

1° Qualitative analysis of dynamical systems

1. 1. Dynamical systems

Def: Dynamical system (in continuous time)

is a system of 1st order diff. eqs.

$$\frac{dx_i}{dt} = \dot{x}_i = f_i(x_1, x_2, \dots, x_n) \quad i=1, \dots, n$$

- The trajectory $(x_1(t), \dots, x_n(t))$ is fully specified by initial condition $(x_1(0), x_2(0), \dots, x_n(0))$
- Trajectories evolve in the n -dimensional phase space

Example: Hamiltonian mechanics

$$\dot{q}_i = \frac{\partial H}{\partial p_i}, \quad \dot{p}_i = -\frac{\partial H}{\partial q_i}, \quad i=1, \dots, f, \quad n=2f$$

f : # degrees of freedom

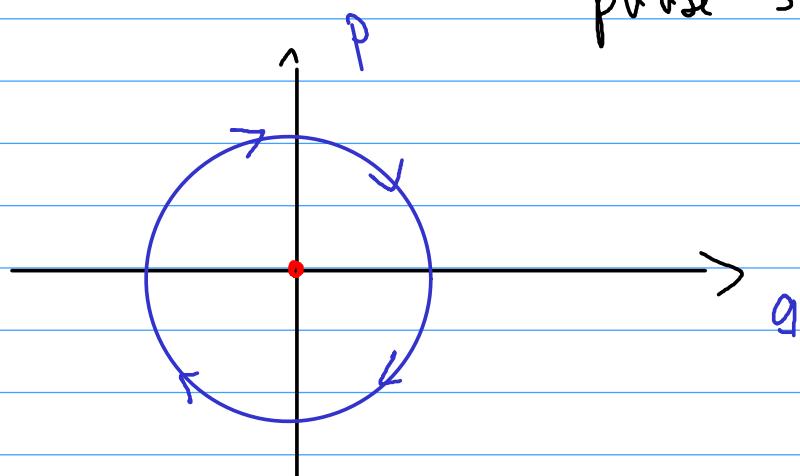
Conservation law:

$$\frac{d}{dt} H(q_1(t), \dots, p_1(t), \dots, p_f(t)) = 0$$

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Harmonic oscillator: $H = \frac{p^2}{2\omega} + \frac{1}{2}m\omega^2q^2$

Phase portrait: Set of trajectories in phase space



fixed point (FP)
 $q=0, p=0$

1.2. Logistic growth (Verhulst 1838)

- $N(t)$: population size (e.g. bacterial colony)

$$\dot{N} = bN - dN \quad \left. \begin{array}{l} b: \text{birth rate} \\ d: \text{death rate} \end{array} \right\}$$

binary cell division: $b = \frac{\ln 2}{T}$ }

T : division time }

$$d=0: \quad N(t) = N(0) e^{bt} = N(0) 2^{t/T} \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

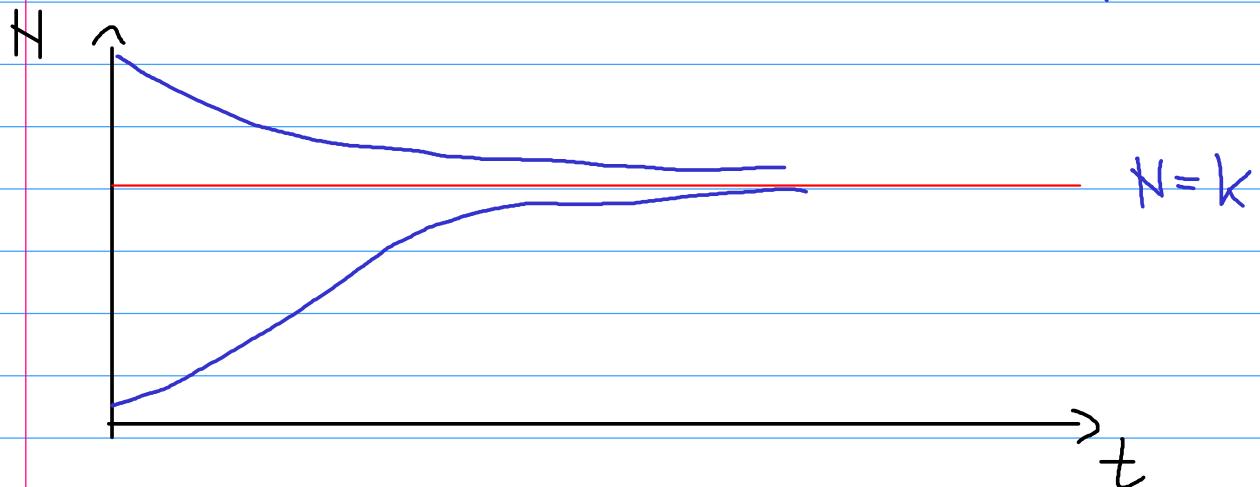
- limited resources \Rightarrow death rate density dependent

$$d = b \frac{N}{K} \quad K: \text{carrying capacity}$$

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$$\Rightarrow \dot{N} = b_N \left(1 - \frac{N}{K}\right) = F(N)$$

explicit solution $N(t) = \frac{N(0) K e^{bt}}{K + N(0)(e^{bt} - 1)}$



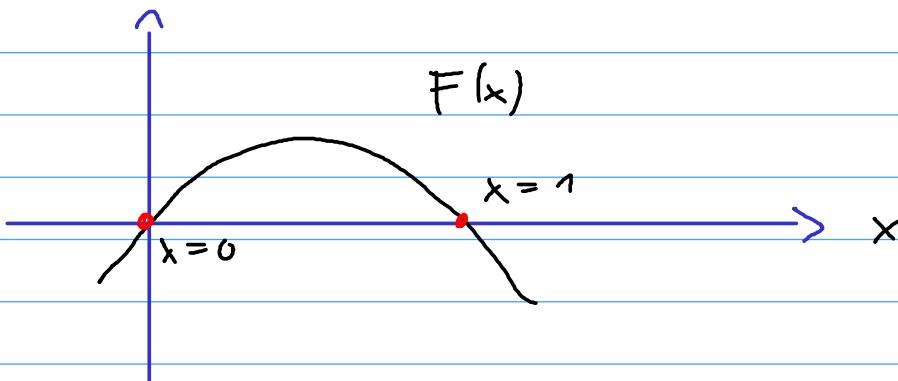
- Qualitative analysis

(i) rescale variables to order unity

$$x = \frac{N}{K} \Rightarrow \dot{x} = b_x (1 - x) = F(x)$$

(ii) identify fixed points (FP) $\dot{x} = 0 \Leftrightarrow F=0$

solutions of $F(x) = 0$



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(iii) linearize dynamics around FP

$$x=0: \quad x = \varepsilon \ll 1 \quad \dot{\varepsilon} = b\varepsilon + \cancel{O(\varepsilon^2)} \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

$$\varepsilon(t) = \varepsilon(0) e^{bt} \rightarrow \infty \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

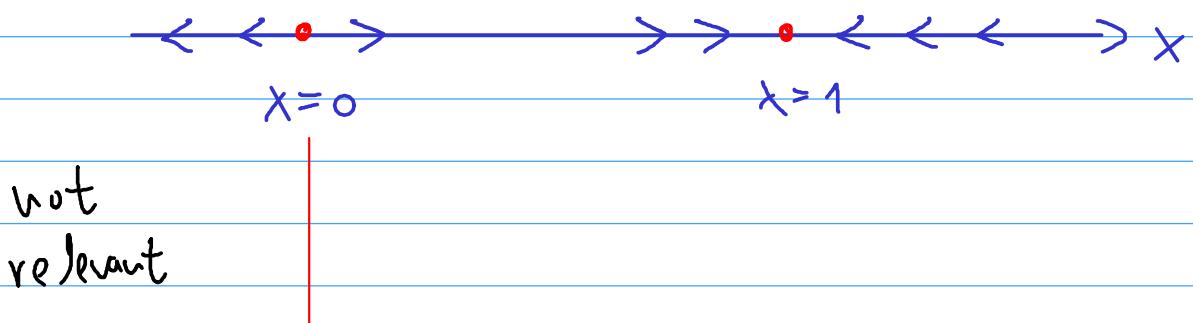
\Rightarrow FP $x=0$ is linearly unstable

$$x=1: \quad x = 1+\varepsilon, \quad |\varepsilon| \ll 1 \quad \dot{\varepsilon} = -b\varepsilon \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

$$\varepsilon(t) = \varepsilon(0) e^{-bt} \rightarrow 0 \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

\Rightarrow FP $x=1$ is linearly stable

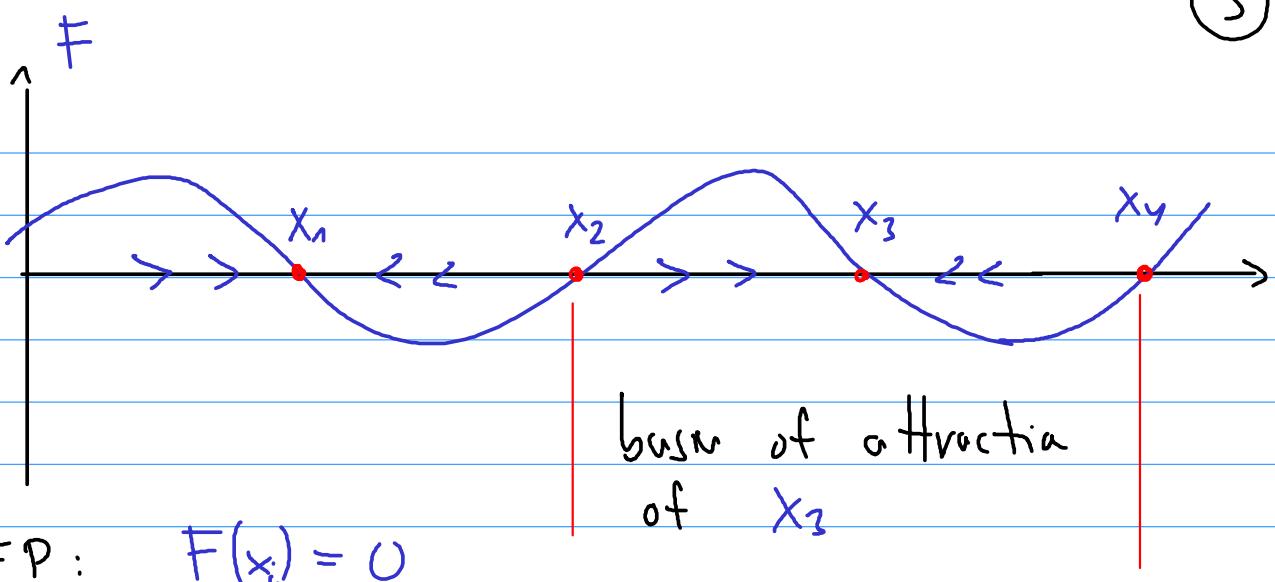
(iv) Construct phase portrait



1.3. Flows on the line

- Phase portrait of a general one-dimensional dynamical system $\dot{x} = F(x)$

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stability: determined by sign of $F'(x_i)$

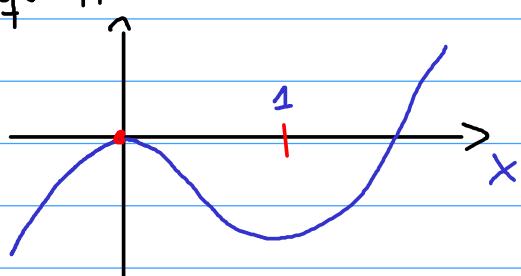
\Rightarrow general phase portrait is a sequence of alternating stable and unstable FP

- Any one-dimensional flow has a potential
- $$\dot{x} = F(x) = -\frac{dV}{dx}$$

Potential $V(x)$ becomes dynamically relevant for stochastic dynamics

Potential of the logistic equation:

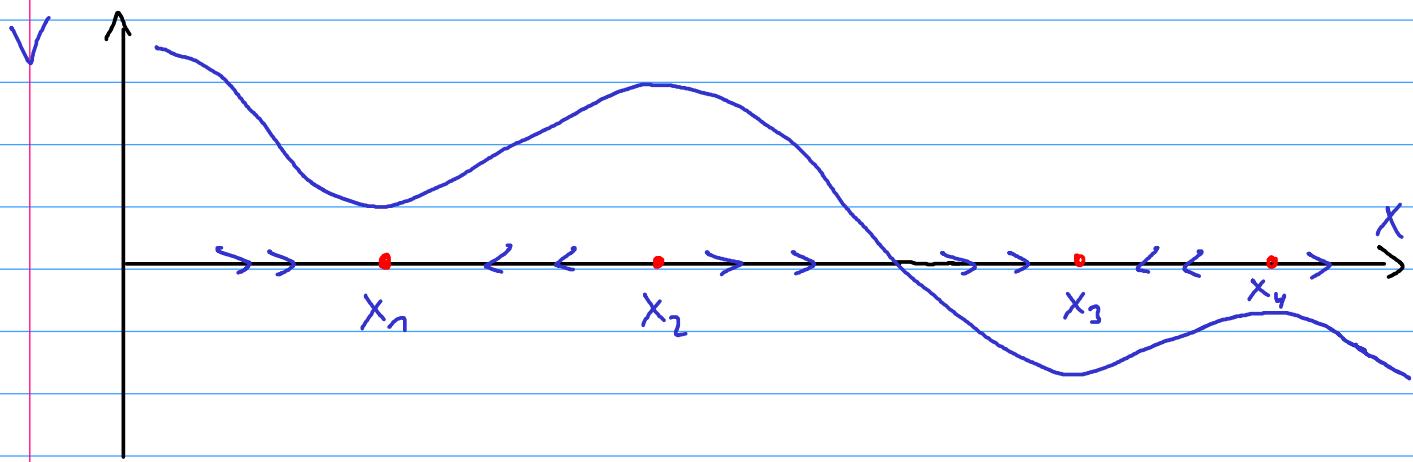
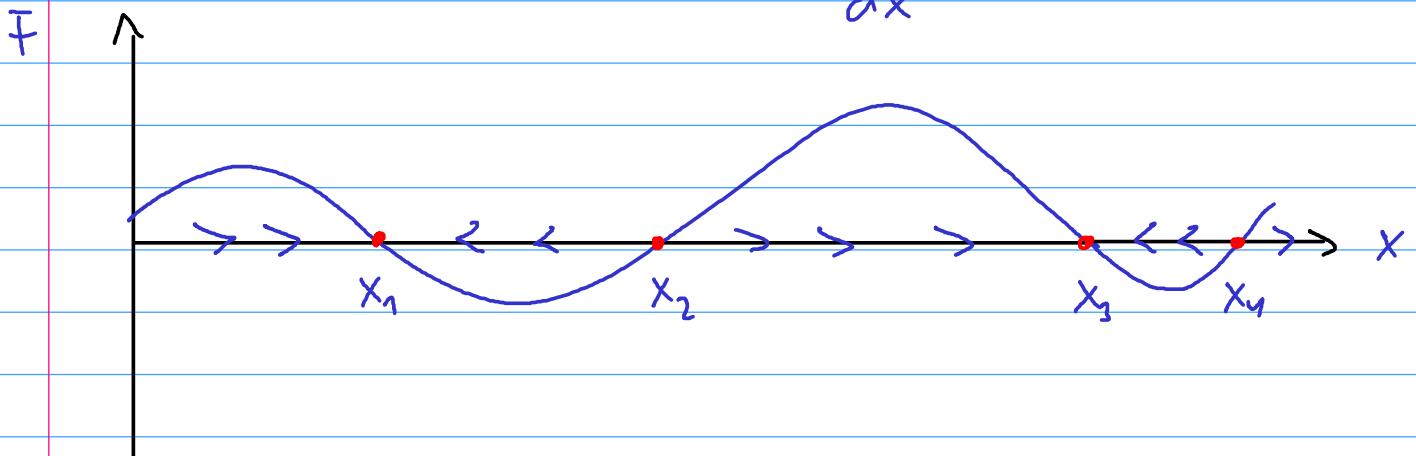
$$V(x) = -\frac{1}{2} b x^2 + \frac{1}{3} b x^3$$



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Recap: One-dimensional dynamical systems

$$\dot{x} = F(x) = -\frac{dV}{dx}$$



- fixed points $x_1, x_2, x_3, x_4 : F(x_i) = 0$

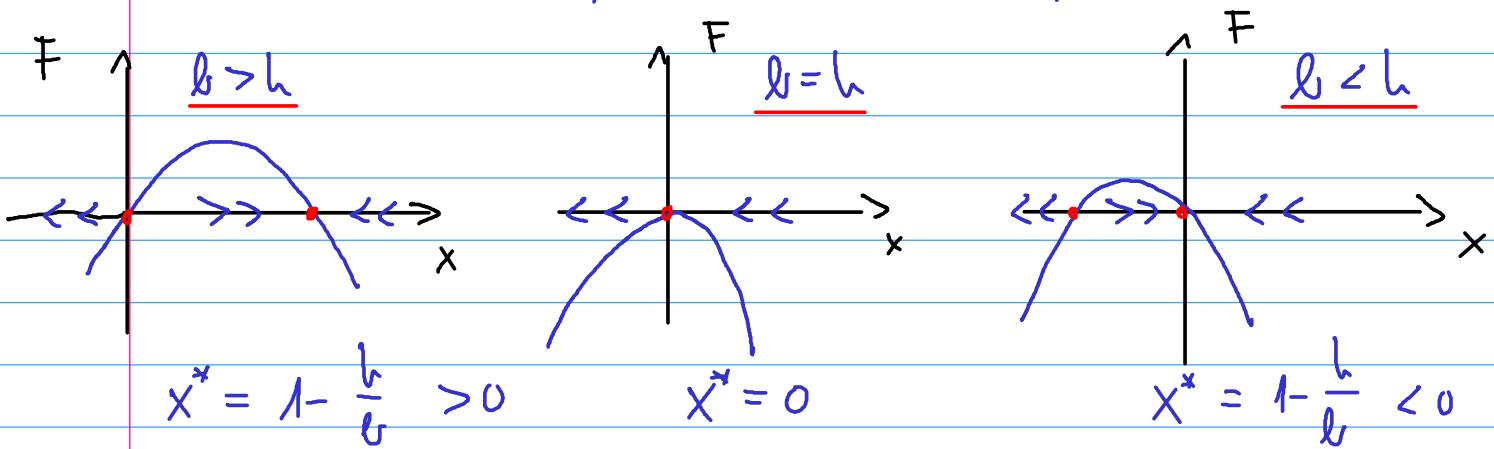
- stability: $F'(x_i)$ $\left\{ \begin{array}{ll} > 0 & \text{unstable} \\ < 0 & \text{stable} \\ = 0 & \text{marginal} \end{array} \right.$

1.4. Bifurcations

Def. A bifurcation occurs when the FP structure of a dynamical system changes as a function of a control parameter

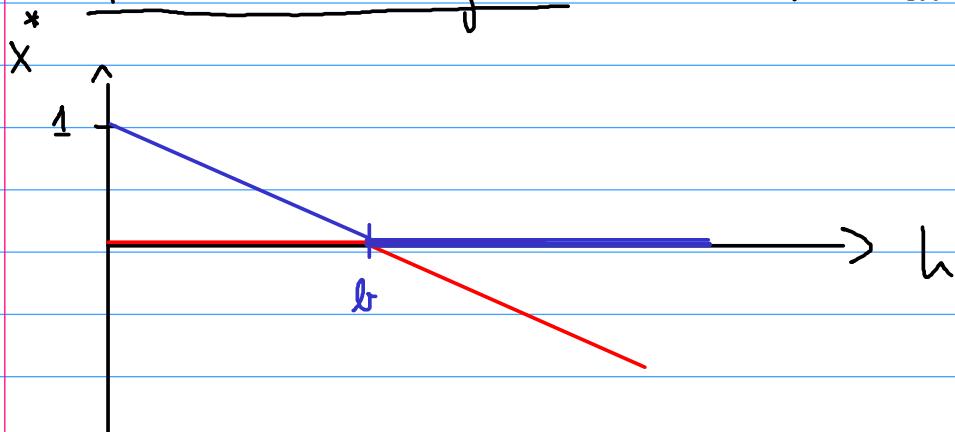
Example: Logistic growth with harvesting

$$\begin{aligned}\dot{x} &= b x (1-x) - h x \quad h: \text{harvesting rate} \\ &= (b-h)x - bx^2 = F(x)\end{aligned}$$



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Bifurcation diagram: Plot x^* as fct. of b



$$\text{FP: } x=0 \\ x^* = 1 - \frac{b}{l}$$

stable
unstable

Transcritical bifurcation: FP $x=0$ and

$x^* = 1 - \frac{b}{l}$ exchange their stability at

$$b = l$$

At $b = l$ there is a single FP $x=0$:

$$\dot{x} = -\beta x^2 \Rightarrow x(t) = \frac{x(0)}{1 + l x(0) \cdot t}$$

$$x(0) > 0 : x(t) \rightarrow 0 \quad t \rightarrow \infty$$

$$x(0) < 0 : x(t) \rightarrow -\infty \quad \text{at} \quad t = -\frac{1}{l x(0)}$$

FP $x=0$ is worflig

Dynamics near $x^* = 1 - \frac{b}{l}$ for $b < l$

$$\text{Expand } F(x) \text{ near } x^* : F'(x^*) = l - l = -(l - l)$$

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Small perturbation: $x = x^* + \varepsilon$

$$\dot{\varepsilon} = F'(x^*) \varepsilon = -(\lambda - b) \varepsilon$$

$$\Rightarrow \varepsilon(t) = \varepsilon(0) e^{-(\lambda - b)t} = \varepsilon(0) e^{-t/\tau}$$

τ : relaxation time $\tau = \frac{1}{\lambda - b}$

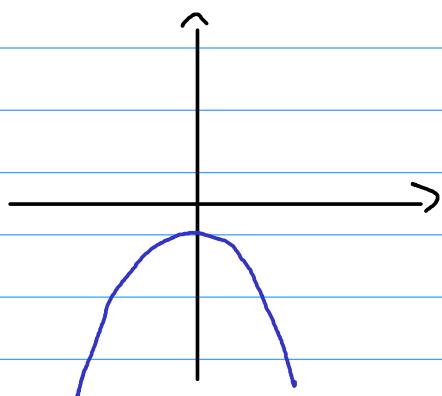
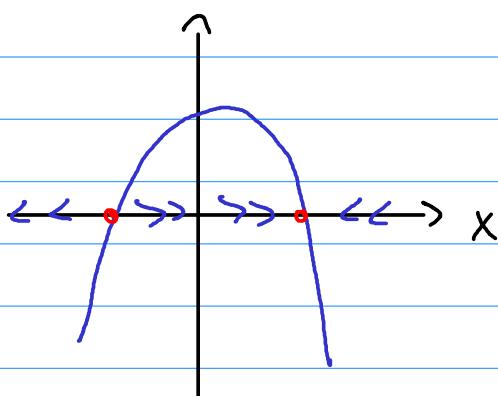
diverges at the bifurcation

"critical slowing down"

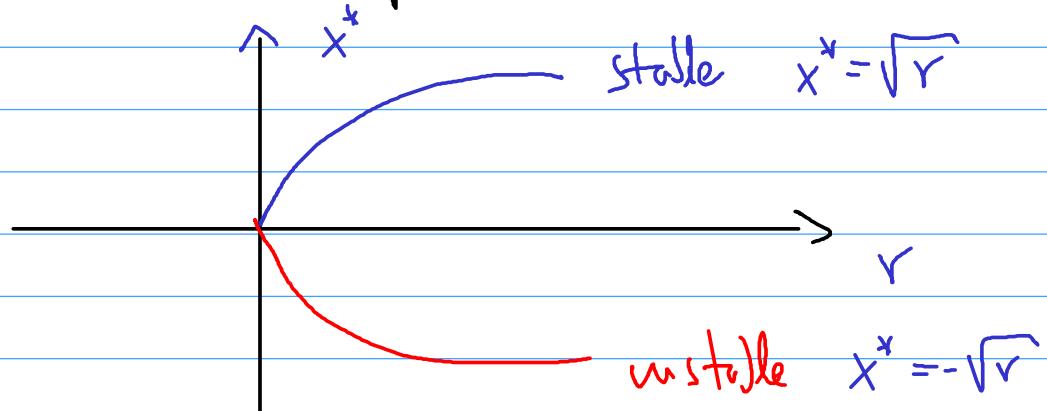
- Saddle-node bifurcation

$$\dot{x} = r - x^2 = F(x) \quad \text{FP: } x^* = \pm \sqrt{r}$$

exist if $r > 0$



Bifurcation diagram:



