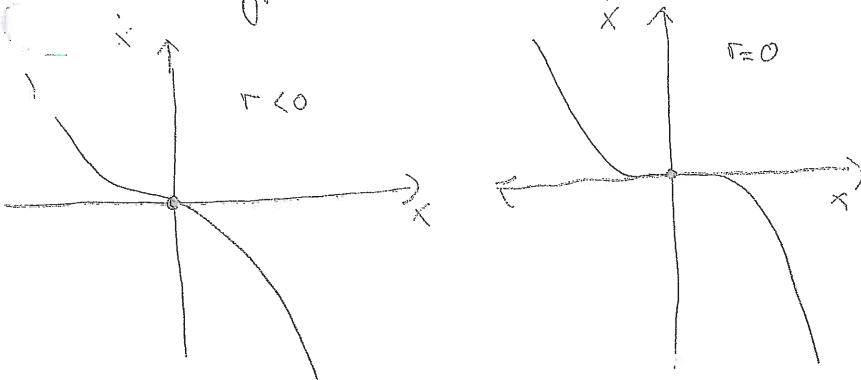


for $0 < \alpha < 1$ we find
positive and stable solutions

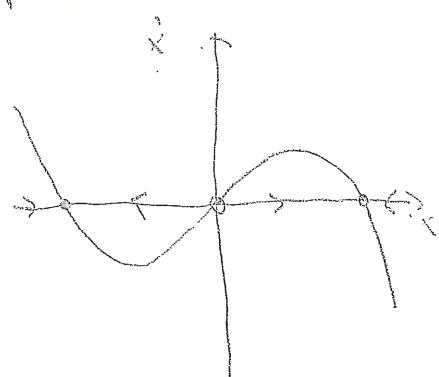
Transcritical bifurcation



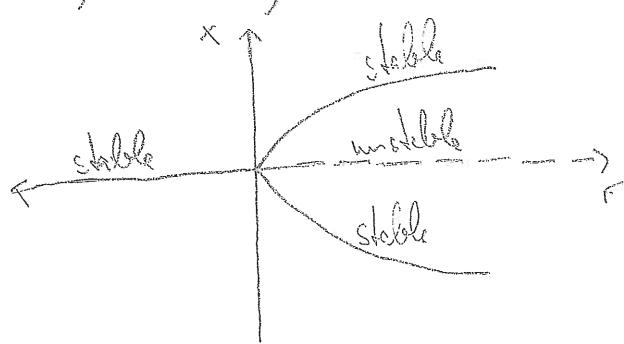
Another type: $\dot{x} = r x - x^3$



Pitchfork bifurcation



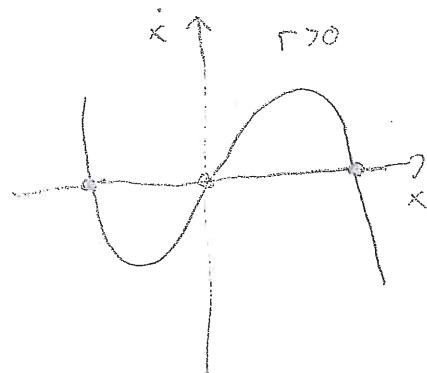
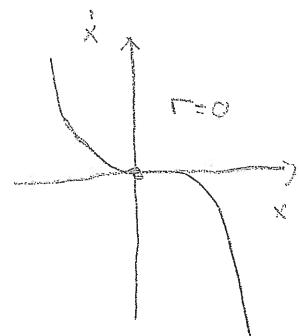
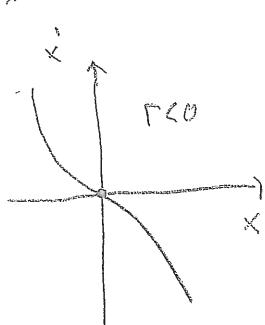
$$\dot{x} = 0 = r x - x^3 \Rightarrow x = 0, x = \pm \sqrt{-r}$$



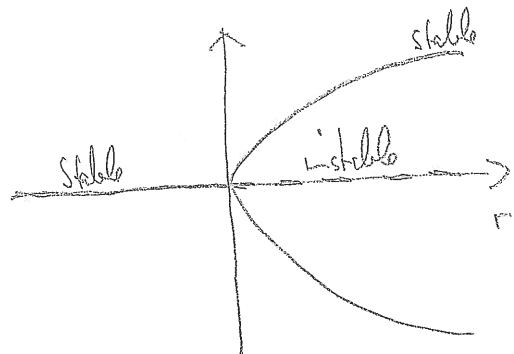
Exercise: Some Bifurcations come in two flavours

