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BI3264 - Math & Comp Bio

Intro class
2 papers - Cohen 2004, Abbot 2008

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→ Abbott 2008 - Theoretical Neuroscience rising

* Equations force a model to be precise, complete and self-consistent & allow its full implications to be worked out.

* Key test of the value of a theory is whether it makes post-dictions that generalize to other systems and provide valuable ways of thinking

* first principles in neuroscience :
  - Efficient coding
  - Bayesian inference
  - Generative Models
  - Causality
  - Positivity of neural code.

(A lot about neural coding and neural network modelling that went over my head).

* Identifying the minimum set of features needed to account for a particular phenomenon and describing these accurately enough to do the job is a key component of model building.

→ Cohen 2004
Current landscape of math as a tetrahedron - 4 vertices are data structures, algorithms, theories & models, and computers and software.

Lec 2 - 18|1|22
Introduction to Chemical kinetics
In the course, we will see how concentrations, populations etc. change in time and space; and build up a formalism. [conc of chemicals in a reaction]
Changes in time ⇒ Dynamical system
Its described well with Ordinary Differential Equations (ODE)
Spatial - Partial Differential Eqns.

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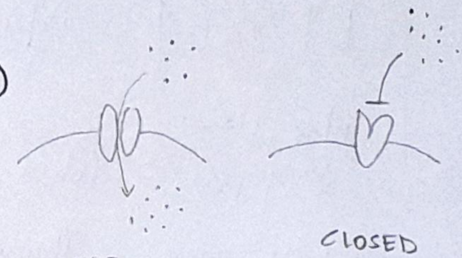
Aims —
i) Write the differential equations governing chemical reactions
ii) Simplify and solve these equations.

Transition between 2 states

Ion channels (like Na^+ channel) can be in either open or closed state with a probability that's dictated by membrane potential.



Slime mold — when food is scarce, it forms an aggregate, multicellular blob, from cAMP cues.
So, based on availability of food, cAMP receptors can be receptive or non-receptive.

Transition states

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$$

A, B : conc, ion channels, receptors
dimension: number/unit volume

k_1, k_2 : Rate constants
dim: 1/unit time (s^{-1})

Such a model is a simplification. Kinetic gating scheme of Hodgkin-Huxley Na channel has 8 states between which the Na channel can switch.

Consider: the ion channel is in state A. After time Δt,
(i) it can remain in state A
(ii) it transitions to state B and remains there.

we choose a Δt small enough that $A \to B \to A$ is very unlikely

Probability that it transitions —

$$P(A \to B) = k_1 \Delta t + \varepsilon(\Delta t)$$

↳ Error as a function of Δt called Absolute error

$$= k_1 \Delta t \left(1 + \underbrace{\frac{\varepsilon(\Delta t)}{k_1 \Delta t}} \right)$$

↳ Fractional error : $E(\Delta t)$

Think of k_1 as a timescale. If k_1 is huge, it means that it takes a long time for $A \to B$??

- Also, if $k_1 \gg k_2$ ⇒ $A \to B$ occurs much 'faster' and B will be the steady state.

- How small should Δt be?

Independent ↙ $P(B \xrightarrow{k_1^{-1}} A \xrightarrow{k_1} B) \ll P(B \xrightarrow{k_1^{-1}} A)$ for the error to be small.

Δt should be small that molecule in state A remains in state A after time Δt or shifts to state B & stays in B

* for instance, membrane potential is constant

$$P(B \to A \to B) \ll P(B \to A)$$

$$(\cancel{k_{-1}\Delta t})(k_1 \Delta t) \ll \cancel{k_{-1}\Delta t}$$

Similarly,

$\Delta t \ll \frac{1}{k_{-1}}$

$\Rightarrow \Delta t \ll \frac{1}{k_1}$ } timescale where interesting stuff happens

Markov Properties

1) Transition between states are random (independent events)

2) Prob of transitions in a time interval doesn't depend on the history of transitions

3) If 'conditions are fixed'*, transitions don't depend on the time when they're observed

Now we construct equations to get the conc. of channels open at $(t + \Delta t)$ given that $A(t)$

$$A(t+\Delta t) = A(t) - \underbrace{(k_1 \Delta t)}_{P(A \to B)} A(t) + \underbrace{(k_{-1}\Delta t)}_{P(B \to A)} B(t)$$

$$\lim_{\Delta t \to 0} \frac{A(t+\Delta t) - A(t)}{\Delta t} = -k_1 A(t) + k_{-1} B(t) \quad \text{\# Applying } \lim \to 0$$

$$\frac{dA}{dt} = -k_1 A + k_{-1} B \quad \text{for} \quad A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$$

Similarly,

$$\frac{dB}{dt} = k_1 A - k_{-1} B$$

Initial cond: $A(t=0) = A_0$
$B(t=0) = B_0$

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Lecture 3 - Recorded

We are looking at transitions at a population level

A : conc : $\frac{\text{no. of molecules in state A}}{\text{Volume}}$

The equations we derived are linear ODEs

$$\frac{dA}{dt} + \frac{dB}{dt} = 0 \Rightarrow (A+B) = \text{constant} = M$$

This means that total no. of molecules is going to be the same

$$\Rightarrow A_0 + B_0 = \boxed{A(t) + B(t) = M}$$

$$A = M - B \quad - (1)$$

Use (1) :

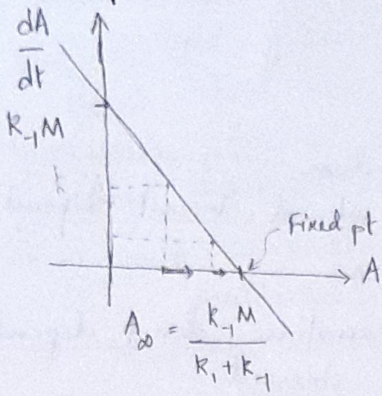
$$\frac{dA}{dt} = -k_1 A + k_{-1}(M - A)$$

(4)

$$\frac{dA}{dt} = -(k_1 + k_{-1}) A + k_{-1} M$$

We need to solve this differential eqn to understand how A changes with time

Phase space plot



$$A_\infty = \frac{k_{-1} M}{k_1 + k_{-1}}$$

When $\frac{dA}{dt} = 0$, $\boxed{A_\infty = \frac{k_{-1} M}{k_1 + k_{-1}}}$

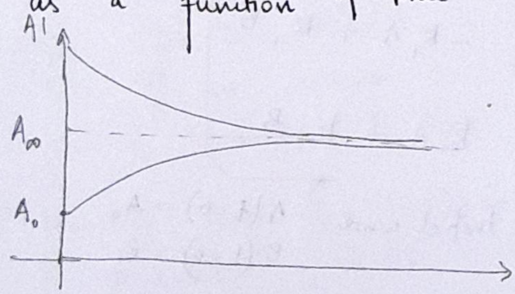
* If $A(t=0) = A_\infty$
  $A(t = 0 + \Delta t) = A_\infty$
  So, A_∞ is called fixed point because $dA/dt = 0$ there.

* If $A(t=0) = A_\infty - \delta A = A_0$
  $\left.\frac{dA}{dt}\right|_{A_0} > 0 \Rightarrow A(t = 0 + \Delta t)$ will increase based on $\left|\frac{dA}{dt}\right|$

* If $A(t=0) = A_\infty + \delta A = A_0$
  $\left.\frac{dA}{dt}\right|_{A_0} < 0 \Rightarrow A(t = 0 + \Delta t)$ will decrease

So if we perturb the system either to the left or the right, we get a stable fixed point.
(Like a pendulum)

A as a function of time



If we start from $A_0 \neq A_\infty$, the system will asymptote towards the stable fixed point.

The solution to the differential eqⁿ will be -

How to find these solutions?

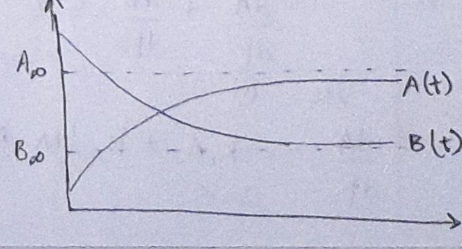
$$A(t) = A_\infty - (A_\infty - A_0)\, e^{-(k_1 + k_1)t}$$

$t \to \infty \quad A(t_\infty) = A_\infty$

$t \to 0 \quad A(t_0) = A_0$

If A increases with time, B has to decrease with time because $A(t) + B(t) = M$

$$A_\infty = \frac{k_1 M}{k_1 + k_{-1}} \qquad B_\infty = M - A_\infty$$



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Lecture 4

Enzyme Kinetics

Reactions with more than one reactant

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} P$$

Such reactions are governed by law of Mass Action: the rate / speed of a reaction is proportional to the product of concentrations of the reactants.

If we increase conc, the probability that the reaction occurs goes up and so the speed increases.

The molecules shouldn't be so densely packed that other interactions come into play.

$$\frac{dP}{dt} = k_1 [A][B] - k_{-1} [P]$$

For reaction $3A \xrightarrow{k} C$

$$\frac{dC}{dt} = k[A]^3 = k[A][A][A]$$

Its important to keep stoichiometry of reactions in mind

Consider: $2A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$

Forward Reaction

Molecules	Stoichiometry
A	-2
B	-1
C	+1

Reverse reaction

Molecules	Stoichiometry
A	+2
B	+1
C	-1

Differential equations:

$$\frac{dA}{dt} = -\underbrace{2}_{\text{no. of mol consumed (stoichiometry)}}\underbrace{k_1 A^2 B}_{\text{Rate of consumption}} + 2 k_{-1} C$$

$$\frac{dC}{dt} = k_1 A^2 B - k_{-1} C$$

$$\frac{dB}{dt} = -k_1 A^2 B + k_{-1} C$$

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Example : Dimerization

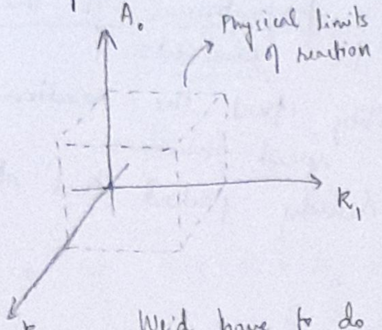
$$A + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$\frac{dA}{dt} = -2k_1 A^2 + 2k_{-1} C \qquad \frac{dC}{dt} = k_1 A^2 - k_{-1} C$$

Note that : $\frac{dA}{dt} + \frac{2C}{dt} = 0 \Rightarrow \boxed{A + 2C = A_0}$: constant

3 parameters in the expt : A_0 - total no. of monomers at the start of the reaction (assuming no dimers)

k_1 , k_{-1} - rate constants.



We'd have to do X^n experiments where n is no. of parameters

If we can find ways to combine parameters into a composite parameter (dimensionless) [or find relations between them] such that we can vary the composite parameter and study the system.

Enzyme Kinetics

Enzymes catalyse reactions by <u>lowering the energy barrier</u> so the molecules can cross it to a thermodynamically favorable state. It lowers the <u>activation energy</u> of the reactions.

Substrates enter the active site and enzyme changes shape to hold them (induced fit) and lowers E_A so they can form products which are released.

The enzyme can further catalyse many more molecules.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$$

\# $E + P \rightarrow C$ is negligible

$$\frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C$$

$$\frac{dS}{dt} = -k_1 ES + k_{-1} C$$

$$\frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C$$

$$\frac{dP}{dt} = k_2 C$$

Conservation statements.

- $E_{tot} = E(t) + C(t) = E_0$
- $S(t) + P(t) + C(t) = S_0$

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Lecture 5

Recap: Enzyme - substrate interaction

We'll focus of how substrate is consumed.

$$\frac{dS}{dt} = -k_1 ES + k_{-1} C \qquad E(t) = E_0 - C(t)$$

$$\frac{dS}{dt} = -k_1 (E_0 - C(t)) + k_{-1} C$$

$$\frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C = k_1 (E_0 - C(t)) S - (k_{-1} + k_2) C$$

Assumptions -

① E-S complex is formed rapidly i.e. C forms at a much smaller time scale than S changes

② Enzyme is working at full capacity - it reaches steady state $\Rightarrow$ $\boxed{\frac{dc}{dt} \approx 0}$

$$\Rightarrow k_1 \; E_0 - C(t) = \frac{(k_{-1} + k_2) C}{k_1 S} \qquad \boxed{k_m = \frac{k_{-1} + k_2}{k_1}}$$

Somehow, $C(t) = \frac{E_0 S}{k_m + S} \Rightarrow \frac{dP}{dt} = \frac{k_2 E_0 S}{k_m + S}$

$$\frac{dS}{dt} = -\frac{dP}{dt} \; \therefore \; \frac{dS}{dt} = -k_2 C = -\frac{k_2 E_0 S}{k_m + S} \qquad V_{max} = k_2 E_0$$

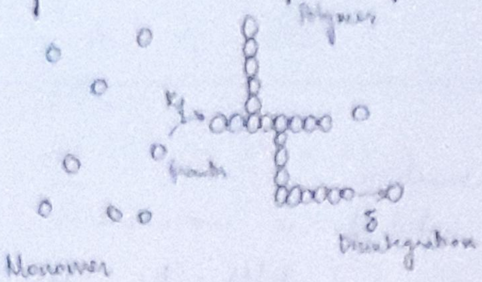
$$\therefore \boxed{\frac{dS}{dt} = -\frac{V_{max} S}{k_m + S}}$$ Rate at which substrate $\rightarrow$ product assuming that $\frac{dc}{dt} = 0$

Michaelis - Menten Kinetics equation

If $S \gg k_m$, $\frac{dS}{dt} \rightarrow V_{max}$

⑧ # Simple model of polymer dynamics

* Why?
$F + C \rightleftharpoons F$
↳ find a why!!



: Simplified description, but a good way to start

In reality, the rate of addition of monomer may not be constant – it could decrease with polymer growth because of hinderance

$C(t)$: no. of monomers in volume V at time t 4C 7F

$F(t)$: amount of polymer (in monomer subunits) at time t

A : Total amount of material

$$\frac{dC}{dt} = -k_f CF + \delta F$$
$$\frac{dF}{dt} = k_f CF - \delta F$$

Conservation:

$$\boxed{C(t) + F(t) = A}$$
$$F = A - C$$

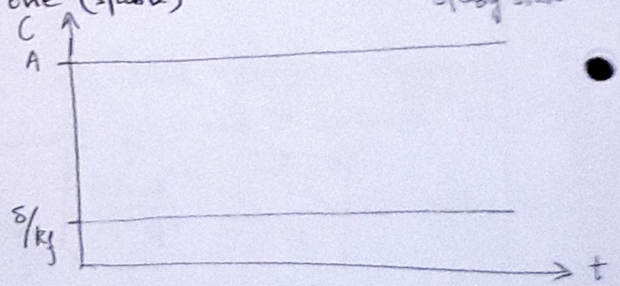
Non-linear (Quadratic) differential eq^n

So, $\underbrace{\frac{dC}{dt} = (\delta - k_f C)(A - C)}$

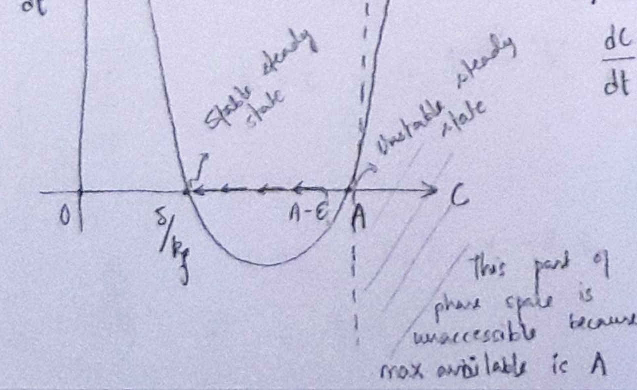
What are the steady states? i.e. $\frac{dC}{dt} = 0$

If the system is perturbed, it can move away, or come back to the same one (stable)   (unstable) steady state

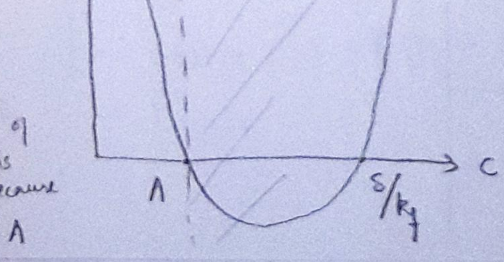
$$\frac{dC}{dt} = 0 \begin{cases} C = A \\ C = \delta / k_f \end{cases}$$



i) Case I



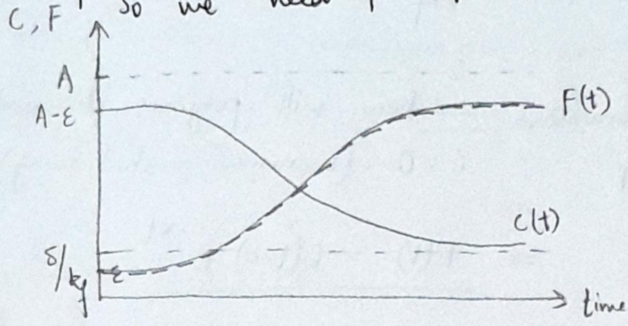
ii) Case II



i) Case I – how C evolves with time

If $C(t=0) = A$, then system will remain there.

So we need to start with some amount of polymer



If $C(t=0) = A - \varepsilon$, then system will exponentially move towards the other steady state because $\frac{dC}{dt}$ is negative (phase-space plot)

$C(t_\infty) \rightarrow \delta/k_f$

$F(t_\infty) \rightarrow A - \delta/k_f$

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Lecture 6

$C(t_\infty) \rightarrow \delta/k_f$: It'll asymptote towards the limit, but it will never reach it because rate of increase becomes smaller

$F(t_\infty) \rightarrow A - \delta/k_f$

ε is the seed polymer that nucleates the reaction.

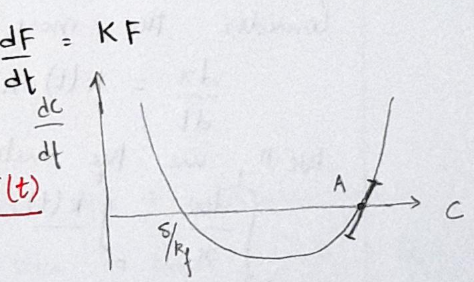
$C(t=0) = A - \varepsilon$

$\varepsilon \ll A$

Recall: $\frac{dF}{dt} = k_f CF - \delta F$

$$\frac{dF}{dt} = F(k_f C - \delta) = F(k_f(A - \cancel{\varepsilon}) - \delta)$$

$$\frac{dF}{dt} = \underbrace{(k_f A - \delta)}_{\text{const. } K} F \Rightarrow \frac{dF}{dt} = KF$$



So, $F(t) = F(t=0) \times e^{Kt} = \varepsilon e^{Kt} = F(t)$

$$\boxed{K = k_f(A - \delta/k_f)}$$

This is called linearization – it allows us to examine the region around a fixed point for a short period of time by approximating a non-linear ODE as linear ODE.

