Systems Biology: Mathematics for Biologists

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Introduction to 2D systems

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- Qualitative analysis of system dynamics
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One differential equation

A single differential equation:

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

For example:

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

In this system there is only a single variable x

The rate of change $\frac{dx}{dt}$ only depends on the values of the parameters (r and K) and on the value of the variable x

Systems of two differential equations

A system of two **coupled** differential equations:

$$\begin{cases} \frac{dx}{dt} = f(x, y) \\ \frac{dy}{dt} = g(x, y) \end{cases}$$

This system contains two variables, x and y

Note that $\frac{dx}{dt} = f(x, y)$ and $\frac{dy}{dt} = g(x, y)$

Thus, the rate of change of x depends on x itself and y.
Similarly, the rate of change of y depends on y itself and x.

The dynamics of x and y are **co-dependent**

Example systems: Linear system

Decaying and converting chemicals:

$$\begin{cases} \frac{dx}{dt} = ax + by \\ \frac{dy}{dt} = cx + dy \end{cases},$$

with $a = -2$, $b = 1$, $c = 1$, $d = -2$

Example systems: Non-linear system

Predator-prey system:
Prey have logistic growth and predators eat prey as only foodsource
What should the systems of equations look like:

A

$$\frac{dx}{dt} = rx(1 - \tfrac{x}{K}) - by$$
$$\frac{dy}{dt} = cx - dy$$

B

$$\frac{dx}{dt} = rx(1 - \tfrac{x}{K}) - bxy$$
$$\frac{dy}{dt} = cxy - dy$$

C

$$\frac{dx}{dt} = rx(1 - \tfrac{x}{K}) - bxy$$
$$\frac{dy}{dt} = bxy - dy$$

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Example systems: Non-linear system

Predator-prey system:

$$\begin{cases} \frac{dx}{dt} = rx(1 - \frac{x}{K}) - bxy \\ \frac{dy}{dt} = cxy - dy \end{cases},$$

with $r = 3$, $K = 1$, $b = 1.5$, $c = 0.5$, $d = 0.25$

Qualitative Analysis: Phase Portrait

How to understand the long term dynamics of 2D systems?

We will develop a similar approach as for 1D systems:
- qualitative
- graphical
- not requiring solution

To do so, as for 1D systems, we first look at the solutions of 2D systems and see how we can generalize from thereon.
But....we will only consider *numerical* solutions.

Intermezzo: Numerical Solutions for 1D systems

For a 1D system:

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

The *analytical solution* $x(t) = F(x) + c$ describes behavior of x over time

We can *approximate* the behavior of x over time as follows:
$x_1 = x_0 + \Delta t \times f(x_0)$
$x_2 = x_1 + \Delta t \times f(x_1)$
$x_3 = x_2 + \Delta t \times f(x_2)$
....
$x_n = x_{n-1} + \Delta t \times f(x_{n-1})$
This stepwise computation is called the *numerical solution*

Note:
Only a solution for **specific initial value** $x(0) = x_0$
For idea of **general solution** many such computations needed

Intermezzo: Numerical Solutions for 2D systems

Let us now numerically solve a general 2D system:

$$\begin{cases} \frac{dx}{dt} = f(x, y) \\ \frac{dy}{dt} = g(x, y) \end{cases}$$

Mind the co-dependence of the variables!
We can not do first: $x_0 \rightarrow x_1 \rightarrow x_2 \rightarrow x_3$ etc
and after that: $y_0 \rightarrow y_1 \rightarrow y_2 \rightarrow y_3$ etc
To compute $x_2 = x_1 + \Delta t \times f(x_1, y_1)$ we need x_1 and y_1

Therefore, we need to do it in parallel:
$x_1 = x_0 + \Delta t \times f(x_0, y_0)$ and $y_1 = y_0 + \Delta t \times g(x_0, y_0)$
$x_2 = x_1 + \Delta t \times f(x_1, y_1)$ and $y_2 = y_1 + \Delta t \times g(x_1, y_1)$
$x_3 = x_2 + \Delta t \times f(x_2, y_2)$ and $y_3 = y_2 + \Delta t \times g(x_2, y_2)$ etc

Again: only solution for specific initial value x_0, y_0

Trajectories: computing and drawing a solution

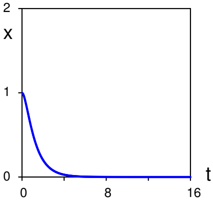
Let us compute a numerical solution for:

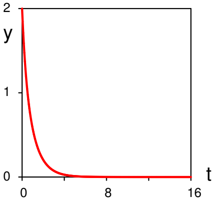
$$\begin{cases} \frac{dx}{dt} = -2x + 1y \\ \frac{dy}{dt} = 1x - 2y \end{cases}$$

for $x_0 = 1.1$ and $y_0 = 2$, using a $\Delta t = 0.1$

$x_1 = 1.1 + 0.1(-2 \times 1.1 + 2) = 1.08$ and
$y_1 = 2 + 0.1(1.1 - 2 \times 2) = 1.71$

$x_2 = 1.08 + 0.1(-2 \times 1.08 + 1.71) = 1.035$ and
$y_2 = 1.71 - 0.1(1.08 - 2 \times 1.71) = 1.476$
etcetera....