Supercritical Pitchfork Bifurcation

$$\dot{x} = rx - x^3$$



↳ Bifurcation diagram

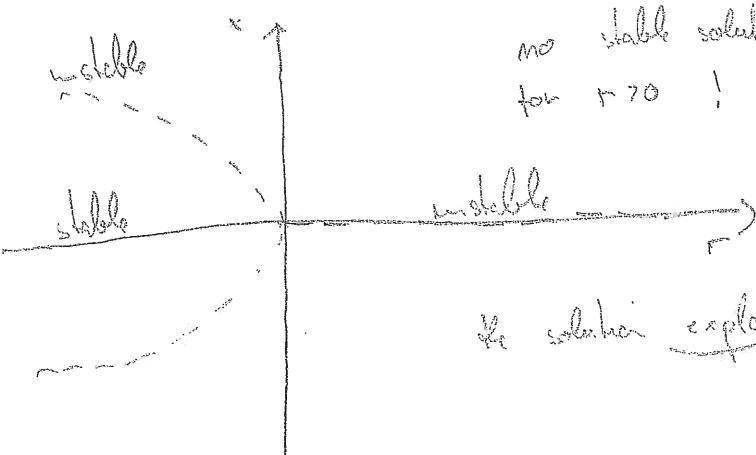


coming from $r < 0$ we obtain
two new stable solutions which
originate smoothly from the "old"
stable solution

Subcritical Pitchfork Bifurcation

Now consider:

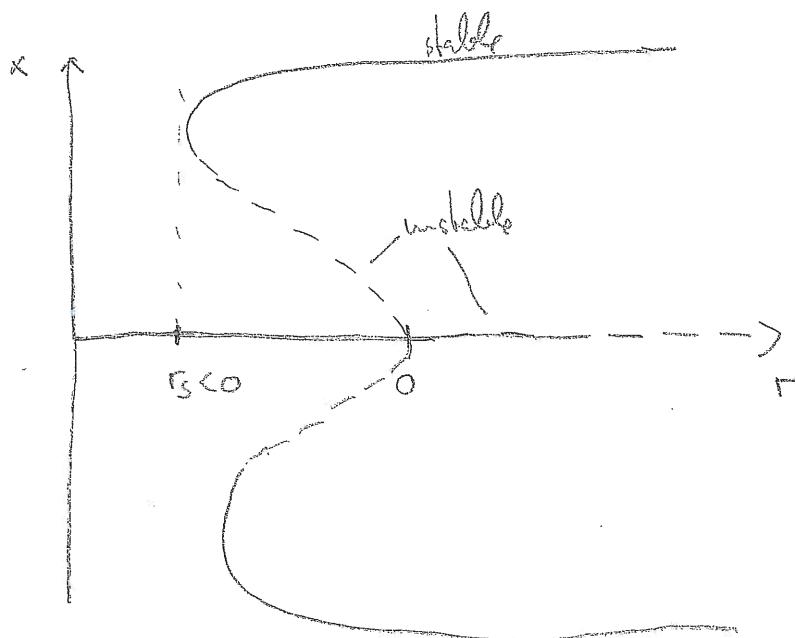
$$\dot{x} = rx + x^3$$



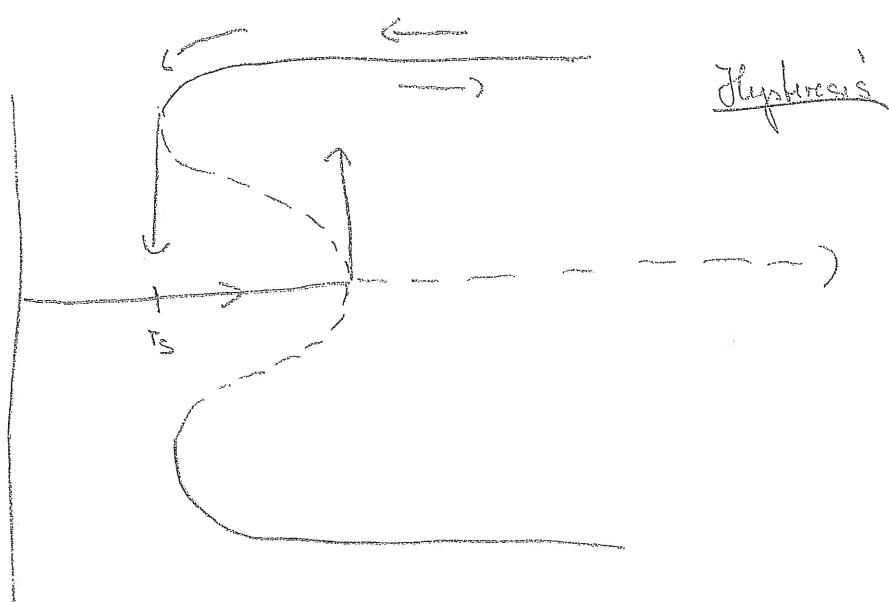
The solution explodes!

Rights and turns become important

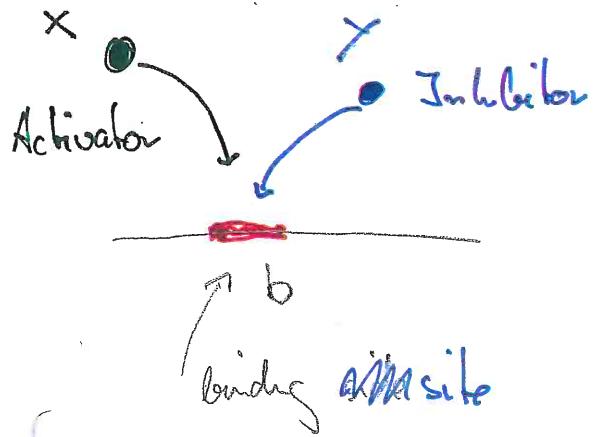
$$\dot{x} = rx + x^3 - x^5$$



The system ~~jumps~~!