Approximating a nonlinear ODE by a linear ODE.

Its done by taking a slope at the fixed point

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$S/k_f = C_{crit}$: minimum conc of c for polymer to be produced

$K = k_f (A - S/k_f)$ Polymerisation will happen only if $c > C_{crit}$ i.e. K +ve

If K is +ve, system moves away from A

K is -ve i.e. $S/k_f > A$ [case II] then no polymerisation ? (~35 min)

* Wash away all monomers — how will polymers dissociate?

$$\frac{dF}{dt} = k_f cF - SF \quad , \quad c = 0 \text{ (monomers washed away)}$$

$$\frac{dF}{dt} = -SF \quad \Rightarrow \quad \underline{F(t) = F(t=0)\, e^{-St}}$$

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Lecture 7

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Differential Equations - Recorded (Ch. 3 Primer)

First Order Linear ODE

→ Exponential growth : $\frac{dx}{dt} = rx \quad \rightarrow \quad x(t) = c.\exp(rt)$

We can find c by : $x(t=0) = c$

If
- $r > 0$: exponential growth
- $r = 0$: no change
- $r < 0$: exponential decay

Consider the more general form —

$$\frac{dx}{dt} = k(t) \cdot x \qquad k(t) : \text{function that varies with time}$$

We'll use the method of Separation of variables —

$$\int_0^t \frac{dx}{x} = \int_0^t k(t) \cdot dt$$

$$\ln(x)\Big|_{x(0)}^{x(t)} = \int_0^t k(\xi) \cdot d\xi$$

$$\ln(x(t)) - \ln(x(0)) = \int_0^t k(\xi) \cdot d\xi$$

$$x(t) = x(0) \cdot \exp\left(\int_0^t k(\xi)\, d\xi\right)$$

If $k(\xi) = r$, then $x(t) = x_0 \exp(rt)$

Production and Decay

$$\frac{dx}{dt} = I - \gamma x$$

I : Production

γx : Decay term

I, γ - constants $\quad x(t=0) = x_0$

$$\int_{x(0)}^{x(T)} \frac{dx}{I - \gamma x} = \int_0^T dt$$

Change of variable

$u = I - \gamma x$

$\frac{du}{dx} = -\gamma \Rightarrow du = -\gamma dx$

$$\Rightarrow -\frac{1}{\gamma} \int_0^T \frac{du}{u} = \int_0^T dt$$

$$\ln\left(\frac{u(T)}{u(0)}\right) = -\gamma T \quad \Rightarrow \quad u(T) = u(0) \exp(-\gamma T)$$

$$I - \gamma x = [I - \gamma x(0)] \exp(-\gamma T)$$

$$x(t) = \frac{I}{\gamma} - \left[\frac{I}{\gamma} - x_0\right] \exp(-\gamma t)$$

These are linear and homogenous equations

$$\frac{dx}{dt} = f(t) + rx$$: Inhomogenous (explicit dependence on t)

$f(t)$ - production term varies with t

(i) Find general solution of homogenous eqn

$$\frac{dx}{dt} = rx \quad \Rightarrow \quad x(t) = ce^{rt}$$

(ii) Find a particular solution

$x(t) =$ general soln of homogenous eqn + particular soln

a) If $f(t) = \text{const}$, then particular soln is const : $ce^{rt} + c_2$

b) If $f(t) = \exp(kt)$, then particular soln is Ae^{kt} : $ce^{rt} + Ae^{kt}$

Eg 3.3 $$\frac{dx}{dt} = rx + \alpha \cdot e^{\beta t} \qquad x(0) = x_0 \ ; \ r, \alpha, \beta - \text{const.}$$

Particular sol^n of $f(t)$: $x = A\exp(\beta t)$

$$\frac{dx}{dt} = A\beta \cancel{e^{\beta t}} = rA\cancel{e^{\beta t}} + \alpha \cancel{e^{\beta t}}$$

$$\Rightarrow \beta A = rA + \alpha \quad \Rightarrow \quad A = \frac{\alpha}{\beta - r} \quad \text{for } \beta \neq r$$

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If $\beta = r$, then we use the particular solution Ate^{rt}
Look in TB

General solution :-

$$x(t) = c\exp(r) + \frac{\alpha}{\beta - r}\exp(\beta t)$$ — Exercise : verify.

Consider :

$$\frac{dy}{dt} = ay + q(t)$$

y : amt. of money in bank at time t
a : rate of interest unit : $1/t$

If $\frac{dy}{dt} = ay$ $t=0$: y_0 rupees in the bank
$y = y_0 \exp(at)$: money at time t

So, $q(t)$: withdrawals / deposits — Source / sink term

$$y(t) = \underbrace{y_0 \exp(at)}_{\text{growth of initial capital}} + \underbrace{\int_{s=0}^{s=t} e^{a(t-s)} q(s).ds}_{\text{particular solution}}$$

If we put in money at time s, it grows exponentially from time s

If we solve the integral, we'll get the particular sol^n.

Verify —

$$\frac{dy}{dt} = y_0 . a\exp(at) + \frac{d}{dt}\left[e^{at}\int_{s=0}^{s=t} e^{-as} q(s).ds\right]$$

$$\frac{dy}{dt} = y_0 a\exp(at) + \frac{de^{at}}{dt}\left(\int_0^t e^{-as} q(s).ds\right) + e^{at}\frac{d}{dt}\left(\int_0^t e^{-as} q(s).ds\right)$$

$$\frac{dy}{dt} = y_0 a\exp(at) + ae^{at}\int_0^t e^{-as} q(s)\, ds + \underbrace{e^{at}.e^{-at}}_{1}.q(t)$$

$$\frac{dy}{dt} = a(y) + q(t)$$

If we take a common, we'll get $y(t)$ in common

Other special cases. $q(t) = \cos(\omega t)$
$q(t) = H(t-T)$ — step fn
$q(t) = \delta(t-T)$ — delta fn
$q(t) = t^n$ (polynomial)

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Lecture 8 - Recorded

Linear 2nd order ODEs with constant coefficients

General form : $\hat{a}\frac{d^2x}{dt^2} + \hat{b}\frac{dx}{dt} + \hat{c}x = 0$

Rewritten : $\frac{d^2x}{dt^2} - \beta\frac{dx}{dt} + \gamma x = 0$ where $\beta = -\frac{\hat{b}}{\hat{a}}$ $\gamma = \frac{\hat{c}}{\hat{a}}$

Euler's method - solution of this equation, guessing wildly,
$y = e^{mt}$, m is a const.

Put it in the differential eq^n -

$$\frac{d^2 e^{mt}}{dt^2} - \beta\frac{de^{mt}}{dt} + \gamma e^{mt} = 0$$

$$m^2 \cancel{e^{mt}} - \beta . m e^{mt} + \gamma e^{mt} = 0$$

$m^2 - \beta m + \gamma = 0$: Characteristic equation for the differential eq^n

$\Rightarrow$ $y = e^{mt}$: this solution will work if m satisfies the characteristic equation -

$$\boxed{m_{1,2} = \frac{1}{2}\left[\beta \pm \sqrt{\beta^2 - 4\gamma}\right]}$$: roots of eq^n : also called eigenvalues.

Real roots : $\beta^2 - 4\gamma > 0$

$m_1 = \frac{1}{2}\left(\beta + \sqrt{\beta^2 - 4\gamma}\right)$ $m_2 = \frac{1}{2}\left(\beta - \sqrt{\beta^2 - 4\gamma}\right)$

Solution can be written as superposition of two solutions - c_1, c_2 : constants.

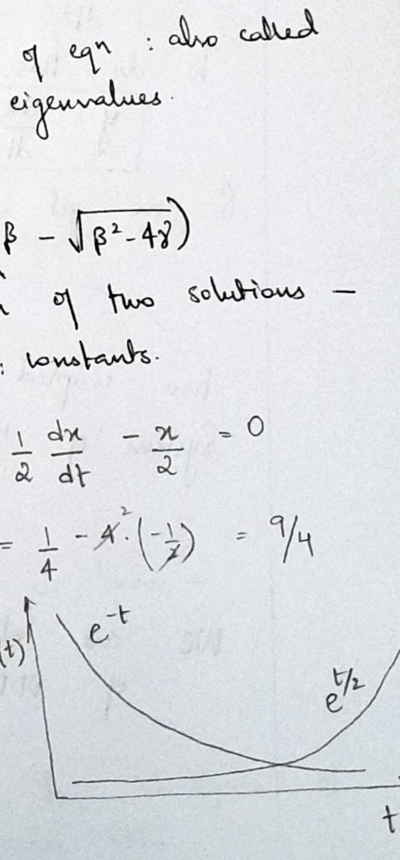
$$x(t) = c_1 e^{m_1 t} + c_2 e^{m_2 t}$$

Eg : $2\frac{d^2x}{dt^2} + \frac{dx}{dt} - x = 0$ $\Rightarrow$ $\frac{d^2x}{dt^2} + \frac{1}{2}\frac{dx}{dt} - \frac{x}{2} = 0$

$\Rightarrow$ $\beta = -\frac{1}{2}$ $\gamma = -\frac{1}{2}$ $\Rightarrow$ $\beta^2 - 4\gamma = \frac{1}{4} - \cancel{4}^2 . \left(-\frac{1}{\cancel{2}}\right) = 9/4$

$m_1 = \frac{1}{2}\left(-\frac{1}{2} + \sqrt{\frac{9}{4}}\right) = 1/2$ $m_2 = -1$

$$x(t) = c_1 e^{t/2} + c_2 e^{-t}$$



2nd term acts in the initial time period, but it diminishes as $t \to \infty$

(14)

Complex roots : $\beta^2 - 4\gamma < 0$

$m_1 = p + iq \qquad m_2 = p - iq$

$p = \frac{1}{2}\beta \qquad q = \frac{1}{2}\sqrt{|\beta^2 - 4\gamma|}$

$x_1(t) = e^{(p+iq)t} = e^{pt} \cdot e^{iqt}$

$x_2(t) = e^{(p-iq)t} = e^{pt} \cdot e^{-iqt}$

de Moivre's theorem : $\boxed{e^{i\theta} = \cos\theta + i\sin\theta}$

$\Rightarrow \left.\begin{aligned} x_1(t) &= e^{pt}(\cos qt + i\sin qt) \\ x_2(t) &= e^{pt}(\cos qt - i\sin qt) \end{aligned}\right\}$ Oscillatory solutions

Linear combinations of the solutions are also a solution.

$\Rightarrow x(t) = c_1 e^{pt} \cdot \cos qt + c_2 e^{pt} \sin qt$ L.C. ? Why no i in 2nd term?

Because : $\left.\begin{aligned} \frac{1}{2}(x_1(t) + x_2(t)) &= \cos qt \, e^{pt}, \text{ and} \\ \frac{i}{2}(x_2(t) - x_1(t)) &= e^{pt}\sin(qt) \end{aligned}\right\}$ Also solutions

??

2nd order ODE can be written as a set of 2 1st order ODEs

$$\frac{d^2x}{dt^2} - \beta\frac{dx}{dt} + \gamma x = 0$$

To do this, we define another dependent variable y –

$\boxed{y = \frac{dx}{dt}} \Rightarrow \frac{dy}{dt} = \frac{d^2x}{dt^2}$

So, we get : $\frac{dx}{dt} = y$

$$\frac{dy}{dt} = \beta\frac{dx}{dt} - \gamma x = \beta y - \gamma x = \frac{dy}{dt}$$

two coupled 1st order ODEs in place of 2nd order ODEs

System of 1st order ODEs : $\left[\begin{aligned} \frac{dx}{dt} &= ax + by \\ \frac{dy}{dt} &= cx + dy \end{aligned}\right.$

We are interested in qualitative solutions of system of ODEs.

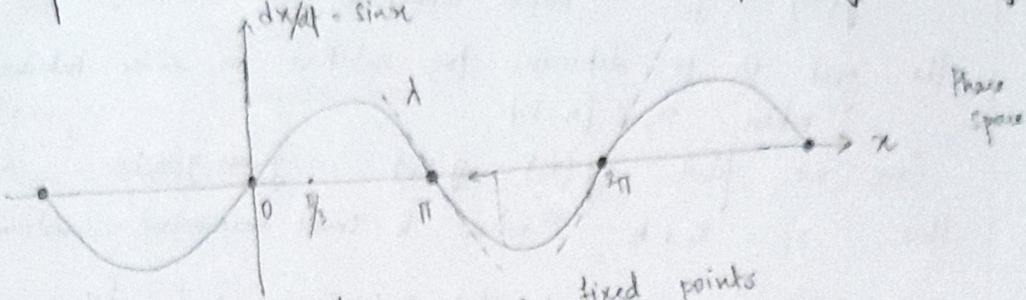
Example of qualitative solution (Strogatz book)

Consider : $\frac{dx}{dt} = \sin x$ $\qquad \int dt = \int \frac{dx}{\sin x}$

$\Rightarrow t + c = \int \operatorname{cosec} x \cdot dx$

$t = \ln\left(\frac{\operatorname{cosec} x_0 + \cot x_0}{\operatorname{cosec} x + \cot x}\right)$

If $x(t=0) = x_0$ $\quad x(t \to \infty) = ?$ — Hard to do analytically. So think geometrically.



$\frac{dx}{dt} = 0 \Rightarrow$ fixed points

$x = n\pi$

When $\frac{dx}{dt} > 0$, it moves towards increasing x

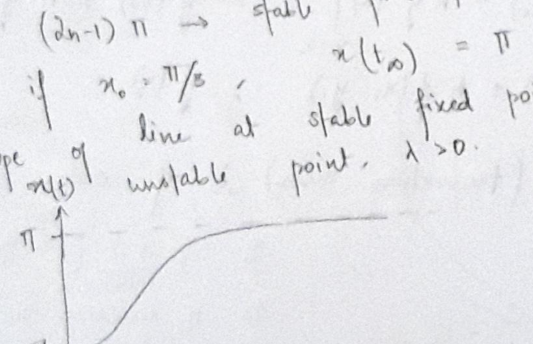
$\Rightarrow$ if $x = \pi - x.5$, as $t \to \infty$, $x = \pi \to$ stable fixed pt

$2n\pi \to$ unstable fixed point

$(2n-1)\pi \to$ stable fixed point

$\Rightarrow$ if $x_0 = \pi/3$, $\quad x(t_\infty) = \pi$

Slope of line at stable fixed point is negative. for unstable point, $\lambda > 0$.



We looked at the system qualitatively. but we know —

1. Fixed points
2. Stability of fixed points
3. Past and future trajectories of the system

This is a 1D system, we need to do this for 2d system of 1st order ODEs.

(16)

$$\begin{bmatrix} dx/dt \\ dy/dt \end{bmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

Slope $\lambda \sim$ Eigenvalues of the matrix.

Lecture ~~9~~ - Tutorial 01 — Ch. 21 - Adv. Eng. Mathematics - Kreyszig → 5th Ed — 3/2/22

Method of Numerical Integration : Euler-Cauchy Method

ODE - Initial value problem

$$y' = f(x, y) \qquad ' : \frac{d}{dx}$$

$$y(x_0) = y_0 \quad : \text{initial condition}$$

The goal is to determine the solution in some interval $[a, b]$ when $x_0 \in [a, b]$

Can we find $y(x_1)$, $y(x_2)$ ... given $y(x_0)$?

Here, $x_1 = x_0 + h$ where h : small increment, constant

$$y(x+h) = y(x) + h y'(x) + \frac{h^2}{2!} y''(x) + \dots \quad \text{[Taylor series]}$$

If h is small, $h^2, h^3 \dots$ will be negligible.

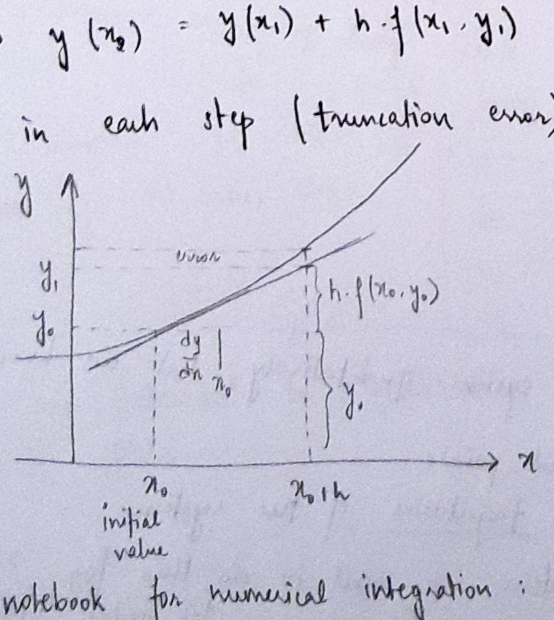
then, $y(x+h) \simeq y(x) + h \cdot y'(x)$

$y(x+h) = y(x) + h \cdot f(x, y)$ WKT. $y(x_0) = y_0$

So, $y(x_1) = y(x_0 + h) = y(x_0) + h y'(x)\Big|_{x=x_0} = y(x_0) + h \cdot f(x_0, y_0)$

$\Rightarrow y(x_2) = y(x_1) + h \cdot f(x_1, y_1)$; $y(x_3) = \dots$

Error in each step (truncation error) is of order $O(h^2)$



$y_1 = y_0 + h \cdot f(x_0, y_0)$

As h decreases, the error also decreases

Geometric interpretation of Euler-Cauchy Method

Adaptive step counter - smaller h for smaller slope, even smaller h for higher slope

Python notebook for numerical integration : Rishika - PSST

Lecture 9 (Recorded)

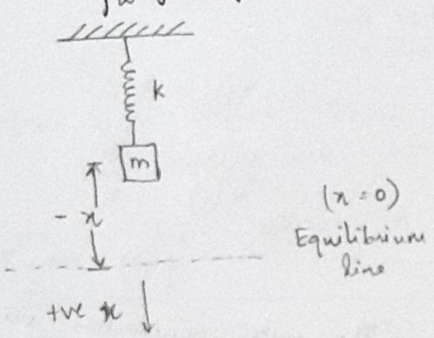
$$\frac{dx}{dt} = ax + by \qquad \frac{dy}{dt} = cx + dy$$

$$\begin{pmatrix} dx/dt \\ dy/dt \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} \; : \; \frac{d\bar{x}}{dt} = A\bar{x}$$

The solutions can be visualised as trajectories in the XY plane.