At the bifurcation point the stable and unstable FP annihilate

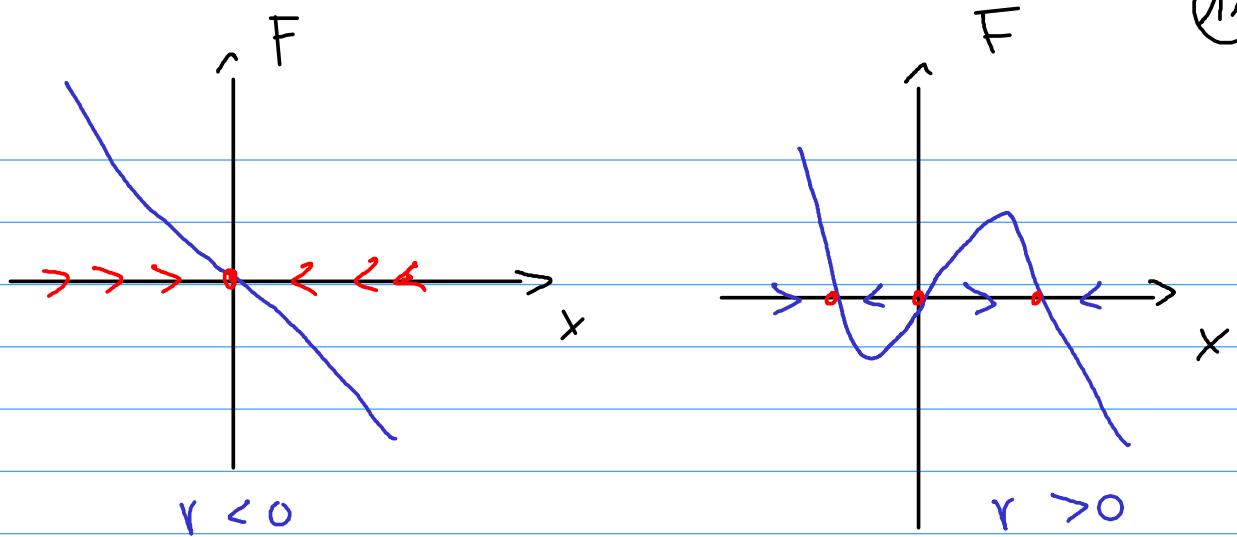
- Pitchfork bifurcation

$$\dot{x} = rx - x^3 = -\frac{\partial V}{\partial x}$$

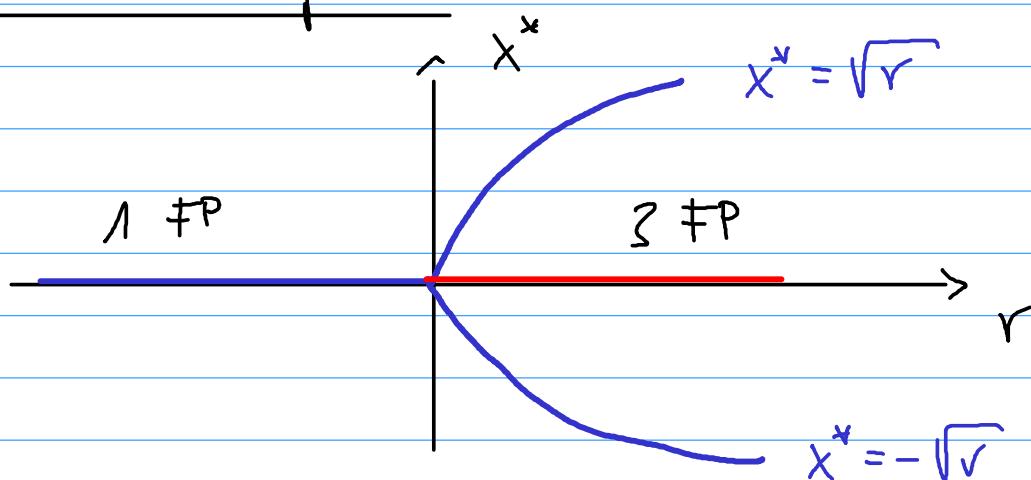
$$V(x) = -\frac{1}{2}x^2 + \frac{1}{4}x^4 \Rightarrow \text{compare to Landau theory of phase transition}$$

Dynamics is symmetric under $x \rightarrow -x$, which prevents a quadratic term in $F(x)$ (similar to Ising model at zero field)

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Bifurcation diagram



Supercritical w forward pitchfork bifurcation,
because multiple FP appear in the supercritical

regime $r > 0$

• Subcritical pitchfork bifurcation

Consider a situation where cubic term is positive,

but $X \rightarrow -X$ symmetry is preserved:

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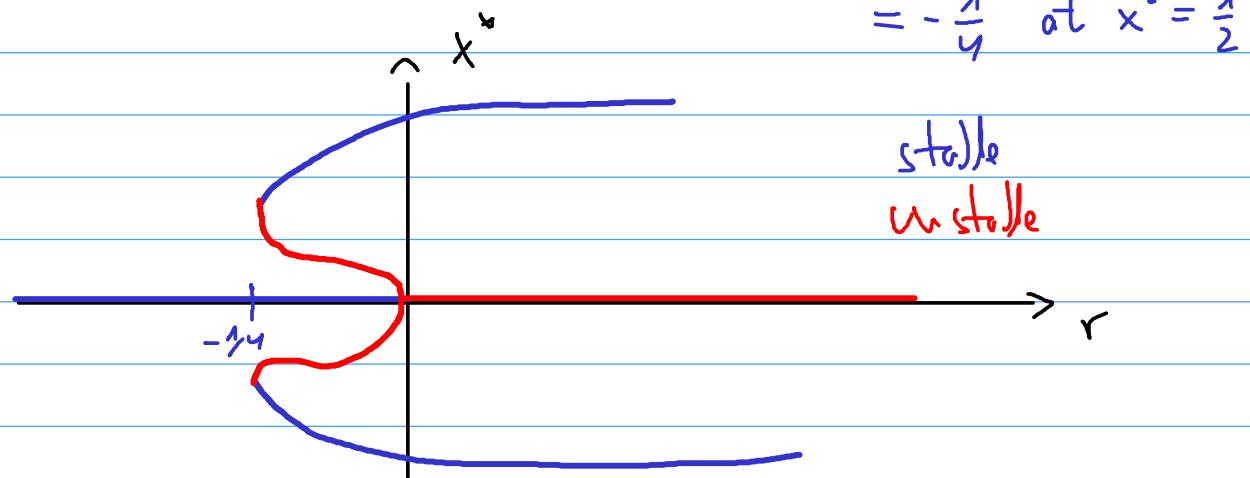
$$\dot{x} = rx + x^3 - \boxed{x^5}$$

odd odd for stability

$$= x(r + x^2 - x^4) = F(x)$$

$$\text{FP: } x=0, \quad r = x^4 - x^2 = \underbrace{x^2(x^2-1)}_{= -\frac{1}{4}} \geq -\frac{1}{4}$$

at $x^2 = \frac{1}{2}$



This can lead to hysteresis under periodic changes of r

1.5 Higher-dimensional flows

- n -dim. dynamical system

$$\dot{\underline{x}} = \underline{F}(\underline{x}) \quad \underline{x} = (x_1, \dots, x_n), \quad \underline{F} = (F_1, \dots, F_n)$$

- Fixed point: \underline{x}^* solves $\underline{F}(\underline{x}^*) = 0$

$$\Leftrightarrow F_i(x_1, \dots, x_n) = 0 \quad \forall i = 1, \dots, n$$

- Linearize dynamics around FP: $\underline{x}(t) = \underline{x}^* + \underline{\varepsilon}(t)$

$$\dot{\underline{\varepsilon}} = \underline{F}(\underline{x}^* + \underline{\varepsilon}) = \underline{F}(\underline{x}^*) + D\underline{F}(\underline{x}^*) \cdot \underline{\varepsilon} + O(|\underline{\varepsilon}|^2)$$

$$D\underline{F}(\underline{x}^*) = \begin{pmatrix} \frac{\partial F_1}{\partial x_1}(\underline{x}^*) & \frac{\partial F_1}{\partial x_2} & \dots & \frac{\partial F_1}{\partial x_n} \\ \vdots & & & \\ \frac{\partial F_n}{\partial x_1}(\underline{x}^*) & \dots & & \frac{\partial F_n}{\partial x_n}(\underline{x}^*) \end{pmatrix}$$

$n \times n$ -matrix: Jacobian at \underline{x}^*

- Solution of linearized dynamics:

- diagonalize $D\underline{F}(\underline{x}^*)$

- expand $\underline{\varepsilon}(t)$ in eigenvectors of $D\underline{F}(\underline{x}^*)$

$$\underline{\xi}(0) = \sum_{i=1}^n c_i \underline{v}_i \quad \underline{v}_i : \text{eigenvectors}$$

- time-dep. solution $\underline{\xi}(t) = \sum_{i=1}^n c_i e^{\lambda_i t} \underline{v}_i$

λ_i : eigenvalues (generally complex)

- Stability of FP is determined by the eigenvalues
real parts of

- We say that the FP is

stable: $\operatorname{Re}(\lambda_i) < 0$ for all i

unstable: $\operatorname{Re}(\lambda_i) > 0$ for some i

marginal: $\operatorname{Re}(\lambda_i) = 0$ for all i

→ { saddle: $\operatorname{Re}(\lambda_i) < 0$ for some i ,

$\operatorname{Re}(\lambda_j) > 0$ for some j

repellor: $\operatorname{Re}(\lambda_i) > 0$ for all i

2^o Dynamics of interacting populations

2.1. Predator-prey dynamics

a) Lotka-Volterra equation

A. J. Lotka (1920): chemical oscillations

V. Volterra (1926): fish populations in the Adriatic sea

$N(t)$: prey population

$P(t)$: predator population

$$\dot{N} = N(a - bP)$$

$$\dot{P} = P(cN - d)$$

$a > 0$: prey growth rate

$d > 0$: predator death rate

$c, b > 0$: interaction coefficients

- rescaled equations:

Scale time by $1/d$: $t \rightarrow \tau = d \cdot t$

$$\dot{N} = \frac{dN}{d\tau} = \frac{1}{d} \frac{dN}{dt} = N \left(\frac{a}{d} - \frac{b}{d} P \right)$$

α $=: y$

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$$\dot{P} = \frac{dP}{d\tau} = P \left(\underbrace{\frac{c}{d} N - 1}_{=x} \right)$$

$$\dot{x} = x(\alpha - y), \quad \dot{y} = y(x - 1), \quad \alpha = \frac{c}{d}$$

b) Fixed points and their stability

Two FP: $(x_0^*, y_0^*) = (0, 0)$ }
 $(x_1^*, y_1^*) = (1, \alpha)$ }

Jacobian matrix:

$(0, 0)$: $D\mathbf{F} = \begin{pmatrix} \alpha & 0 \\ 0 & -1 \end{pmatrix}$ saddle

$(1, \alpha)$: $x = 1 + \varepsilon, \quad y = \alpha + \delta$

$\Rightarrow \dot{\varepsilon} = -\delta, \quad \dot{\delta} = \alpha\varepsilon$

$$\begin{pmatrix} \dot{\varepsilon} \\ \dot{\delta} \end{pmatrix} = \underbrace{\begin{pmatrix} 0 & -1 \\ \alpha & 0 \end{pmatrix}}_{D\mathbf{F}} \begin{pmatrix} \varepsilon \\ \delta \end{pmatrix}$$

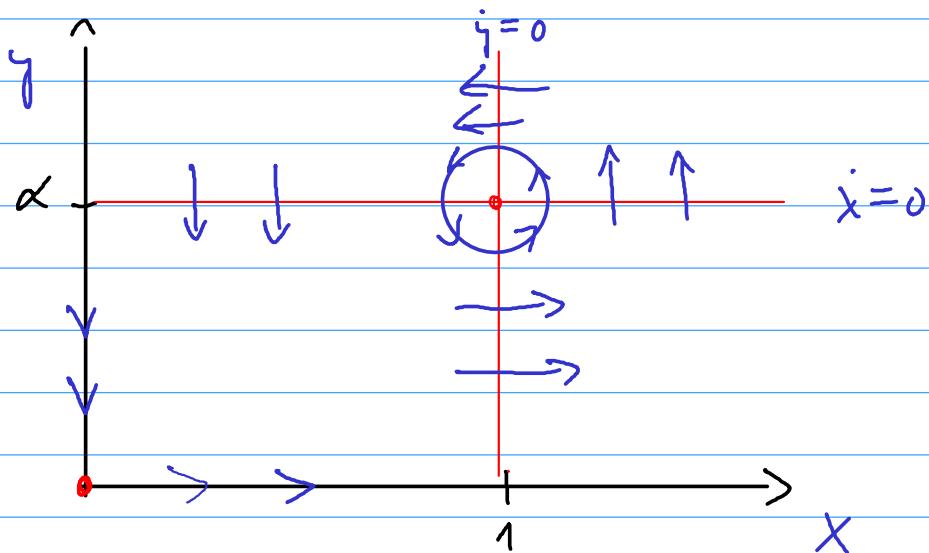
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Eigenvalues satisfy $\lambda^2 + \alpha = 0$

$$\Rightarrow \lambda = \pm i\sqrt{\alpha}$$

imaginary

c) Phase portrait



- Along the null-clines $\dot{x}=0$ ($y=\alpha$) and $\dot{y}=0$ ($x=1$) the flow is vertical and horizontal, respectively

\Rightarrow the flow is a rotation around the

FP $(1, \alpha)$



d) Conservation law

- The function

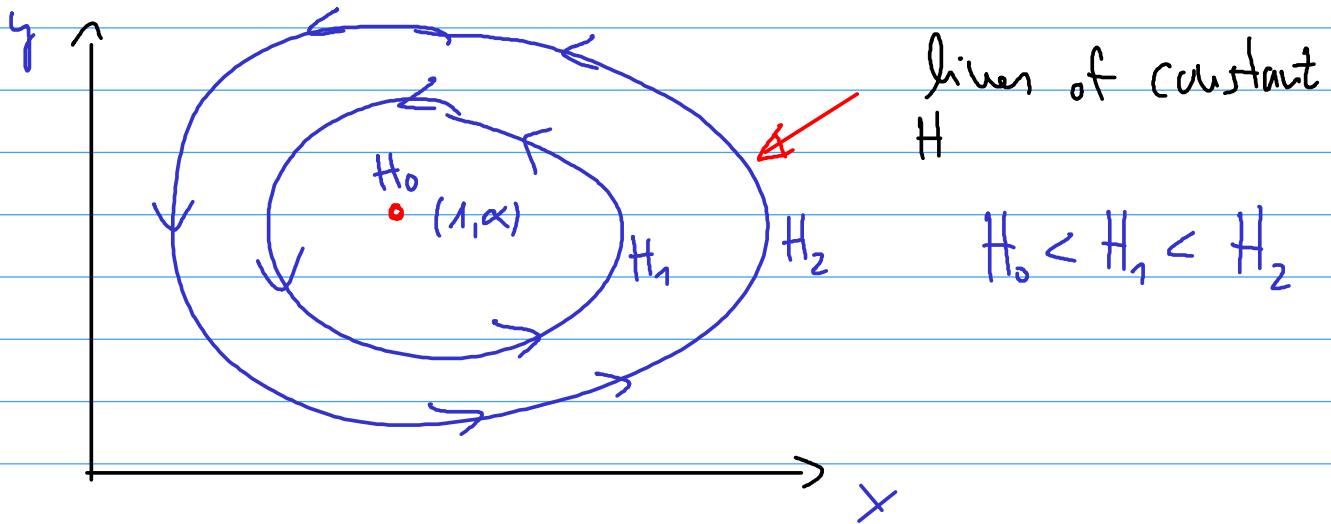
$$H(x, y) = x + y - \ln x - \alpha \ln y$$

is conserved under the dynamics:

$$\frac{d}{dt} H(x(t), y(t)) = \dot{x} + \dot{y} - \frac{\dot{x}}{x} - \alpha \frac{\dot{y}}{y} = 0$$

\Rightarrow all trajectories are lines of constant H

- $(1, \alpha)$ is the global minimum of H



- In fact, this is a Hamiltonian system:

Def: $p = \ln x, q = \ln y$

$$H = H(q, p) = e^p + e^q - p - \alpha q$$

Hamilton's equations:

$$\begin{aligned} \frac{\partial H}{\partial p} &= e^p - 1 = x - 1 = \dot{y} = \dot{q} \\ \frac{\partial H}{\partial q} &= e^q - \alpha = y - \alpha = -\frac{\dot{x}}{x} = -\dot{p} \end{aligned} \quad \left. \begin{array}{l} \text{---} \\ \text{---} \end{array} \right\}$$

e) Vulterra's principle

Consider a periodic trajectory with period T

$$0 = \ln x(T) - \ln x(0) = \int_0^T dt \frac{d}{dt} \ln x(t) =$$

$$= \int_0^T dt \frac{\dot{x}}{x} = \int_0^T dt \dot{p} = \int_0^T dt (\alpha - y) =$$

$$\alpha T - \underbrace{\int_0^T dt y(t)}_{\bar{y}} = 0$$

$$T \cdot \text{time average of } y : \bar{y} = \frac{1}{T} \int_0^T dt y(t)$$

$$\Rightarrow \boxed{\bar{y} = \alpha, \bar{x} = 1}$$

\Rightarrow time averages of x and y are equal to the FP values

- Back to the original variables:

$$\bar{N} = \frac{d}{c} \bar{x} = \frac{d}{c}, \quad \bar{P} = \frac{d}{b} \alpha = \frac{d}{b}$$

Fishing increases d and decreases a

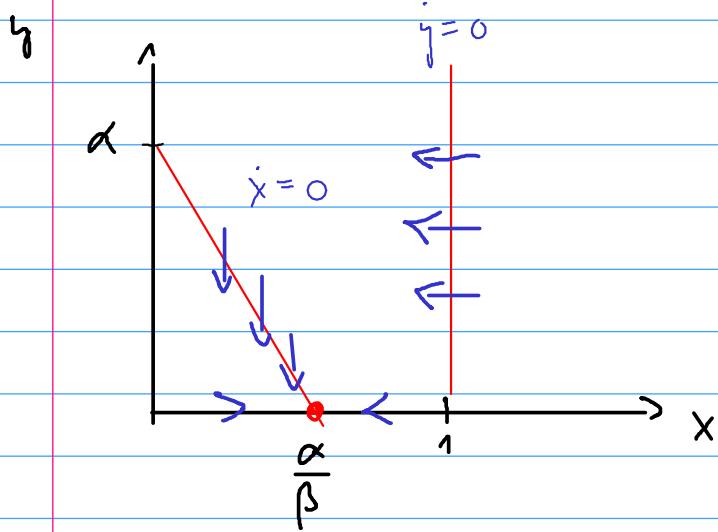
Assuming that b, c do not change:

\Rightarrow less fishing during WW1 leads to
less prey and more predators

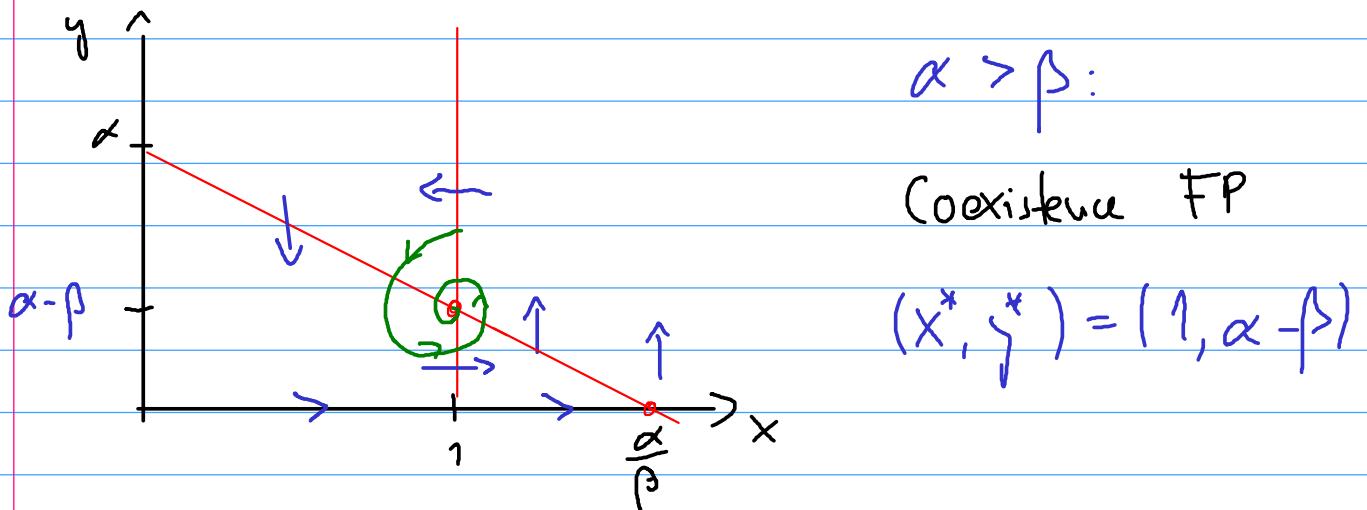
f) Prey with finite carrying capacity

$$\dot{x} = x(\alpha - y - \beta x), \quad \dot{y} = y(x-1)$$

Null clines: $\dot{x} = 0 : y = \alpha - \beta x$ "tilted"
 $\dot{y} = 0 : x = 1$



$\alpha < \beta$: Predator goes extinct



Stability of FPs

$$\underline{(\alpha/\beta, 0)}: \quad x = \frac{\alpha}{\beta} + \varepsilon, \quad \gamma = \delta$$

$$\begin{pmatrix} \dot{\varepsilon} \\ \dot{\delta} \end{pmatrix} = \begin{pmatrix} -\alpha & -\frac{\alpha}{\beta} \\ 0 & \frac{\alpha}{\beta} - 1 \end{pmatrix} \begin{pmatrix} \varepsilon \\ \delta \end{pmatrix}$$

eigenvalues $-\alpha, \frac{\alpha}{\beta} - 1$

$\alpha < \beta$: stable $\alpha > \beta$: saddle

$$\underline{(1, \alpha-\beta)}: \quad x = 1 + \varepsilon, \quad \gamma = \alpha - \beta + \delta \quad (\alpha > \beta)$$

$$\begin{pmatrix} \dot{\varepsilon} \\ \dot{\delta} \end{pmatrix} = \begin{pmatrix} -\beta & -1 \\ \alpha - \beta & 0 \end{pmatrix} \begin{pmatrix} \varepsilon \\ \delta \end{pmatrix}$$

eigenvalues: $\lambda_{1,2} = -\frac{\beta}{2} \pm \frac{\sqrt{\beta^2 - 4(\alpha - \beta)}}{2}$

\Rightarrow FP is stable (attracting)

small β : $\lambda_{1,2} = -\frac{\beta}{2} \pm i\sqrt{\alpha}$

\Rightarrow flow spirals into the FP,
no sustained oscillations ("friction")

What happens to the conserved quantity?

Consider the modified "Hamiltonian"

$$H(x, y) = x + y - \lambda x - (\alpha - \beta) \ln y$$

Then

$$\frac{d}{dt} H(x(t), y(t)) = -\beta(1-x)^2 < 0$$

H decreases monotonically with the flow,
and is an example of a Lyapunov function.