Competitive inhibition



Three possible states

$$\left. \begin{aligned} \dot{b} &= -\alpha x b - \beta y b + \alpha' c_1 \\ \dot{c}_1 &= \alpha x b - \alpha' c_1 \\ \dot{c}_2 &= \beta y b - \beta' c_2 \end{aligned} \right\} \begin{matrix} \text{bind} \\ \text{process} \end{matrix}$$

$$\dot{z} = \mu c_1 - \lambda z$$

$$b_0 = b + c_1 + c_2 \Rightarrow b = b_0 - c_1 - c_2$$

$$\dot{c}_1 = \alpha x (b_0 - c_1 - c_2) - \alpha' c_1$$

use quasi-steady-state assumption

$$\dot{c}_2 = \beta y (b_0 - c_1 - c_2) - \beta' c_2$$

$$c_1 (\alpha x + \alpha') = \alpha x b_0 - \alpha x c_2$$

$$c_2 (\beta y + \beta') = \beta y b_0 - \beta y c_1 \Rightarrow c_2 = \frac{\beta y b_0 - \beta y c_1}{\beta y + \beta'}$$

$$c_1 (\alpha x + \alpha') = \alpha x b_0 - \alpha x \frac{\beta y b_0 - \beta y c_1}{\beta y + \beta'}$$

$$(\Rightarrow) c_1 (\alpha x + \alpha') (\beta y + \beta') = \alpha x b_0 (\beta y + \beta') - \alpha \beta b_0 x y + \alpha \beta x y c_1$$

$$c_1 [\alpha x y + \alpha \beta' x + \alpha' \beta y + \alpha' \beta' - \alpha \beta x y] = \alpha \beta x b_0$$



$$\Rightarrow c_1 = \frac{\alpha' \beta' b_0}{\lambda \beta' x + \alpha' \beta' y + \alpha' \beta'}$$

$$c_1 = \frac{\alpha' \beta' b_0 x}{\lambda + \alpha' \beta' x + \beta' \beta' y}$$

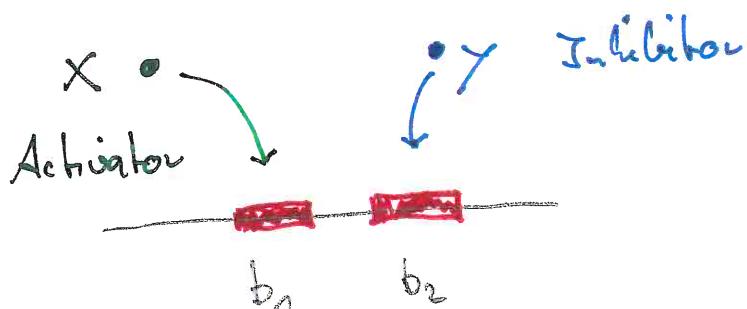
check units

$$\left[\frac{1}{x} \right] = v$$

$$\Rightarrow z = \frac{\mu \alpha' \beta' b_0 x}{\lambda + \alpha' \beta' x + \beta' \beta' y} - \lambda t$$

complementary
inhibition

Uncompetitive inhibition



4 possible states

$$C_{00} = -\alpha X C_{00} - \beta Y C_{00} + \delta' C_{10} + \gamma' C_{01}$$

$$C_{10} = \alpha X C_{00} - \delta' C_{10} - \beta Y C_{10} + \gamma' C_{01}$$

$$C_{01} = \beta Y C_{00} - \delta' C_{01} - \alpha X C_{01} + \delta' C_{11}$$

$$C_{11} = \alpha X C_{01} + \beta Y C_{10} - \delta' C_{11} - \gamma' C_{01}$$

$$b_0 = C_{00} + C_{10} + C_{01} + C_{11}$$

Again, use QSS assumption:

$$\dot{0} = +\alpha X (b_0 - C_{10} - C_{01} - C_{11}) - \delta' C_{10} - \beta Y C_{10} + \gamma' C_{01}$$

$$\dot{0} = \beta Y (b_0 - C_{10} - C_{01} - C_{11}) - \delta' C_{01} - \alpha X C_{01} + \delta' C_{11}$$

$$\dot{0} = \alpha X C_{01} + \beta Y C_{10} - \delta' C_{01} - \beta' C_{01}$$

$$\Rightarrow \boxed{C_{01} = \frac{\alpha' \beta' b_0 \gamma}{(\alpha' + \alpha x)(\beta' + \beta y)} \quad ; \quad C_{10} = \frac{\alpha \beta' b_0 x}{(\alpha' + \alpha x)(\beta' + \beta y)}}$$

$$\boxed{C_{11} = \frac{\alpha \beta' b_0 x y}{(\alpha' + \alpha x)(\beta' + \beta y)} \quad ; \quad C_{00} = \frac{\delta' \beta' b_0}{(\alpha' + \alpha x)(\beta' + \beta y)}}$$