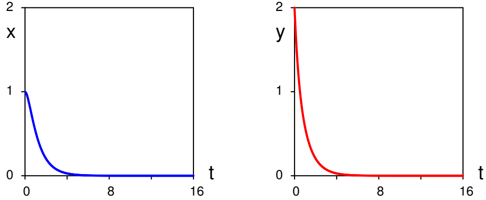




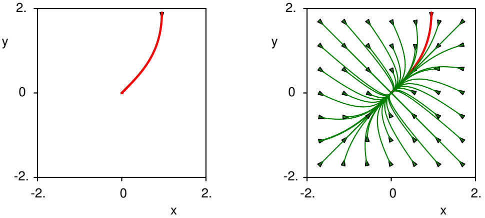
x and y exponentially decrease over time

Trajectories: computing and drawing multiple solutions

We need 3D graph to depict dynamics in single graph:
x-axis for x, y-axis for y and z axis for time



We can simplify to 2D by using arrows to depict time dynamics (left):
We can draw multiple solutions for different x_0, y_0 (right)



Convergence to point $(0, 0)$, stable equilibrium?!

Equilibria

When do we have an equilibrium for a 2D system?

$$\begin{cases} \frac{dx}{dt} = f(x, y) \\ \frac{dy}{dt} = g(x, y) \end{cases}$$

What if $\frac{dx}{dt} = f(x^*, y^*) = 0$ and $\frac{dy}{dt} = g(x^*, y^*) \neq 0$?
at next timepoint x stays at x^* but y will go from y^* to y'
then $\frac{dx}{dt} = f(x^*, y') \neq 0$ so x willgo to x', while y moves on to y''

Similar story for $\frac{dy}{dt} = g(x^*, y^*) = 0$ and $\frac{dx}{dt} = f(x^*, y^*) \neq 0$

Therefore (x^*, y^*) is an **equilibrium** only if *both*
$\frac{dx}{dt} = f(x^*, y^*) = 0$ and $\frac{dy}{dt} = g(x^*, y^*) = 0$

How to find equilibria

In equilibrium $\frac{dx}{dt} = f(x^*, y^*) = 0$ and $\frac{dy}{dt} = g(x^*, y^*) = 0$

So we need to solve system of equations:

$$\begin{aligned} f(x,y) = & \ 0 \\ g(x,y) = & \ 0 \end{aligned}$$

Step 1: solve simplest equation
Step 2: fill in solution into second equation
Step 3: now also solve second equation
Step 3b: if necessary fill back in into solution first equation
Step 4: repeat steps 2&3 if step 1 gave multiple solutions

Keep track which x and y values belong together!

Equilibria DIY

Example: Find equilibria of the following linear system:

$$\begin{cases} \frac{dx}{dt} = -2x + y \\ \frac{dy}{dt} = x - 2y \end{cases}$$

What are the equilibria of this system?
A (1,1)
B (0,0)
C (0,0) & (1,1)

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Linear systems always have a single equilibrium at (0,0)

Equilibria DIY

Example: Find equilibria of the following non-linear system:

$$\begin{cases} \frac{dx}{dt} = 3x(1-x) - 1.5xy \\ \frac{dy}{dt} = 0.5xy - 0.25y \end{cases}$$

What are the equilibria of this system?
A (0,0) & (1,0)
B (0,0) & (0.5,1)
C (1,0) & (0.5,1)
D(0,0), (1,0) & (0.5,1)

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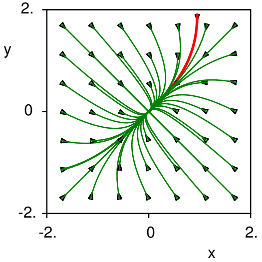
Non-linear systems may have multiple equilibria

Vectorfield

How to move from solutions to phase portrait?