For $t \rightarrow \infty$ system evolves to the global
minimum of H , which is at $(1, \alpha - \beta)$

\Rightarrow this FP is globally attracting (for $\alpha > \beta$)

2.2. Competitive exclusion

- General model of two competing species:

$$\dot{x} = x(a - bx - cy) \quad a, b, c, d, e, f > 0$$

$$\dot{y} = y(d - ex - fy)$$

- Null-clines: $\dot{x} = 0 : y = \frac{1}{c}(a - bx)$
- $\dot{y} = 0 : y = \frac{1}{f}(d - ex)$

- Coexistence: Are there (stable) FP with

$$x^* > 0, y^* > 0 ?$$

FP are crossing points of the null-clines

- Three scenarios:

(i) Null-clines do not intersect

\Rightarrow one species goes extinct

(ii) Null-clines intersect at stable FP

\Rightarrow coexistence

(iii) Null-clines intersect at unstable FP

Special case: Both species feed on the same resource R

$$R = \bar{R} - c_1 x - c_2 y \quad c_1, c_2 > 0$$

\Rightarrow birth rates of both species are proportional to R

$$\dot{x} = x(\lambda_1 R - d_1) =$$

$$= x(\lambda_1 \bar{R} - d_1 - \lambda_1 c_1 x - \lambda_1 c_2 y)$$

$$\dot{y} = y(\lambda_2 R - d_2) =$$

$$= y(\lambda_2 \bar{R} - d_2 - \lambda_2 c_1 x - \lambda_2 c_2 y)$$

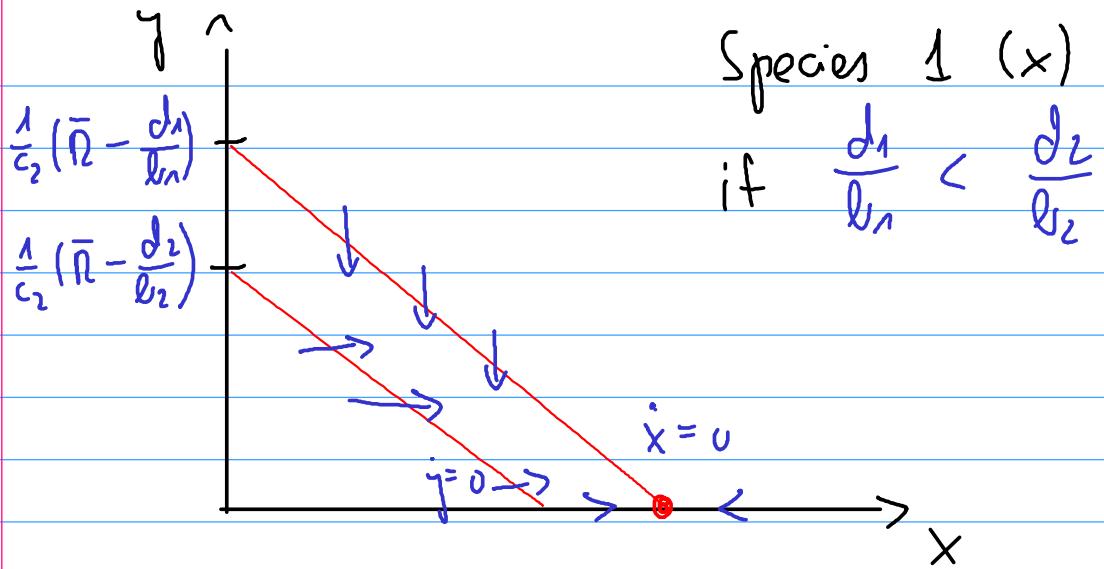
Null-clines:

$$\dot{x} = 0: \quad y = \frac{1}{c_2} \left(\bar{R} - \frac{d_1}{\lambda_1} - \underline{c_1 x} \right)$$

$$\dot{y} = 0: \quad y = \frac{1}{c_1} \left(\bar{R} - \frac{d_2}{\lambda_2} - \underline{c_2 x} \right)$$

\Rightarrow null-clines are parallel:

(26)



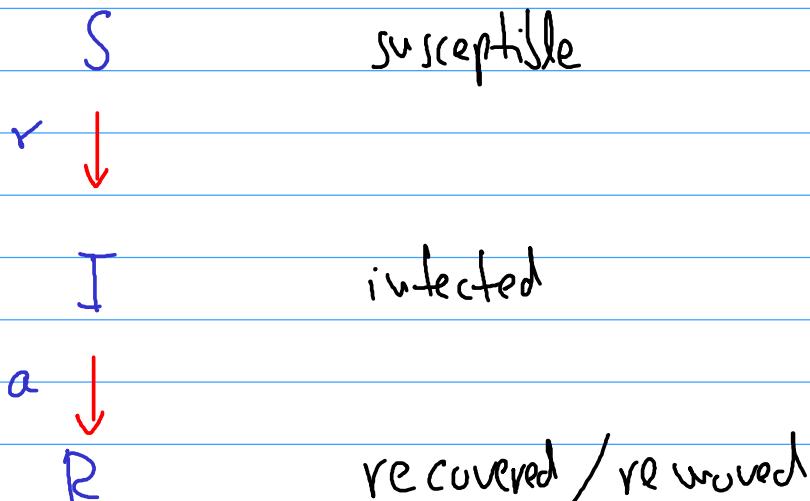
Competitive exclusion principle

One ecological niche (= resource) can accommodate at most one species

2.3. Epidemic modeling

- SIR-model (Kermack, Mc Kandrick 1927)

Population is divided into "compartments"



r : infection rate a : recovery rate

differential equations:

$$\left. \begin{array}{l} \dot{S} = -r SI \\ \dot{I} = r SI - a I \\ \dot{R} = a I \end{array} \right\} \quad N = S + I + R \text{ conserved}$$

initial conditions: $S(0) = S_0$, $I(0) = I_0$, $R(0) = 0$

$R(t)$ does not affect the dynamics
 \Rightarrow two-dimensional problem

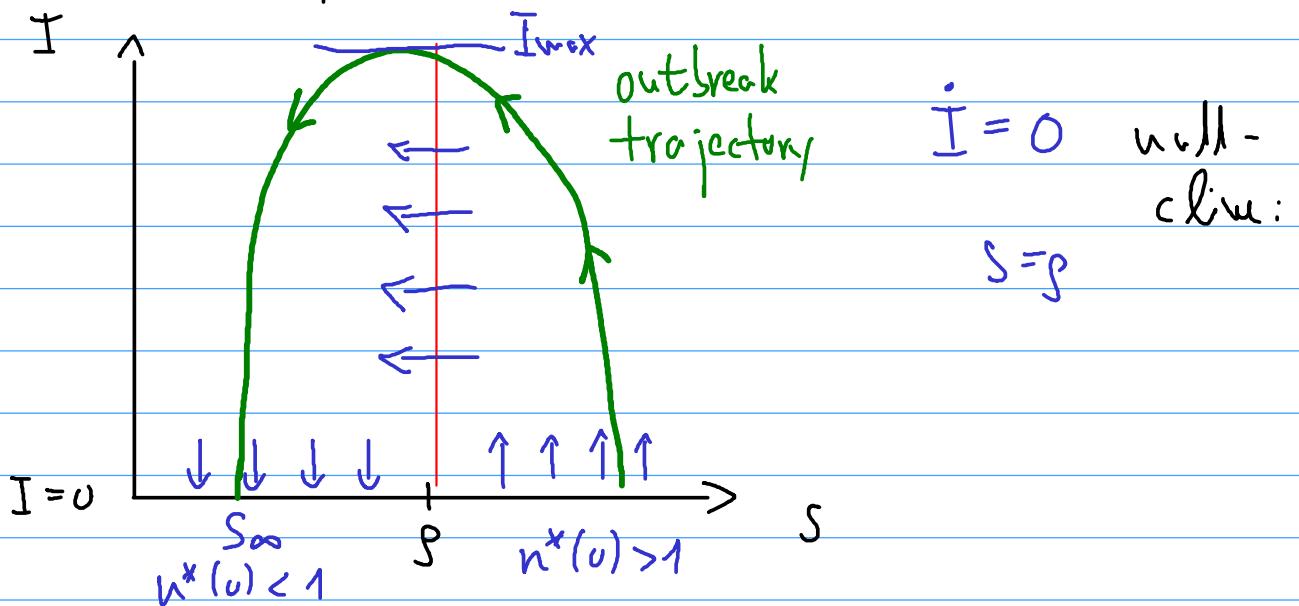
- $\dot{I} = 0$ is a line of FPs

$$\dot{I} = I(rS - \alpha)$$

FP are unstable if $S > \frac{\alpha}{r} =: g$

stable if $S < g$

- Phase portrait:



- Reproductive number: n^*

n^* : Number of other individuals that are
infected by an infected person

Duration of an infection?

Probability to still be infected after time T

$$p_I(t) = e^{-at} \quad a: \text{recovery rate}$$

Number of infected increases at rate rS

$$\Rightarrow n^*(t) = \int_t^\infty dt' p_I(t'-t) r S(t')$$

assume $S(t)$ changes slowly

$$\Rightarrow n^*(t) \approx r S(t) \int_t^\infty dt' e^{-a(t'-t)} = \frac{r}{a} S(t)$$


$$t=0: \quad n^*(0) = \frac{r}{a} S_0 = \frac{S_0}{\rho} \approx 1/\rho$$

Example: Covid-19 in Germany

$$S_0 \approx 8 \cdot 10^7, \quad a \approx 0.1 \cdot \text{day}^{-1}, \quad n^*(0) = 3$$

$$r = 4 \cdot 10^{-9} \text{ day}^{-1}$$

- Relation to Lotka-Volterra model:

S, I satisfy predator-prey dynamics without prey birth ($\alpha = 0$)

- As a consequence there is a conserved quantity ("Hamiltonian")

$$H = r(S+I) - \alpha \ln S = \\ = r(S+I - \beta \ln S)$$

- Peak of the epidemic:

$$I = I_{\max} \text{ when } S = \rho \text{ (at } t = t_{\max})$$

$$H(t=0) = r(S_0 + I_0 - \beta \ln S_0)$$

$$I_0 \ll S_0 \approx N \text{ total population size}$$

$$H(t=0) = \underline{r(N - \beta \ln N)} = \\ = H(t=t_{\max}) = \underline{r(\rho + I_{\max} - \beta \ln \rho)}$$

$$\Rightarrow \underline{I_{\max}} = N - \rho - \rho \ln \left(\frac{N}{\rho} \right) = \\ = N \left(1 - \underline{\frac{1 + \ln(u^*(0))}{u^*(0)}} \right)$$

$$u^*(0) = 1 + \varepsilon, \quad \varepsilon \ll 1 : \quad \frac{I_{\max}}{N} = \frac{\varepsilon^2}{2} \quad \} \\ u^*(0) = 3 \quad I_{\max}/N \approx 0.30 \quad \}$$

- Final size of the epidemic

$$H(t=0) = r(N - \beta \ln N) =$$

$$= H(t \rightarrow \infty) = r(S_\infty - \beta \ln S_\infty)$$

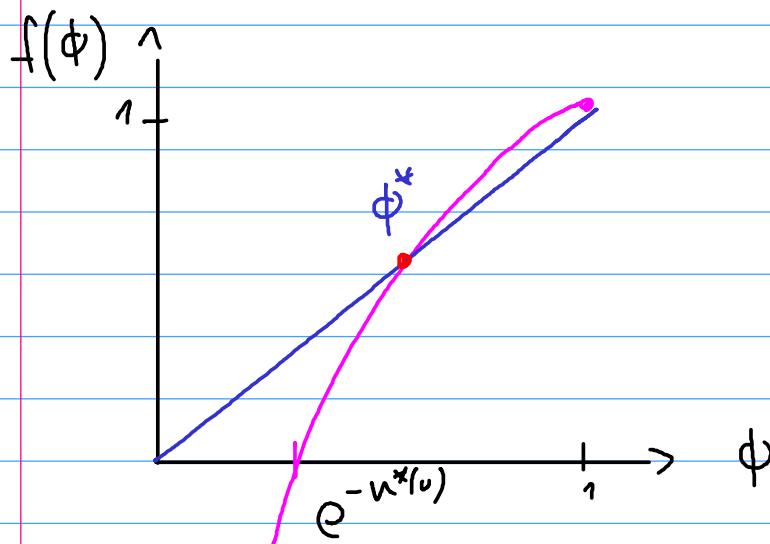
$$\Rightarrow S_\infty = N - \beta \ln \left(\frac{N}{S_\infty} \right) =$$

$$= N \left(1 - \frac{1}{\bar{N}^*(0)} \ln \left(\frac{N}{S_\infty} \right) \right)$$

Fraction of unaffected individuals $\phi = \frac{S_\infty}{N}$

satisfies

$$\phi \stackrel{?}{=} 1 - \frac{\ln(1/\phi)}{\bar{N}^*(0)} =: f(\phi)$$



$$f(\phi) = 0 \text{ at}$$

$$\phi = e^{-\bar{N}^*(0)}$$

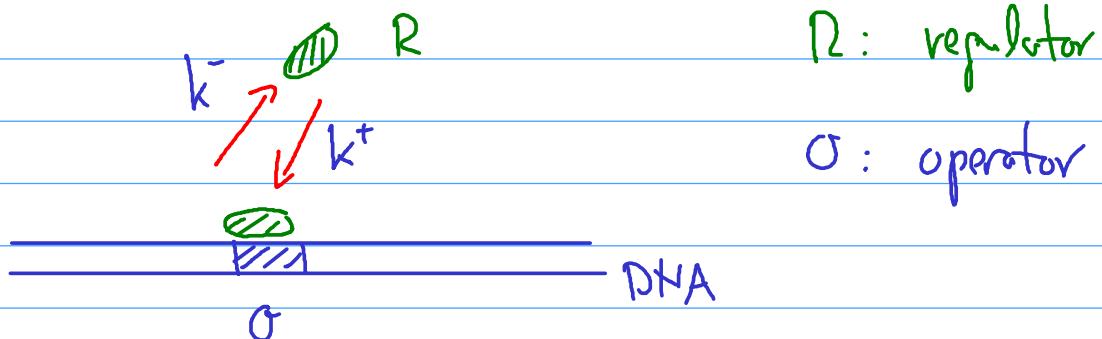
$$0 < e^{-\bar{N}^*(0)} < \phi^* < 1$$

3° How linear dynamics in gene regulation

3.1. Molecular mechanisms

a) Mass-action kinetics

- basic situation



- chemical reaction: $R + O \xrightleftharpoons[k^-]{k^+} RO$
- chemical rate equations:

Concentrations x_R , x_O , x_{RO}

$$\dot{x}_R = k^- x_{RO} - k^+ x_R \cdot x_O = 0 \quad \text{equilibrium}$$

$$\Rightarrow x_{RO} = \frac{k^+}{k^-} x_R \cdot x_O$$

chemical notation: $x_R = [R]$, $x_O = [O]$, $x_{RO} =$

$$\Rightarrow \frac{[R][O]}{[RO]} = \frac{k^-}{k^+} =: K \quad = [RO]$$

dissociation constant

(33)

\Rightarrow "law of mass action"

Note: K is a concentration

- Total concentrations of R and O :

$$[O]_T = [O] + [RO], \quad [R]_T = [R] + [RO]$$

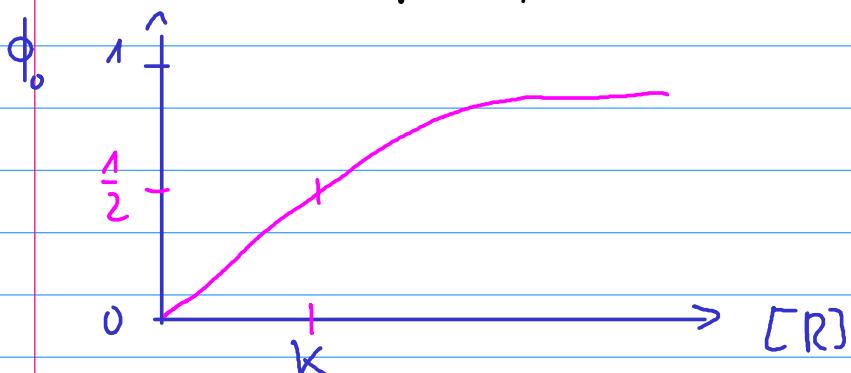
\uparrow \uparrow
 free bound

Fraction (of time) that operator is occupied:

$$\phi_o = \frac{[RO]}{[O]_T} = \frac{1}{K} \frac{[R][O]}{[O] + \frac{1}{K}[R][O]} =$$

$$= \frac{[R]}{K + [R]} \underset{\approx}{\sim} \frac{[R]_T}{K + [R]_T}$$

because typically $[R] \gg [RO], [O]$

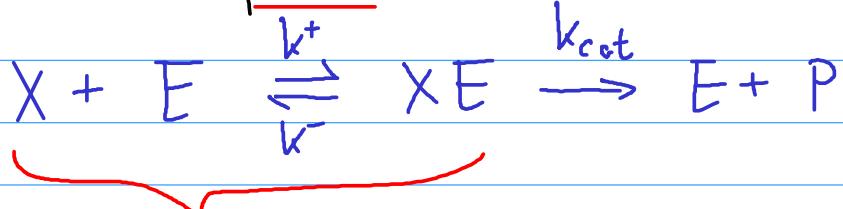


1st order kinetics

b) Michaelis-Menten kinetics (Sweppen, 10.2)

Enzyme E catalyses the reaction of a substrate

X into a product P:



law of mass action:

$$\frac{([X]_T - [XE])([E]_T - [XE])}{[XE]} = K = \frac{k^-}{k^+}$$

Assume reaction $XE \rightarrow E + P$ quickly depletes

$[XE]$, i.e. $[XE]^2 \ll [X]_T [E]_T$, then

$$\underline{[XE]} = \frac{[X]_T [E]_T}{K + [X]_T + \cancel{[E]_T}} \approx \frac{[X]_T [E]_T}{K + [X]_T}$$

$\cancel{[X]_T \gg [E]_T}$

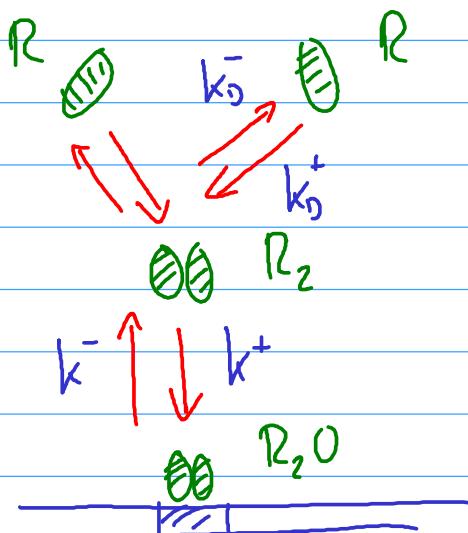
Rate of enzymatic reaction:

$$r_{X \rightarrow P} = k_{cat} \cdot [XE] = \frac{k_{cat} [X]_T [E]_T}{K + [X]_T}$$

Michaelis-Menten law (1913)

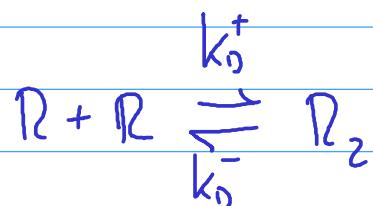
c) Cooperativity

- Suppose the regulator can bind to the operator only in the form of a dimer:



dimerization equilibrium

$$\frac{[R]^2}{[R_2]} = K_D = \frac{k_D^-}{k_D^+}$$



- Fraction of occupied operators:

$$\phi_o = \frac{[R_2 O]}{[O]_T} = \frac{[R_2]}{K + [R_2]} = \frac{[R]^2}{KK_D + [R]^2}$$

1st order result

- Total concentration of regulators.

$$[R]_T = [R] + 2[R_2] = [R] \left(1 + \frac{2[R]}{K_D} \right)$$

\uparrow \uparrow
 monomer dimer

- Limiting cases:

(i) $[R]_T \ll K_D : [R]_T \approx [R]$

$$\Rightarrow \phi_o \approx \frac{[R]_T^2}{KK_D + [R]_T^2}$$

second
order
kinetics

(ii) $[R]_T \gg K_D : [R]_T \approx \frac{2[R]^2}{K_D}$

$$\Rightarrow \phi_o \approx \frac{[R]_T}{2K + [R]_T}$$

first order
kinetics

- Summarize and generalize these expressions in the form of a Hill function

$$\phi_o(x) = \frac{(x/\tilde{K})^h}{1 + (x/\tilde{K})^h}$$

$x = [R]_T$ concentration of regulator

$h=1, \tilde{K}=K$: first-order kinetics

$h=2, \tilde{K}=\sqrt{KK_D}$: second-order kinetics

h : Hill coefficient

(A.V. Hill, 1910)

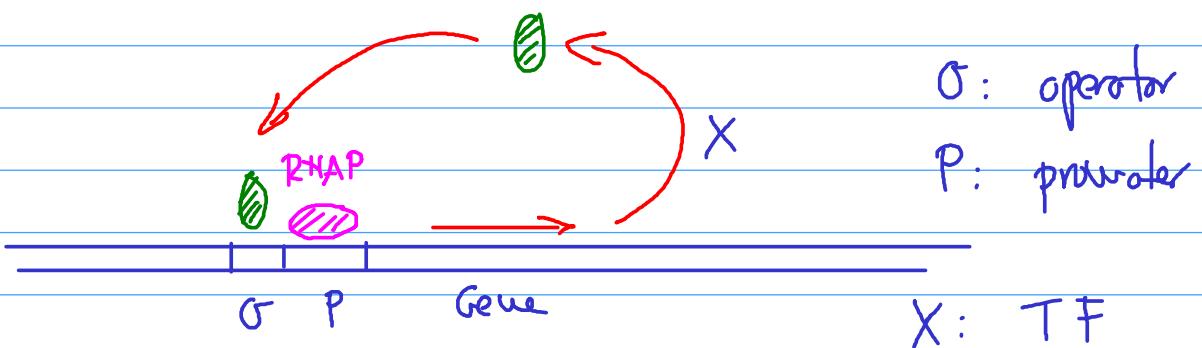
In applications to empirical data, h can take on non-integer values

Review: Goutelle et al. 2008 (\rightarrow ILIAS)

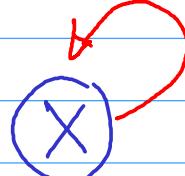
3.2. Genetic switches

a) Self-activating (autocatalytic) gene

- Gene codes for its own activation



Short hand notation:



- $x(t)$ concentration of X in rescaled form:

$$\dot{x} = \frac{x^h}{1+x^h} - kx = f(x), h \geq 1$$

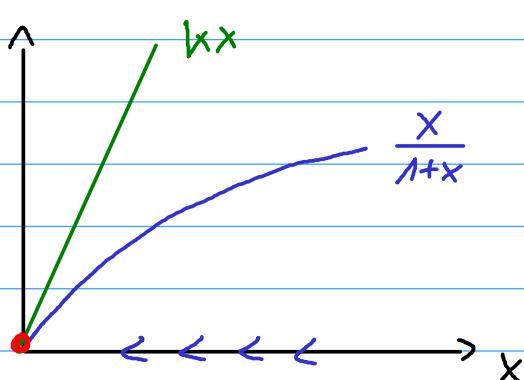
activation degrading/dilution $k > 0$

- FP: $x^* = 0$ is always a FP

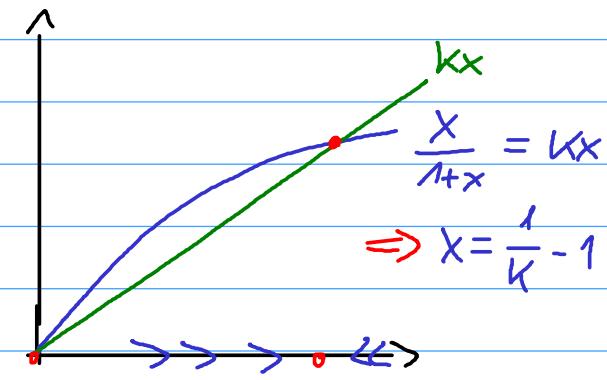
stability: $f'(0) = \begin{cases} 1-k & h=1 \\ -k & h>1 \end{cases}$

$h > 1$: $x^* = 0$ always stable

$h=1$:

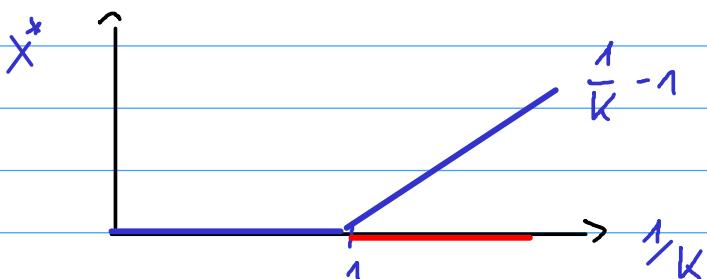


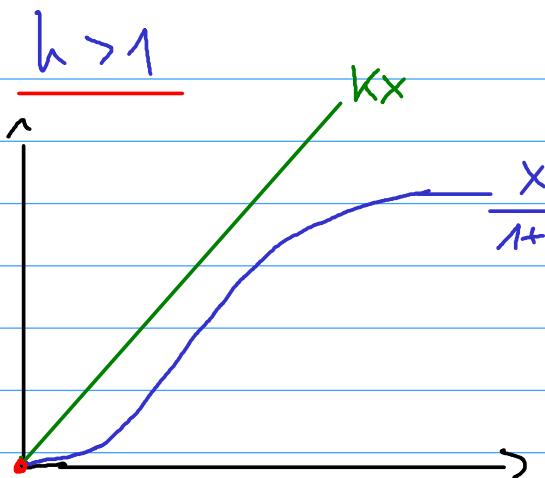
$k > 1$



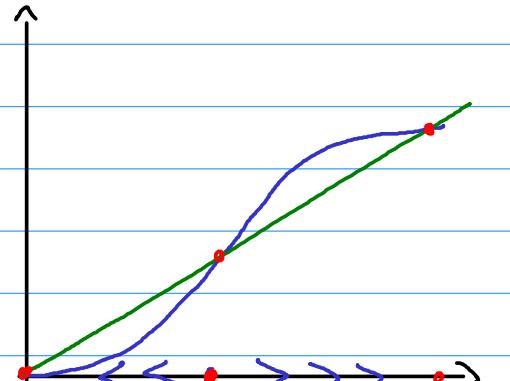
$k < 1$

\Rightarrow at $k=1$ new FP appears through a
transcritical bifurcation



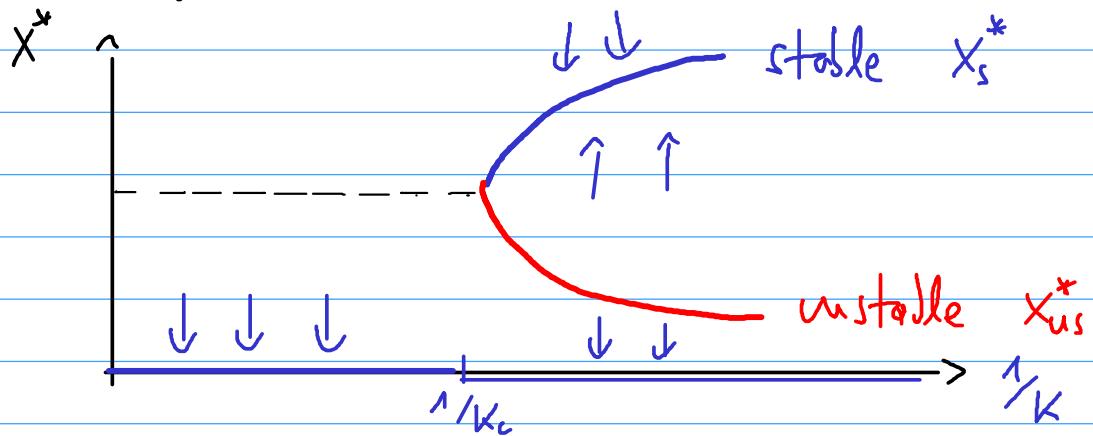


$$K > K_c$$

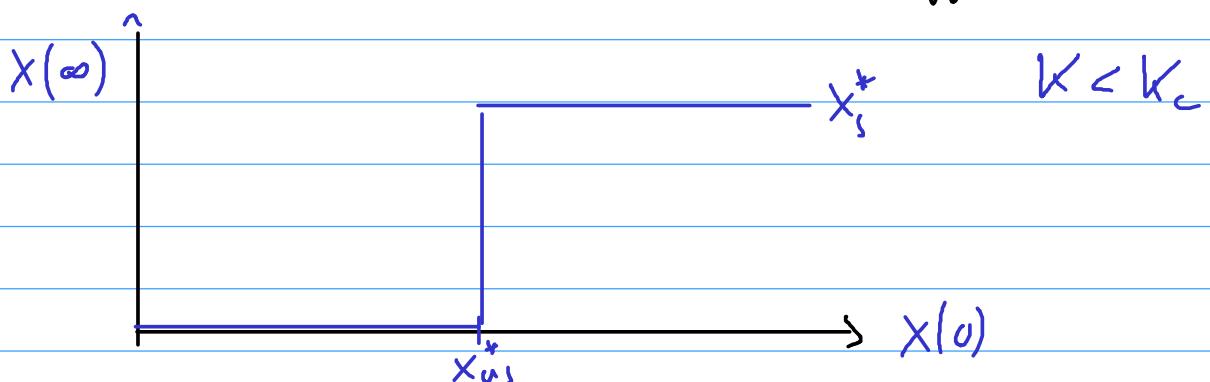


$$K < K_c$$

\Rightarrow supercritical saddle-node bifurcation at K_c



- For $K < K_c$ system is bistable; one can be switched on and off by changing the initial concentration ("toggle switch")