We can now have the cases:

$$\dot{z} = \mu (c_{01} + c_{10} + c_{11}) - \alpha t \quad \text{OR} \quad A \vee B$$

$$\dot{z} = \mu c_{11} - \alpha t \quad \text{AND} \quad A \wedge B$$

$$\dot{z} = \mu c_{10} - \alpha t \quad \text{AND} \quad A \wedge \bar{B}$$

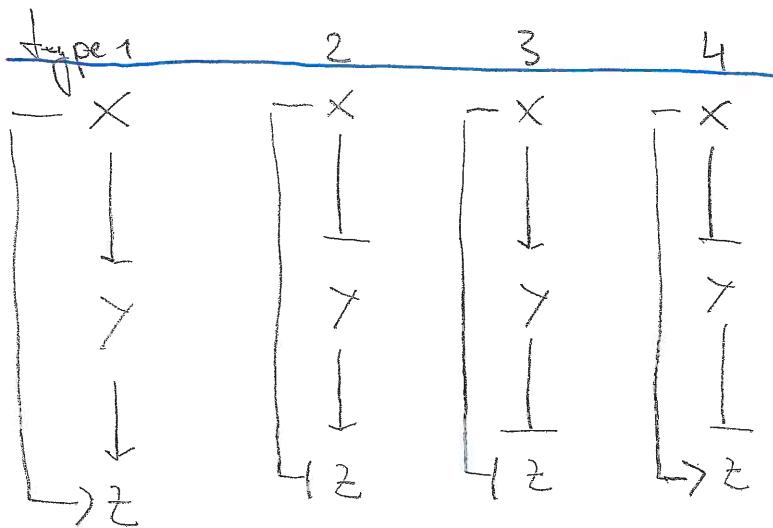
$$\dot{z} = \mu (c_{01} + c_{00}) - \alpha t \quad \text{XOR} \quad A \vee \bar{B}$$

Consider $A \wedge \bar{B}$ (uncompetitive inhibition)

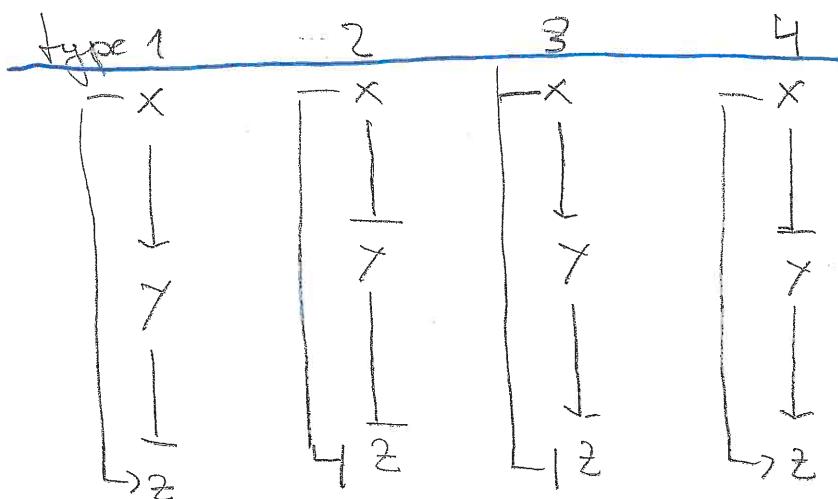
$$\dot{z} = \mu \frac{\alpha' \beta' b_0 x}{(\alpha' + \alpha x)(\beta' + \beta x)} - \alpha t$$

$$\boxed{\dot{z} = \frac{\mu \alpha' \beta' b_0 x}{(1 + \beta'/\beta x)(1 + \alpha'/\alpha x)} - \alpha t}$$

Feed forward network motifs

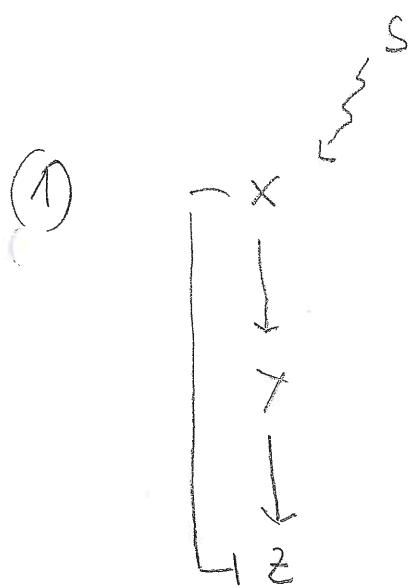


Coherent



Incoherent

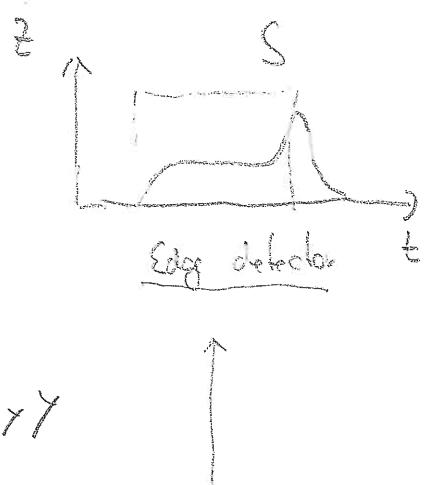
We assume: x and y join into z in an uncompetitive manner (two binding sites)



$$\dot{x} = S - \lambda_x x$$

$$\dot{y} = \frac{\mu_y x}{1 + K_1 x} - \lambda_y y$$

$$\dot{z} = \frac{\mu_z y}{(1 + K_2 x)(1 + K_3 y)} - \lambda_z z$$

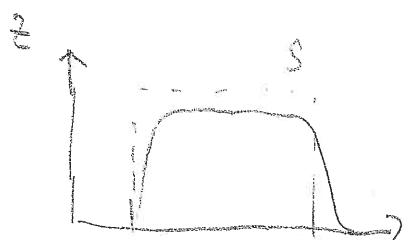
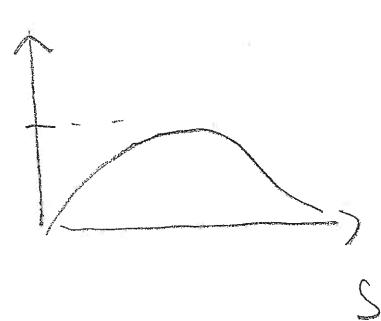