Examples – (Strogatz book)

1. Mass spring system



$$m\frac{d^2x}{dt^2} + kx = 0$$

Assuming: no friction, small displacement

Say. $\frac{dx}{dt} = v \qquad \frac{dv}{dt} = -\frac{k}{m} \cdot x$

where $\frac{k}{m} = w^2$ (frequency)

$$\Rightarrow \frac{dv}{dt} = -w^2 x$$

a : maximum compression possible i.e. one end of the oscillation $\Rightarrow v = 0$

$$\begin{pmatrix} dx/dt \\ dv/dt \end{pmatrix} = \begin{bmatrix} 0 & 1 \\ -w^2 & 0 \end{bmatrix} \begin{bmatrix} x \\ v \end{bmatrix}$$

(a) $\frac{dx}{dt} = 0 = v$

$\frac{dv}{dt} = -w^2 x = w^2(-x)$ $\Rightarrow$ velocity increases

(b) At equilibrium $(x = 0)$ ↓

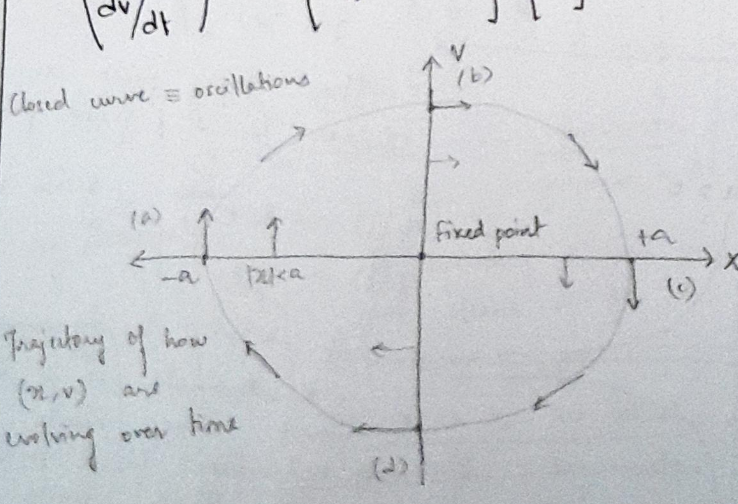
$\frac{dx}{dt} = v \quad \frac{dv}{dt} = 0$

(c) Max stretching $(v = 0)$

$\frac{dx}{dt} = 0 \quad \frac{dv}{dt} = \underbrace{(-w^2)x}_{-ve}$

(d) At equilibrium $(x = 0)$ ↑

$\frac{dv}{dt} = 0 \quad \frac{dx}{dt} = v$



(18) 2.

$$\frac{d\bar{x}}{dt} = A\bar{x} \qquad \bar{x} = \begin{pmatrix} x \\ y \end{pmatrix} \qquad A = \begin{bmatrix} a & 0 \\ 0 & -1 \end{bmatrix}$$

off diagonal elements are 0

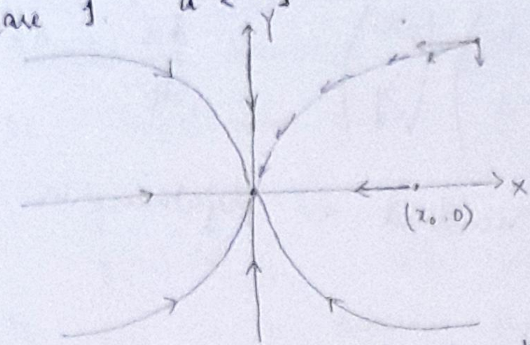
$$\Rightarrow \frac{dx}{dt} = ax \qquad \frac{dy}{dt} = -y$$

: Uncoupled ODEs

$$x(t) = x_0 e^{at} \qquad y(t) = y_0 e^{-t}$$

(x_0, y_0) - initial condtn.

★ Case 1 $a < -1$

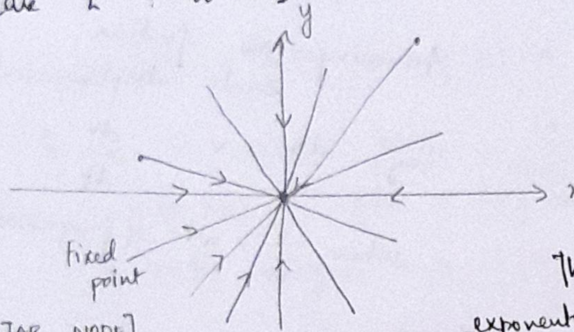


Since the exponent is negative, as $t \to \infty$, both $x, y \to 0$

Since $a < -1$, the vector decreases along y closer than it does x.

If initial condn is $(x_0, 0)$, then the vector is on x axis, and it moves to origin in an exponential way.

★ Case 2 : $a = -1$



[STAR NODE]

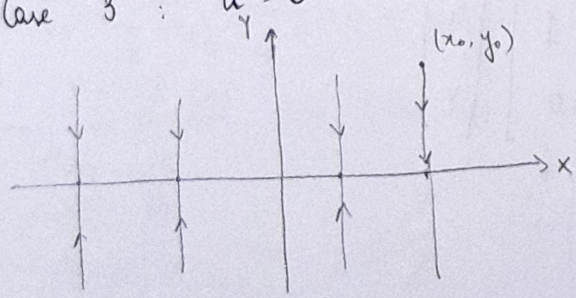
$$x(t) = x_0 e^{-t} \qquad y(t) = y_0 e^{-t}$$

$$\frac{y(t)}{x(t)} = \frac{y_0}{x_0}$$

$$\Rightarrow y(t) = m \cdot x(t)$$

The vector approaches origin exponentially i.e. asymptotes to 0.

★ Case 3 : $a = 0$



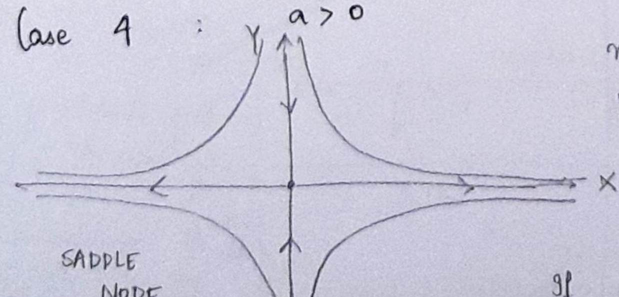
$$x(t) = x_0$$

$$y(t) = y_0 e^{-t}$$

$$y(t \to \infty) = 0$$

Here, every point on the X axis is a fixed point

★ Case 4 : $a > 0$



SADDLE NODE

$$x(t) = x_0 e^{at} \Rightarrow t \to \infty \; x(t_\infty) \to \infty$$

$$y(t) = y_0 e^{-at} \Rightarrow t \to \infty \; y(t_\infty) \to 0$$

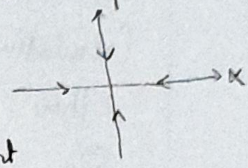
At $x \gg 0$, the dynamics along X dominate, so Y values won't change much

If perturbed from fixed point, it'll fly off to infinity.

Lecture 10 - Recorded (8/2)

Coupled ODEs

$$\frac{d\bar{x}}{dt} = A\bar{x}$$: How to solve general form of coupled ODEs ?



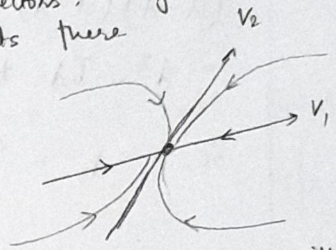
Some insights from last lecture -

- There's a fixed point at the origin
- There are certain special directions - if we start on x axis ($y_0 = 0$), then it'll stay on x axis.

If $x(t) = e^{at} \cdot x_0$ $\quad y(t) = e^{-t} \cdot y_0$

$$\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} = x_0 \underbrace{\begin{bmatrix} 1 \\ 0 \end{bmatrix}}_{\text{unit vector in x-direction}} e^{at} + y_0 \underbrace{\begin{bmatrix} 0 \\ 1 \end{bmatrix}}_{\text{unit vector in Y-direction}} e^{-t}$$ - this is for uncoupled ODEs

Even for coupled ODEs, there will be vectors, along which the system will remain if it starts there



$$\frac{d\bar{x}}{dt} = A\bar{x} \quad \text{where} \quad A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

$$\boxed{x(t) = e^{\lambda_1 t} \cdot \vec{v_1} \qquad y(t) = e^{\lambda_2 t} \vec{v_2}}$$

Perhaps the solution will be like this.

$$\frac{d\bar{x}}{dt} = \frac{d}{dt}\left(e^{\lambda_1 t} \vec{v_1}\right) = \lambda_1 \underbrace{e^{\lambda_1 t} v_1}_{x} \quad ; \quad \frac{d\bar{x}}{dt} = A\bar{x}$$

So, we get :

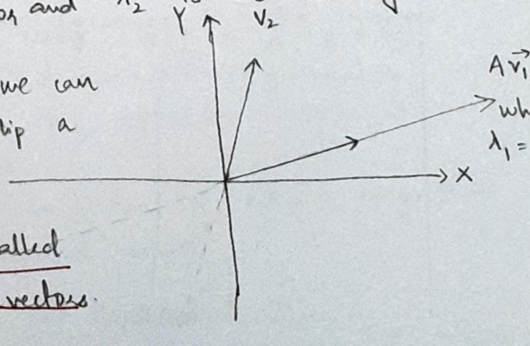
$$A \cancel{e^{\lambda_1 t}} \vec{v_1} = \lambda_1 \cancel{e^{\lambda_1 t}} \cdot \vec{v_1}$$

: ODEs connect to linear algebra

$$A\vec{v_1} = \lambda_1 \vec{v_1}$$

Here, $\vec{v_1}$ is called an eigenvector, and λ_1 is an eigenvalue

Similarly, $\vec{v_2}$ is also eigenvector and λ_2 is also an eigenvalue.



$\vec{V_1} = (v_{11}, v_{12})$

$$A \begin{bmatrix} v_{11} \\ v_{12} \end{bmatrix} = \begin{bmatrix} \lambda_1 v_{11} \\ \lambda_2 v_{12} \end{bmatrix}$$

By operating A, we can just stretch of flip a point on v_1 & v_2.

So, v_1 & v_2 are called invariant vectors - eigenvectors.

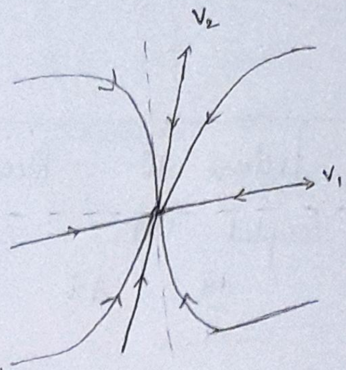
20

Solution for it would be:

$$\bar{x} = x_0 e^{\lambda_1 t} \vec{v_1} + y_0 e^{\lambda_2 t} \vec{v_2}$$

Say, $-1 < \lambda_1 < 0$

$-2 < \lambda_2 < -1$



$\therefore |\lambda_2| > |\lambda_1|$

Calculating eigenvalues

There can be multiple eigenvalues.

Say, $A\vec{v} = \lambda \vec{v}$

To get λ, we've to solve –

$$\det(A - \lambda I) = 0$$

$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$ $\quad I = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$

$$\det\left(\begin{bmatrix} a-\lambda & b \\ c & d-\lambda \end{bmatrix}\right) = 0$$

$(a-\lambda)(d-\lambda) - bc = 0$: Quadratic eqn.

$\lambda^2 - \tau\lambda + \Delta = 0$ where $\tau = a + d$: Trace of A

$\Delta = ad - bc$: determinant of A.

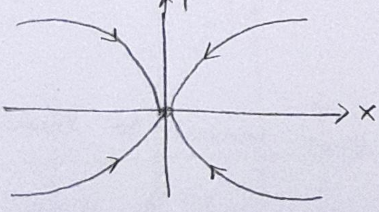
So, $\lambda_1 = \dfrac{\tau + \sqrt{\tau^2 - 4\Delta}}{2}$

$\lambda_2 = \dfrac{\tau - \sqrt{\tau^2 - 4\Delta}}{2}$

wkt, solution is –

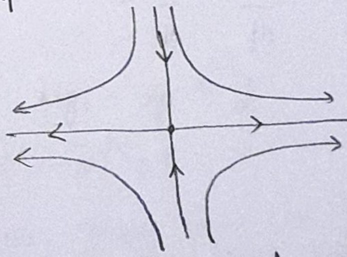
$$x(t) = x_0 e^{\lambda_1 t} \vec{v_1} + y_0 e^{\lambda_2 t} \vec{v_2}$$

① $\lambda_1, \lambda_2 < 0$



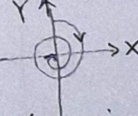
Stable nodes

② $\lambda_1 > 0$, $\lambda_2 < 0$



Saddle node

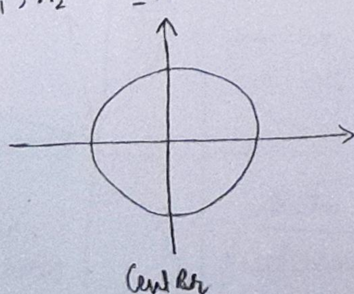
⑤ $Re(\lambda_1) < 0$



Collapse inwa

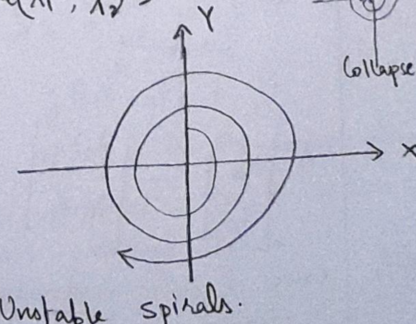
③ $\lambda_1, \lambda_2 = \pm i\omega$ where $A = \begin{pmatrix} 0 & 1 \\ -\omega^2 & 0 \end{pmatrix}$

$Re(\lambda_1, \lambda_2) = 0$



Center

④ $Re(\lambda_1, \lambda_2) > 0$



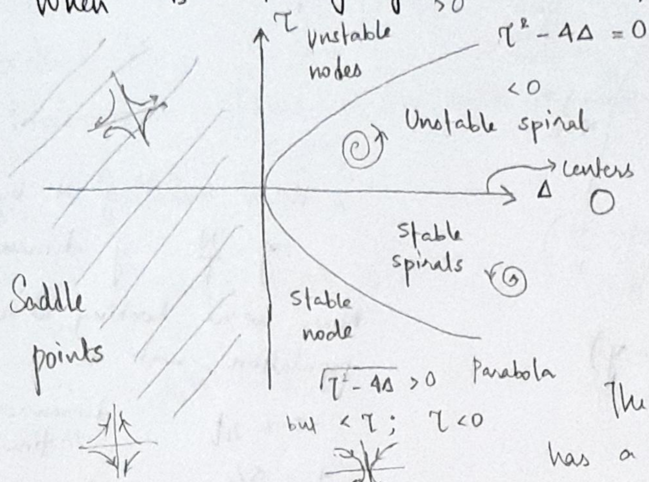
Unstable spirals.

$$\lambda_{1,2} = \frac{1}{2}\left(\tau \pm \sqrt{\tau^2 - 4\Delta}\right) \qquad \tau = tr(A) = a+d = \lambda_1 + \lambda_2$$

$$\Delta = \det(A) = ad - bc = \lambda_1 \lambda_2$$

What matters is the sign of λ_1, λ_2. If +ve, its unstable and if -ve, its stable.

When is it going to be +ve / -ve?



If $\tau^2 - 4\Delta > 0$, $\sqrt{} < \tau$. So, if $\tau^2 - 4\Delta > 0$, λ_1 & λ_2 will be positive $\Rightarrow$ unstable nodes.

In lower quadrant, $\sqrt{\tau^2 - 4\Delta} > 0$, but τ is negative so both λ_1 & λ_2 are -ve.

The area 'inside' the parabola has a complex component to it, so we get spirals

On the LHS of vertical line, among λ_1 & λ_2 — one will be positive & other negative, so we'll get saddle points.

14/2

Lecture 11

Non-dimensionalisation and Scaling

Recall: dimerisation model (pg. 6)

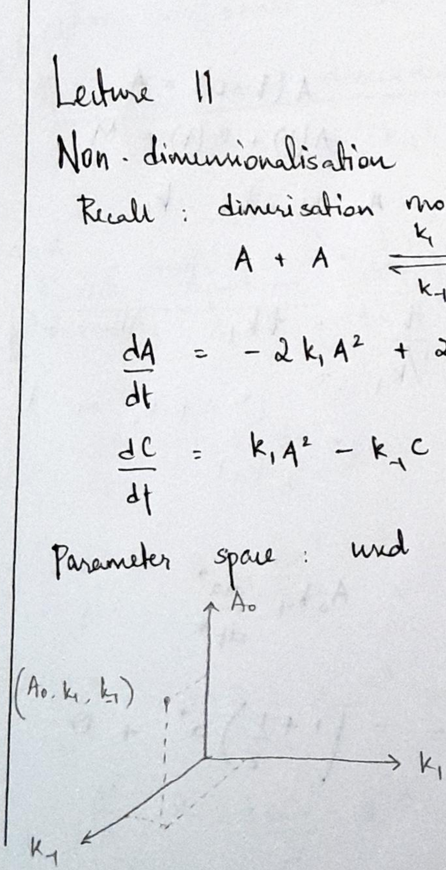
$$A + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

Conservation statement:

$$\frac{dA}{dt} = -2k_1 A^2 + 2k_{-1} C \qquad A + 2C = A_0 \text{ (constant)}$$

$$\frac{dC}{dt} = k_1 A^2 - k_{-1} C$$

Parameter space: used to describe the dynamics of the system



* Can we eliminate some parameters to make the dynamics simpler to understand
* Gives us an idea of relative magnitude of different terms

Function of non-dimensionalisation

(22) → Eg. 1 The logistic equation

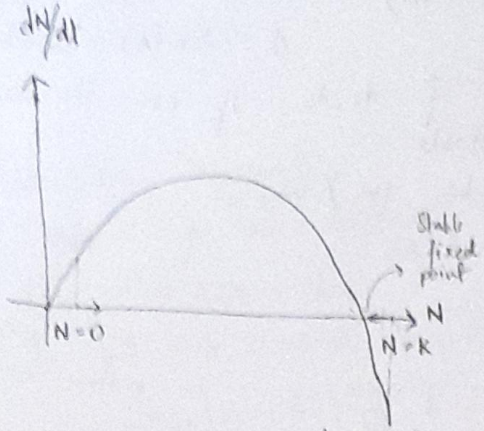
$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

Malthusian population eqⁿ

$$\frac{dN}{dt} = rN$$

$N(t)$: Population
r : rate (timescale)
K : carrying capacity

K has same dim. as N



$$\frac{1}{K}\frac{dN}{dt} = r\frac{N}{K}\left(1 - \frac{N}{K}\right)$$

// We're rescaling N by K

$y = \frac{N}{K}$ y: dimensionless

Now, we're looking at relative population, wrt K.

$$\frac{dy}{dt} = r\,y(1-y)$$

$s = rt$: dimensionless time

$t = s/r$ $\Rightarrow ds = r.dt$

$$\Rightarrow \frac{dy}{ds} = y(1-y)$$

No free parameters

Fixed points are 0 & 1

→ Eg. 2 : $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$

$A(t=0) = A_0$ Why $A_0 \neq M$?