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b) Two mutually repressing genes

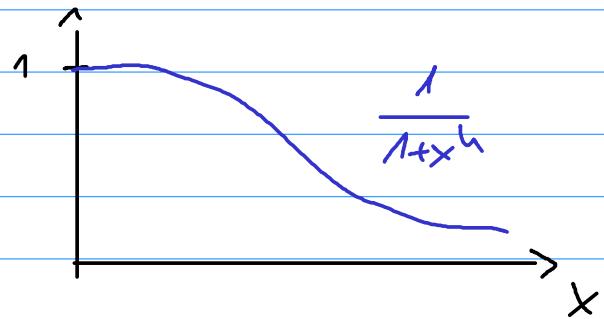
schematic:



$$\text{Prob}[\text{ suppression}] = \phi_0 = \text{Prob}[G \text{ is occupied}]$$

$$\Rightarrow \text{Prob}[\text{ gene is active }] = 1 - \phi_0 = 1 - \frac{x}{1+x^h} =$$

$$= \frac{1}{1+x^h}$$

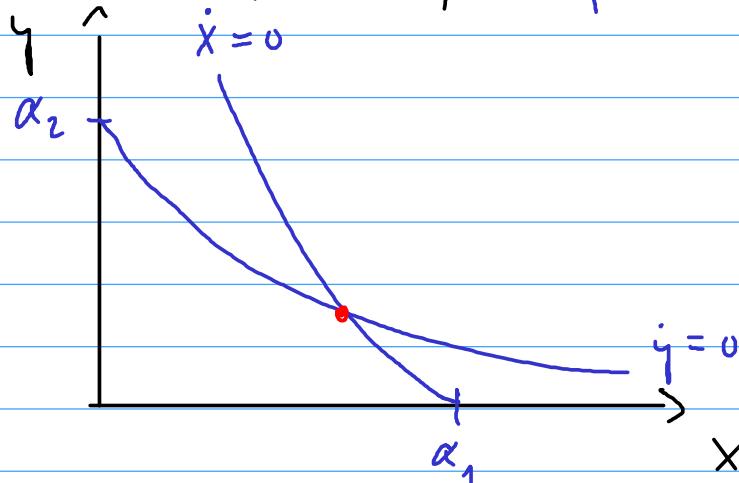


Model: $x = [X]$, $y = [Y]$

$$\begin{aligned} \dot{x} &= \frac{\alpha_1}{1+y^\beta} - x \\ \dot{y} &= \frac{\alpha_2}{1+x^\gamma} - y \end{aligned} \quad \left. \begin{array}{l} \text{parameters:} \\ \alpha_1, \alpha_2, \beta, \gamma \end{array} \right\}$$

$$\begin{aligned} \text{Null-clines: } \dot{x} = 0 : \quad x &= \frac{\alpha_1}{1+y^\beta} \\ \dot{y} = 0 : \quad y &= \frac{\alpha_2}{1+x^\gamma} \end{aligned} \quad \left. \begin{array}{l} \\ \end{array} \right\}$$

No cooperativity: $\beta = \gamma = 1$



\Rightarrow always unique

crossing point / FP

Linear stability of FP: $\alpha_1 = \alpha_2 = 2$

\Rightarrow FP $(x^*, y^*) = (1, 1)$

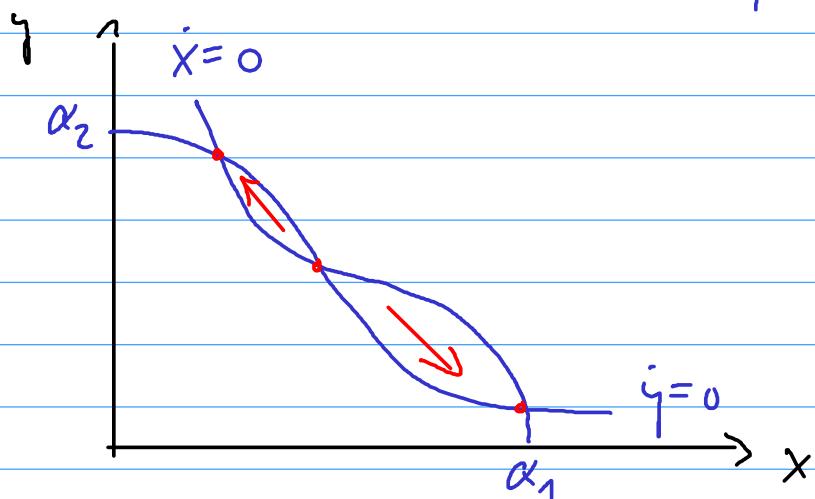
$x = 1 + \varepsilon, y = 1 + \delta$:

$$\begin{pmatrix} \dot{\varepsilon} \\ \dot{\delta} \end{pmatrix} = \begin{pmatrix} -1 & -\frac{1}{2} \\ -\frac{1}{2} & -1 \end{pmatrix} \begin{pmatrix} \varepsilon \\ \delta \end{pmatrix}$$

$$\Rightarrow \lambda_{1,2} = -1 \pm \frac{1}{2} \text{ stable}$$

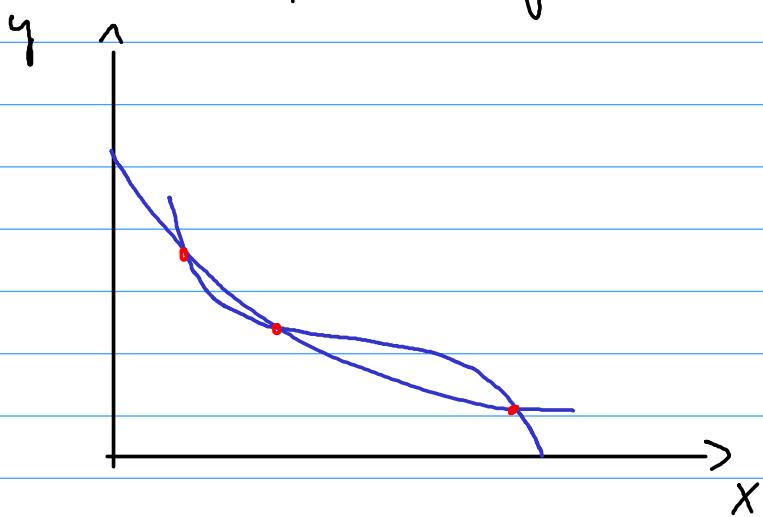
\Rightarrow no bistability, no switching

With cooperativity: $\beta, \gamma > 1$



3 fp,
2 stable, 1 unstable

One cooperative gene



- Generic situation in presence of cooperativity:

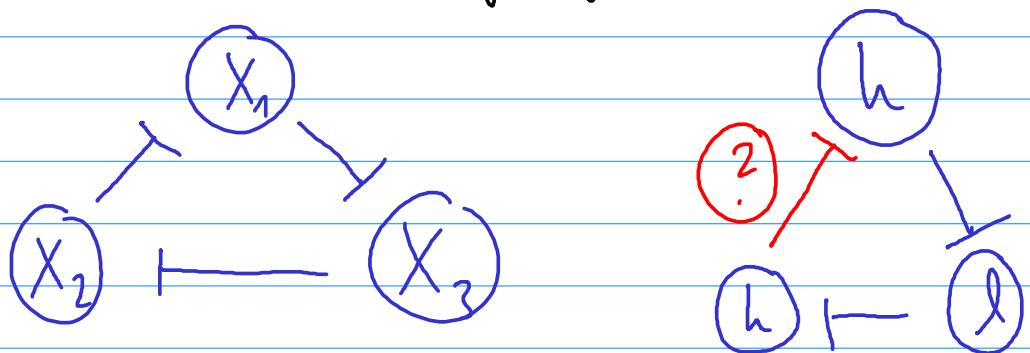
2 stable states $(x_{\text{high}}, y_{\text{low}})$

$(x_{\text{low}}, y_{\text{high}})$

Switching can be induced by pulses of
 x or y

3.3. Genetic oscillators

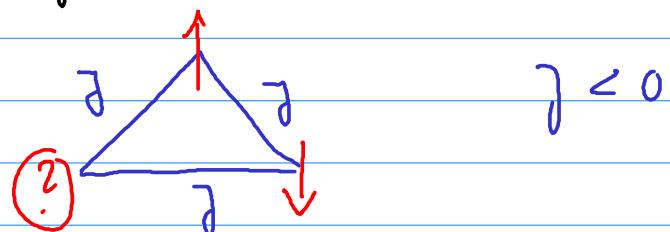
Three mutually repressing genes



Is there a state (FP) where for each pair of genes one is on (high concentration h) and the other is off (l)? No

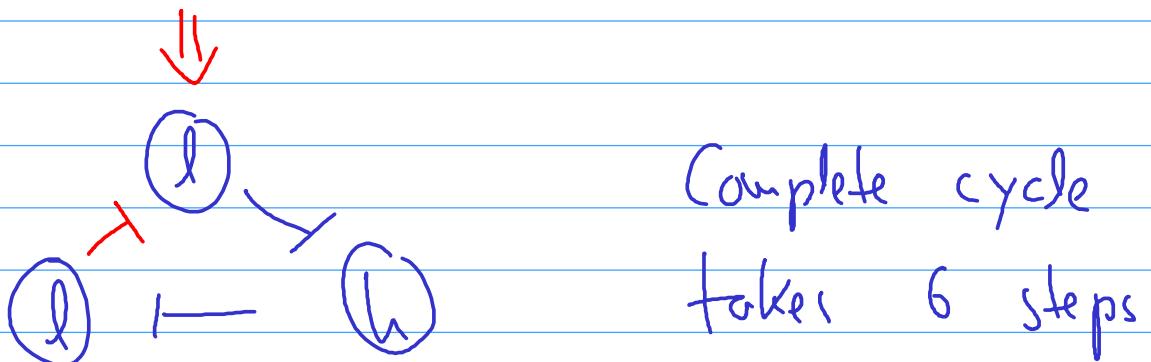
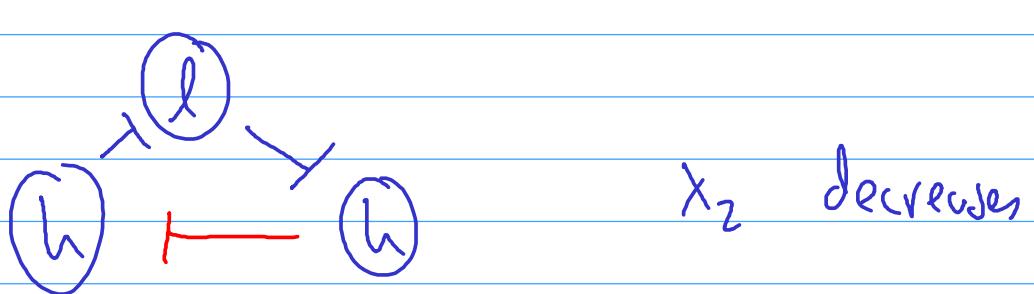
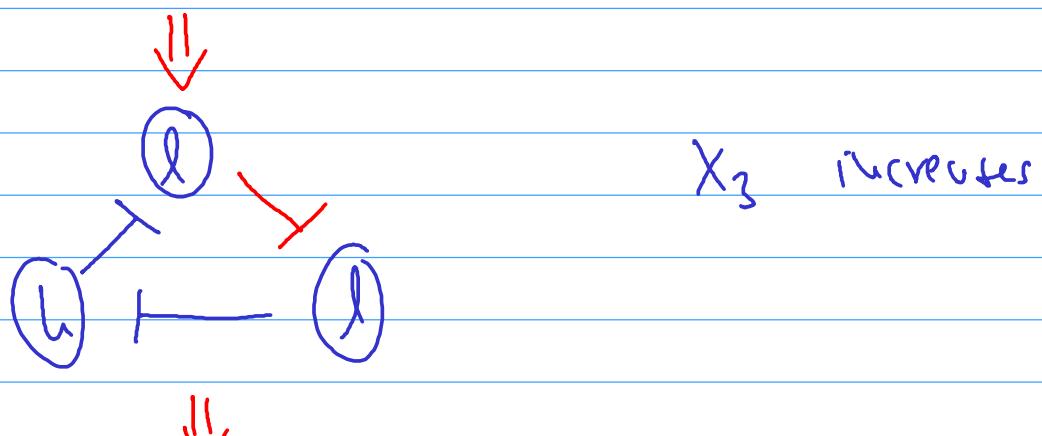
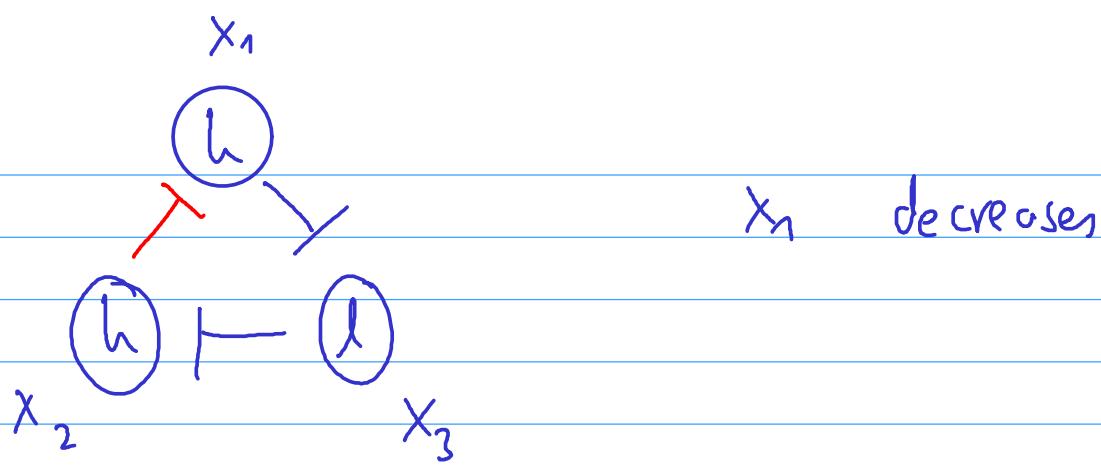
Frustration: All constraints cannot be satisfied simultaneously

Example: Antiferromagnetic Ising model on triangular lattice



Solution in the case of gene expression: Cycle

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Complete cycle
takes 6 steps

Model : Elowitz, Leibler 2000

x_i protein concentration of gene $i=1,2,3$

y_i mRNA - concentration of gene $i=1,2,3$

Model is symmetric, i.e. all three genes have identical properties

$$\dot{x}_i = \beta (y_i - x_i) \quad \text{translation}$$

$$\dot{y}_i = -y_i + \frac{\alpha}{1+x_{i+1}^n} + \alpha_0 \quad \text{transcription}$$

↑
repression leakage

+ periodic boundary conditions $x_4 = x_1$

4° Chaos in dynamical systems

4.1. Iterated maps

a) Dynamical systems in discrete time

Def: One-dimensional dynamical system in discrete time is defined by a first order recursive relation

$$x_{t+1} = f(x_t), \quad x_t \in \mathbb{R}$$

Examples: Population dynamics with non-overlapping generations

(i) exponential growth or decay

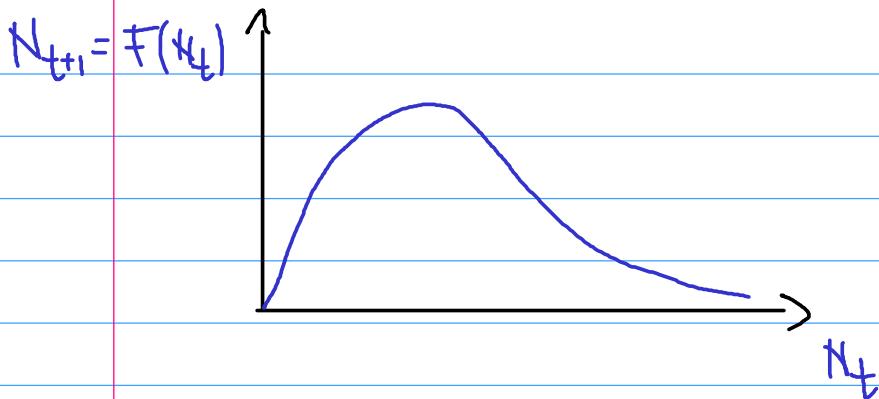
$$N_{t+1} = r N_t = e^{\beta} N_t$$

$r > 1, \beta > 0$: growth $r < 1, \beta < 0$: decay

(ii) population regulation through carrying capacity

$$N_{t+1} = \exp\left(g\left(1 - \frac{N_t}{K}\right)\right) N_t$$

Ricker, 1954



Ricker map

(iii) Verhulst process

$$N_{t+1} = r N_t \left(1 - \frac{N_t}{K}\right)$$

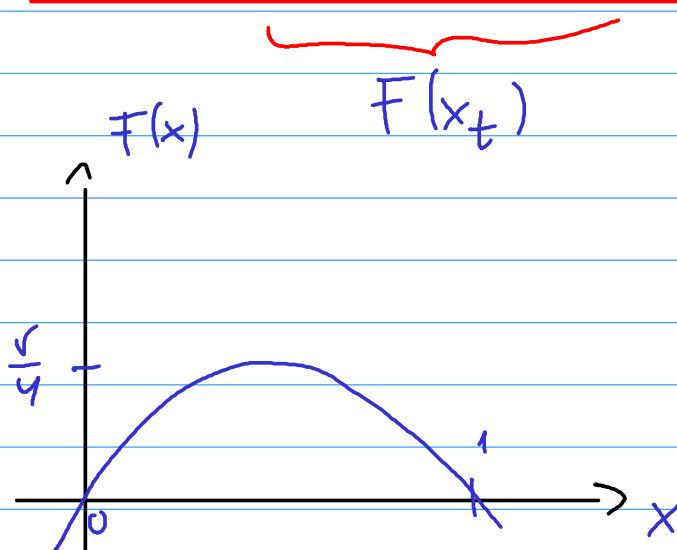
not well-defined
for $N_t > K$

$$x_t = \frac{N_t}{K}$$

\Downarrow

$$X_{t+1} = r X_t (1 - X_t)$$

logistic map



interval $[0,1]$

is mapped to
itself for $r < 4$

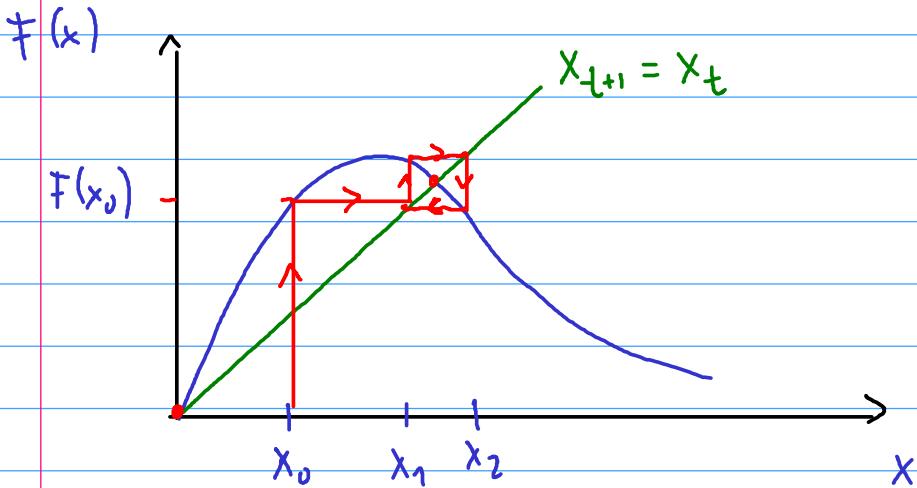
(iv) Fibonacci sequence (1202)

$$N_{t+1} = N_t + N_{t-1}$$

second-order

b) Fixed points and their stability

- Visualization of trajectories: "Cobwebbing"



- Fixed points are solutions of $F(x^*) = x^*$
- Linear stability analysis: $x_t = x^* + \varepsilon_t$

$$x_{t+1} = x^* + \varepsilon_{t+1} = F(x^* + \varepsilon_t)$$

$$\approx F(x^*) + \varepsilon_t F'(x^*)$$

$$\Rightarrow \varepsilon_{t+1} = F'(x^*) \varepsilon_t \Rightarrow \boxed{\varepsilon_t = F'(x^*)^t \varepsilon_0}$$

$|F'(x^*)| < 1$: FP stable }

$|F'(x^*)| > 1$: FP unstable }

$F'(x^*) = 0$: FP superstable }

(4g)

Example: Logistic map $0 \leq r \leq 4$

$$F(x) = r \times (1-x) \Rightarrow x^* = r x^* (1-x^*)$$

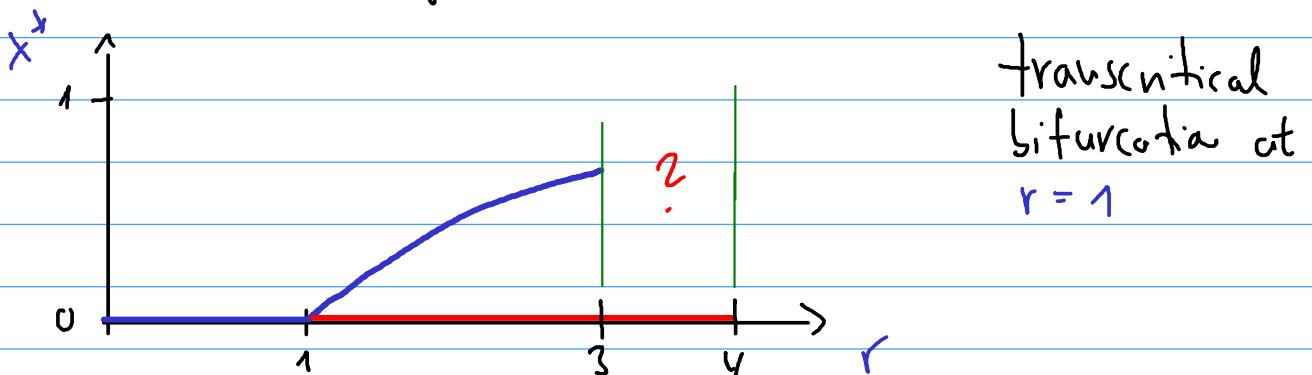
$$x_0^* = 0, \quad x_1^* = 1 - \frac{1}{r}$$

$$F'(0) = r, \quad F'\left(1 - \frac{1}{r}\right) = 2 - r$$

$0 < r < 1$: x_0^* stable, $x_1^* < 0$

$1 < r < 3$: x_0^* unstable, x_1^* stable

Bifurcation diagram:



$3 < r < 4$: No stable FP, but trajectories are confined to $[0, 1]$

c) Period doubling

- To understand what happens at $r=3$

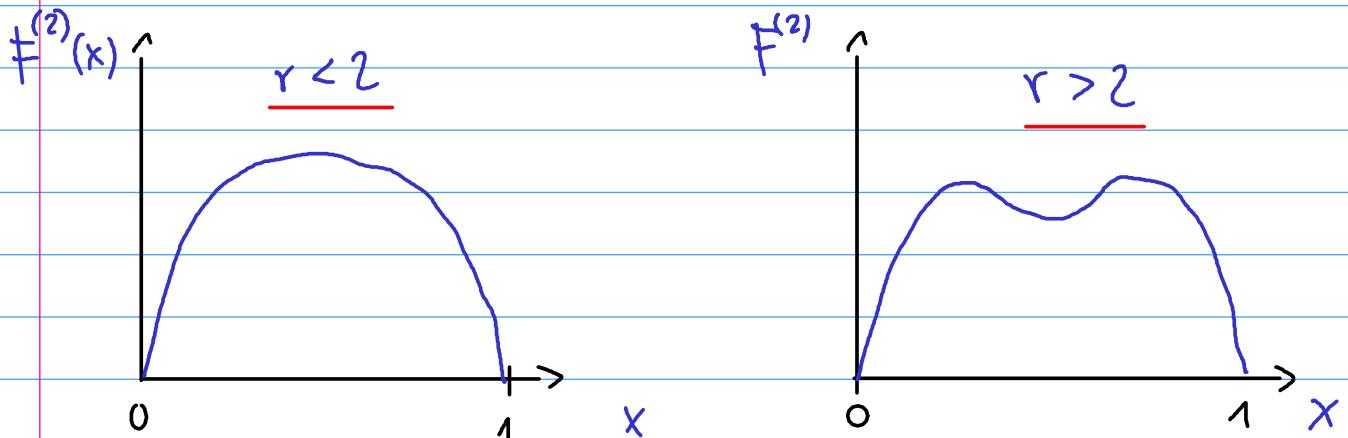
Consider the second iteration of F :

$$F^{(2)}(x) = F(F(x)) \Rightarrow x_{t+2} = F^{(2)}(x_t)$$

- Logistic map: $F(x) = r \times (1-x)$

$$F^{(2)}(x) = r^2 \times (1-x)(1-r \times (1-x))$$

polynomial of degree 4



- FP of F is also a FP of $F^{(2)}$, but converse is not true

- At $r=3$, $F^{(2)}$ undergoes a saddle-node bifurcation leading to the birth

of a 2-cycle

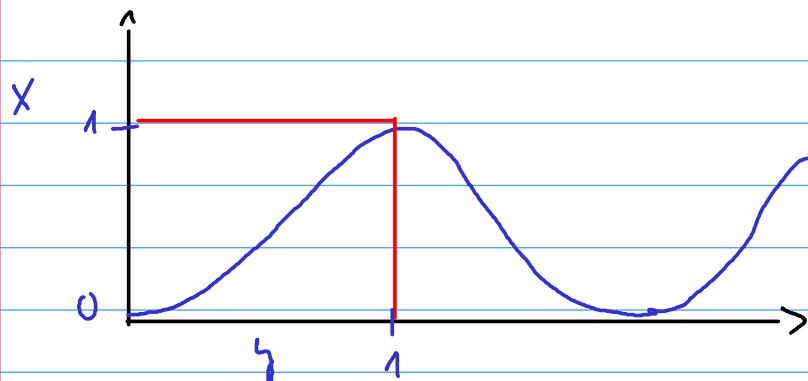
4.2. Deterministic chaos (reading: Ott)

a) Logistic map at $r = 4$

$$x_{t+1} = 4x_t(1-x_t)$$

- Variable transformation:

$$x \in [0,1] \rightarrow y \in [0,1] \text{ with } x = \sin^2\left(\frac{\pi y}{2}\right)$$



$$\begin{aligned} \sin^2\left(\frac{\pi y}{2}\right) &= \\ &= \frac{1}{2}(1 - \cos(\pi y)) \end{aligned}$$

$$x(1-x) = \frac{1}{4} \sin^2(\pi y)$$

$$\Rightarrow \boxed{\sin^2\left(\frac{\pi y_{t+1}}{2}\right) = \sin^2(\pi y_t)}$$

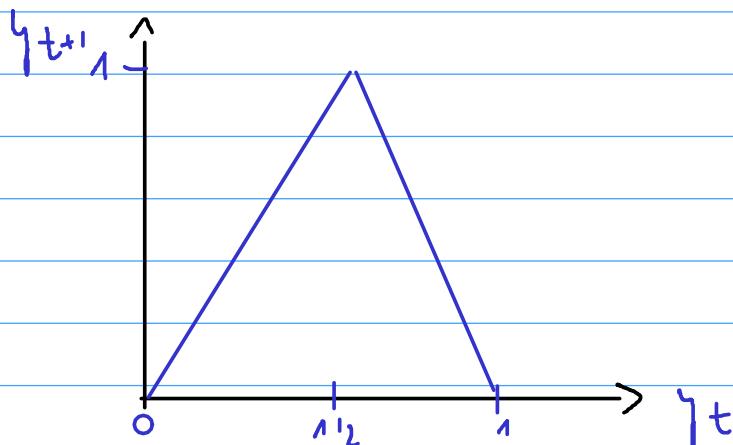
$$\Rightarrow \frac{\pi y_{t+1}}{2} = \pm \pi y_t + k\pi \quad k \in \mathbb{Z}$$

Requirement that $y \in [0, 1]$ and that
the map $y_t \rightarrow y_{t+1}$ is continuous
leads to the following:

$$\underline{0 \leq y \leq \frac{1}{2}} : \quad y_{t+1} = 2y_t \quad (k=0)$$

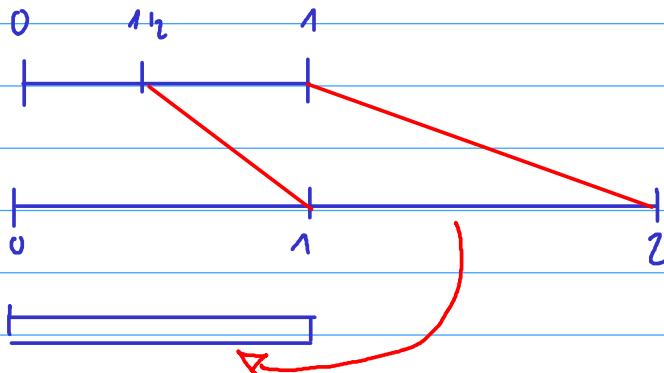
$$\underline{\frac{1}{2} \leq y \leq 1} : \quad y_{t+1} = 2(1-y_t) \quad (k=1)$$

$$\Rightarrow \boxed{y_{t+1} = 1 - 2 \left| y_t - \frac{1}{2} \right|}$$



"tent map"
piecewise linear,
continuous

- Geometric interpretation: Stretching and folding

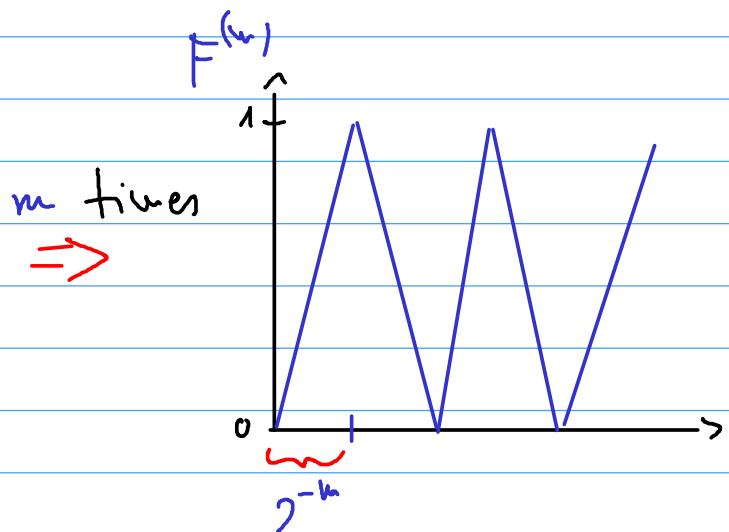
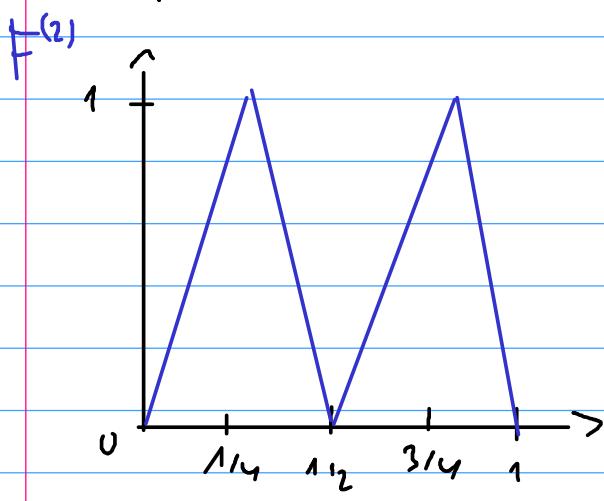


stretching: $y \rightarrow 2y$

folding

- Iterations of the tent map remain

piecewise linear



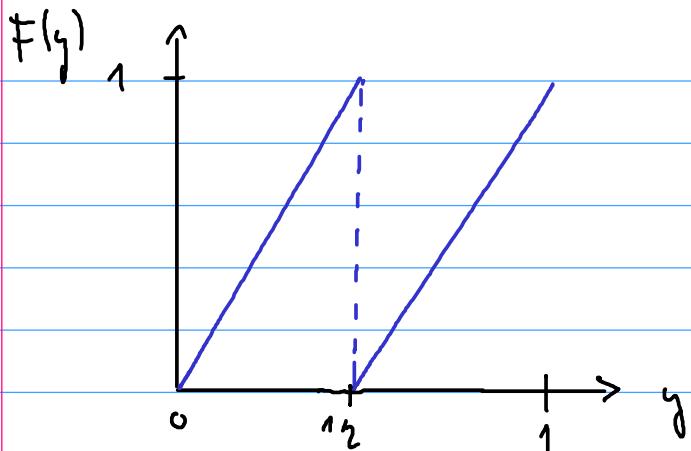
After n iterations, an interval of size $2^{-n} = \varepsilon$
is mapped to the entire interval $[0, 1]$

\Rightarrow Sensitive dependence on initial conditions

Two points at initial distance ε are at
distance $2^n \varepsilon$ after n iterations

b) Bernoulli shift

$$y_{n+1} = 2y_n \bmod 1 = \begin{cases} 2y_n & y_n < \frac{1}{2} \\ 2y_n - 1 & y_n > \frac{1}{2} \end{cases}$$



piecewise linear,
discontinuous

Represent y as a binary sequence:

$$y_0 = \sum_{k=1}^{\infty} a_{k-1} 2^{-k} = a_0 \frac{1}{2} + a_1 \cdot \frac{1}{4} + \dots$$

coefficients are $a_k \in \{0, 1\}$ and form a sequence

$$\{a_0, a_1, a_2, \dots\}$$

\Rightarrow map shifts the sequence by one digit

to the left and discards the first digit

if it is = 1

$$y_0 \stackrel{\wedge}{=} \{a_0, a_1, a_2, \dots\}$$



$$y_1 \stackrel{\wedge}{=} \{a_1, a_2, a_3, \dots\}$$

Binary expansion of a generic (\sim irrational) real number is a random sequence

\Rightarrow leading digit of y_t is equivalent to a random coin toss

c) Chaos in continuous time dynamics

- Def: Deterministic chaos: Banded aperiodic fluctuations with sensitive dependence on initial conditions
 - quantity for continuous time dynamics:
- Lyapunov exponents: Eigenvalues of the Jacobian evaluated along the trajectory
- Chaos: At least one Lyapunov exponent is positive

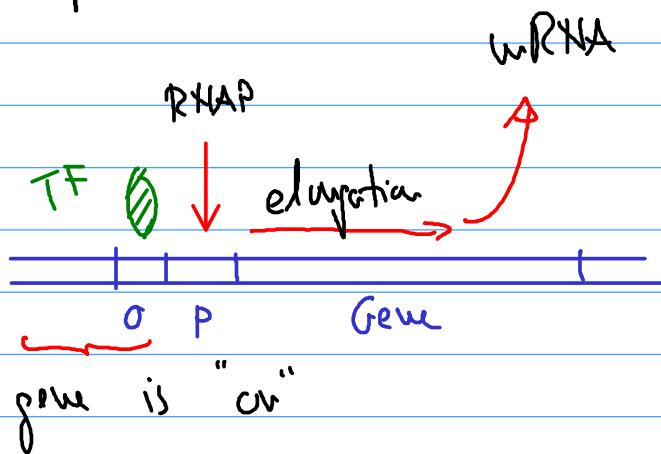
5° Elementary stochastic processes

Reading: van Kampen, Amir

5.1. Poisson distribution and Poisson process

Some molecular species is being produced at constant rate ✓

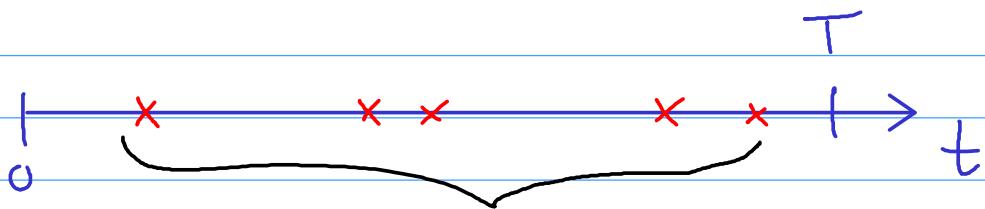
Example: mRNA transcription



- Assume transcription is limited by the attachment of the RNAP (= initiation).

Then the production of mRNA molecule reflects the random attachment events of the RNAP.

a) Random events



random events occurring at rate r

\Rightarrow what does this mean?

- (i) divide interval $[0, T]$ into N segments of size $\Delta t = T/N$, such that expected number of events in a segment $r \cdot \Delta t \ll 1$

\Rightarrow at most one event per segment:

$$\text{Prob}[\text{one event in } (t, t + \Delta t)] = p = r \cdot \Delta t \quad \}$$

$$\text{Prob}[\text{no event } \dots] = 1 - p \quad \}$$

- (ii) Distribution of the number of events n

in $[0, T]$ is binomial with success rate p

$$\begin{aligned} p_n &= \text{Prob}[n \text{ events in } [0, T]] = \\ &= p^n (1-p)^{N-n} \binom{N}{n}, \quad \binom{N}{n} = \frac{N!}{n!(N-n)!} \end{aligned}$$

(iii) Limit $\Delta t \rightarrow 0, N \rightarrow \infty, r, T$ fixed:

$$\binom{N}{u} = \frac{N!}{u!(N-u)!} = \frac{1}{u!} \prod_{k=0}^{u-1} (N-k) \rightarrow \frac{1}{u!} N^u$$

$$p^u = (r \Delta t)^u = (rT)^u N^{-u}$$

$$(1-p)^{N-u} \approx (1-r \Delta t)^{T/\Delta t} \rightarrow e^{-rT}$$

$$\lim_{\Delta t \rightarrow 0} \binom{N}{u} p^u (1-p)^{N-u} = \boxed{\frac{(rT)^u}{u!} e^{-rT}}$$

Poisson distribution

with parameter rT

b) Properties of the Poisson distribution

Poisson distribution with parameter λ

$$p_u = e^{-\lambda} \frac{\lambda^u}{u!} \quad u=0, 1, 2, \dots$$

• normalization: $\sum_{u=0}^{\infty} p_u = e^{-\lambda} \underbrace{\sum_{u=0}^{\infty} \frac{\lambda^u}{u!}}_{e^{\lambda}} = 1$

- mean: ($=$ expectation of n)

$$\text{IE}(n) = \langle n \rangle = \sum_{v=0}^{\infty} v p_v = e^{-\lambda} \sum_{v=1}^{\infty} \frac{\lambda^v}{(v-1)!}$$

↑ ↑

work physics

$$= \lambda e^{-\lambda} \sum_{v=1}^{\infty} \frac{\lambda^{v-1}}{(v-1)!} = \lambda$$

$\underbrace{= e^{-\lambda}}$

- Variance: $\text{Var}(n) = \text{IE}(n^2) - (\text{IE}(n))^2 =$

$$= \langle n^2 \rangle - \langle n \rangle^2$$

$$\text{IE}(n(n-1)) = \sum_{v=2}^{\infty} e^{-\lambda} \frac{n(n-1) \lambda^n}{n!} =$$

$$= e^{-\lambda} \sum_{v=2}^{\infty} \frac{\lambda^n}{(v-2)!} = \lambda^2 e^{-\lambda} \sum_{v=2}^{\infty} \frac{\lambda^{v-2}}{(v-2)!}$$

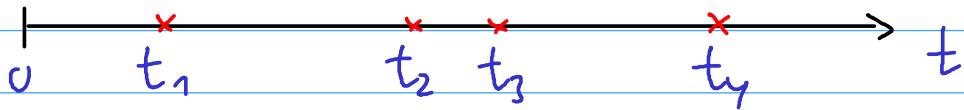
$\underbrace{= e^{-\lambda}}$

$$= \lambda^2 = \text{IE}(n^2) - \text{IE}(n)$$

$$\underline{\text{Var}(n) = \text{IE}(n^2) - (\text{IE}(n))^2 = \lambda^2 + \lambda - \lambda^2 = \lambda}$$

$\text{Var}(n) = \text{IE}(n)$

c) Waiting times



t_i : time of i -th event

$\tau_i = t_i - t_{i-1}$ waiting time for i -th event

Poisson process with rate r

$$\text{Prob}[\tau_i > \tau] = \text{Prob}[\text{no event in } (t_{i-1}, t_{i-1} + \tau)]$$

$$= e^{-r\tau}$$



according to Poisson dist.

Probability density of waiting time: $p_w(s)$

$$\text{Prob}[\tau_i > \tau] = \int_{\tau}^{\infty} ds p_w(s) = e^{-r\tau}$$

$$p_w(\tau) = -\frac{d}{d\tau} e^{-r\tau} = \underline{r e^{-r\tau}}$$

exponential distribution
with parameter r

\Rightarrow waiting times between random events
are exponentially distributed

- Generalization: Renewal process

Point process (= process of points on the line)

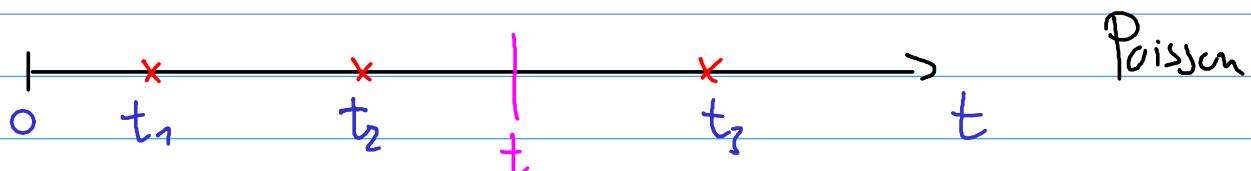
where waiting times are independent,
identically distributed random variables with
some p.d.f. density $p_w(\tau)$

- Properties of the exponential distribution:

$$\langle \tau \rangle = \int_0^\infty ds s r e^{-rs} = 1/r$$

$$\text{Var}(\tau) = 1/r^2$$

- Waiting time paradox



Observe process from random time point t

- expected time to next event = $\frac{1}{\lambda}$
 - expected time since last event = $\frac{1}{\lambda}$
- \Rightarrow expected time between two events = $\frac{2}{\lambda}$

Resolution of the "paradox":

Probability for a random point to lie between two events is proportional to the waiting time

\Rightarrow larger waiting times are overrepresented

$$p_w(\tau) \longrightarrow \tau p_w(\tau)$$

effective waiting time

distribution seen from a random time pt.

d) Measures of randomness

General: Compare variance of a ~~random~~ variable to its mean

~~non-negative~~

(i) Index of dispersion / Fano factor

Meaningful for counting processes, i.e.

random variable $n = 0, 1, 2$ is non-negative

integer

$$f(n) = \frac{\text{Var}(n)}{\text{E}(n)}$$

$f = 1$ for Poisson process

\Rightarrow quantifies deviation from Poisson process

- overdispersed : $f > 1$
- underdispersed : $f < 1$

Example : Distribution of secondary infections

in an epidemic

n : # secondary infections

well expectation: n is Poisson distributed
with mean R_0

SARS-CoV2 is overdispersed: "Superspreading"

$$\text{Var}(n) = R_0 \left(1 + R_0/k\right)$$

$k \approx 0.1$ dispersion parameter

(ii) Coefficient of variation

Applicable to any non-negative RV X ,

by construction dimensionless:

$$CV(X) = \frac{\text{Std}(X)}{\text{IE}(X)} = \frac{\sqrt{\text{Var}(X)}}{\text{IE}(X)}$$

Exponential distribution: $\text{Var}(X) = \text{IE}(X)^2$

$$\Rightarrow \underline{CV = 1}$$

Poisson: $CV = \sqrt{\lambda}$

(iii) Randowness parameter (Schmitz, Block 1995)

$$R(X) = CV(X)^2 = \frac{\text{Var}(X)}{\text{IE}(X)^2}$$

Motivation: For a general renewal process at long times

$$R(\tau) = \frac{\text{Var}(\tau)}{|\text{E}(\tau)|^2} = \frac{\text{Var}(n)}{|\text{E}(n)|} = f(n)$$

Waiting times

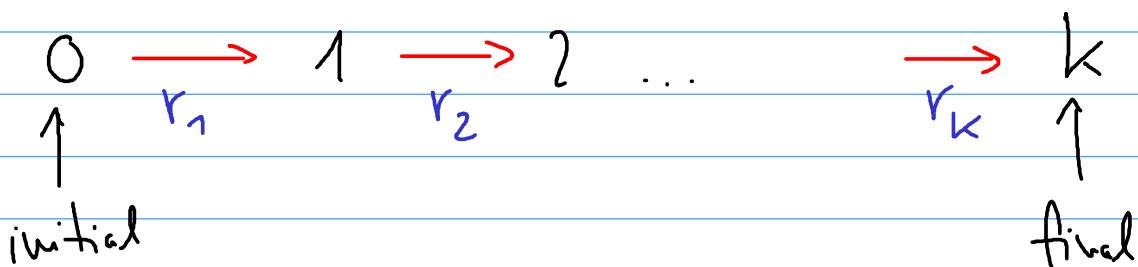
counting process of

the number of events

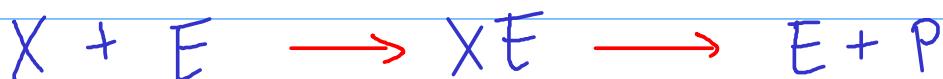
For the Poisson process $R = f = 1$

e) Multi-step processes

Process consisting of k steps with exponentially distributed waiting times



Example: Enzymatic reaction



Total waiting time is the sum:

$$\tau = \sum_{i=1}^k \tau_i$$

τ_i : independent exponentially distributed random variables

Mean and variance of independent random variables are additive

$$E(\tau) = \sum_{i=1}^k E(\tau_i) = \sum_{i=1}^k \lambda r_i$$

$$\text{Var}(\tau) = \sum_{i=1}^k \text{Var}(\tau_i) = \sum_{i=1}^k \lambda r_i^2$$

randomness parameter:

$$R(\tau) = \frac{\sum_{i=1}^k \lambda r_i^2}{\left(\sum_{i=1}^k \lambda r_i\right)^2} < 1$$

If all rates are the same ($r_i = r$)

$$R(\tau) = \frac{1}{k}$$

In this case the distribution of τ is

$$p_w(\tau) = \frac{\gamma^k \tau^{k-1}}{(k-1)!} e^{-\gamma\tau}$$

Erlang distribution / Γ -distribution

Conclusion: The timing of a random

process can be made more precise by
introducing intermediate stages

(cf. cooperativity in molecular reactions)

Example: Cell division

Generalization (Aldous & Schupp 1987)

For general reaction network with k states,
the randomness parameter of the process
completion time is bounded by

$$R(\tau) \geq \frac{1}{k} \Rightarrow k \geq k_{\min} = \frac{1}{R(\tau)}$$

Statistical kinetics:

Make use of fluctuations to estimate
 the effective number of states in
 a biophysical process
 (Moffitt, Bustamante 2014)