Steady state: $x = \frac{S}{\lambda_x}$; $y = \frac{\mu_y/\lambda_y x}{1 + K_1 x} = \frac{S \mu_y / (\lambda_x \lambda_y)}{1 + K_1 x / \lambda_x S}$

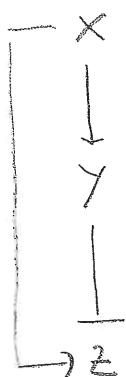
$$z = \frac{\frac{S \mu_y \mu_z}{\lambda_x \lambda_y \lambda_z}}{\left(1 + K_2 / \lambda_x S\right) \left(1 + K_3 \frac{S \mu_y}{\lambda_x \lambda_y}\right) \left(1 + K_1 / \lambda_x S\right)}$$

To simplify, set $K_1 = K_2 = K_3 = \mu_y = \mu_z = \lambda_x = \lambda_y = \lambda_z = 1$

$$\Rightarrow z = \frac{s}{(1+s)(1+\frac{s}{1+s})(1+s)} \stackrel{(\equiv)}{=} \boxed{z = \frac{s}{(1+s)(1+2s)}}$$



(2)



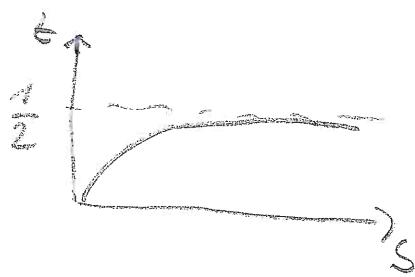
$$\dot{x} = s - x$$

$$\dot{y} = \frac{x}{1+x} - y$$

$$\dot{z} = \frac{x}{(1+x)(1+y)} - z$$

fast response module

$$\Rightarrow z = \frac{s}{(1+s)(1+\frac{s}{1+s})} \stackrel{(\equiv)}{=} \boxed{z = \frac{s}{1+2s}}$$



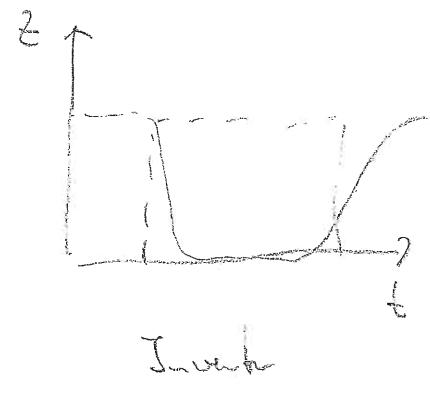
(3)



$$\dot{x} = s - x$$

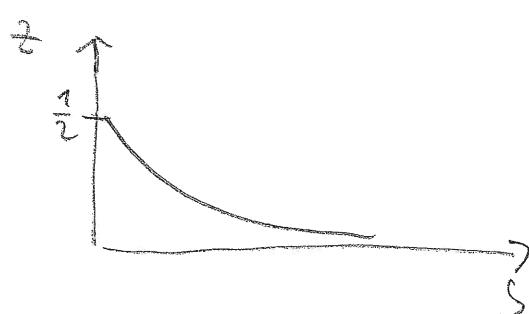
$$\dot{y} = \frac{1}{1+x} - y$$

$$\dot{z} = \frac{y}{(1+x)(1+y)} - z$$



Invert

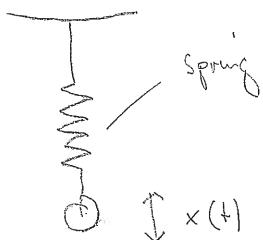
$$\Rightarrow z = \frac{1}{(1+s)(1+s)(1+\frac{1}{1+s})} \Leftrightarrow z = \frac{1}{(1+s)(2+s)}$$



Oscillations

Linear oscillations

Simple example:



force of the spring

$$m \ddot{x} = -\gamma \dot{x} - Kx \quad (=) \quad \ddot{x} = -\gamma \dot{x} - \omega^2 x$$

$$T = \frac{2\pi}{\omega} \quad | \quad \omega^2 = \frac{K}{m}$$

force
~ to velocity

Rewrite:

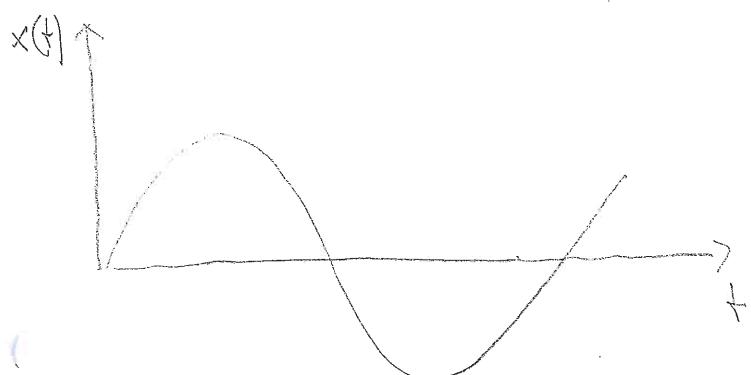
$$\begin{cases} \dot{x} = y \\ \ddot{x} = -\gamma y - \omega^2 x \end{cases}$$

first order ordinary differential equation

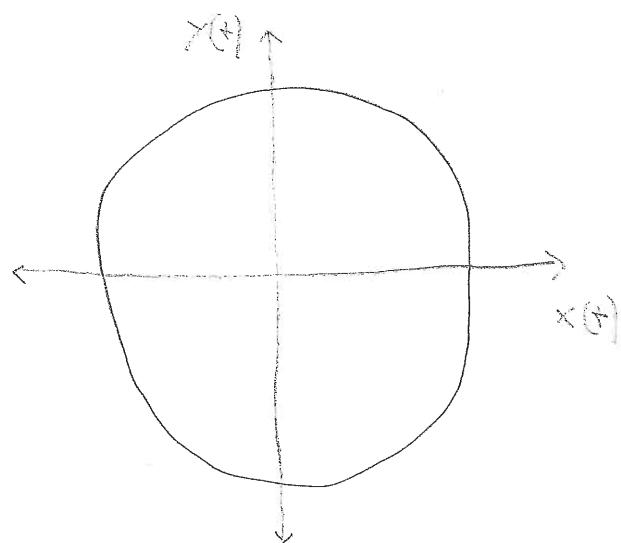
General: $\begin{cases} \dot{x} = f(x) \end{cases}$

Property of the oscillatory solution: $\vec{x}(t+T) = \vec{x}(t)$ $T > 0$ is the period

Two way of plotting



Time plot



Phase plot
or phase portrait

Is very useful for nonlinear systems

Show mathematica file, linear oscillations

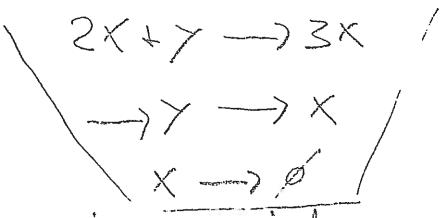
The orbits of a linear system are not isolated \rightarrow [mathematica]

However, biological oscillations exhibit very specific properties

\rightarrow we have to consider nonlinear oscillators

[Discuss phase portraits]

Example: Glycolytic oscillator

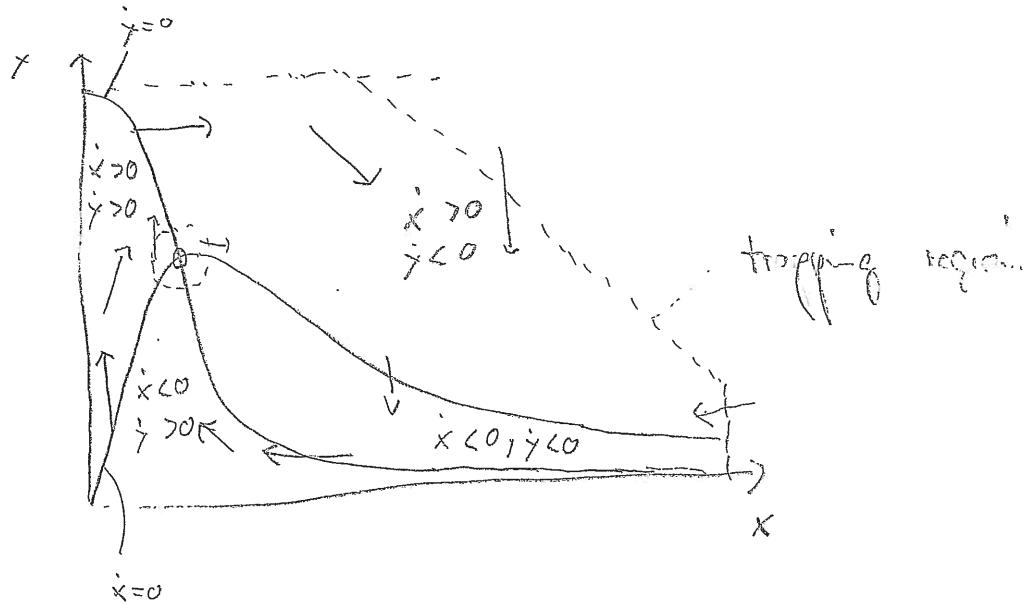


$$\dot{x} = -x + ay + x^2y$$

$$\dot{y} = b - ay - x^2y$$

The nullclines are given by:

$$y = \frac{x}{a+x^2} \quad \text{and} \quad y = \frac{b}{a+x^2}$$



We have a trapping region, but there is a fixed point inside
 \rightarrow the Poincaré-Bendixson theorem does not hold

But: the fixed point is a repeller

Jacobian: $J = \begin{pmatrix} -1 + 2xy & a + x^2 \\ -2xy & -(a + x^2) \end{pmatrix}$