$A(t) + B(t) = M$

$$\frac{dA}{dt} = -(k_1 + k_{-1})A + k_{-1}M$$

A_0, M, $\underbrace{k_{-1}, k_1}$ dims.

conc $\quad$ 1/time

Define a dimensionless time : $t^* = \frac{t}{1/k_{-1}} = t k_{-1}$ Alternately,

$t^* = t.k_1$ or $t.\sqrt{k_1 k_{-1}}$

No/unit volume $\quad [A] = L^{-3}$ Dimensionless conc : $a^* = \frac{A}{A_0}$ $\quad t^* = k_{-1}t$

$$\frac{dA}{dt} = A_0\frac{da^*}{dt} = A_0\frac{da^*}{dt^*}\cdot\underbrace{\frac{dt^*}{dt}}_{k_{-1}} = A_0 k_{-1}\cdot\frac{da^*}{dt^*}$$

$$\frac{da^*}{dt^*} = -\left(1 + \frac{k_1}{k_{-1}}\right)\frac{A}{A_0} + \frac{M}{A_0} = -\left(1 + \frac{1}{\varepsilon}\right)a^* + \theta$$

$\varepsilon = \frac{k_{-1}}{k_1}$ $\quad \theta = \frac{M}{A_0}$

$$\therefore \frac{da^*}{dt^*} = -\left(1 + \frac{1}{\varepsilon}\right) a^* + 0$$

We've non-dimensionalized all the terms and the no. of independent variables have reduced.

10/2/22

Lecture 12

Dimerisation [NDs in a series of steps]

$$A + A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$\frac{dA}{dt} = -2k_1 A^2 + 2k_{-1} C$$

$$\frac{dC}{dt} = k_1 A^2 - k_{-1} C$$

Conservation statement

$A + 2C = A_0$: const

k_1, k_{-1}, A_0 - can we reduce the no. of parameters.

1. Determine the dimensions of each parameter & variable

$[A] = [A_0] = [C] = L^{-3}$ $[k_{-1}] = T^{-1}$ $[k_1] = L^3 T^{-1}$

Rate coefficients can have different dimensions.

2. Introduce new dimensionless dependent & independent variable

$$t^* = \frac{t}{1/k_{-1}} = k_{-1} t \qquad a^* = \frac{A}{A_0} \qquad c^* = \frac{C}{A_0}$$

3. Rewrite equations in terms of new variables

$$A = A_0 a^* \qquad t = \frac{t^*}{k_{-1}} \qquad C = A_0 c^*$$

$$\frac{dA}{dt} = A_0 k_{-1} \frac{da^*}{dt^*} = -2k_1 A_0^2 a^{*2} + 2k_{-1} A_0 c^*$$

$$\frac{dC}{dt} = A_0 k_{-1} \frac{dc^*}{dt^*} = A_0^2 k_1 a^{*2} - k_{-1} A_0 c^*$$

$$\frac{da^*}{dt^*} = -2\frac{k_1}{k_{-1}} A_0 a^{*2} + 2c^* = -2\phi a^{*2} + 2c^*$$

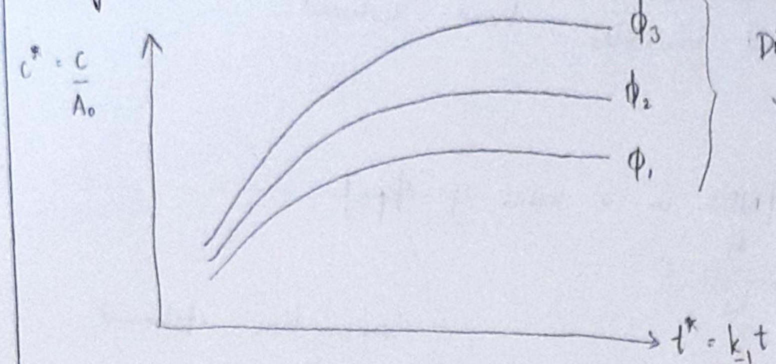
$$\frac{dc^*}{dt^*} = \frac{A_0 k_1}{k_{-1}} a^{*2} - c^* = \phi a^{*2} - c^*$$

Say, $\phi = \dfrac{A_0 k_1}{k_{-1}}$

4. <u>Interpret the dimensionless parameters</u>

$\phi = \frac{k_1}{k_{-1}} \Rightarrow [\phi] = L^3 : \frac{1}{\text{Conc}}$: It can be thought of as a characteristic conc of the system

5. <u>Analyse</u> the behaviours of dimensionless model : situation-specific



Dictionary of dynamics by varying ϕ

ϕ : k_1, k_{-1}, A_0

6. <u>Convert the results back</u> into unit carrying form.

$\phi \rightarrow k_1, k_{-1}, C, A_0, A$

This is a excercise to the reader

Tutorial 03 - read it 17/2/22

Tutorial

Euler's method for numerical integration

Solutions of 2D ODEs.

See tutorial 5 python file.

24/2

Lecture 13 (rec)

Stability and Bifurcations

Stability of fixed points and bifurcations (changes in solution of ODE) help us qualitatively understand the nature of ODE.

I : growth

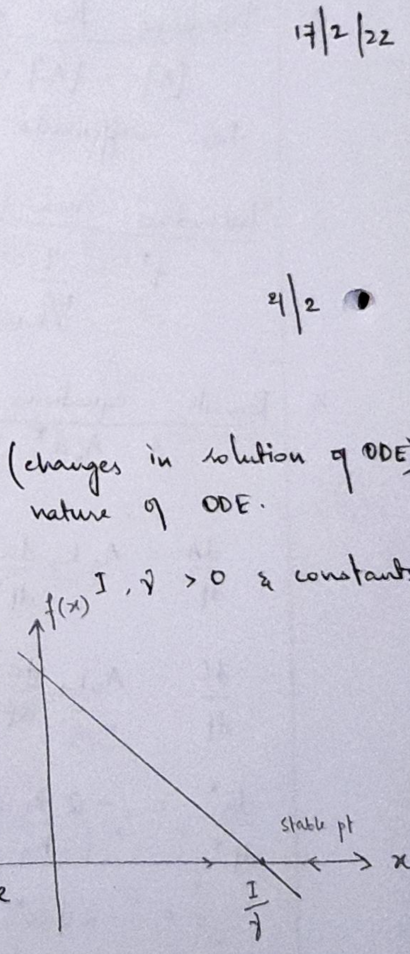
$-\gamma x$: decay

$I, \gamma > 0$ & constants

→ Example : $\frac{dx}{dt} = I - \gamma x$

x is a state variable

Steady state : $x_{ss} = \frac{I}{\gamma}$ is a stable fixed pt.



What determines the stability ?

To left of x_{ss}, $\frac{dx}{dt}$ = +ve & to the right, its -ve

Slope is -ve (m = -γ), so fixed pt is stable

If slope were +ve (m = γ), then it would be unstable

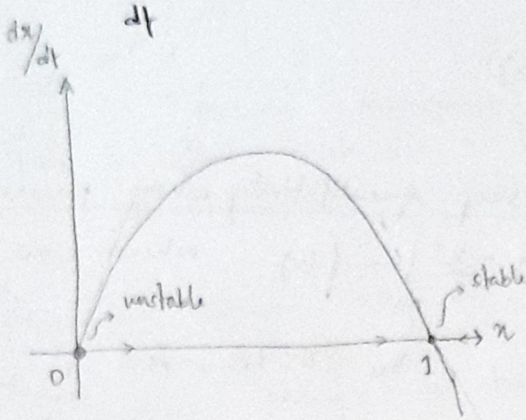
Stable fixed point is also called an attractor

x_{ss} is a globally stable stable state

→ Example 2 logistic growth curve

$$\frac{dx}{dt} = x(1-x)$$

Non-dimensionalised form of logistic eqⁿ



To predict stability of non-linear system, we take a slope at the fixed point

Making small perturbations (local prediction of slope aligns with the curve) around f.p

we can predict stability through sign of slopes

i) Both attractor & repeller are not 'global'
for -ve values of x, $x_{ss} = 1$ is NOT an attractor

ii) Local dynamics depend on the tangent at the fixed point

Stability of steady states

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

Suppose x_{ss} is the steady state

$$\Rightarrow \left.\frac{dx}{dt}\right|_{x_{ss}} = f(x_{ss}) = 0$$

Suppose we perturb the system close to the steady state

$$x(t) = x_{ss} + \underbrace{x_p(t)}_{\text{small perturbation}}$$

$$\frac{d}{dt}\left(x_{ss} + x_p(t)\right) = f\left(x_{ss} + x_p(t)\right)$$

If $x_p(t)$ grows in time, then x_{ss} is unstable, but its stable if $x_p(t)$ decreases in time

$\frac{d}{dt}(x_{ss}) = 0$

$$\frac{dx_p}{dt} = f(x_{ss} + x_p)$$

$$= \underset{\overset{\shortparallel}{0}}{f(x_{ss})} + x_p f'(x_{ss}) + \frac{x_p^2}{2!} f''(x_{ss}) + \dots$$

↳ ignore

where $f' = \left.\frac{df}{dx}\right|_{x_{ss}}$

$\Rightarrow \dfrac{dx_p}{dt} = x_p f'(x_{ss})$ $\quad$ x_p : fn of time
$f'(x_{ss}) = \lambda$ constant

$\dfrac{dx_p}{dt} = \lambda x$: describes the dynamics of small perturbation

$x_p(t) = x_p(0)\, e^{\lambda t}$

If $\lambda > 0$ - exponentially growing perturbation $\Rightarrow$ unstable f.p.
$\lambda < 0$ - exponentially decreasing perturbation $\Rightarrow$ stable f.p.

λ is called an eigenvalue. In 2D systems & higher order ODEs, the system would have multiple eigenvalues.

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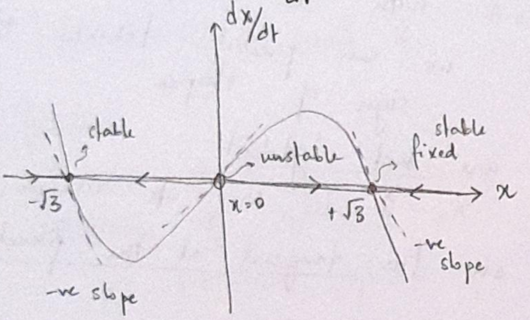
Lecture 14 - Recorded (22/2)

Bifurcations

How solutions of ODEs vary quantitatively when parameters change

Example : $\dfrac{dx}{dt} = c\left(x - \dfrac{x^3}{3}\right) = f(x)$ where $c > 0$ [neurons]

$x_{ss} = 0, +\sqrt{3}, -\sqrt{3}$

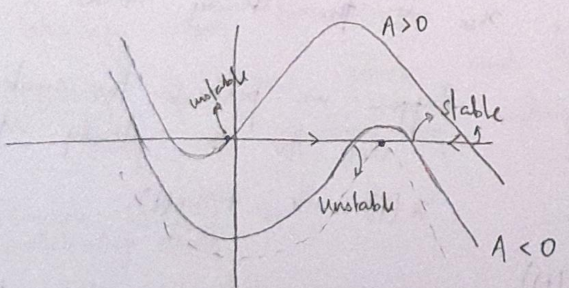


BISTABLE SYSTEM $(A = 0)$

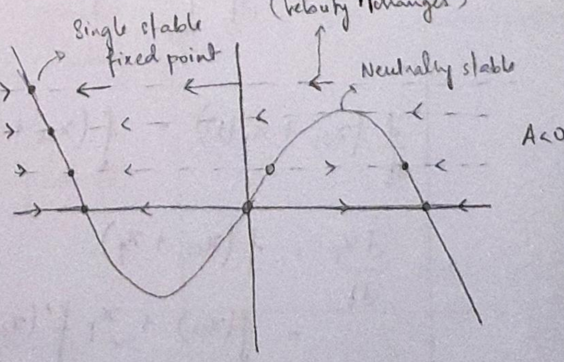
$\dfrac{dx}{dt} = c\left(x - \dfrac{x^3}{3} + A\right) = f(x)$ Parameter

When $A = 0$, we got 3 fixed points, 2 stable & one unstable

A - Bifurcation parameter



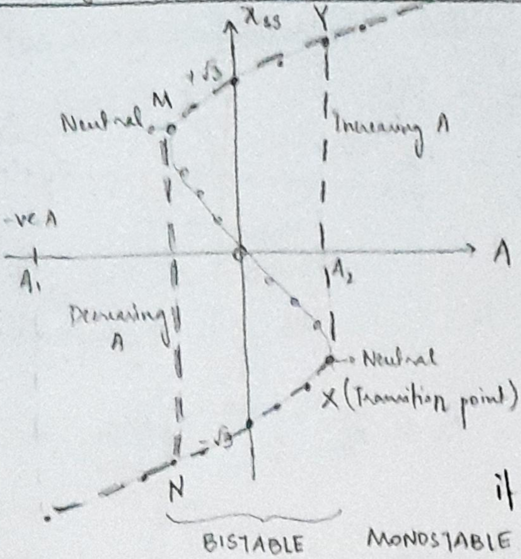
We can vary A, but also, moving the x-axis up/down has the same effect. (velocity changes)



When $A << 0$, then 2 fixed pts disappear, but there are ghosts of fixed points, reflected in the trajectory

Bifurcation plot

Conditions for bifurcation :- $f(x) = 0$; $f'(x) = 0$ at $x = x_{ss}$, $r = r_0$



When we start varying the value of A from A_1 it settles on a fixed point that steadily increases, until a transition point (X) when it suddenly jumps to another totally different x_{ss}, (Y).

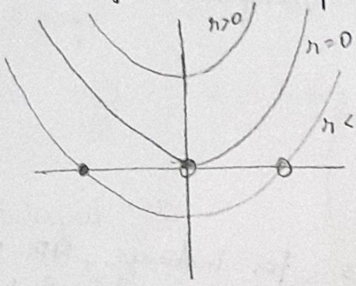
Similarly, when we steadily decrease A, at a transition point M, (not Y) it jumps to another steady state (N).

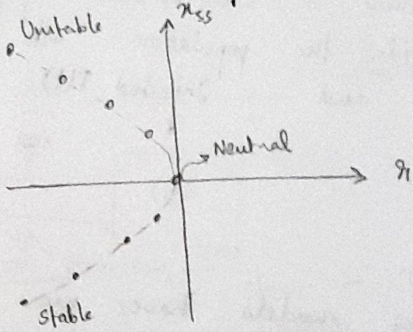
This is called hysteresis - the transition point depends on the direction in which A is varied.

* There are different ways in which character of solution can change.

The above example is that of Fold Bifurcation.

Another example : $\frac{dx}{dt} = r + x^2 = f(x)$





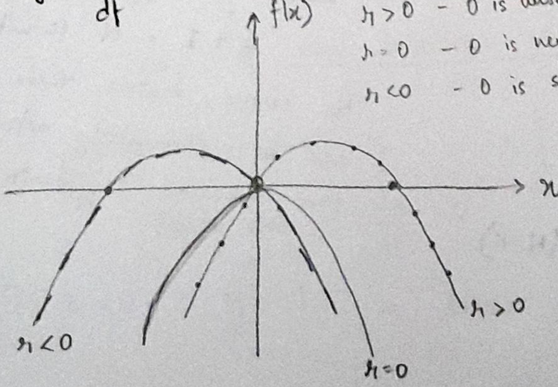
* Transcritical bifurcation

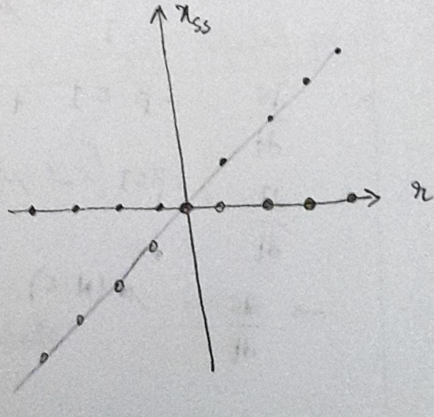
Eg: $\frac{dx}{dt} = rx - x^2 = x(r - x)$ $\Rightarrow$ $x = 0$ $\quad x = r$ - fixed pts

$r > 0$ - 0 is unstable

$r = 0$ - 0 is neutral

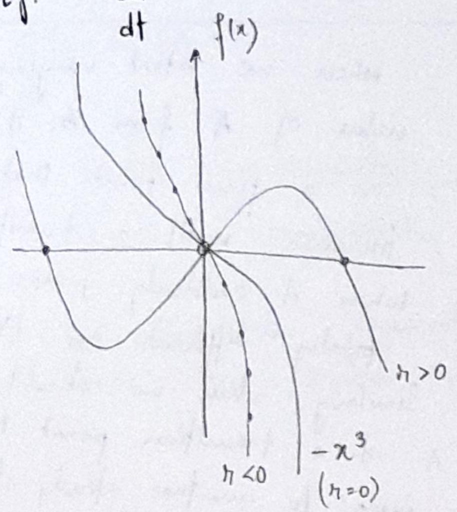
$r < 0$ - 0 is stable

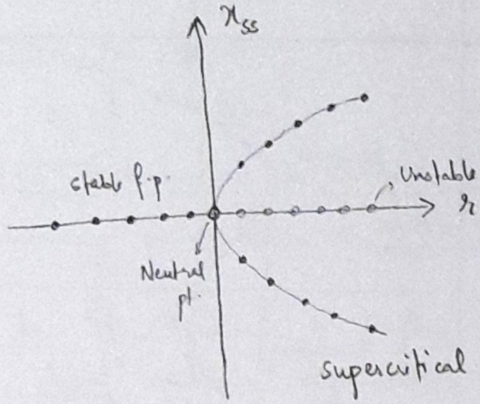




28 ★ Pitchfork bifurcation

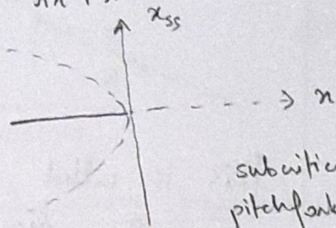
Eg: $\frac{dx}{dt} = rx - x^3$ $\qquad x = 0 \ , \ x = \pm\sqrt{r}$





supercritical pitchfork

$\frac{dx}{dt} = rx + x^3$



subcritical pitchfork.