5.2. Markov chains and the master equation

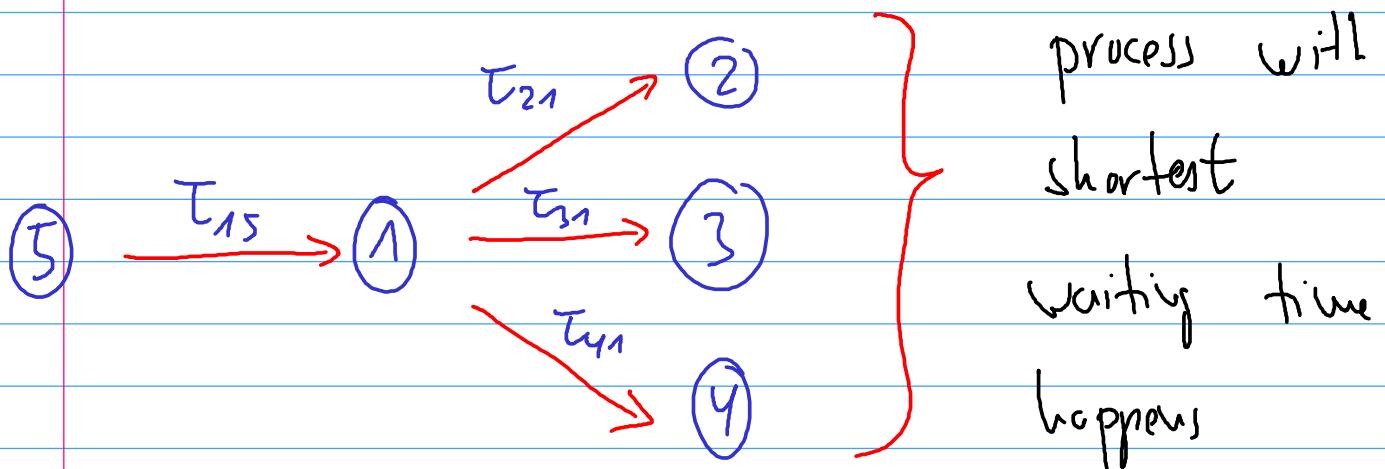
a) Continuous-time Markov chains

Def: • A continuous-time Markov chain
 is defined by a set of states
 $i = 1, 2, 3 \dots$ and transition rates

$$r_{j \leftarrow i} = r_{ji} \geq 0$$

- System is in state i at time t , then transition to state j with $r_{ji} > 0$ occurs after waiting time T_{ji} with exponential distribution

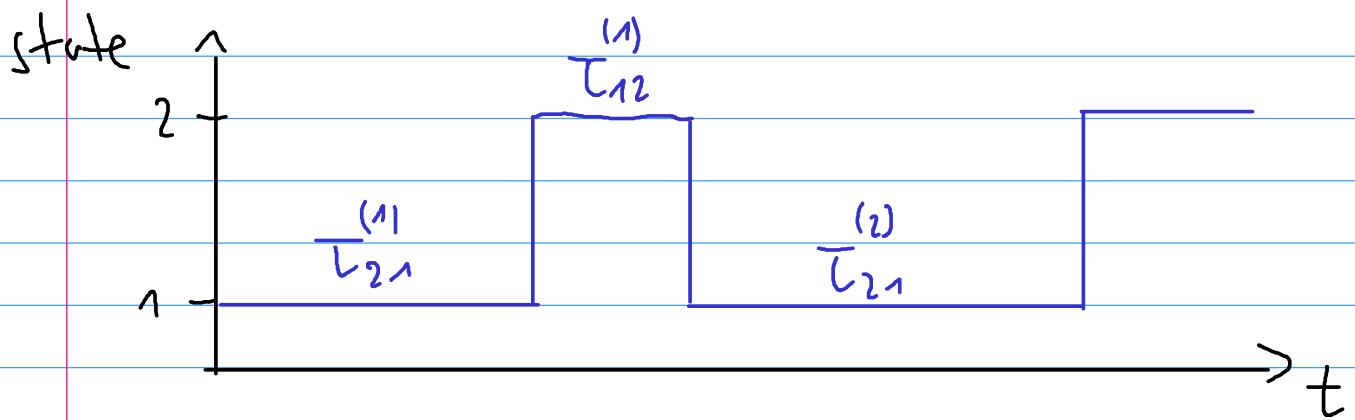
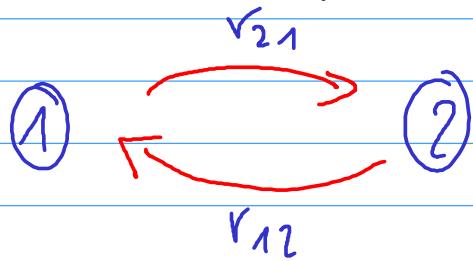
$$P_{ji}(T) = r_{ji} e^{-r_{ji} T}$$



Numerical implementation: Gillespie algorithm

- Markov property: Because processes with exponential waiting times are memoryless, the future evolution is fully determined by the present state

- Example: Two-state process
(e.g., gene that is "on" or "off")



b) Master equation

$P_i(t) = \text{Prob}[\text{System is in state } i \text{ at time } t]$

evolves in time according to the
Master equation

$$= \sum_j \hat{r}_{ij} P_j \quad \text{matrix multiplication}$$

with $\hat{r}_{ij} = \begin{cases} r_{ij} & i \neq j \\ -\sum_k r_{ki} & i = j \end{cases}$

- Conservation of probability

$$\frac{d}{dt} \sum_i P_i = \sum_{i,j} r_{ij} P_j - \sum_{i,j} r_{ji} P_i = 0$$

- Example: Two-state system

$$\dot{P}_1 = r_{12} P_2 - r_{21} P_1$$

$$\dot{P}_2 = r_{21} P_1 - r_{12} P_2$$

$$P_1 + P_2 = 1 \Rightarrow P_2 = 1 - P_1$$

$$\begin{aligned} \Rightarrow \dot{P}_1 &= r_{12} (1 - P_1) - r_{21} P_1 = \\ &= r_{12} - (r_{12} + r_{21}) P_1 \end{aligned}$$

$$\text{General solution: } P_1(t) = P_1^* + (P_1(0) - P_1^*) e^{-rt}$$

with $P_1^* = \frac{r_{12}}{r_{12} + r_{21}}$, $r = r_{12} + r_{21}$

$$P_2^* = \frac{r_{21}}{r_{12} + r_{21}}$$

P_1^* , P_2^* : stationary distribution

In terms of the transition matrix

$$\begin{pmatrix} \hat{r}_{11} & \hat{r}_{12} \\ \hat{r}_{21} & \hat{r}_{22} \end{pmatrix} = \begin{pmatrix} -r_{21} & r_{12} \\ r_{21} & -r_{12} \end{pmatrix}$$

eigenvalues $\lambda_1 = 0$, $\lambda_2 = -r = -(r_{12} + r_{21})$

stationary distribution is eigenvector

corresponding to $\lambda_1 = 0$

- General case: If state space is finite, and if transition rate matrix is irreducible

(= all pairs of states can be reached from each other in finite time)

then there is a unique stationary distr.

$\{P_i^* \mid P_i^* > 0\}$ which is an eigenvector
of the transition rate matrix with
eigenvalue 0:

$$\sum_j r_{ij} P_j^* = 0$$

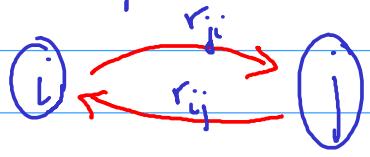
(Frobenius - Perron theorem)

P_i^* : Fraction of time spent in state i

c) Reversibility / detailed balance

- Stationary distribution is the solution of

$$0 = \sum_j (r_{ij} P_j^* - r_{ji} P_i^*) = \sum_j J_{ij}^* \quad \forall i$$

$$J_{ij}^* = r_{ij} P_j^* - r_{ji} P_i^* \quad \text{net probability current between states } i, j$$


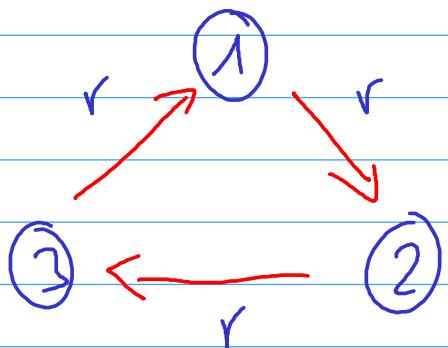
- Markov chain is called reversible if

all probability currents vanish:

$$J_{ij}^* = 0 \iff r_{ij} P_j^* = r_{ji} P_i^* \quad \text{"detailed balance"}$$

- In statistical physics, reversible Markov chains describe systems in thermal equilibrium, whereas irreversible chains describe nonequilibrium stationary states

- Example: Irreversible 3-state Markov chain



$$p_i^* = \frac{1}{3}, \quad i = 1, 2, 3$$

stationary probability
current

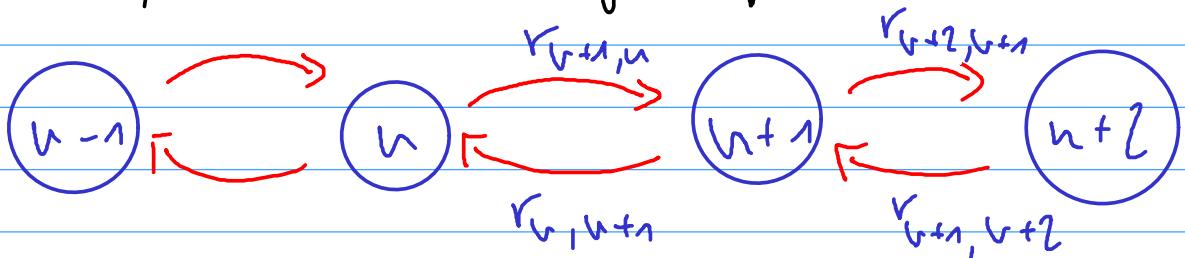
$$\pi_i^* = \frac{1}{3} \checkmark$$

5.3 One-step processes

reading: van Kampen, Chapter VI

a) Definition

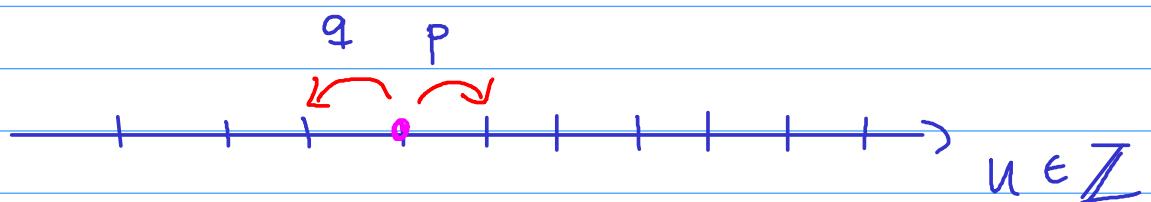
- Continuous time Markov chain where states are integers $n \in \mathbb{Z}$ and transitions occur only between neighboring states



- Master equation:

$$\dot{P}_v = r_{v,v+1} P_{v+1} + r_{v,v-1} P_{v-1} - (r_{v+1,v} + r_{v-1,v}) P_v$$

- Example: Random walk



$$r_{v+1,v} = p, \quad r_{v,v+1} = q$$

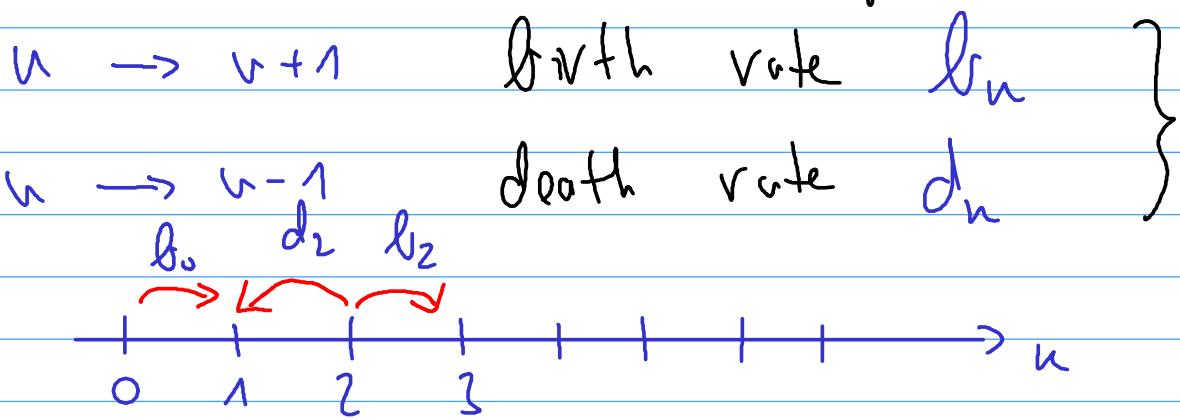
$p = q$: symmetric

$p \neq q$: biased

Example of biased random walk:
Molecular motor }

b) Birth - Death processes

$n > 0$ describes size of a population
(of molecules or organisms)



Example: Production and degradation of
a molecular species (e.g. mRNA)

$$b_n = r \quad \text{production rate}$$

$$d_n = kn \quad K: \text{degradation rate}$$

- Master equation:

$$P_n = \frac{K(n+1) P_{n+1}}{} + \frac{r P_{n-1}}{} - \frac{(r + kn) P_n}{}$$

- Condition for stationary distribution:

$$(K(u+1) P_{u+1}^* - r P_u^*) -$$

$$(Ku P_u^* - r P_{u-1}^*) = 0$$

Get each term to vanish individually

by

$$\boxed{K(u+1) P_{u+1}^* = r P_u^* \quad \forall u}$$

detailed balance / reversibility

Solve recursively starting at $u=0$:

$$P_1^* = \frac{r}{K} P_0^*, \quad P_2^* = \frac{1}{2} \left(\frac{r}{K} \right)^2 P_0^*, \dots$$

$$\Rightarrow P_u^* = \frac{1}{u!} \left(\frac{r}{K} \right)^u P_0^*$$

Normalization: $\sum_{u=0}^{\infty} P_u^* = P_0^* e^{r/K} = 1$

$$\Rightarrow P_0^* = e^{-r/K}$$

\Rightarrow number of molecules is Poisson-distr.

$$P_u^* = e^{-r/K} \frac{(r/K)^u}{u!}$$

- Moment dynamics

Mean number of ∞ molecules

$$\langle u \rangle(t) = \sum_{v=0}^{\infty} v P_v(t)$$

master eq.

$$\Rightarrow \frac{d}{dt} \langle u \rangle(t) = \sum_{v=0}^{\infty} v \dot{P}_v =$$

$$= r - K \langle u \rangle$$

linear ODE

cf. Chapter 3

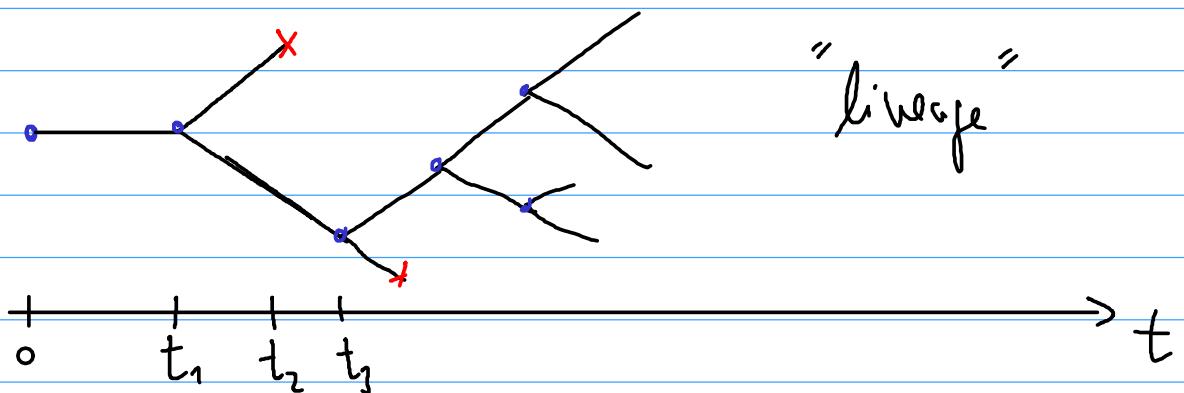
Similar equations can be derived for

higher moments $\langle u^k \rangle = \sum_{v=0}^{\infty} v^k P_v(t)$

Closed ODE for the moments can be derived because d_u, d_v are linear fcts. of u

c) Branching processes

- Bacterial population where cells divide at rate b and die at rate d



- Number of cells n follows a birth-death process with rates

$$b_n = b \cdot n, \quad d_n = d \cdot n$$

- Average number of cells:

$$\frac{d}{dt} \langle n \rangle = (b - d) \langle n \rangle$$

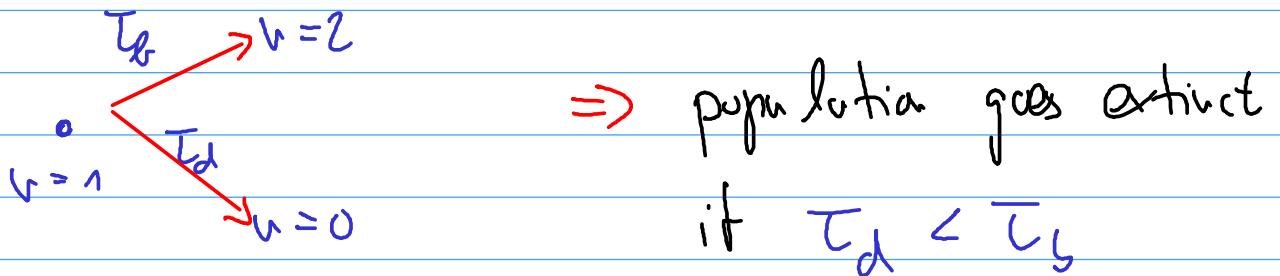
$b > d$: exponential growth

$b < d$: extinction

\Rightarrow no stationary distribution

- Because of stochasticity, population may go extinct even if $b > d$

Start with single cell:



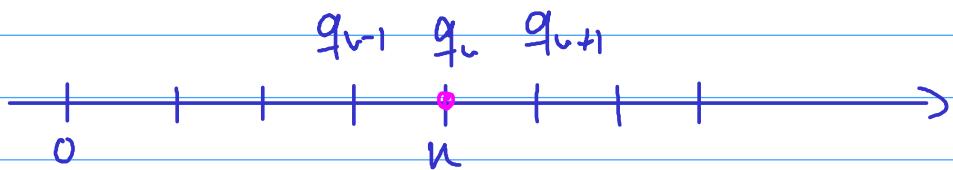
- Using exponential distribution of waiting times:

$$\text{Prob} [T_d < \bar{T}_b] = \frac{d}{b + d}$$

This is a lower bound on the extinction probability

- Denote by q the probability that population ever goes extinct, and q_n probability that a population starting from n cells ever goes extinct
($q = q_1$: start from single cell)

- Recursive calculation of q_n



Next event is a birth with probability

$$p_b = \frac{b}{b+d}$$

and a death with prob. $1-p_b$.

$$\Rightarrow q_n = p_b q_{n+1} + (1-p_b) q_{n-1}, \quad n \geq 1$$

Because of independence of cells $q_n = q^n$,

where $q = q_1$ is the extinction prob. of

a single cell

$$\cancel{q}^n = p_b \cancel{q}^{n+1} + (1-p_b) \cancel{q}^{n-1}$$

$$\Rightarrow 1 = p_b q + (1-p_b)/q$$

$$\Rightarrow q = \frac{1-p_b}{p_b} = \frac{b+d}{b} \cdot \frac{d}{b+d} = \frac{d}{b}$$

If $d > b$ the population goes extinct, $q = 1$

$$q = \min\left(\frac{d}{b}, 1\right)$$

6° Noise in gene expression

6.2. The "standard model"

Consider two special cases of the general expression of Paulsson (2005)

a) Translation noise

Assume gene is always "on": $P_{on} = 1$

\Rightarrow protein randomness parameter

$$\frac{\sigma_3^2}{\langle u_3 \rangle^2} = \frac{1}{\langle u_3 \rangle} + \frac{1}{\langle u_2 \rangle} \underbrace{\frac{\tau_2}{\tau_2 + \tau_3}}$$

$$\tau_2 \ll \tau_3$$

$$\simeq \tau_2 / \tau_3$$

Fano factor:

$$\frac{\sigma_3^2}{\langle u_3 \rangle} = 1 + \frac{\langle u_3 \rangle}{\langle u_2 \rangle} \cdot \frac{\tau_2}{\tau_3}$$

- Steady state: $\frac{d}{dt} \langle u_3 \rangle = \lambda_3 \langle u_2 \rangle - \frac{\langle u_3 \rangle}{\tau_3} = 0$

$$\Rightarrow \frac{\langle u_2 \rangle}{\langle u_1 \rangle} = \tau_2 \lambda_2$$

$$\Rightarrow \frac{\sigma_2^2}{\langle u_2 \rangle} = 1 + \underbrace{\lambda_2 \tau_2}_{\text{number of proteins produced}} = b$$

number of proteins produced

during mRNA life time =

= b "protein burst size"

b) Transcription noise

- Randomness parameter of mRNA:

$$\frac{\sigma_2^2}{\langle u_2 \rangle^2} = \frac{1}{\langle u_2 \rangle} + \frac{1 - p_{on}}{\langle u_1 \rangle} \cdot \frac{\tau_1}{\tau_1 + \tau_2}$$

- Fano factor *intrinsic*

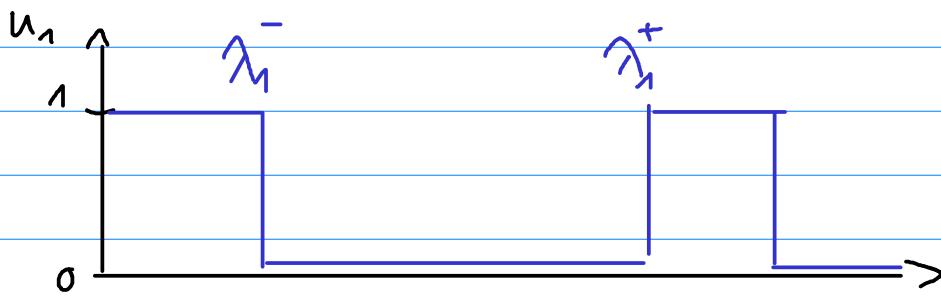
$$[u_1^{max} = 1]$$

$$\frac{\sigma_2^2}{\langle u_2 \rangle} = 1 + (1 - p_{on}) \frac{\langle u_2 \rangle}{\langle u_1 \rangle} \frac{\tau_1}{\tau_1 + \tau_2}$$

- Steady state $\frac{d}{dt} \langle u_2 \rangle = \lambda_2 \langle u_1 \rangle - \frac{1}{\tau_2} \langle u_2 \rangle = 0$

$$\Rightarrow \frac{\langle u_2 \rangle}{\langle u_1 \rangle} = \lambda_2 \tau_2$$

- in RNA burst size : \tilde{b}



\Rightarrow average on-time is $1/\lambda_1^-$

$$\Rightarrow \tilde{b} = \lambda_2 / \lambda_1^- \Rightarrow \lambda_2 = \tilde{b} \lambda_1^-$$

$$\bullet P_{on} = \frac{\lambda_1^+}{\lambda_1^+ + \lambda_1^-}, \quad 1 - P_{on} = \frac{\lambda_1^-}{\lambda_1^+ + \lambda_1^-} \quad \left. \right\}$$

$$\tau_1 = \frac{1}{\lambda_1^+ + \lambda_1^-}$$

$$\Rightarrow \frac{\sigma_2^2}{\langle u_2 \rangle} = 1 + \tilde{b} (1 - P_{on})^2 \frac{\tau_2}{\tau_1 + \tau_2}$$

$$\leq \boxed{1 + \tilde{b}}$$

- Maximal overdispersion is reached when

$$P_{on} \ll 1, \quad \tau_2 \gg \tau_1 \approx \frac{1}{\lambda_1^-} \quad \text{duration of burst}$$

$\lambda_1^+ \ll \lambda_1^-$

\Rightarrow short, infrequent bursts

6.3. The distribution of protein copy numbers

Friedman et al. 2006

- Assume proteins are produced in bursts with rate ν and exponentially / geometrically distributed protein numbers per burst
- Continuum approximation: Replace protein number n by cellular concentration $x = n/V$ V : cell volume

$$x = n/V \quad V: \text{cell volume}$$

- Dilution / degradation dynamics:

$$p_n = K(n+1) p_{n+1} - Kn p_n$$

↓ continuum limit

$$\frac{\partial}{\partial t} p(x,t) = K \frac{\partial}{\partial x} x p(x,t)$$

- Protein production dynamics:

Burst increases concentration $X \rightarrow X + Y$

where γ is drawn from probability density

$$\nu(\gamma)$$

- Master equation for $p(x,t)$:

$$\frac{\partial}{\partial t} p(x,t) = K \frac{\partial}{\partial x} \times p(x,t) +$$

$$+ r \int_0^x dx' \nu(x-x') p(x',t) - r p(x,t)$$

gain from states with
concentration $0 \leq x' \leq x$
loss

- Stationary state: $p(x)$

$$\frac{d}{dx} \times p(x) = \frac{r}{K} \left[\int_0^x dx' \nu(x-x') p(x') - p(x) \right]$$