Fixed points: $x^* = b$

$$y^* = \frac{b}{a+b^2}$$

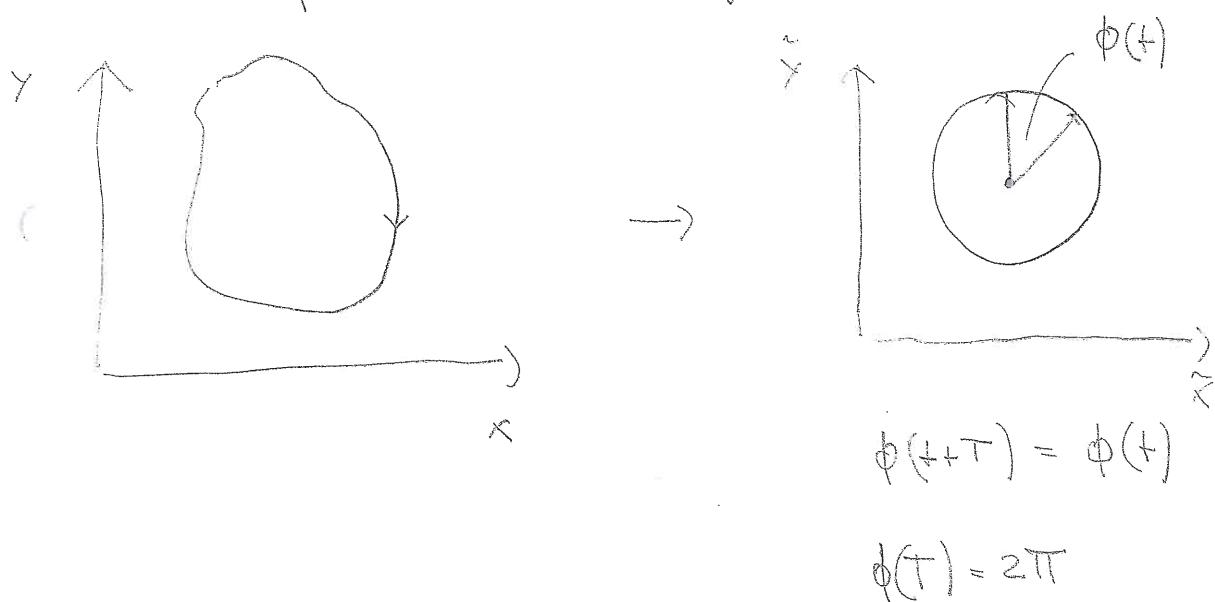
$$\chi = \det J = a + b^2 > 0$$

$$\beta = \operatorname{tr} J = -\frac{b^4 + (2a-1)b^2 + a + a^2}{a + b^2} ; \text{ the fixed point is stable for } \beta < 0$$

The location $b=0$ defines a curve in the (a,b) plane

Entrainment

One can map the close trajectory on a circle:



Now consider a simple model for the entrainment of the fireflies:

$\dot{\phi} = \omega$ flashing of the firefly

$\dot{\theta} = \omega$; ω = speed the firefly goes through its cycle

$\dot{\theta} = \sigma$ periodic stimulus

$\dot{\sigma} = S$ speed of the stimulus

Assume that the fireflies want to catch up with the stimulus



Simple phasor model.

$$\dot{\phi} = \omega + A \sin(\theta - \phi) ; \quad \theta = \Omega t$$

(working strength)

Analysis: look at the phase difference between supply and stimulus

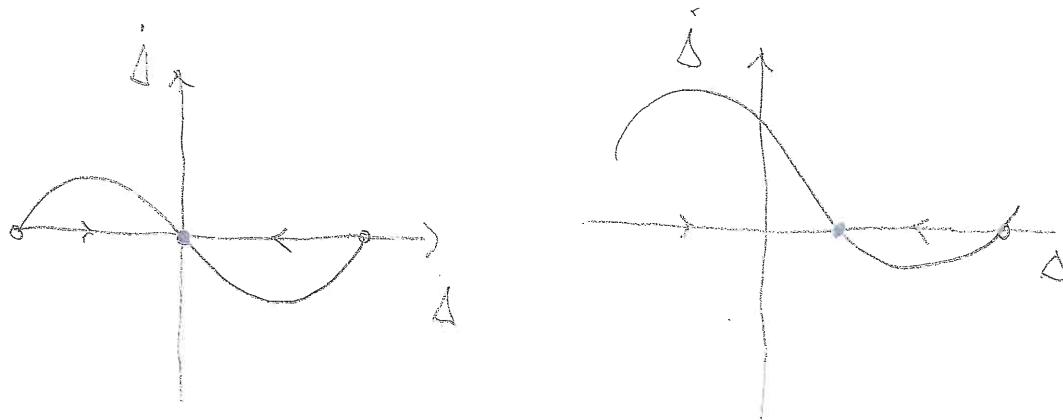
$$\Delta = \theta - \phi$$

$$[E = A \cdot t]$$

$$\Rightarrow i = \dot{\theta} - \dot{\phi} = \Omega \cdot \omega - A \sin \Delta$$