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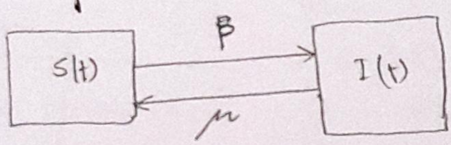
Lecture 15

Ch. 6 of the 'Primer'

Building a model from scratch

Assume a 'well-mixed' population

Divide the population into two classes/compartments — Susceptible $S(t)$ and Infected $I(t)$



Other models have more compartments. For instance, SIR models also have a Recovered compartment, along with S & I.

$$S + I \xrightarrow{\beta} 2I$$
$$I \xrightarrow{\mu} S$$

Conservation statement

$S + I = N$ (const)

No births, deaths, immigration

I can be associated with a decay term connected to death const

$$\frac{dS}{dt} = -\beta . SI + \mu I$$

$$\frac{dI}{dt} = \beta SI - \mu I$$

$$\rightarrow \frac{dS}{dt} = \mu(N-S) - \beta S(N-S)$$

Non-dimensionalization & Scaling

$[\mu] = T^{-1}$ $\qquad$ $[\beta] = \text{population}^{-1} . T^{-1}$

$t^* = \mu t$; $\quad y^* = \frac{S}{N} \quad x^* = \frac{I}{N} \qquad x^* + y^* = 1$

Rewrite the equation

$dy^* = \frac{1}{N} dS \qquad dt^* = \mu . dt$

$$\Rightarrow \frac{N . dy^*}{dt^*/\mu} = \mu . N . x^* - \beta (x^* . N)(y^* . N)$$

$$\frac{dy^*}{dt^*} = x^* - \frac{\beta N}{\mu} x^* . y^* \quad — (1)$$

$$\frac{N . dx^*}{dt^*/\mu} = \beta (x^* . N)(y^* . N) - \mu . x^* . N$$

Say $\boxed{R_0 = \frac{\beta N}{\mu}}$

$$\frac{dx^*}{dt} = \frac{\beta N}{\mu} x^* y^* - x^* \quad — (2)$$

Forget the $*$'s

$\frac{dy}{dt} = x - R_0 xy \qquad \frac{dx}{dt} = R_0 xy - x \qquad$ where $x + y = 1$

$\qquad = R_0 x(1-x) - x$

Interpret R_0

$R_0 = \frac{\beta N}{\mu} \qquad \frac{1}{\mu} \rightarrow$ typical recovery time

[time that person stays in I state, and can infect a susceptible person]

Since $N \gg 1$, $S \simeq N$.

Suppose $I = 1 \quad S = N-1$

βN : no. of new infections per unit time

Total no. of new infections due to a single infected person, $\frac{\beta N}{\mu}$

$$\frac{dx}{dt} = R_0 x(1-x) - x = x\left[(R_0 - 1) - R_0 x\right]$$

Steady state : $\frac{dx}{dt} = 0$

(i) $x = 0$, $y = 1 \Rightarrow$ Disease free state.

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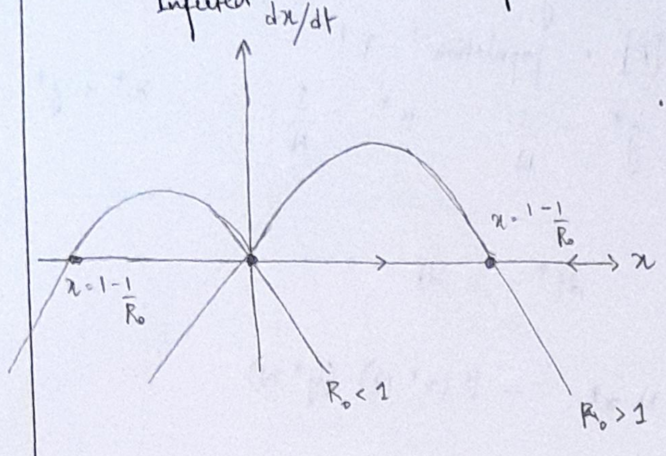
(ii) Disease endemic state

$\underbrace{x = 1 - \frac{1}{R_0}}_{\text{Infected}}$ $\underbrace{y = \frac{1}{R_0}}_{\text{Susceptible}}$



When $R_0 > 01$,
- 0 is unstable x_{ss}, $1 - \frac{1}{R_0}$ is stable

When $R_0 < 1$,
- 0 is stable x_{ss}, $1 - \frac{1}{R_0}$ is -ve which is forbidden

If $R_0 < 1$, then the system comes back to the $x_{ss} = 0$ steady state.

So, R_0 is a very important.

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Lecture 16

2D non-linear ODEs

With 2D linear ODEs, the eigenvalues could tell us whether the fixed pt. was stable, unstable, saddle or oscillatory.
The eigenvectors gave us invariant directions.
With 2D nonlinear ODEs there's no closed form, analytical solution for the system. So we look at qualitative nature of solutions.

$$\left\{ \frac{dx}{dt} = f(x, y) \qquad \frac{dy}{dt} = g(x, y) \right\}$$ where f, g are non-linear fns of x, y

Null clines

$\frac{dx}{dt} = f(x, y) = 0$: x - null cline $\Rightarrow$ flow is vertical

$\frac{dy}{dt} = g(x, y) = 0$: y - null cline $\Rightarrow$ flow is horizontal

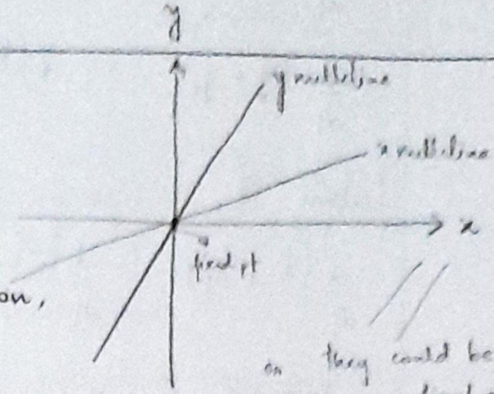
At the intersection of nullclines, $\frac{dx}{dt} = 0$ & $\frac{dy}{dt} = 0$, so the system will be stuck at the point i.e fixed point.

In a linear system,

$f(x, y) = 0 \Rightarrow y = m_f x + c_f$

$g(x, y) = 0 \Rightarrow y = m_g x + c_g$

There can be one or zero intersection, so we can figure out global value of fixed point.



or they could be parallel → no fixed pt.

But with non-linear systems, it can have <u>multiple intersections</u> of nullclines, hard to say.

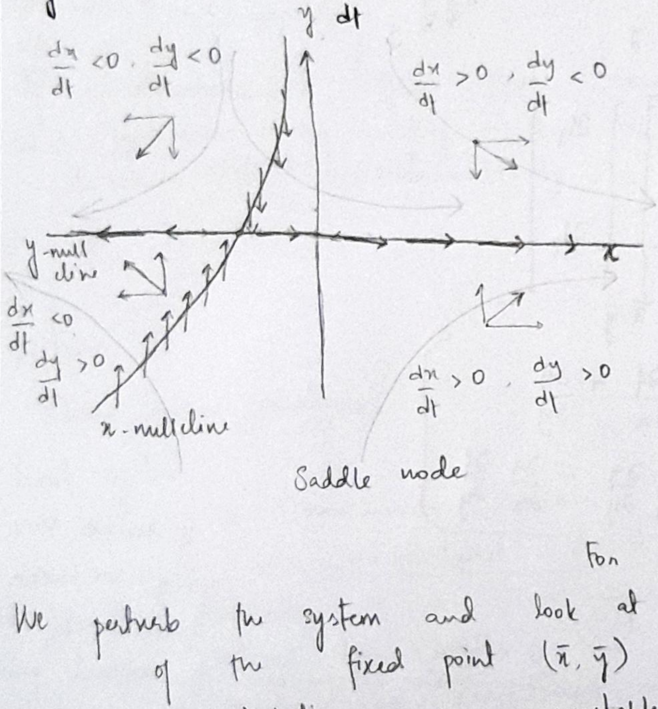
Example –

$$\frac{dx}{dt} = e^{-y} + x \qquad \frac{dy}{dt} = -y$$

x-nullcline : $\frac{dx}{dt} = 0 \Rightarrow x = -e^{-y}$

y nullcline : $\frac{dy}{dt} = 0 \Rightarrow y = 0$ (i.e. x-axis)

Remember, flow is vertical along the x nullcline



Saddle node

This gives us local dynamics – there could be another entirely different fixed pt.

How to think about stability of this fixed point?

For linear eqn, we had slope/eigenvector

We perturb the system and look at the dynamics in the vicinity of the fixed point $(\bar{x}, \bar{y})$

If the perturbation grows – unstable, if it decays – stable

perturb the system from $\bar{x} \longrightarrow \bar{x} + x_p$

$\bar{y} \longrightarrow \bar{x} + y_p$

(32)

$$\frac{d}{dt}(\underset{\text{const}}{\bar{x}} + \underset{x_p(t)}{x_p}) = f(\bar{x} + x_p, \bar{y} + y_p)$$

$$\frac{d}{dt}(\bar{y} + y_p) = g(\bar{x} + x_p, \bar{y} + y_p)$$

to perturb the system around the fixed point - does it shift system away or back to the fixed pt?

2/3/22

Lecture 17

$$\frac{d}{dt}(\bar{x} + x_p) = \cancel{\frac{d}{dt}(\bar{x})}^{0} + \frac{d}{dt}(x_p)$$

We use taylor expansion in 2D

$$f(\bar{x} + x_p, \bar{y} + y_p) = \frac{dx_p}{dt} = \cancel{f(\bar{x}, \bar{y})}^{0} + x_p \frac{\partial f}{\partial x}\bigg|_{\bar{x},\bar{y}} + y_p \frac{\partial f}{\partial y}\bigg|_{\bar{x},\bar{y}} + \dots$$

$$+ \frac{1}{2!} x_p^2 \frac{\partial^2 f}{\partial x^2} + \frac{1}{2!} y_p^2 \frac{\partial^2 f}{\partial y^2} + \frac{1}{2!} x_p y_p \frac{\partial^2 f}{\partial x \partial y} + \dots$$

For <u>small</u> x_p & y_p we can ignore the higher order terms

$$\frac{dx_p}{dt} = x_p \frac{\partial f}{\partial x}\bigg|_{\bar{x},\bar{y}} + y_p \frac{\partial f}{\partial y}\bigg|_{\bar{x},\bar{y}}$$

$$\frac{dy_p}{dt} = x_p \frac{\partial g}{\partial x}\bigg|_{\bar{x},\bar{y}} + y_p \frac{\partial g}{\partial y}\bigg|_{\bar{x},\bar{y}}$$

$\frac{\partial f}{\partial x}$ are numbers

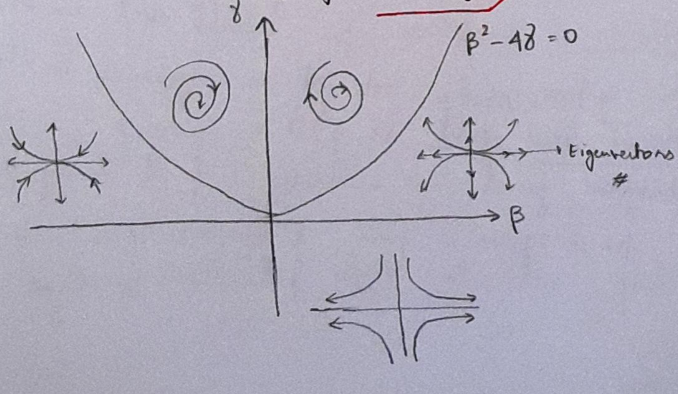
So, near the fixed point, we are linearizing the system.
When x_p & y_p are small, the slopes are somewhat close to the curves, the deviation is not much.

$$\begin{bmatrix} \frac{dx_p}{dt} \\ \frac{dy_p}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix}_{\bar{x},\bar{y}} \begin{bmatrix} x_p \\ y_p \end{bmatrix}$$

Jacobian Matrix ?? (~40 mins)

$$\boxed{\begin{aligned} \beta &= \text{trace}(J) = \frac{\partial f}{\partial x} + \frac{\partial g}{\partial y} \\ \gamma &= \det(J) = \frac{\partial f}{\partial x}\cdot\frac{\partial g}{\partial y} - \frac{\partial g}{\partial x}\cdot\frac{\partial f}{\partial y} \end{aligned}}$$

\# eigenvectors needn't be orthogonal



Given a non-linear system, we can talk qualitatively about the fixed point in a small region around it.

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Tutorial 8 - 3/3/22

SIR Model (1927)

$$\text{susceptible } S \xrightarrow{\beta} \text{infected } I \xrightarrow{\gamma} \text{recovery } R$$

Total no: N

$S + I + R = N$

β: effective contact rate

γ: mean recovery rate $1/\gamma$: mean recovery time

$$\frac{dS}{dt} = -\frac{\beta S I}{N}$$

I no of infected individuals come in contact with $\frac{\beta S}{N}$ fraction of susceptible individuals

$$\frac{dI}{dt} = \frac{\beta S I}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Using scipy.integrate from which odeint is imported.

Modifying β can can decrease the intensity of the peak and shift the peak - "flatten the curve".

If we decrease γ then time taken to go from $I \to R$ decreases very quickly - kind of like vaccination. This decreases the peak dramatically, & susceptible fraction doesn't go to zero.

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Lecture 18

Phase plane analysis

Limit cycles

↳ unique to non-linear systems

Limit cycle is an isolated closed trajectory.

In the vicinity of a limit cycle orbit, we don't have other closed loop orbits.

isolated ⇒ neighbouring trajectories are not closed

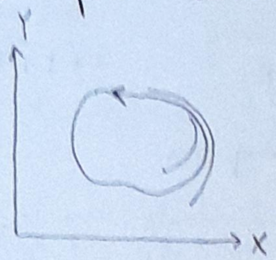
There are 3 types of limit cycles.

1) If there's a small perturbation, the system will slowly asymptote towards the orbit. This is called a stable limit cycle

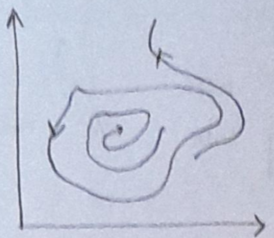
(34)

2) <u>Unstable limit cycle</u> - when the system is perturbed, the system moves away to a different fixed point

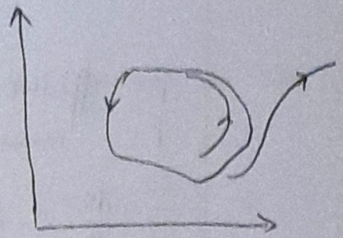
3) Half-stable l. cycle - The perturbation towards the inside is stable, whereas outside is unstable.



Stable



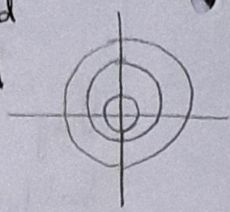
Unstable



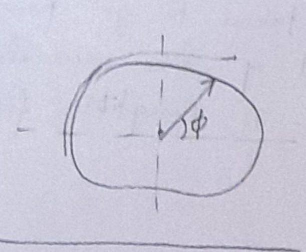
Half-stable

Recall : SHO - linear dynamic system

$\frac{d^2x}{dt} = -w^2 x$: Here, we can find closed orbits in the vicinity of other closed orbits.



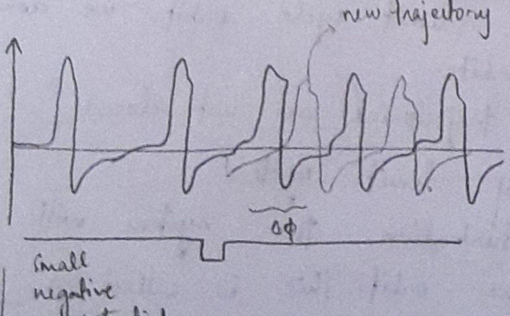
Describing a limit cycle



Limit cycle can be described using the angle of vector (?), phase ϕ. After a perturbation, the system comes back, the amplitude is the same but ϕ changes.

Biological systems that show limit-cycle oscillations - neurons, heart muscle, predator-prey, central pattern generators (lobster - stomatogastral ganglion).

Say we insert an electrode in the neuron and stimulate it

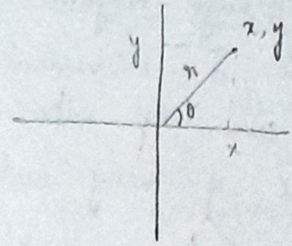


Since ~~excitable~~ neurons are excitable, after a stimulation above threshold, they have huge oscillations.

When there's a perturbation, <u>phase changes</u>, but <u>amplitude is the same</u>

Example (Strogatz)

* $\dfrac{dr}{dt} = r(1-r^2)$; $\dfrac{d\theta}{dt} = 1$

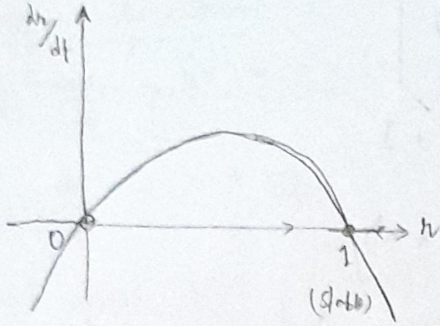


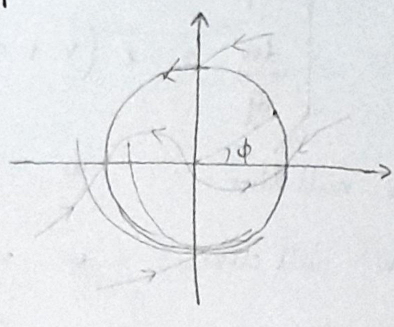
$x = r\cos\theta$

$y = r\sin\theta$

$\Rightarrow \theta = t + \phi$ ϕ : initial phase

$\dfrac{dr}{dt} = 0 \Rightarrow r = 0, \; r = 1$: fixed pts.