Take similar approach as for 1D phase portraits:

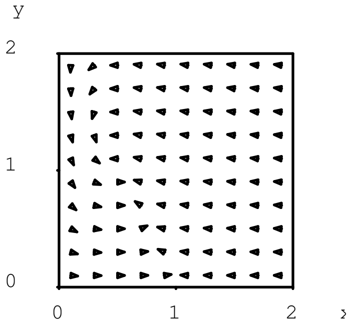
- get rid of the the time axis
- consider only qualitative change
- use functions, not their solution

How:
Fill in x,y values to obtain vectorfield $\vec{v} = (\frac{dx}{dt}, \frac{dy}{dt}) = (f(x,y), g(x,y))$.
In 2D plane depict the sign of these derivatives (direction of vectors)

Vectorfield

So we draw:

If $\frac{dx}{dt} = f(x, y) > 0$, x increases: $\rightarrow$
If $\frac{dx}{dt} = f(x, y) < 0$, x decreases: $\leftarrow$
If $\frac{dy}{dt} = g(x, y) > 0$, y increases: $\uparrow$
If $\frac{dy}{dt} = g(x, y) < 0$, y increases: $\downarrow$



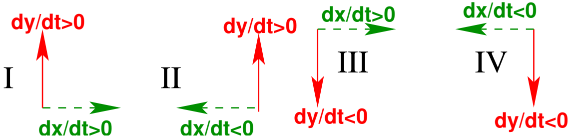
Quite unsatisfying:

Hard to see what long term dynamics will be!

Null-clines

Vectorfield: a lot of work, and still unclear.
Can we do this in a smarter, more insightful way?

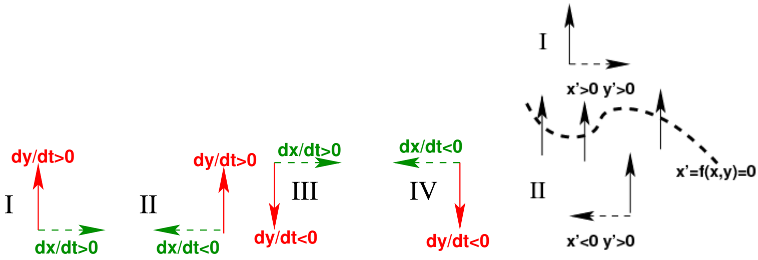
Important: only 4 qualitatively different vectors are possible:



More efficient approach:

1. Divide vectorfield into different regions by finding boundaries.
2. Assign all vectorfield regions to one of these 4 categories.

x null-clines

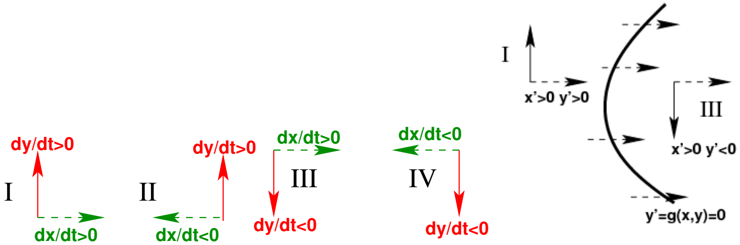


From I to II, and from III to IV, the direction of $\frac{dx}{dt}$ changes.

x null-clines are *boundary lines* at which $\frac{dx}{dt} = f(x, y) = 0$, separating vectorfield regions I from II and III from IV

At an x null-cline, the horizontal part of the vectorfield is zero, hence the vectorfield has only a vertical component.

y null-clines



From I to III, and from II to IV, the direction of $\frac{dy}{dt}$ changes.

y null-clines are boundary lines at which $\frac{dy}{dt} = g(x, y) = 0$, separating vectorfield regions I from III and II from IV

At an y null-cline, the vertical part of the vectorfield is zero, hence the vectorfield has only a horizontal component.

Combining null-clines and vectorfield

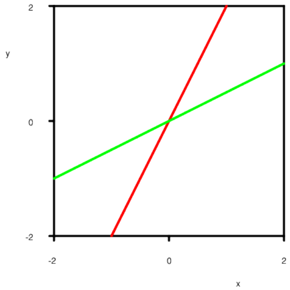
Let us draw a phase portrait by combining null-clines and vectorfield for:

$$\begin{cases} \frac{dx}{dt} = -2x + y \\ \frac{dy}{dt} = x - 2y \end{cases}$$

First we will determine the nullclines:

For the x **null-cline** we solve $\frac{dx}{dt} = -2x + y = 0$ to obtain $y = 2x$

For the y **null-cline** we solve $\frac{dy}{dt} = x - 2y = 0$ to obtain $y = 0.5x$

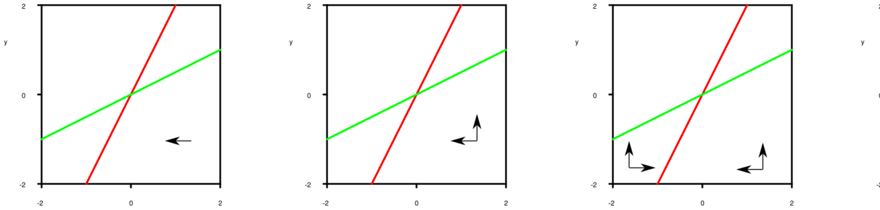


Combining null-clines and vectorfield

Next we determine the vectorfield:

Determine vectorfield **in one region** of the phase portrait
For example, lower right corner so fill in $x = 1$ $y = -1$
gives $\frac{dx}{dt} = -3$ so $\leftarrow$ and $\frac{dy}{dt} = 3$ so $\uparrow$

Determine vectorfield **in other regions** by using that
if you cross x null-cline *horizontal* vector switches direction
if you cross y null-cline *vertical* vector switches direction
For example, for lower left corner, you cross x null-cline
so now we get $\rightarrow$ while we keep $\uparrow$



Together, null-clines and vectorfield give more information

Relation null-clines and equilibria

At x null-cline $\frac{dx}{dt} = f(x, y) = 0$

At y null-cline $\frac{dy}{dt} = g(x, y) = 0$

If x and y null-clines intersect,
$f(x, y) = 0$ and $g(x, y) = 0$: **equilibrium**!

However:
Intersections of two nullclines *of the same type*
are not equilibria!

Global plan

General plan of phase portrait analysis:

$$\begin{cases} \frac{dx}{dt} = f(x,y) \\ \frac{dy}{dt} = g(x,y) \end{cases}$$

1. Draw $\frac{dx}{dt} = f(x,y) = 0$ and $\frac{dy}{dt} = g(x,y) = 0$ null-clines.
2. Identify equilibria as intersections of different null-clines.
3. Choose a region of the x, y plane to find vector $\vec{v} = (f(x,y), g(x,y))$.
4. Find the vectorfield in the adjacent regions using:
   - Flip the horizontal component when crossing x null-cline.
   - Flip the vertical component when crossing y null-cline.
5. Show the direction of the vectorfield on the null-clines
   - horizontal on y, vertical on x null-clines.
6. Try determine the dynamics around an equilibrium
   - convergence so stable or divergence so unstable.
7. Try to derive the global dynamics of the system
   - attractors, basins of attraction.

Example

Example: Draw a vectorfield of the following system:

$$\begin{cases} \frac{dx}{dt} = 3x(1-x) - 1.5xy \\ \frac{dy}{dt} = 0.5xy - 0.25y \end{cases}$$

Parameters and bifurcations

Consider a system in which

- x and y disappear through decay
- and promote each others production:

$$\begin{cases} \frac{dx}{dt} = -ax + by \\ \frac{dy}{dt} = c\frac{x^2}{x^2+d^2} - ey \end{cases}$$

a, b, c, d and e are all parameters.

Let us fix b, c, d and e and study the influence of a.

Does a influence the number and/or stability of equilibria?
That is, does changing a cause bifurcations?

Parameters and bifurcations

Depending on a we have:
A zero or one equilibrium
B zero or two equilibria
C one or three equilibria
D one or two equilibria

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Parameters and bifurcations

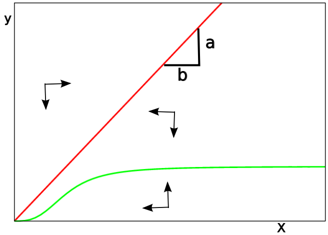
Start by finding null-clines:

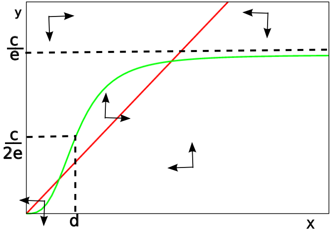
x **null-cline**:
$\frac{dx}{dt} = -ax + by = 0$ so $y = \frac{a}{b}x$
straight increasing line
slope proportional to a

y **null-cline**:
$\frac{dy}{dt} = c\frac{x^2}{x^2+d^2} - ey = 0$ so $y = \frac{c}{e}\frac{x^2}{x^2+d^2}$
saturating function,
maximum value $\frac{c}{e}$,
reaches half-max. at $x = d$
independent of a

Parameters and bifurcations

Depending on the value of *a*, one or three equilibria:





So *a* determines if there is a non-trivial stable equilibrium.

So changing *a* causes a **bifurcation**, a qualitative change in the number and/or stability of the equilibria of a system.

Parameters and bifurcations

Note that if we replace $\frac{x^2}{x^2+d^2}$ by $\frac{x}{x+d}$:

- we change from a sigmoid to normal Hill function
- now we have maximum of two intersection points
- after bifurcation zero equilibrium unstable, non-zero one stable
- thus we loose the possibility for bistability