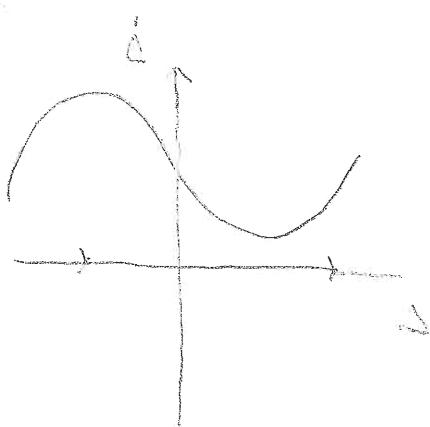
Change of variables: $i = m - \sin \Delta$ $m = \frac{\Omega \cdot \omega}{A}$

lumping parameters
together



$\mu = 0$

$0 < \gamma < \pi$



Cases:

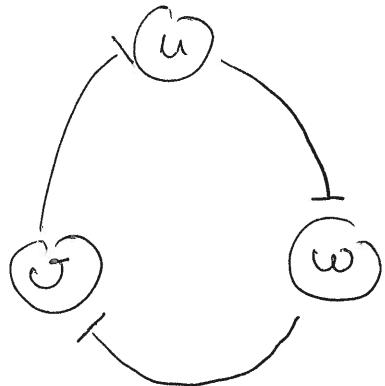
1. $\mu = 0$, Synchrony, no phase difference

2. $\mu > 0$; phase-locked, constant phase difference

3. $\mu > 1$; phase drift

Show mathematica file

Repression/Activation



$$\frac{dm_1}{dt} = -m_1 + \frac{\alpha}{1+U^n} + \delta_0$$

$$\frac{dm_2}{dt} = -m_2 + \frac{\alpha}{1+W^n} + \delta_0$$

mRNA

$$f(x) = \frac{\alpha}{1+x^n}$$

reflects
Synthesis of
mRNA

$$\frac{dm_3}{dt} = -m_3 + \frac{\alpha}{1+U^n} + \delta_0$$

$$\frac{du}{dt} = -\beta(u - m_1)$$

protein

$$\frac{dv}{dt} = -\beta(v - m_2)$$

$$\frac{dw}{dt} = -\beta(w - m_3)$$

n : cooperativity
reflects multimerization
of proteins needed to
affect the promoter

δ_0 : leaky gene expression
uncontrolled

If $\rho \ll 1$ we can do a QSS assumption.

$$\Rightarrow m_1 = \frac{\rho}{1+\rho^n} + d_0$$

$$m_2 = \frac{\rho}{1+\rho^n} + d_0$$

$$m_3 = \frac{\rho}{1+\rho^n} + d_0$$

Further, neglect d_0

$$\left. \begin{aligned} \dot{u} &= \frac{\rho}{1+\rho^n} - u \\ \dot{\sigma} &= \frac{\rho}{1+\rho^n} - \sigma \\ \dot{w} &= \frac{\rho}{1+\rho^n} - w \end{aligned} \right\}$$

Simplified system

(time is rescaled with ρ)

Look for the steady state :

$$\Rightarrow u = \frac{d}{1+u^n}$$

$$v = \frac{k}{1+w^n}$$

$$w = \frac{\lambda}{1+u^n}$$

} define 3 null planes

$$\left(\frac{d}{1+u^n}, v, w \right)$$

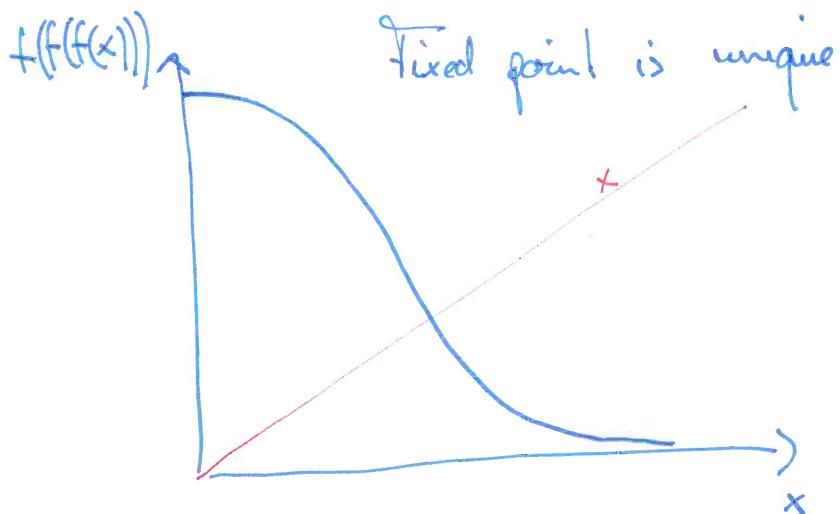
; Define $f(x) = \frac{d}{1+x^n}$

$$\Rightarrow \left(u, \frac{d}{1+w^n}, w \right)$$

(=) $f(f(f(x))) - x = 0$

$$\left(u, v, \frac{\lambda}{1+u^n} \right)$$

specifies the fixed point of the system



The equation $f(f(f(x))) = x$ is certainly fulfilled if $f(x) = x$ holds.

$$f(x) = \frac{x}{1+x^n} = x \Rightarrow \boxed{x = x + x^{n+1}}$$

~~Asymptotic behavior~~

$$\text{cases : } x \ll 1 \Rightarrow x \approx x$$

$$x \gg 1 \Rightarrow x \approx x^{\frac{1}{n+1}} \quad n > 1$$