Solution

* Van der Pol Oscillator

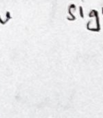
Well known, well analysed and standard model of limit cycle oscillator

$$\left[\frac{d^2x}{dt^2} = \underbrace{-\mu(x^2-1)\frac{dx}{dt}}_{\text{non-linear term}} + x = 0\right]$$

If non-linear term is removed, it becomes SHO with $\omega^2 = 1$

If this term were linear : $-k\dfrac{dx}{dt}$: similar to having drag or frictional force acting against motion, proportional to the instantaneous velocity

Linear : Damped oscillations : of dissipating energy



For us, $\underline{k = \mu(x^2-1)}$.

If the sign is positive : it's like injecting energy into system

negative : it's like dissipating energy

$\Rightarrow$ if $|x| > 1$, μ +ve $\Rightarrow$ damped oscillation

$|x| < 1$, μ +ve $\Rightarrow$ oscillation is amplified (unstable spiral)

$\Rightarrow$ When amplitude increases, the system drives it down, and when it decreases, the system drives it up $\Rightarrow$ <u>keep it b/w limit cycles</u>.

Lecture

Limit cycle oscillators

Fitzhugh - Nagumo Model

This is a variant of Van der pol oscillator. They independently came up with electrical circuits to model neuronal activity.

One of many realisations of FHN model -

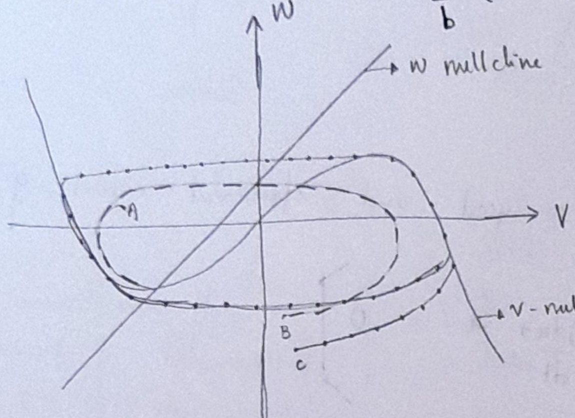
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

$$\frac{dw}{dt} = e\,(v + a - bw)$$

Like injecting external current

v nullcline : $w = v - \dfrac{v^3}{3} + I$

w null cline : $w = \dfrac{1}{b}(v + a)$



* As we increase the value of I, the cubic nullcline moves up, so the point of intersection changes – fixed point becomes limit cycle.
* Tilting the slope (b) takes us to bistable system – bifurcation!

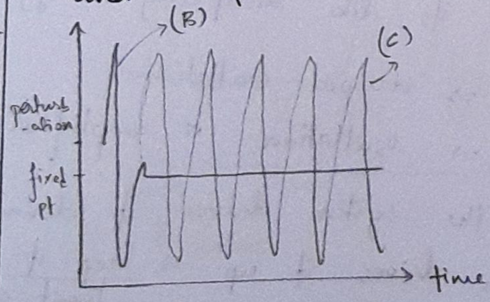
Forward Euler ??

subthreshold

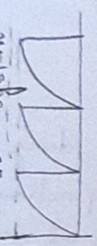
If there's a small perturbation (A), the system comes back to fixed point in the way it was perturbed.

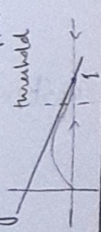
If the perturbation is above threshold, then the system has to follow the flow, take a long circulation and then come back to the fixed point.

If the perturbation is even greater, it goes to a limit cycle oscillator



We can get an oscillation in 1D system using a reset system –





Lecture

Limit cycles

In the previous example, the equations were decoupled and relatively simple to solve analytically. The other example was the Van der Pol oscillator.

Hopf bifurcation

Given that: $r > 0$, limit cycles exist

$$f(x,y) = \frac{dx}{dt} = rx - y - x(x^2+y^2)$$

$$g(x,y) = \frac{dy}{dt} = x + ry - y(x^2+y^2)$$

The fixed point: $(\bar{x}, \bar{y}) = (0,0)$. We'll write the Jacobian -

$$J = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{bmatrix}_{\bar{x},\bar{y}} = \begin{bmatrix} r - 3x^2 + y^2 & -1 - 2xy \\ 1 - 2x & r - x^2 - 3y^2 \end{bmatrix}_{(0,0)}$$

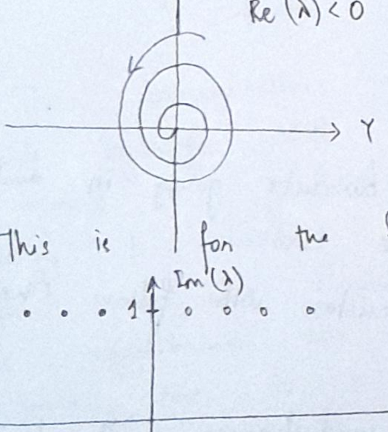
$$J = \begin{bmatrix} r & -1 \\ 1 & r \end{bmatrix}$$

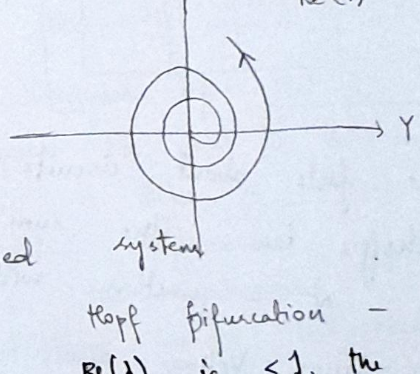
Do $\det(J - \lambda I) = (r-\lambda)^2 + 1 = 0$

$r - \lambda = \pm i$

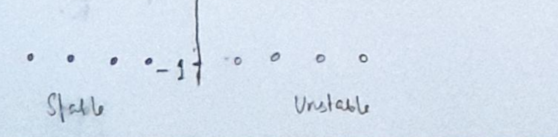
$\therefore \lambda = r \pm i$

We get $\lambda = r \pm i$ $\quad Re(\lambda) = r$



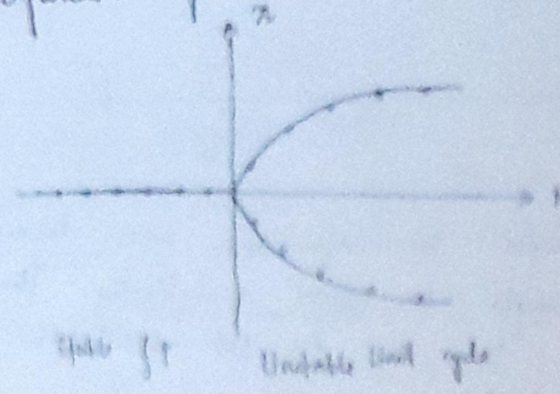


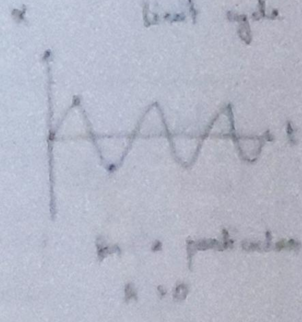
This is for the linearised system



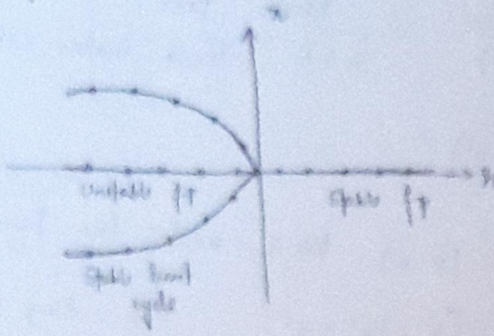
Hopf bifurcation - when $Re(\lambda)$ is < 1, the fixed pt. is stable, when it crosses the imaginary axis, the fixed points become unstable

Bifurcation plot.





This is called a supercritical Hopf bifurcation.



: Subcritical Hopf bifurcation.

\# In pitchfork bifurcation, the fixed points are coalescing. here the limit cycle is merging to give fixed points

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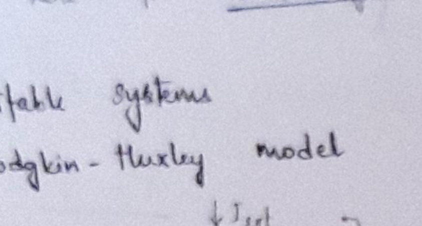
Excitable systems

Hodgkin - Huxley model



Equivalent circuit to model the membrane of the neuron.

Some facts about circuits -

1. Kirchoff's law : The sum of currents going in and going out at a junction will be zero.

2. Ohm's law : Voltage across a resistor will follow Ohm's law:

$$V = IR$$

By convention, we'll focus on conductances : $g = \frac{1}{R}$.

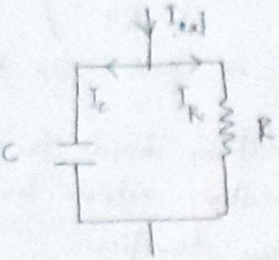
Giant squid axon was used by Hodgkin & Huxley to measure membrane potential difference under various conditions.

The membrane is made of a lipid bilayer and there are transmembrane proteins which let different ions across the membrane, called ion channels.

lipid bilayer - capacitor

Ion channel - resistor

Ignore the ion channels for now. If we just consider the lipid membrane, there'll be some ions leaking across. The equivalent circuit is given by -



$$I_{ext} + I_c + I_R = 0 \qquad I_R = \frac{V}{R}$$

$$Q = CV$$

$$\frac{dQ}{dt} = I_c = C.\frac{dV}{dt}$$

$$\boxed{C\frac{dV}{dt} = -\frac{V}{R} + I_{ext}}$$

$+ I_{ext}$ = acknowledging different # signs?

Ion	Intracellular	Extracellular
Na^+	5 - 15 mM	145 mM
K^+	140 mM	5 mM
Cl^-	4 mM	110 mM

There are also more anions inside the cell - -vely charged protein.

These concentrations are maintained by Na^+ - K^+ pump which hydrolyse ATP, to push Na^+ out & K^+ inside against a gradient. This is like a battery — expending energy to maintain a potential difference.

There are also channels in the membrane. This equilibrium ion concentration across the membrane gives rise to a V_m called the Nernst Potential.

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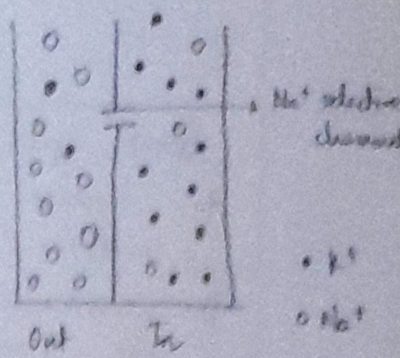
Because of conc. difference in Na^+, the ion will diffuse from 'out' to 'in'. Once some ions have crossed, the -ve charge in the 'out' compartment increases, which holds Na^+ ions back. The potential established by this electrochemical gradient is called Nernst p.



Gerstner, Kistler ... 'Neuronal dynamics' - Derivation

Probability of molecule to take an energy E :

$$P(E) \propto \exp\left(\frac{-E}{kT}\right)$$ k : Boltzmann's constant

Consider a static (electric field), $\mu(x)$

$$E(x) = q \cdot \mu(x) \Rightarrow P(E) \propto \exp\left(\frac{-q\mu(x)}{kT}\right)$$

Assume there are a large no. of ions → prob. can be based on ion densities

$$\frac{P(E(x_1))}{P(E(x_2))} = \frac{\eta(x_1)}{\eta(x_2)}$$

x_1 : positions inside the cell
x_2 : position outside the cell
η : ion densities

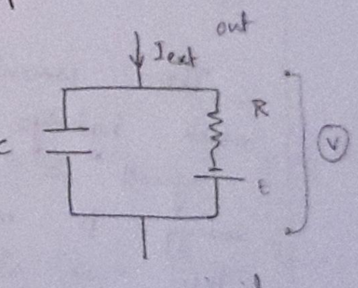
$$= \exp\left[\frac{-q(\mu_1 - \mu_2)}{kT}\right]$$

$\Delta\mu = \mu_1 - \mu_2$
↳ potential difference

$$\boxed{\Delta\mu = \frac{kT}{q} \ln\left(\frac{n_2}{n_1}\right)}$$

Because the concentrations are being actively maintained, there's now a battery in the circuit.

So, we have —



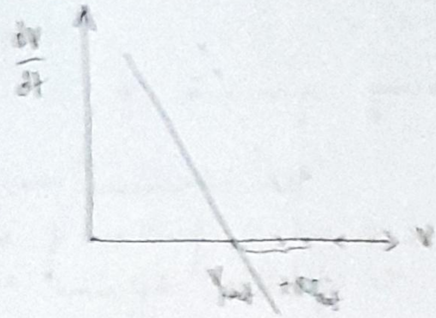
$$C \cdot \frac{dV}{dt} = -\frac{(V - V_{rest})}{R} + I_{ext}$$

$$\tau \frac{dV}{dt} = -V + V_\infty$$ where $\tau = RC$

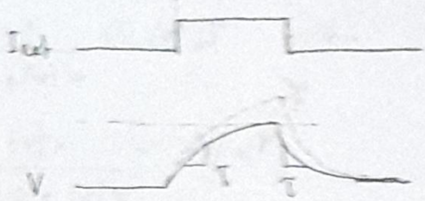
$V_\infty = R \cdot I_{ext} + V_{rest}$

τ : timescale

V_∞ : equilibrium value ie when $\frac{dV}{dt} = 0$, $V = V_\infty$



When I_{ext} (external current) is injected, the fixed point shifts to $V_{rest} + RI_{ext}$, so the system moves asymptotically towards the new fixed point.



This is a simple R-C circuit.

It's also ___linear___ — as I_{ext} increases, the ___V also increases proportionally.___

But in a neuron, above a certain threshold, the membrane potential spikes and then comes back down.

To get this ___excitable property___, we've to introduce ___non-linearity___ in the system.

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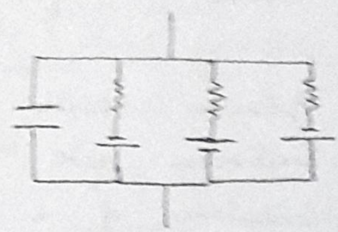
Lecture

Recall: Nernst potential

$$E = \frac{kT}{q}\ln\left(\frac{n_2}{n_1}\right)$$



Now resistors and batteries represent different ion channels.

$$I = C\frac{dV}{dt} + I_{Na} + I_K + I_L$$

This would still show linear response to external current. To get NLD, we need to introduce non-linearity in the ion current.

Hodgkin-Huxley used Squid Giant Axon because —
- It's easy to take recordings from ___giant axon___
- It only has ___Na^+ & K^+ channels___, nothing else

They are ___voltage-gated channels___ — open probability depends on potential difference across the membrane

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Channels are -

i) transmembrane proteins

ii) voltage gated

iii) have 4 subunits

→ Say prob. of one subunit being open is n

$$\Rightarrow P(K_{open}) = n^4$$

This introduces non-linearity -

$$\text{closed} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \text{open}$$

α, β are a function of V

i.e. potential difference across membrane

$$\frac{dn}{dt} = \alpha(1-n) - \beta n$$

$$\Rightarrow \tau_n(V) \cdot \frac{dn}{dt} = n_\infty(V) - n$$

where $\tau_n(V) = \dfrac{1}{\alpha(V) + \beta(V)}$ *

* $n_\infty(V) = \dfrac{\alpha(V)}{\alpha(V) + \beta(V)}$

$$\Rightarrow \boxed{I_K = \bar{g}_K n^4 (V - E_K)}$$: Current through Potassium channel

→ Sodium channel

The sodium channel has an activation & inactivation gate.

Prob of activation gate being open increases with V, where as prob of inactivation gate being open decreases/inc? with V(?)

Activation variable : m

Inactivation rate variable : h

Conductance of a channel :

$$g = \bar{g} m^a h^b$$

where $\bar{g}$ is max. conductance

a, b are obtained from experiments.

$$g_{Na} = \bar{g}_{Na} m^3 h$$

$$\Rightarrow \boxed{I_{Na} = \bar{g}_{Na} m^3 h (V - E_{Na})}$$

For m & h also, we can describe dynamics similar to dn/dt, based on α_m, β_m etc

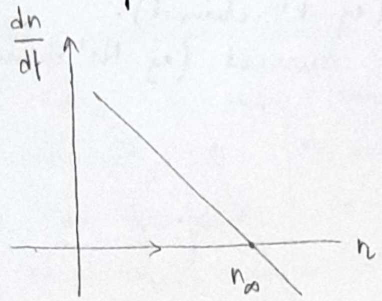
$$C \cdot \frac{dV}{dt} = I - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K) - g_L (V - E_L)$$

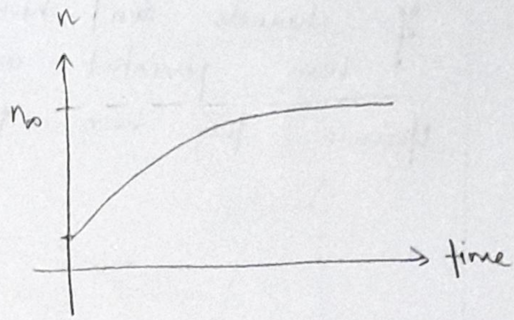
$$\tau_n \frac{dn}{dt} = n_\infty(V) - n$$

$$\tau_m \frac{dm}{dt} = m_\infty(V) - m$$

$$\tau_h \frac{dh}{dt} = h_\infty(V) - h$$

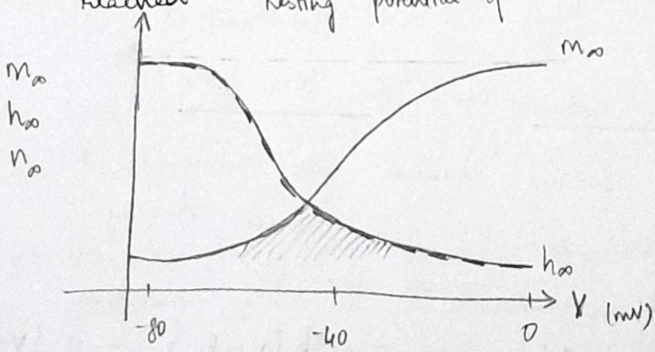
To find τ & n_∞ (steady state value), we need to charecterise $\alpha(V)$ & $\beta(V)$ for n, m and h.