- Laplace transformation:

$$\hat{p}(s) = \int_0^\infty dx e^{-sx} p(x), \quad \hat{\nu}(s) = \int_0^\infty dx e^{-sx} \nu(x)$$

$$\Rightarrow s \frac{d\hat{p}}{ds} = \left(\frac{r}{K} \right) (\hat{v}(s) - 1) \hat{p}(s)$$

$\hat{v}(s) = a$

- Exponential burst size distribution

$$v(x) = b^{-1} e^{-x/b} \Rightarrow \hat{v}(s) = \frac{1}{b} \frac{1}{s + 1/b}$$

$$\Rightarrow \hat{p}(s) = \left(s + \frac{1}{b} \right)^{-a}$$



$$p(x) = \frac{x^{a-1} e^{-x/b}}{b^a \Gamma(a)}$$

$\frac{1}{b}$ = cell division time

$\Rightarrow a = \# mRNAs$ produced in
one cell cycle

7° Exclusion models for gene expression and transport

7.2. Totally asymmetric simple exclusion process (TASEP)

- Def: - One-dimensional lattice of L sites

- Occupation numbers $i=1, \dots, L$

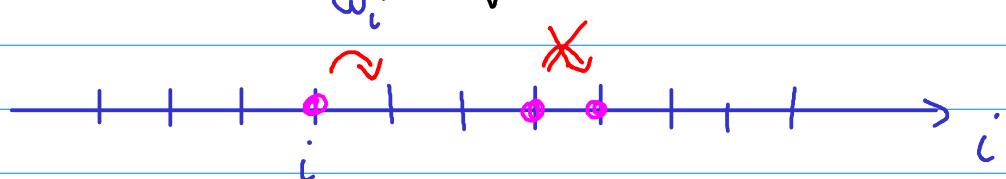
$$n_i = \begin{cases} 1 & \text{occupied} \\ 0 & \text{vacant} \end{cases}$$

- Exclusion: $n_i \leq 1$

- Totally asymmetric simple dynamics:

Particles jump to nearest neighbor

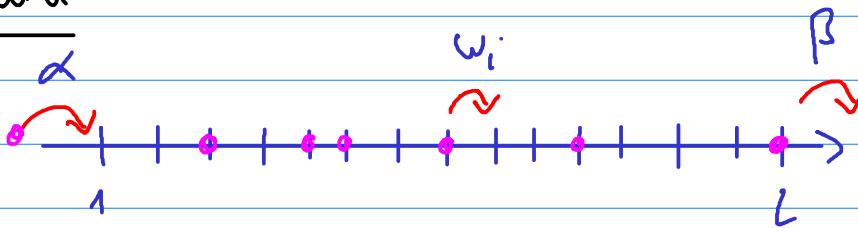
sites to the right, if vacant



- Continuous time Markov chain on the space of configurations

Configuration space

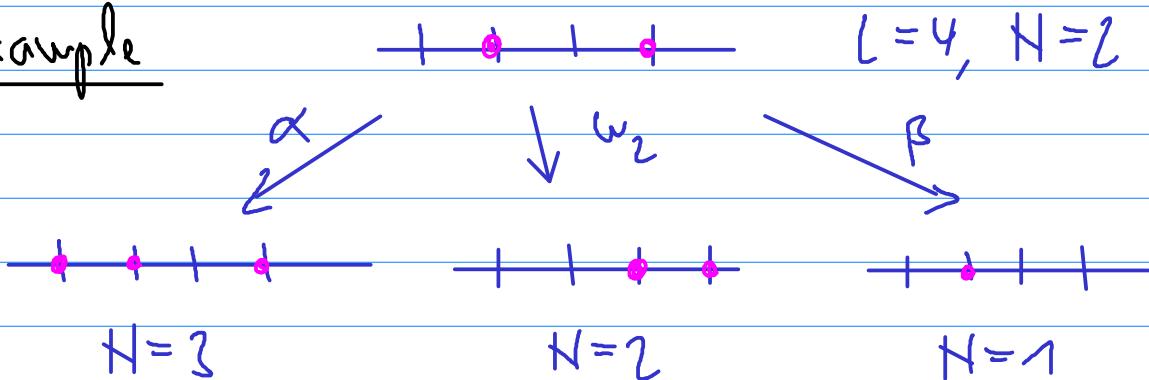
(i) "Open chain"



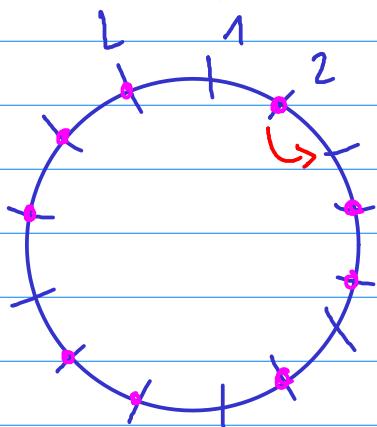
- 2^L configurations

- particle number $H = \sum_{i=1}^L n_i$ is fluctuating
and can take any value $0 \leq H \leq L$

Example



(ii) Ring (= periodic boundary conditions)



- particle number is conserved

- $\binom{L}{N}$ configurations

7.3 TASEP on the ring

Consider homogeneous system where all jump rates are the same $w_i \equiv w$

a) Master equation

- Configuration $\varrho = \{u_1, u_2, \dots, u_L \mid u_i \in \{0, 1\}\}$
- L sites, N particles : $\sum_{i=1}^L u_i = N$
- Probability distribution $P(\varrho, t)$ evolves as

$$\frac{d}{dt} P(\varrho, t) = \sum_{\varrho'} r(\varrho \leftarrow \varrho') P(\varrho', t) - \sum_{\varrho'} r(\varrho' \leftarrow \varrho) P(\varrho, t)$$

$$r(\varrho' \leftarrow \varrho) = \begin{cases} w & \text{if } \varrho' \text{ can be reached} \\ & \text{from } \varrho \text{ in a single jump} \\ 0 & \text{else} \end{cases}$$

- Stationary state? TASEP is irreversible
 \Rightarrow no detailed balance

b) Stationary state

Simplesst ansatz? Equipartition:

$$p^*(e) = \left(\frac{L}{N}\right)^{-1}$$

This requires the condition

$$\sum_{e'} r(e \leftarrow e') p^*(e') - \sum_{e'} r(e' \leftarrow e) p^*(e) =$$

$$= \left(\frac{L}{N}\right)^{-1} \left[\sum_{e'} r(e \leftarrow e') - \sum_{e'} r(e' \leftarrow e) \right] = 0$$

for all configurations e .

$$\sum_{e'} r(e' \leftarrow e) = (\text{total number of particles, that can move in } e) \cdot w$$

$$= w \# \{ \rightarrow \} (e) = w \cdot \sum_{i=1}^L n_i (1 - u_{i+1})$$

↑
number of elements in a set

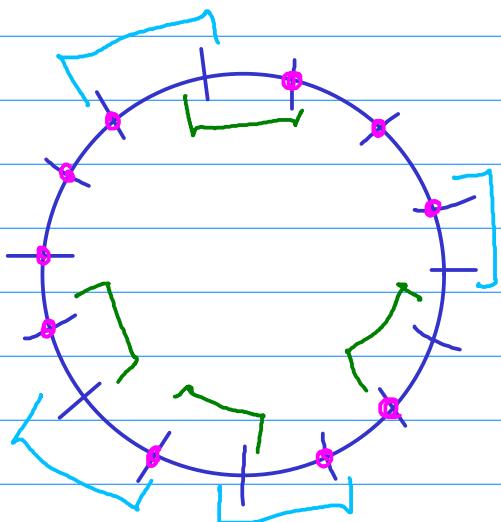
$$\sum_{\epsilon'} r(\epsilon \leftarrow \epsilon') = w \# \{ \text{++} \} =$$

$$= w \sum_{i=1}^L (1-u_i) u_{i+1}$$

For any configuration ϵ

$$\sum_{i=1}^L u_i (1-u_{i+1}) = \sum_{i=1}^L (1-u_i) u_{i+1} =$$

= number of clusters of particles



$$\# \{ \text{++} \} = 4 \quad \square$$

$$\# \{ \text{+-} \} = 4 \quad \square$$

- "Pairwise Influence"

c) Stationary current

- Current: Number of particles that jump across a bond in unit time

$$\begin{aligned} J_{i,i+1} &= \omega \cdot \text{Prob} [u_i = 1, u_{i+1} = 0] = \\ &= \omega \cdot \mathbb{E}(u_i(1-u_{i+1})) \end{aligned}$$

- By stationarity $J_{i,i+1} \equiv J$ indep. of i
- By equipartition:

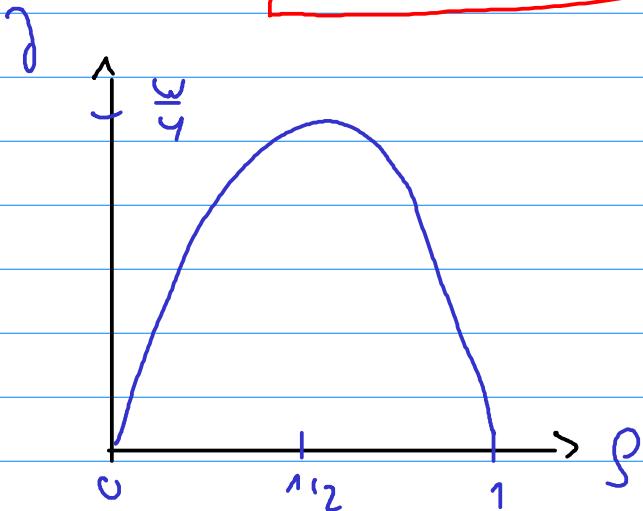
$$\begin{aligned} \text{Prob} [u_i = 1, u_{i+1} = 0] &= \binom{L-2}{N-1} \\ &= \frac{\#\{e : u_i(e) = 1, u_{i+1} = 0\}}{\#\{e\}} \\ &= \binom{L}{N} \end{aligned}$$

$$= \binom{L}{N}^{-1} \binom{L-2}{N-1} = \frac{N(L-N)}{L(L-1)} = \varrho(1-\varrho) \frac{L}{L-1}$$

- particle density: $\varrho = \frac{N}{L}$

- Stationary current for large L :

$$\boxed{j = \omega \rho (1 - g)}$$



current-density

relation

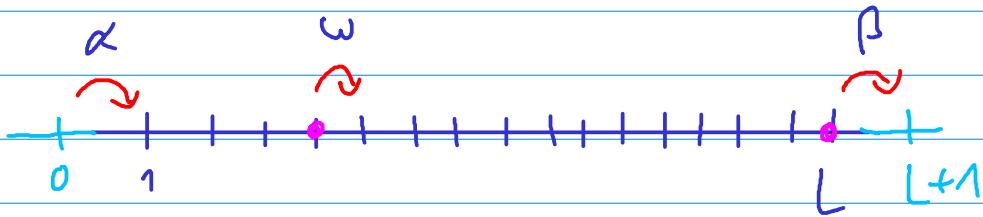
"fundamental
dispersion"

- $j(g)$ is nonlinear because of jamming / queueing

- Hydrodynamic picture: $j = v \rho$

$v = \omega(1 - g)$ speed of a particle, which
is reduced by jamming

7.4. TASEP on the open chain



- Normalize rates to $\omega=1 \Rightarrow$ parameters α, β
- α, β define effective boundary densities

$$\rho_L = \rho_0 = \alpha, \quad \rho_{L+1} = 1 - \beta$$

- Consider three approaches to the problem

a) Mean field approximation (Mac Donald et al. 1968)

- Average occupation numbers $\rho_i = \langle u_i \rangle$

satisfy a discrete continuity equation

$$\frac{d}{dt} \rho_i = - (\bar{\gamma}_{i,i+1} - \bar{\gamma}_{i-1,i}) \quad (\omega=1)$$

$$= - \langle u_i (1-u_{i+1}) \rangle + \langle u_{i-1} (1-u_i) \rangle$$

exact

Not a closed eq. for $\rho_i(t)$

- Mean field / factorization approximation:

$$\beta_{i,i+1} = \langle u_i \cdot (1-u_{i+1}) \rangle \approx \langle u_i \rangle \langle 1-u_{i+1} \rangle = \\ = p_i \cdot (1-p_{i+1})$$

- Stationary state: $\beta_{i,i+1} = \beta = \text{const.}$

$$p_i \cdot (1-p_{i+1}) = p_i - p_i p_{i+1} = \beta$$

$$\Rightarrow 1 - p_{i+1} = \beta/p_i$$

$$\Rightarrow p_{i+1} = 1 - \beta/p_i$$

iterated
map

- The (unknown) stationary current is

determined such that the boundary

conditions $p_0 = \alpha$, $p_{L+1} = 1-\beta$

are satisfied

\Rightarrow phase diagram in the (α, β) -plane

b) Matrix product ansatz

(Demida et al. 1992; Schadschneider 4.2.3)

- Exact stationary proj. distribution is of the form

$$\text{Prob}[u_1, u_2, \dots, u_L] \sim \langle w | \prod_{i=1}^L D^{u_i} E^{1-u_i} | v \rangle$$

$$\rightarrow D^{u_i} E^{1-u_i} = \begin{cases} D & u_i = 1 \\ E & u_i = 0 \end{cases}$$

D, E are matrices, $\langle w |, | v \rangle$ are vectors with

$$(i) \quad DE = D + E$$

$$(ii) \quad D | v \rangle = \frac{1}{\beta} | v \rangle$$

$$(iii) \quad \langle w | E = \frac{1}{\alpha} \langle w |$$

- D, E are generally infinite-dimensional matrices

- Special case: Assume D, E are scalar

numbers (= one-dimensional representation)

$$(ii), (iii): \quad D = \frac{1}{\beta}, \quad E = \frac{1}{\alpha}$$

$$(i) \quad \frac{1}{\alpha} \cdot \frac{1}{\beta} = \frac{1}{\alpha} + \frac{1}{\beta} = \frac{\alpha + \beta}{\alpha \beta}$$

$$\Rightarrow \alpha + \beta = 1 \Rightarrow p_L = p_R = \alpha = 1 - \beta$$

Probability of a configuration with N particles:

$$P_N \sim \left(\frac{1}{\beta}\right)^N \left(\frac{1}{\alpha}\right)^{L-N} = (\alpha(1-\alpha))^{-L} \times \alpha^N (1-\alpha)^{L-N}$$

$\uparrow \quad \beta = 1 - \alpha$

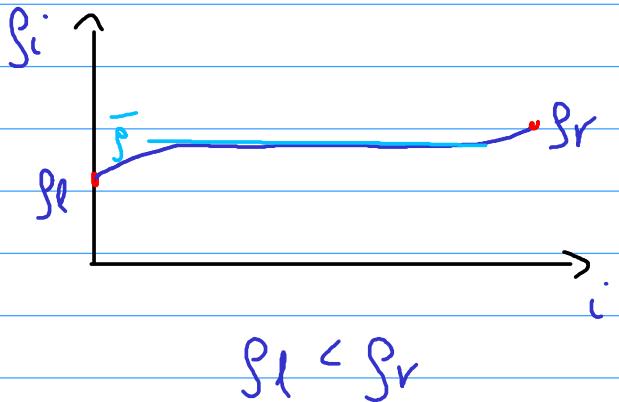
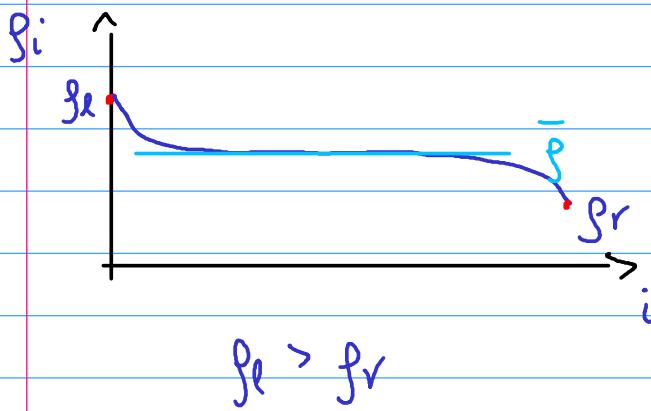
\Rightarrow independent particles with occupation

$$\text{probability } \alpha = 1 - \beta$$

c) Extremal current principle

- Observation: Stationary density profile is essentially flat, with density $\bar{\rho}$ that lies between the boundary densities, ω is equal to one of them

- Two cases:



Stationarity \Rightarrow current is constant in space

Total current is of the form

$$j = j(j_i) + j_{ex}^{(i)}$$

current of uniform system of density j_i

$j(j) = j(1-j)$

"excess current", nonzero only near the boundaries where the density varies

- Assuming that

$$j_{ex} \begin{cases} > 0 & j_e > j_r \\ < 0 & j_e < j_r \end{cases}$$

it can be shown that

$$J = \begin{cases} \max [j(g)] & g_l > g_r \\ g_r \leq g \leq g_l \\ \min [j(g)] & g_r > g_l \\ g_l \leq g \leq g_r \end{cases}$$

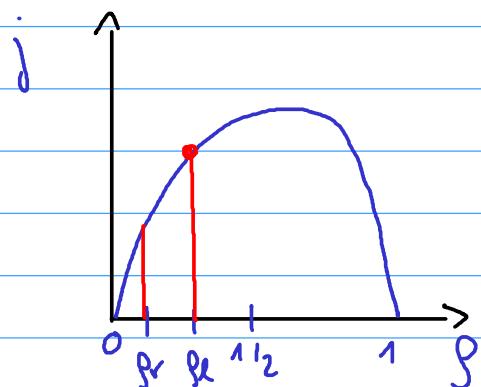
- The density \bar{g} is then such that $J = j(\bar{g})$

d) Phase diagram

(i) $g_l > g_r$ $g_l = \alpha, g_r = 1 - \beta \Rightarrow \alpha + \beta > 1$

Current-density relation: $j(g) = g(1-g)$

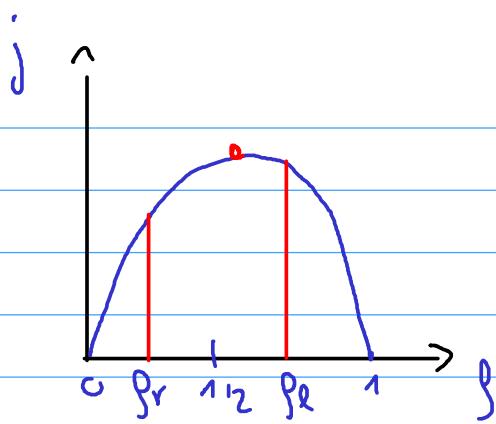
Three cases:



$g_r < g_l < \frac{1}{2}$

$\bar{g} = g_l = \alpha$

$\alpha < \frac{1}{2}, \beta > \frac{1}{2}$



$$\underline{g_r < \frac{1}{2} < g_l}$$

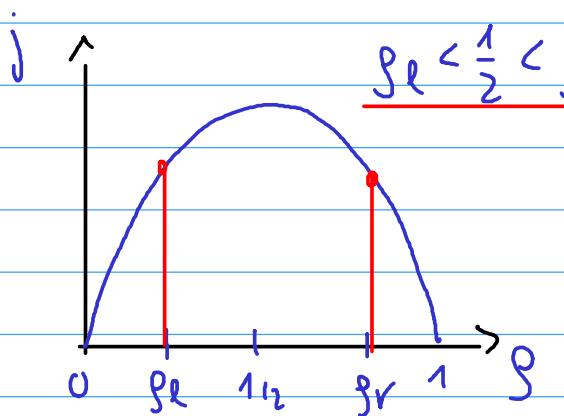
$$\bar{g} = \max[j(g)] = \frac{1}{2}$$

$$\bar{g} = \frac{1}{2}$$

$$\underline{\frac{1}{2} < g_r < g_l} \Rightarrow \bar{g} = g_r = 1 - \beta$$

(ii) $\underline{g_l < g_r} \Rightarrow$

$$\alpha + \beta < 1$$



$$\bar{g} = \min_{g_r \leq g \leq g_l} (j(g))$$

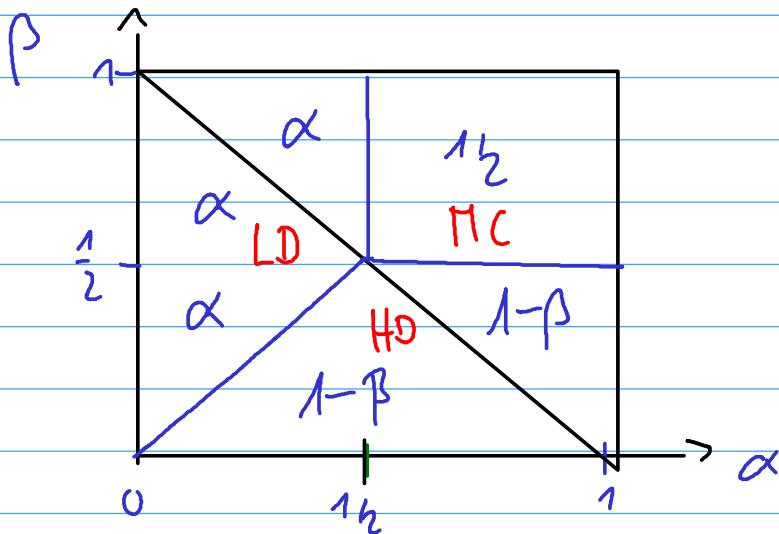
$$\Rightarrow \bar{g} = \begin{cases} g_l & g_l < 1 - \beta \\ g_r & g_l > 1 - \beta \end{cases}$$

$$\Rightarrow \bar{g} = \begin{cases} \alpha & \alpha < \beta \\ 1 - \beta & \alpha > \beta \end{cases}$$

$$\underline{g_l < g_r < \frac{1}{2}} : \quad \bar{g} = \alpha$$

$$\underline{\frac{1}{2} < g_l < g_r} : \quad \bar{g} = g_r = 1 - \beta$$

Phase diagram



Three phases:

$\text{LD}: \bar{\rho} = \alpha$

"initiation limited"

"low density"

MC : "maximal current" "elongation limited"

$\bar{\rho} = \frac{1}{2}$ (= ρ_{max} density of maximal current)

HD : "high density", "termination limited"

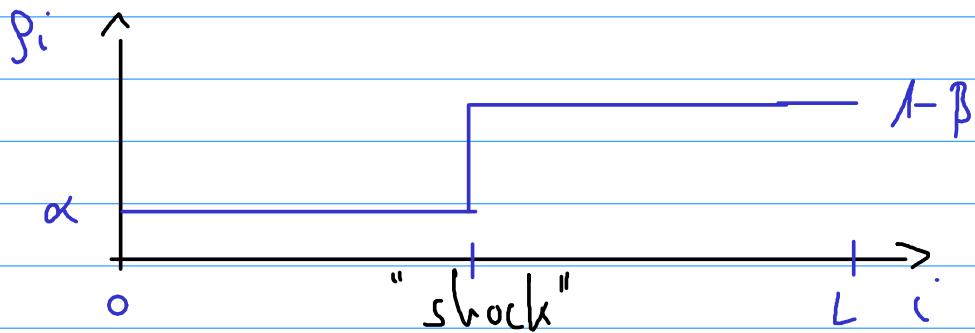
$$\bar{\rho} = 1 - \beta$$

- At the "first order transition line" $\alpha = \beta$

the stationary density jumps from α to $1 - \beta$

- On the "coexistence line" $\alpha = \beta$

the system is inhomogeneous



Shock position diffuses randomly across the system

8° Biological waves

Motivation

- (i) Population dynamics with spatial dispersal
- (ii) Transport of chemical species in cells
and tissues

Problem: Diffusion is often too slow

Example: Typical diffusion coefficient

$$D \sim 10^{-9} - 10^{-8} \text{ cm}^2/\text{s}$$

⇒ diffusion over distance $\lambda = 0.1 \text{ cm}$

$$t_{\text{diff}} \sim \lambda^2 / D \sim 0.3 - 30 \text{ yrs}$$

⇒ biological processes require directed transport

e.g. by molecular motors or chemical waves

↓
reaction-diffusion systems

Example: Min-system in cell division

8.1. Fisher waves

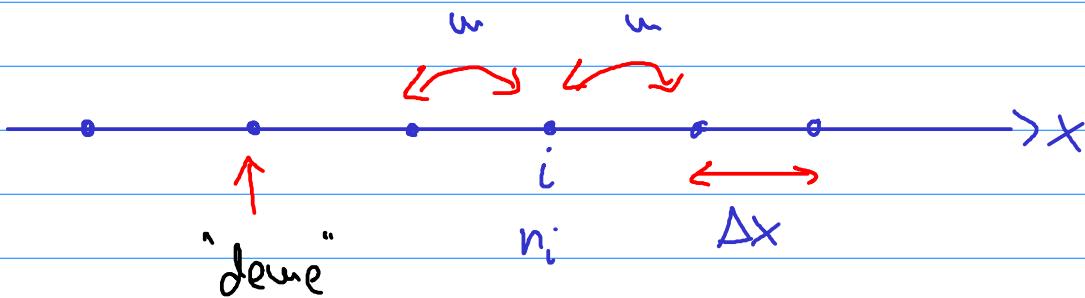
a) Range expansion

Recall: Logistic growth

$$\dot{u} = \delta u (1 - u/K)$$

K: carrying capacity

Population lives in a one-dimensional spatial habitat with migration



$n_i(t)$: Population in the i -th deme

$$\begin{aligned}\dot{n}_i &= \delta n_i (1 - n_i/K) + m(n_{i+1} - n_i) + \\ &\quad + m(n_{i-1} - n_i)\end{aligned}$$