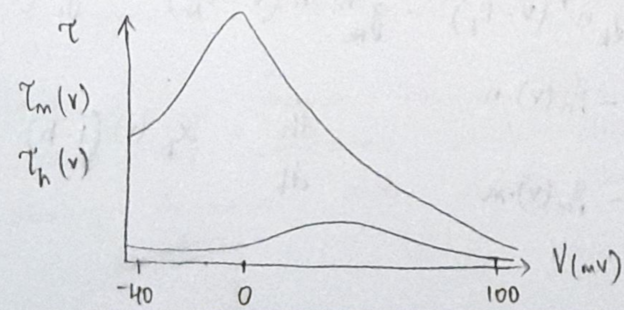


Non-linearity moves the n_∞ fixed point along the axis and changes the rate at which steady state is reached

Resting potential of membrane ~ −65 mV.



At high V, the inactivation gate closes the channel ⇒ there's an optimal region where the channel can conduct.



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Lecture

Izhikevich textbook

Nernst potential – of ions based on the conc difference

In other neurons, along with Na & K, there are also Ca and Cl channels.

Sodium channel :

Open activated

closed: not activated (deactivated), Inactivated

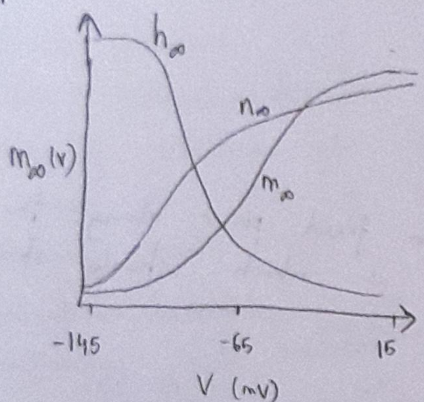
Prob of being open –

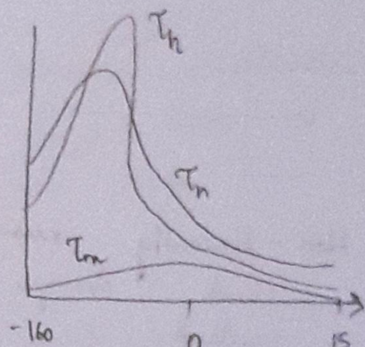
$$p = m^a h^b$$

* Some channels don't have the inactivation gate → $p = n^a$

If channels don't have inactivation gate are said to have persistent current (eg. K^+ channel).

Otherwise, they have transient current (eg. Na^+ channel)





Look up!

τ_n: time taken for system to go to $\frac{1}{e} n_\infty$

$\tau_m << \tau_n, \tau_h$ ⇒ Sodium channel gets activated the quickest

The inactivation gate & K^+ gate react slowly

\# We can fit m, h, n to sigmoid & τ to gaussian

Hodgkin-Huxley equations –

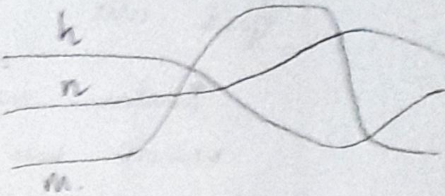
$$C \cdot \frac{dV}{dt} = I - \bar{g}_K n^4 (V - E_K) - \bar{g}_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L)$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V) \cdot n$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V) \cdot m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)\, h$$

- When there's a small increase in V_m, Na^+ activation gate opens, which increases V_m, which further increases m_∞
- Then, K^+ channels open (before inactivation channels) which makes K^+ rush in.
- Then inactivation gate catches up and inactivates Na^+ channels. Since τ_h is large, this keeps going even when V_m goes to -65 mV $\Rightarrow$ there's an after-hyperpolarisation and an absolute refractory period



How variables change -

* $m \to m_\infty$ is very very fast, as compared to n and h

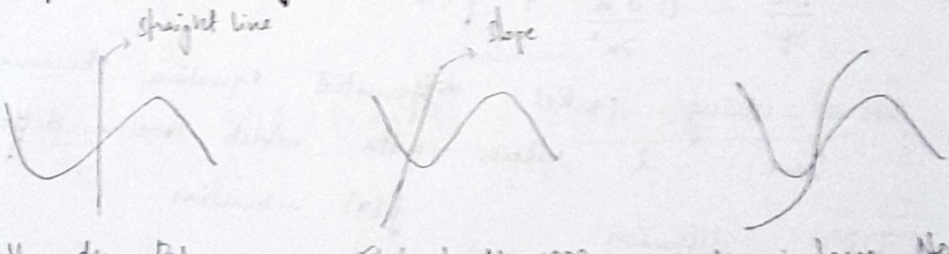
So we approximate $m = m_\infty(v)$

$m \equiv m_\infty$, which eliminates dm/dt equation

* n and h behave reflexively along a horizontal axis.

So we can write : $n(t) = b - h(t)$

So the whole system reduces to 2 equations



Van der Pol oscillator — Fitzhugh-Nagumo neuron — Morris-Lecar Neuron

FHN & ML produces excitatory AP and oscillatory dynamics

Hindmarsh-Rose neuron has an extra variable that moves the cubic curve up and down, which allows it to show bursting dynamics and chaotic behaviour.

Tutorial - HH Model

Python file

11/4

Lecture

Textbook: Mathematical biology by JD Murray.

Studying systems with various spatial constraints.

Pattern generation / formation

Grid cells: present in medial entorhinal cortex of temporal lobe

Random walk of rat, during which grid cell neuron was recorded. Certain neuron fires when the rat is at particular points in the space - the pattern is one of hexagonal symmetry

How could this be related to spots on a leopard?

Turing's paper: Chemical basis of morphogenesis. (1952)

Reaction Diffusion Equations

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u) \quad : \text{1d RDE}$$

We're using partial differential equation because we have 2 values with which we're differentiating - x, t

$f(u)$: reaction

$D\frac{\partial^2 u}{\partial x^2}$: diffusion

$u(x, t)$: 1 dimensional function.

We can think of $f(u)$ (u ?) as degradation of a protein across some space : $-\alpha u$

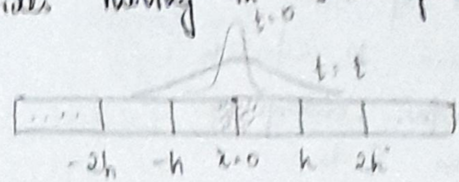
$f(\bar{u})$ where $\bar{u} = [u_1, u_2 \dots u_n]$

u_1 ↓ predator, u_2 ↓ prey → Lotka Volterra Eqn.

Diffusion

Microscopic approach

Consider particles moving in 1-D space



Assume: at $t=0$, all particles are concentrated in the center box, $x=0$

After a time step, probability of –

a) moving right = moving left = $\frac{p}{2}$

b) staying there = $1-p$

$c(x,t)$: conc of particles at x at t.

We need to find conc of particles at a particular box at time $t+\tau$

$$c(x, t+\tau) = \frac{p}{2} c(x+h, t) + \frac{p}{2} c(x-h), t) + \underbrace{(1-p) c(x,t)}_{\text{accounts for the particles that have left}}$$

$$\to \tau \frac{[c(x, t+\tau) - c(x,t)]}{\tau} = \frac{p}{2}\left[c(x+h, t) + c(x-h), t) - 2c(x,t)\right]$$

$\tau \to 0$

take limits to make this continuous – $\tau \to 0$, $h \to 0$

Assume $p = \frac{1}{2}$

$$\tau \frac{\partial u}{\partial t} = \frac{h^2}{2}\left[\frac{c(x+h), t) + c(x-h,t) - 2c(x,t)}{2h^2}\right]$$

$\to \frac{\partial^2 u}{\partial x^2}$

$$\therefore \frac{\partial u}{\partial t} = \frac{h^2}{2\tau}\frac{\partial^2 u}{\partial x^2} \quad \text{where} \quad D = \frac{h^2}{2\tau}$$

Turing proposed RDEs to explain development of pattern formation. But, the timescale of diffusion & development didn't match. This was resolved by Francis Crick in the '70s.

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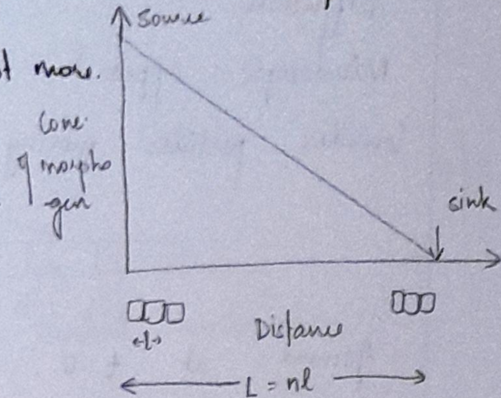
Diffusion in embryogenesis is fast enough

Gradients of morphogens in the developing ~~amp~~ embryo leads to pattern formation – contested hypothesis.



Wolpert : n is 50 - 100 cells, not more.

People were skeptical of the ability of diffusion to establish a gradient in the embryo, given how slow it is.

Crick showed it's possible

$$t = \frac{A(nl)^2}{D}$$

nl : embryonic feild n : no. of cells

D : diffusion coefficient

t is small because l^2 is very small.

A : constant

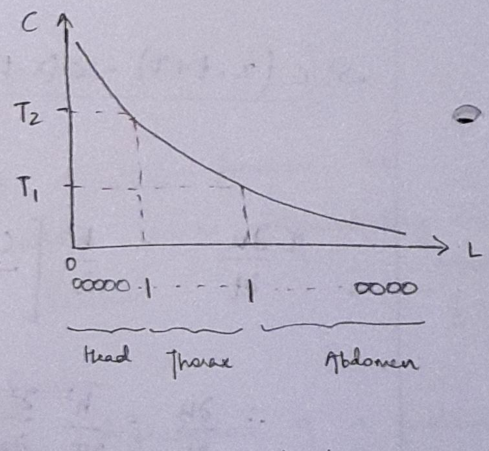
A was calculated by Mary Munro – published later in a different paper

12/4

Lecture

Recall : French-flag model from BI2123.

If conc. is above T_2, then those cells will become head, & if b/w T_1 and T_2, then thorax and so on.



But is it possible to set up this of conc gradient within an hour

$C \equiv C(x, t)$

Boundary conditions –

$c(0, t) = C_0$: Source

$c(L, t) = 0$: Sink

This can be solved analytically as shown in Munro & Crick 1971.

At steady state, $\frac{\partial c}{\partial t} = 0 \Rightarrow D\frac{\partial^2 c}{\partial x^2} = 0$

$\Rightarrow C(x) = C_1 x + C_2$: solution of the differential equation

$C(x=0) = C_0 \Rightarrow c_2 = C_0$

$c(x=L) = 0 \Rightarrow c_1 = -C_0/L$

$$\therefore c(x) = -\frac{C_0}{L}x + C_0$$

They also calculated the time taken —

$$t = \frac{A\,(nl)^2}{2D}$$

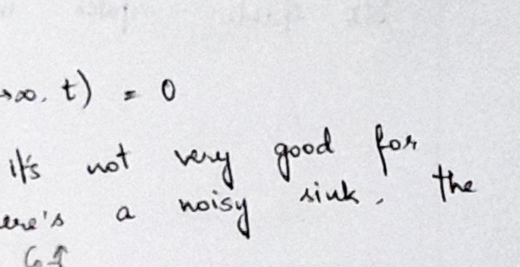
After the model, researchers did find protein morphogens which had a conc. gradient across the embryo axis.

- But the gradient was not a straight line, rather an exponential decay —

$$\Rightarrow \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \underbrace{- \alpha C}_{\text{degradation term}}$$

$c(0,t) = C_0 \qquad c(x \to \infty, t) = 0$

This equation fits nicely, but it's not very good for the robust patterning. If there's a noisy sink, the curve will shift significantly.



error in morphogenesis.

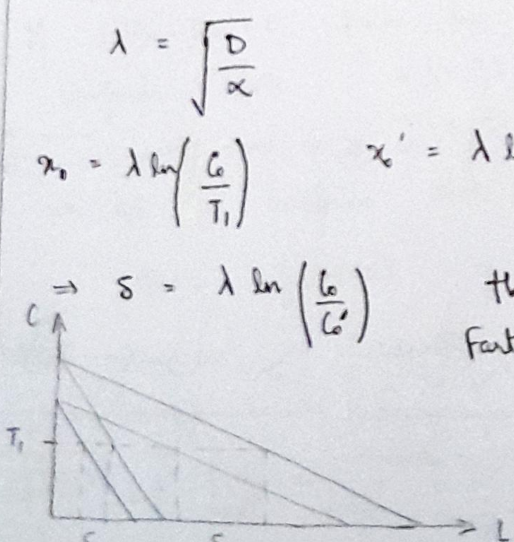
- How to minimise the error?

$$c(x) = C_0 e^{-x/\lambda}$$

$$\lambda = \sqrt{\frac{D}{\alpha}}$$

$x_0 = \lambda \ln\left(\frac{C_0}{T_1}\right) \qquad x_0' = \lambda \ln\left(\frac{C_0'}{T_1}\right) \qquad \delta = x_0 - x_0'$

$\Rightarrow \delta = \lambda \ln\left(\frac{C_0}{C_0'}\right)$ How to minimise δ closer to 0? Farther away, it doesn't matter



If the slope closer to 0 is steeper, then δ would be small.

If RDE was of the form -

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \alpha c^2$$

c^2 in the degradation term

then, curve is steeper near 0 and shallower farther away

Slides

Each cell produces 2 types of ligands - activator (u) & inhibitor (v) that are diffusible

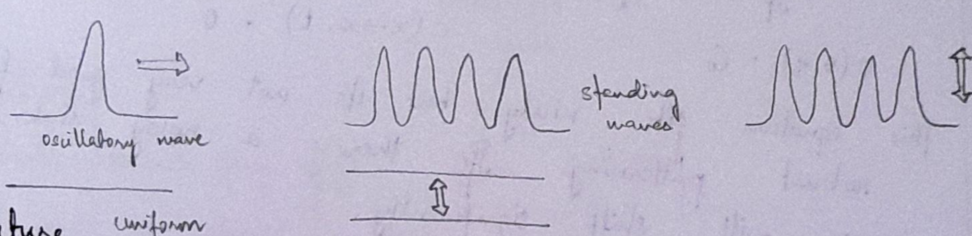
Kondo & Miura (Science)

$$\frac{\partial u}{\partial t} = F(u,v) - d_u u + D_u \Delta u$$

$$\frac{\partial v}{\partial t} = \underbrace{\underbrace{G(u,v)}_{\text{Production}} \underbrace{- d_v v}_{\text{Degradation}}}_{\text{Reaction}} + \underbrace{D_v \Delta v}_{\text{Diffusion}}$$

$\Delta u = \frac{\partial^2 u}{\partial x^2}$ $\quad \Delta v = \frac{\partial^2 v}{\partial x^2}$

Six stable states in Turing's reaction diffusion equations.



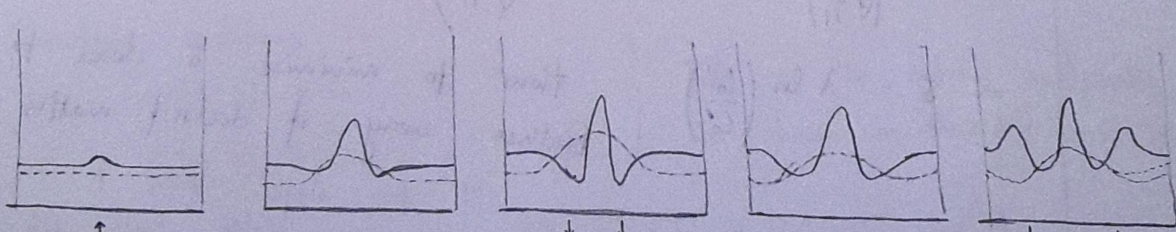
Lecture 18/4/22

Turing linearized the eq^n using Taylor expansion -

- $F(u,v) - d_u u =$
- $G(u,v)$

Intuitive depiction - concentration of u & v over time

—— activator
- - - - inhibitor



Less inhibition in the vicinity increases conc of activator

Here, $D_v > D_u \Rightarrow$ inhibitor diffuses faster than the activator

Features -

1. At least 2 chemicals needed for pattern formation
2. The uniform state is stable in absence of diffusion
3. Diffusion destabilizes the steady state. This is called diffusion driven or Turing instability
4. Pattern formation requires diffusion rates of two reactants differ substantially.

Eg. Belousov - Zabotinsky reaction

Reaction - Diffusion Equations -

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u, v)$$

Degradation term is ignored/ included in the reaction terms

$$\frac{\partial v}{\partial t} = \underbrace{D_v \frac{\partial^2 v}{\partial x^2}}_{\text{Diffusion}} + \underbrace{g(u, v)}_{\text{Reaction}}$$

We need to arrive at Turing patterns - stable, time-independent and heterogenous solutions to the RDEs.

Assumptions -

1) If $D_u . D_v = 0$, then the uniform state is stable

Uniform state : $u(x, t) = u_0$
$v(x, t) = v_0$

$\Rightarrow$ At the uniform state, $\frac{\partial u}{\partial t} = 0 = \frac{\partial^2 u}{\partial x^2}$

Also, $f(u_0, v_0) = g(u_0, v_0) = 0$

We introduce a small perturbation -

$u(x, t) = u_0 + \tilde{u}$ $\qquad$ $v(x, t) = v_0 + \tilde{v}$

$$f(u, v) = f(u_0, v_0) + \tilde{u} \left.\frac{\partial f}{\partial u}\right|_{u_0, v_0} + \tilde{v} \left.\frac{\partial f}{\partial v}\right|_{u_0, v_0} +$$

(52) $$g(u,v) = g(u_0,v_0) + \tilde{u}\frac{\partial g}{\partial u}\Big|_{u_0,v_0} + \tilde{v}\frac{\partial g}{\partial v}\Big|_{u_0,v_0} + \cdots$$

Ignore higher order terms

$$\Rightarrow \frac{\partial u}{\partial t} = \tilde{u}\frac{\partial f}{\partial u} + \tilde{v}\frac{\partial f}{\partial v} + D_u\frac{\partial^2 \tilde{u}}{\partial x^2}$$

$u = u_0 + \tilde{u}$

$$\frac{\partial^2 u}{\partial x^2} = \frac{\partial^2 \tilde{u}}{\partial x^2}$$

$$\frac{\partial v}{\partial t} = \tilde{u}\frac{\partial g}{\partial u} + \tilde{v}\frac{\partial g}{\partial v} + D_v\frac{\partial^2 \tilde{v}}{\partial x^2}$$

$$\begin{bmatrix} \frac{\partial \tilde{u}}{\partial t} \\ \frac{\partial \tilde{v}}{\partial t} \end{bmatrix} = \begin{bmatrix} D_u\frac{\partial^2}{\partial x^2} + \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \frac{\partial g}{\partial u} & D_v\frac{\partial^2}{\partial x^2} + \frac{\partial g}{\partial v} \end{bmatrix}_{u_0,v_0} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix}$$

This is Turing's linearized equations for pattern formation.

19/4

Lecture

Case I : No diffusion

$D_u = D_v = 0$. Perturb in the vicinity of equilibrium –

$u = u_0 + \tilde{u}$ $\quad v = v_0 + \tilde{v}$ $\quad$ We get –

$$\begin{bmatrix} \frac{d\tilde{u}}{dt} \\ \frac{d\tilde{v}}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \frac{\partial g}{\partial u} & \frac{\partial g}{\partial v} \end{bmatrix}_{u_0,v_0} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix}$$

If the eigenvalues of Jacobian, $\lambda_1, \lambda_2 < 0$, then system is stable

Conditions for stability – ie λ_1 and $\lambda_2 < 0$ in absence of diffusion

- Trace : $\tau(J) = \frac{\partial f}{\partial u} + \frac{\partial g}{\partial v} < 0$ – (#)

- Determinant : $\Delta(J) = \frac{\partial f}{\partial u}\frac{\partial g}{\partial v} - \frac{\partial g}{\partial u}\frac{\partial f}{\partial v} > 0$

Now, let's introduce diffusion terms, $D_u, D_v > 0$

$$\begin{bmatrix} \frac{\partial \tilde{u}}{\partial t} \\ \\ \frac{\partial \tilde{v}}{\partial t} \end{bmatrix} = \begin{bmatrix} D_u \frac{\partial^2}{\partial x^2} + \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \\ \frac{\partial g}{\partial u} & D_v \frac{\partial^2}{\partial x^2} + \frac{\partial g}{\partial v} \end{bmatrix}_{u_0, v_0} \begin{bmatrix} \tilde{u} \\ \\ \tilde{v} \end{bmatrix}$$

Ansatz: make stuff up and see if it works –

$$\tilde{u}(x,t) = \sum_q A_q(t) e^{iqx}$$

$$\tilde{v}(x,t) = \sum_q B_q(t) e^{iqx}$$

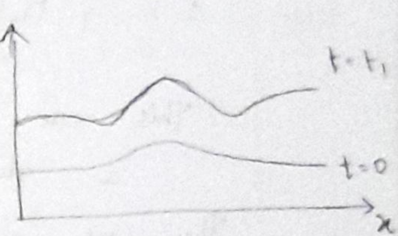
Summing it over q because linear combination of A_q's is also a solution

The solutions have 2 terms – one a function of t and another a function of x $\Rightarrow$ separation of variables

$$e^{iqx} = \cos(qx) + i\sin(qx)$$

Its the sum of cos & sin – it can be written in Fourier series. Also called Fourier modes.

$$\tilde{u}(x, t=0) = \sum_q C_q e^{i2\pi qx} \quad C_q = A_q \; (t=0)$$



q: determines the contribution of q^{th} Fourier mode

$$\tilde{u}(x, t=t_1) = \sum_q C_q(t=t_1)\, e^{i2\pi qx}$$

Let's find solution for one value of q: ie $\tilde{u} = A_q(t) \cdot e^{iqx}$

We get –

$$D_u \frac{\partial^2 \tilde{u}}{\partial x^2} = -q^2 D_u A_q(t) \cdot e^{iqx}$$

$$D_v \times \frac{\partial^2 \tilde{v}}{\partial x^2} = -q^2 D_v B_q(t) \cdot e^{iqx}$$

So, we get –

$$\begin{bmatrix} \frac{\partial \tilde{u}}{\partial t} \\ \\ \frac{\partial \tilde{v}}{\partial t} \end{bmatrix} = \begin{bmatrix} -q^2 D_u + \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \\ \frac{\partial g}{\partial u} & -q^2 D_v + \frac{\partial g}{\partial v} \end{bmatrix}_{u_0, v_0} \begin{bmatrix} A_q(t)\, e^{iqx} \\ \\ B_q(t)\, e^{iqx} \end{bmatrix}$$

This is diffusion induced / Turing instability.

We don't want stability – we want patterns to emerge

Conditions for instability : either has to be violated: $\tau < 0$, $\Delta > 0$

$$\tau = \underbrace{\left(\frac{\partial f}{\partial u} + \frac{\partial g}{\partial v} \right)} - q^2 (D_u + D_v) > 0$$

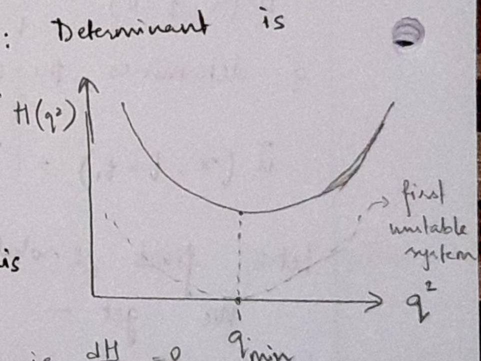
$$\Delta = \left(\frac{\partial f}{\partial u} - q^2 D_u \right)\left(\frac{\partial g}{\partial v} - q^2 D_v \right) - \frac{\partial g}{\partial u} \cdot \frac{\partial f}{\partial v} < 0$$

BUT : Trace cannot be > 0. wkt. the first term < 0 in absence of diffusion (Eqn 7 in pg 52), and the second term is also negative because q, D_u, D_v are +ve values.

So, the system can be unstable only when $\Delta < 0$

$$H(q^2) = \Delta = q^4 D_u D_v - q^2 \left[D_u \frac{\partial g}{\partial v} + D_v \frac{\partial f}{\partial u} \right] + \frac{\partial f}{\partial u}\frac{\partial g}{\partial v} - \frac{\partial g}{\partial u}\frac{\partial f}{\partial v}$$

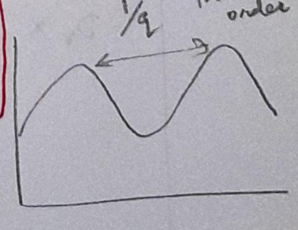
This can be ~~fi~~ thought of as : Determinant is a quadratic function of q^2.



Then we vary D_u & D_v such that the parabola moves up and down, so the curve intersects x-axis

q_{min} : ~~minimum~~ first mode where the system becomes unstable → ie $\frac{dH}{dq^2} = 0$

$$\frac{\partial H}{\partial q^2} = 0 \Rightarrow \boxed{q_{min} = \frac{D_u \frac{\partial g}{\partial v} + D_v \frac{\partial f}{\partial u}}{2 D_u D_v}}$$



Caution : All of this is local analysis

Lecture

Example of Pattern formation : Gierer - Meinhardt Model (1972)

$$\frac{\partial u}{\partial t} = \frac{u^2}{v} - bu + D_u \frac{\partial^2 u}{\partial x^2}$$

u: activator

v: inhibitor

$$\frac{\partial v}{\partial t} = \underbrace{u^2 - v}_{\text{Reaction}} + \underbrace{D_v \frac{\partial^2 v}{\partial x^2}}_{\text{Diffusion}}$$

$$f(u,v) = \frac{u^2}{v} - bu$$

$$g(u,v) = u^2 - v$$

* first, analyse the diffusionless case -

~~J~~ Steady states - $(u_0, v_0) = \left(\frac{1}{b}, \frac{1}{b_0}\right)$ gives $\frac{\partial u}{\partial t} = \frac{\partial v}{\partial t} = 0$

$$J = \begin{bmatrix} \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \frac{\partial g}{\partial u} & \frac{\partial g}{\partial v} \end{bmatrix}_{\left(\frac{1}{b}, \frac{1}{b^2}\right)} = \begin{bmatrix} -b + \frac{2u}{v} & -\frac{u^2}{v^2} \\ 2u & -1 \end{bmatrix}_{\left(\frac{1}{b}, \frac{1}{b^2}\right)}$$

$$J = \begin{bmatrix} b & -b^2 \\ \frac{2}{b} & -1 \end{bmatrix}$$

$$\tau = b - 1$$

$$\Delta = -b - (-b^2)\frac{2}{b} = b$$

For this to be stable, $\tau < 0$ $\Delta > 0$

$\Rightarrow$ $b - 1 < 0$ $\Rightarrow$ $b < 1$ $b > 0$

$\therefore$ This is stable when $\underline{\underline{0 < b < 1.}}$

* Instability with diffusion

We can write the linearised version

$$\frac{\partial \tilde{u}}{\partial t} = b\tilde{u} - b^2\tilde{v} + D_u \frac{\partial^2 u}{\partial x^2}$$

$$\frac{\partial \tilde{v}}{\partial t} = \frac{2}{b}\tilde{u} - \tilde{v} + D_v \frac{\partial^2 u}{\partial x^2}$$

Use ansatz –

$$\begin{bmatrix} \tilde{u}(x,t) \\ \tilde{v}(x,t) \end{bmatrix} = \begin{bmatrix} A(q)\, e^{iqx} \\ B(q)\, e^{iqx} \end{bmatrix}$$

Here, we should be summing over q (Fourier series). But, we'll figure it out for one mode and then see.

Put the solutions in equation and write Jacobian –

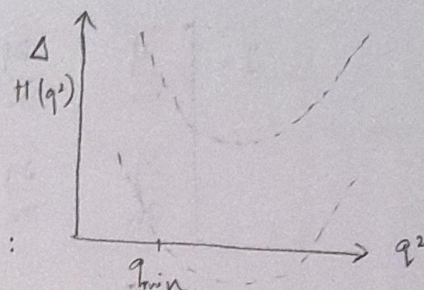
$$J = \begin{bmatrix} b - q^2 D_u & -b^2 \\ \frac{2}{b} & -1 - q^2 D_v \end{bmatrix}$$

For instability, $\lambda_1, \lambda_2 > 0$, for which we need the $\Delta(J)$ to be less than 0.

$$H(q^2) = \Delta = (b - q^2 D_u)(\overset{-1}{\hat{}}\,{-q^2 D_v}) + 2b < 0$$

$$\Delta = q^4 D_u D_v + q^2 (D_u - b D_v) + 2b < 0 \quad \text{— (1)}$$

If b will move the parabola up and down. For some range of q, the system will be unstable.

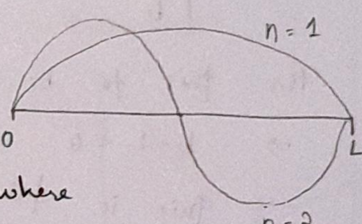


We need to have boundary conditions:

Periodic boundary condition: $u(0,t) = u(L,t)$
i.e. the system is working on a circle.

$$\tilde{u}(x,t) = \sum_q A_q(t) \cos(qx)$$

$q = \frac{n\pi}{L}$ where $n = 1, 2, 3 \ldots$



$q = \frac{\pi}{L}$ at $n = 1$ is the first value where instability is formed

$q_{min} \geq \frac{\pi}{L}$ (q_{min} from Eqn 1)

$\Rightarrow$ There's a critical length scale (L_c) at which pattern formation can occur. If $L < L_c$, no pattern.

Another model: Gray-Scott equations
The size of domain & boundary conditions determine the pattern: narrow 1d → stripes; square 2d → spots.

Stochastic modelling of channel dynamics (16th May)

$$C\frac{dV}{dt} = \underbrace{-g_K(V-V_K)}_{\text{K current}} - \underbrace{g_{Na}(V-V_{Na})}_{\text{Na Current}} - \underbrace{g_L(V-V_L)}_{\text{Leak current}} + \underbrace{I_{ext}}_{\text{Ext current}}$$

$$g_K = \frac{O_K}{N_K}\cdot\bar{g}_K \qquad g_{Na} = \frac{O_{Na}}{N_{Na}}\cdot\bar{g}_{Na}$$

$\bar{g}$ max conductance
O no of open channels
N total no. of channels

$$n_0 \underset{\beta_n}{\overset{4\alpha_n}{\rightleftharpoons}} n_1 \underset{2\beta_n}{\overset{3\alpha_n}{\rightleftharpoons}} n_2 \underset{3\beta_n}{\overset{2\alpha_n}{\rightleftharpoons}} n_3 \underset{4\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n_4$$

K channel

$$\begin{array}{ccccccc}
m_0h_0 & \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} & m_1h_0 & \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} & m_2h_0 & \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} & m_3h_0 \\
\alpha_h \Big\Downarrow\!\Big\Uparrow \beta_h & & \beta_h \Big\Downarrow\!\Big\Uparrow \alpha_h & & \alpha_h \Big\Downarrow\!\Big\Uparrow \beta_h & & \beta_h \Big\Downarrow\!\Big\Uparrow \alpha_h \\
m_0h_1 & \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} & m_1h_1 & \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} & m_2h_1 & \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} & m_3h_1
\end{array}$$

Na channel Markov chain
3 activating gates.
1 inactivating gate

→ Channel conductance is governed by gates, which can be in either 'open' or 'closed' position –

$$\text{Open} \underset{\beta\ \alpha}{\overset{\alpha\ \beta}{\rightleftharpoons}} \text{closed}$$

→ K channels are composed of 4 identical activating gates. When all gates are in ~~active~~ open state, the K channel is 'Open'.

→ Na channels have 3 identical activating gates and 1 inactivating gate. When depolarising current is given, 3 activating gates are 'open' & ~~dea~~ inactivating gate is 'closed', but it closes slowly, so all 4 subunits are 'open' for some time — AP occurs in this time

→ Simulate channels closing & opening – At time t, choose timestep δt

Case I : Channel is closed.

$P(\text{gate opens in } \delta t) = \alpha\,\delta t$

$P(\text{gate remains closed}) = 1 - \alpha\,\delta t$

$\left(\delta t \ll \frac{1}{\alpha}\right)$ Why?

Case II : Channel is open at t. After time δt -

$$P(\text{gate closes}) = \beta \delta t$$

$$P(\text{gate remains open}) = 1 - \beta \delta t \qquad \delta t << \frac{1}{\beta}$$

Using this, we can write Markov chain with 5 states for ~~N~~ K and 8 states for Na. *

* Pick a random no. b/w 0 & 1, and based on its value, decide whether it opens or closes

But this method is very inefficient ∵ it's computationally heavy as we need to keep track of every gate

For 10 Na & 10 K channel, how many calculations are needed to simulate 1-timestep

Markov Process for Occupation Number

Consider that a channel is in one of many states. Define states for K and Na. Now we can talk about no. of channels in a particular state (occupation number)

$$n_0 \underset{\beta}{\overset{4\alpha}{\rightleftarrows}} n_1$$

	n_0	n_1	n_2	n_3	n_4
States	s_1	s_2	s_3	s_4	s_5
Occup. no:	50	25	20	4	1

$$P(s_1 \to s_2) = 4\alpha \delta t \qquad P(\text{not } s_{2\to 1}) = 1 - 4\alpha \delta t$$
?

No. of transitions in each channel is binomially distributed. How many channels in $s_1 \to s_2$?

Take each channel in s_1 and toss a biased coin with $P(H) = 4\alpha \delta t$. If heads, the transition to s_2.

Suppose $N_{s1} = 4$,

$$P(n \text{ transitions}) = {}^{N_{s1}}C_n \cdot p^n (1-p)^{N_{s1} - n} \quad \text{— Binomial distribution}$$

For each state, we pick a single no. from a binomial distribution — that is, no. of state transitions.

We do same for all states, and we have simulated 1 timestep

Gillespie's Algorithm

What is total reaction rate?

r_{ij} : outward rxn rate from state $m_i h_j$ in Na^+ channel (Eg. $r_{21} = 2\beta_m + \alpha_m + \alpha_h$)

r_K : outward rxn rate from state n_K in K^+ channel

Total reaction rate is given by –

$$\lambda = \sum_{j=0}^{1} \sum_{i=0}^{3} r_{ij} N_{ij} + \sum_{k=0}^{4} r_K N_K$$

Sum of all state transitions

Time to next reaction chosen from exponential probability distribution with rate = λ

??

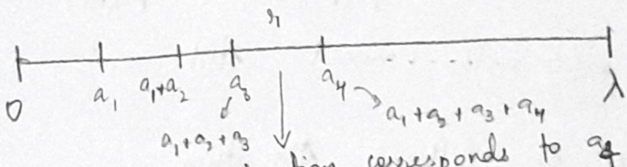
Which reaction occurs?

For each transition rate, define : $a_i = n_i r_i$

Eg: $a_1 = [m_0 h_0] \, 3\alpha_m$ (β_h ?)

$$\Rightarrow \lambda = \sum_{i=1}^{28} a_i$$

Pick r from $U[0, \lambda]$



reaction corresponds to a_4 occurring

Stochastic simulations I

Monte-Carlo method involves using inferential statistics to make predictions about a large sample via sampling of smaller subsets of a larger population.

Our confidence in MC method depends on N (sample size) and Var (sample) [$\uparrow$ var $\Rightarrow$ need larger N to be sure of underlying structure]

Suppose we wish to model this reaction –

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C$$

To model, convert it to a DE.

(60) ODE assumes –

1) well-mixed system (no spatial structure) and
2) very high concentrations so as to have smooth changes in particulate concentrations

This gives us –

$$\frac{dA}{dt} = \frac{dB}{dt} = -k_f AB + k_b C$$

$$\frac{dC}{dt} = k_f AB - k_b C$$

What if the concentrations are not high?

Gillespie algorithm

$n_A = 30$ $n_B = 20$ $n_c = 10$

1. Get the time of next reaction

$$K_{tot} = k_f N_A N_B + k_b N_c$$

Then, we draw δt, the timestep for next reaction as the time from an exponential distribution with $\mu = \frac{1}{K_{tot}}$

2. Which reaction occurs?

Prob. of $A + B \rightarrow C$: $P(R_1) = \frac{k_f N_A N_B}{K_{tot}}$

$$P(R_2) = 1 - P(R_1)$$

Assume it's well mixed still.

Adding space to Gillespie Algorithm

Divide the system into grids where each grid has its own set of independent reactions going on. We also have particles moving from one grid to another based on conc. gradients (acc. to diffusion coefficients). This is still ~~poorish~~ poor-ish spatial resolution. In practice, tetrahedral volumes are used instead of cubes

MCell program – tracks the motion of individual molecules

PDF for a particle having moved dist. r in time t : $f(r,t) = \frac{1}{(4\pi Dt)^{3/2}} e^{-r^2/4Dt}$

Each particle has a radius of interaction. Apply Gillespie within the cylinder.