↓ continuum limit → $\sim m(\Delta x)^2$

$$\frac{\partial}{\partial t} n(x,t) = \delta n (1 - n/K) + D \frac{\partial^2 n}{\partial x^2}$$

- Rescale population density by K : $u = \frac{u}{K}$

$$\Rightarrow \boxed{\frac{\partial u}{\partial t} = -d_r u(1-u) + D \frac{\partial^2 u}{\partial x^2}} \quad \text{FKPP}$$

↑ reaction ↑ diffusion
reaction-diffusion equation

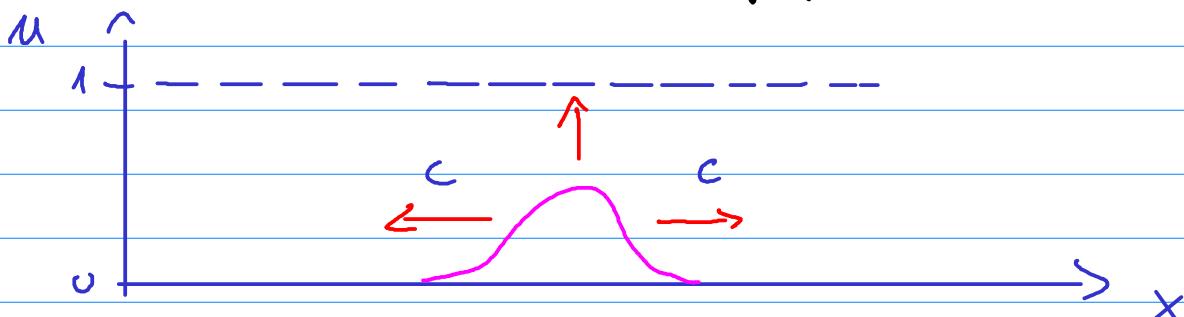
- History:

R. A. Fisher (1937): Spreading of a favorable genetic mutation

Kolmogorov, Petrovsky, Piscounoff (1937)

For further reading see Murray, Chapter 13

- Question: Spreading of an initially localized population

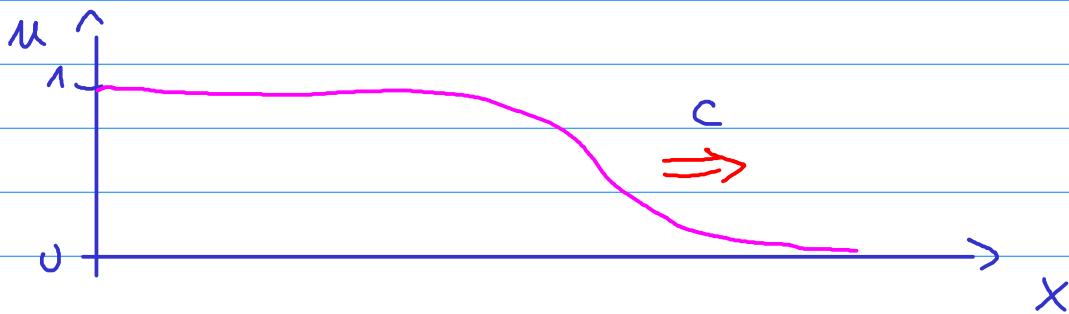


• Dimensional analysis

$$[D] = \frac{x^2}{t}, [b] = \frac{1}{t} \Rightarrow [Db] = \frac{x^2}{t^2}$$

$\Rightarrow \sqrt{Db}$ is a characteristic speed

b) Traveling waves



Ansatz for traveling wave of constant shape:

$$u(x, t) = f(\underbrace{x - ct}_z)$$

right-moving
wave

Insert into FKPP:

$$-\underline{c} f' = b f(1-f) + D f'' \quad \text{ODE}$$

For which values of c is there a solution such that

$$f(z) \rightarrow \begin{cases} 1 & z \rightarrow -\infty \\ 0 & z \rightarrow \infty \end{cases}$$

and $f' < 0$, $f \in [0,1]$?

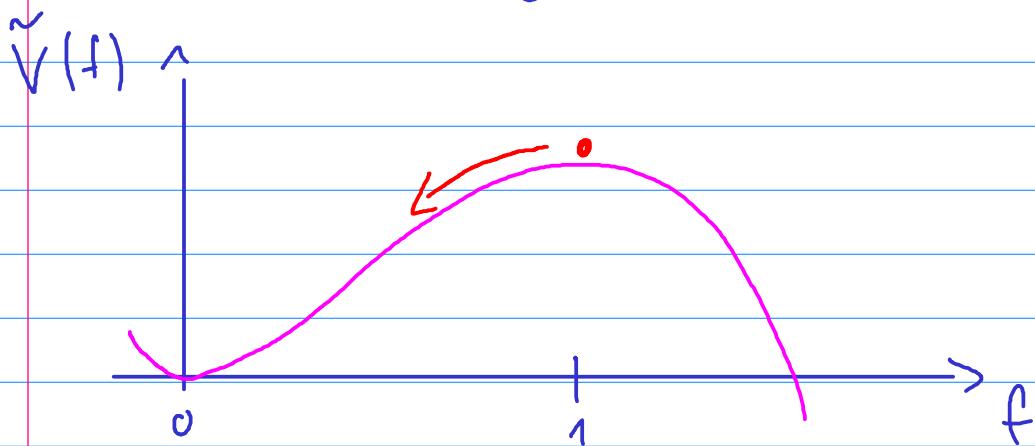
- Mechanical analogue:

$$Df'' = -c f' - b f(1-f)$$

↑ ↑ ↑
 mass x acceleration friction potential force

interpretation: f is the coordinate of a particle moving in time z with friction c and potential

$$\tilde{V}(f) = b \int_0^f dy y(1-y) = b \left(\frac{1}{2} f^2 - \frac{1}{3} f^3 \right)$$



\Rightarrow over damped motion for $c \geq c^* > 0$

c) Selection of the wave speed

Analyze the tail of the wave ($z \rightarrow \infty$):

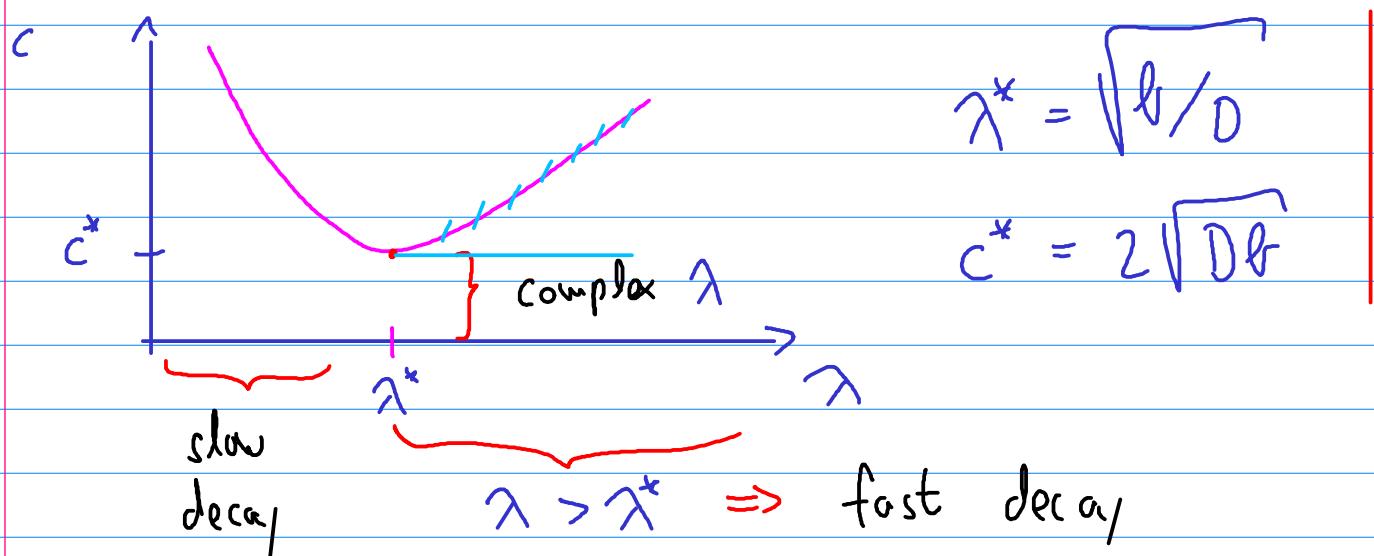
Linearize ODE w.r.t. $u=0$ (harmonic approx.)
 $f=0$

$$Df'' + cf' + bf = 0$$

Exponential ansatz: $f(z) \sim e^{-\lambda z}$, $\lambda > 0$

$$\Rightarrow D\lambda^2 - c\lambda + b = 0$$

$$\Rightarrow c(\lambda) = D\lambda + b/\lambda$$



Expect: Slow decay implies fast wave propagation

Further analysis shows that the actual wave speed is determined by the initial profile: If $u(x, 0) \sim e^{-\lambda x}$, then

$$c = \begin{cases} c(\lambda) & \lambda < \lambda^* \\ \underline{c^*} & \lambda > \lambda^* \end{cases}$$

For an initially localized profile the wave moves at the minimal speed

$$\underline{\text{speed}} \quad c^* = 2\sqrt{D b r}$$

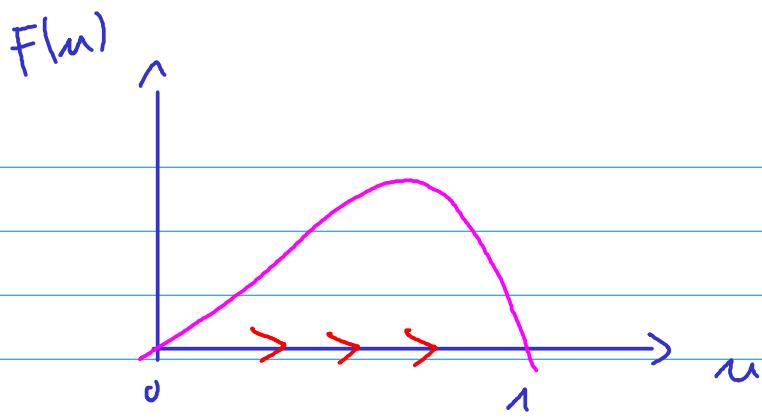
8.2. Pulled and pushed waves

a) Definition

Generalization of the Fisher equation

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + F(u)$$

local pop. dynamics $u = F(u)$



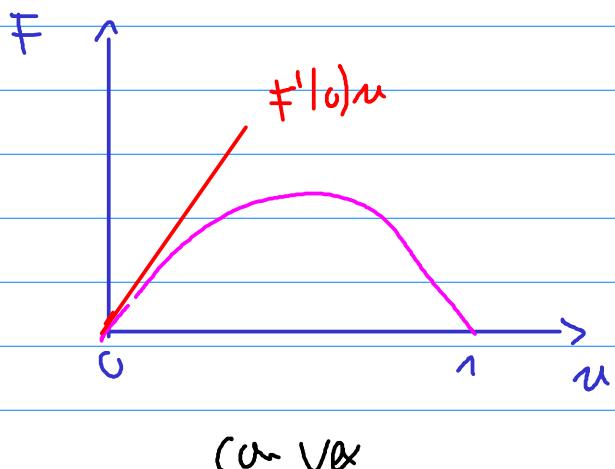
$u=0$: unstable

$u=1$: stable

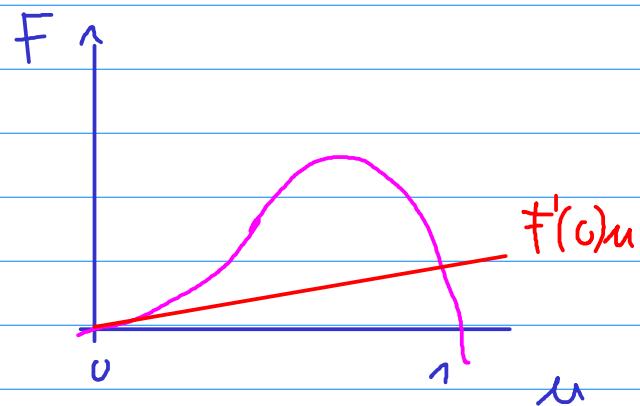
$$F(0) = F(1), \quad F'(0) > 0, \quad F'(1) < 0$$

- linearized analysis predicts wave speed
- $$\underline{c^* = 2 \sqrt{D F'(0)}}$$
- linear prediction is correct provided $F(u)$ is convex, in the sense

(C) $\underline{F(u) \leq F'(0)u} \quad \forall u \in [0, 1]$



convex



non-convex

- If (C) is violated, the spreading speed of a localized initial condition may exceed c^*

Terminology (Stokes 1976)

- Denote by c_l the spreading speed of a localized initial profile
- Then the wave is pulled if $c_l = c^*$ and pushed if $c_l > c^*$
- Pulled waves are governed by the linear behavior in the tail of the profile
- For pushed waves the speed depends on the entire function $F(u)$, in particular on the carrying capacity.

b) Allee effect

- Biological interpretation of \textcircled{C} :

$$\dot{u} = F(u) = r(u)u$$

$r(u)$: per capita growth rate

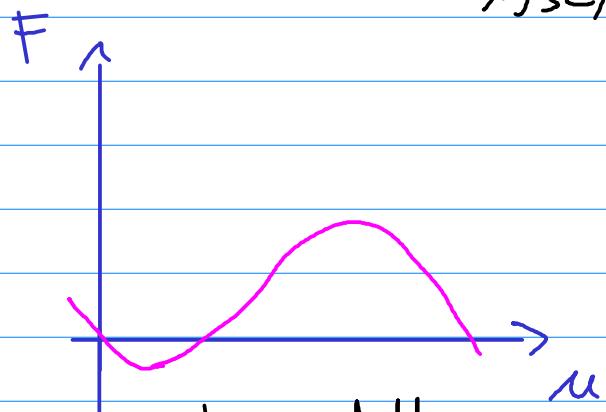
$$\textcircled{C}: r(u) = \frac{F(u)}{u} \leq F'(u) = r(u \rightarrow 0)$$

- Competition: $r(u)$ decreases with increasing u
- In the presence of cooperation, this condition can be violated (Allee, Bower 1932)



weak Allee effect

$$r(u) > 0$$



strong Allee effect

$$r(u) < 0$$

Example: $F(u) = b u (1-u) (1+au)$

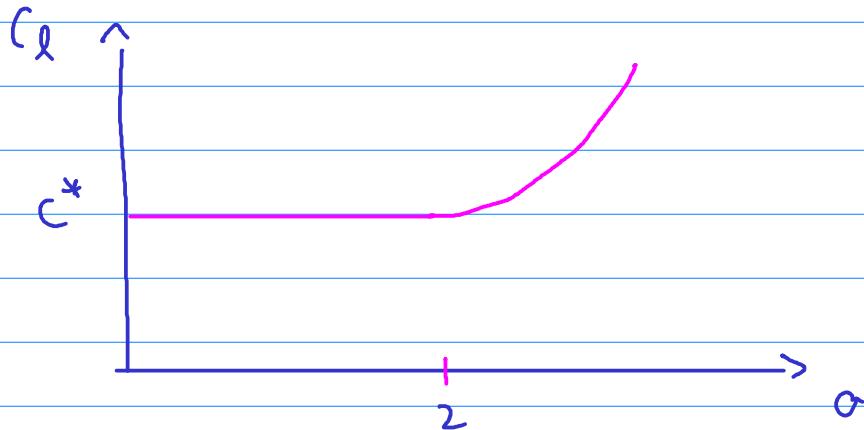
$$\Rightarrow r(u) = b (1-u) (1+au) =$$

$$= b (1 + (a-1)u - au^2)$$

\Rightarrow weak Allee effect for $a > 1$.

\Rightarrow transition from pulled to pushed waves at $a = 2$

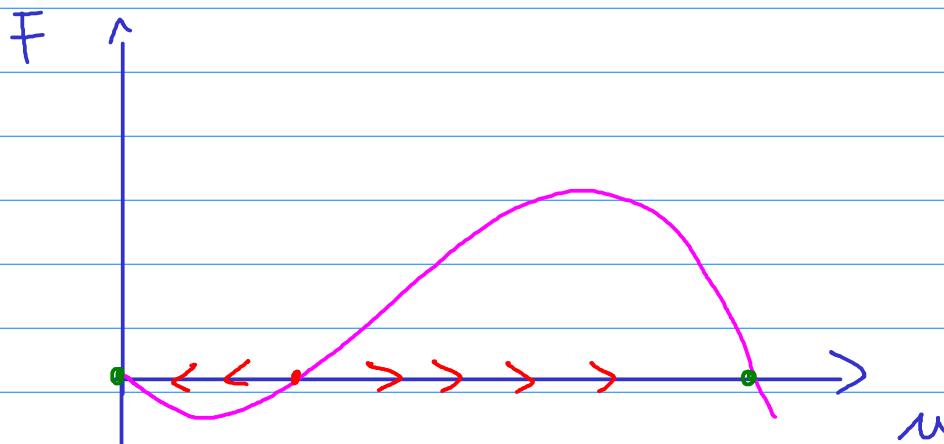
$$c_x = \begin{cases} c^* = 2\sqrt{Df} & a < 2 \\ 2\sqrt{Df} \left(\sqrt{\frac{2}{a}} + \sqrt{\frac{a}{2}} \right) & a \geq 2 \end{cases}$$



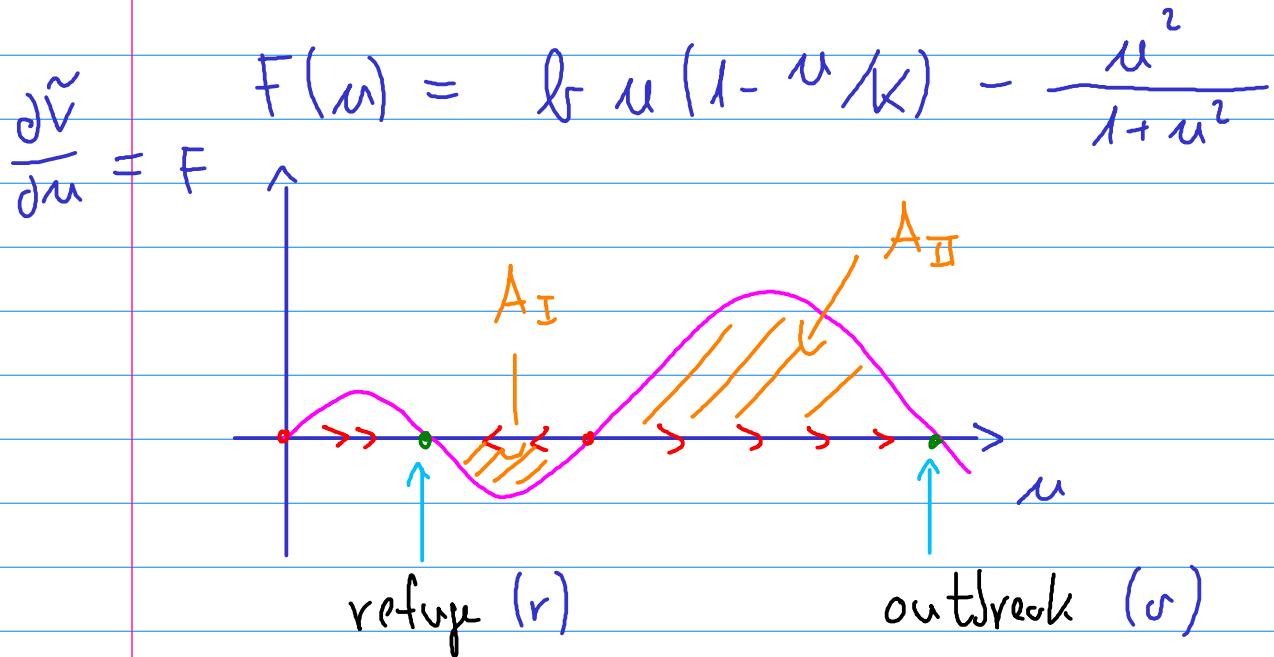
8.3. Wave propagation between stable states

Q: What happens if the local population dynamics displays multiple stable FP?

Example 1: Strong Allee effect



Example 2: Infect population dynamics
(Problem Set 1)



- Consider reaction-diffusion eq.

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + F(u)$$

with $F(u)$ as in the example.

- Recall: One-dim. dynamical systems are simple because they always admit a potential $V(u)$ such that

$$\dot{u} = F(u) = -\frac{\partial V}{\partial u}$$

- Claim: $V(u) = -\tilde{V}(u)$, where \tilde{V} is the potential of the mechanical analogue

Proof:

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + F(u)$$

traveling wave: $u(x,t) = f(x-ct)$

$$\Rightarrow -c f' = D f'' + F(f) = D f'' - \frac{\partial V}{\partial f}$$

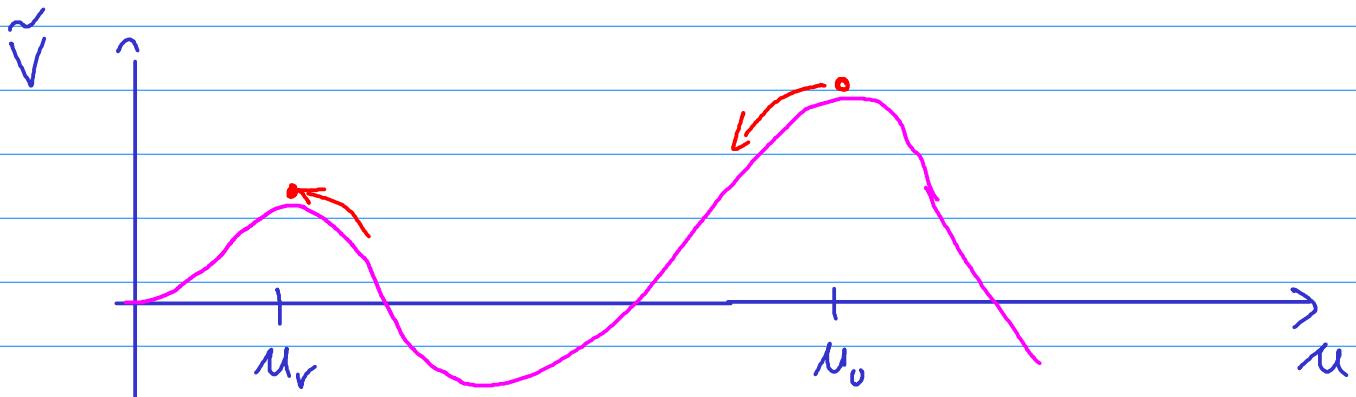
$$\Rightarrow D f'' = -c f' + \frac{\partial V}{\partial f} = -c f' - \frac{\partial \tilde{V}}{\partial f}$$

FPIs

\Rightarrow stable (states) of the local dynamics

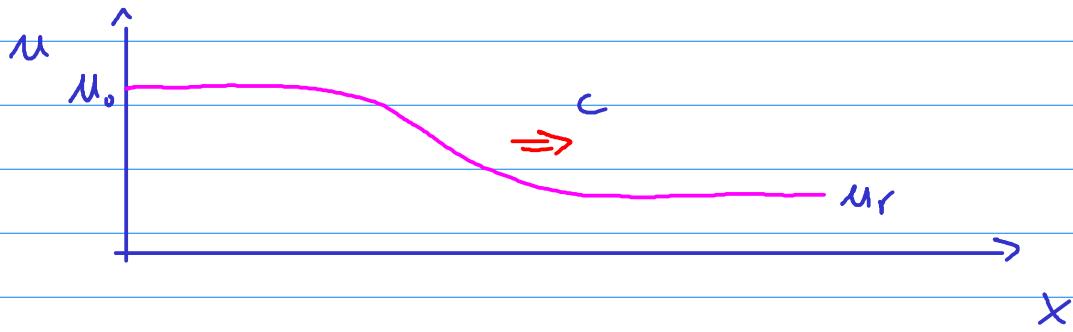
are local maxima of $\tilde{V}(f)$

Example 2:



- In this situation the outbreak state can spread at the expense of the vintage state

but not vice versa:



- Spreading speed c is uniquely determined
- The wave is pushed, not pulled
- This scenario requires that $\tilde{V}(u_0) > \tilde{V}(u_r)$

$$\Leftrightarrow V(u_0) < V(u_r)$$

\Leftrightarrow outbreak state is "more stable" than refuge state

$$\Leftrightarrow A_{\text{II}} > A_{\text{I}}$$

- Statistical physics remark:

$V(u)$ is analogous to a Landau free energy, and the waves are domain walls between different phases