* What is a "Physiological System"?

- It is a "system", i.e., it is a set of interacting or interdependent components forming an integrated whole ⇒ Hence it has a structure and its behavior results from the interaction between the components in the structure

→ A model can be necessary to study the structure and/or the behavior of the system

- It is "physiological", i.e., its components are organs, cells, or biomolecules that interact to carry out a specific chemical or physical function in a living organism

Examples:

- The cardio-vascular system is composed by the heart and the blood vessels. These components interact to pump blood through the body, thus bringing oxygen and removing waste products

- The endocrine system is made of glands throughout the body that secrete hormones in a coordinated way to regulate the internal environment of the body

→ A model can be necessary to study the dynamics of the various components (i.e., how they evolve in time because of the interactions) and/or how the specific chemical or physical function stems from the mechanisms of these interactions

⇓

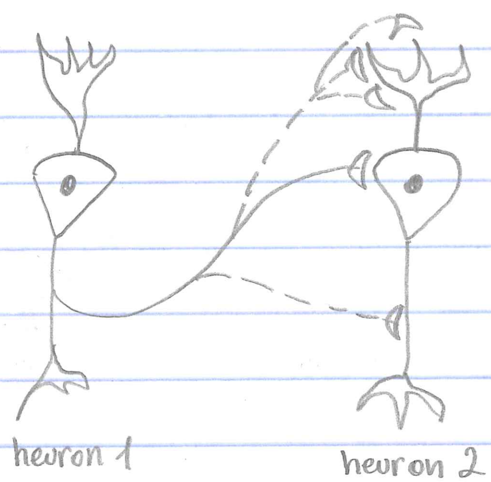
NOTE: The study of the mechanisms of the interaction pertains to the physiologists

* What makes modeling a physiological system challenging?

- Complexity. It deals with the number of options and combinations that one has to take into account when a model is built. It depends on:

  - Number of components in the system
    (the more components, the more complex system)

  - Number of interconnections between components
    (the more interconnections, the more complex system)



Example:
depending on how many synapses are made by neuron 1 on neuron 2 and where, the behavior of neuron 2 may change deeply

  - Nonlinearity
    (components and interactions have nonlinear dynamics)

  - Asymmetry
    (components with similar properties and inputs in the same system behave differently)

  Example: differential growth of cells and specialization

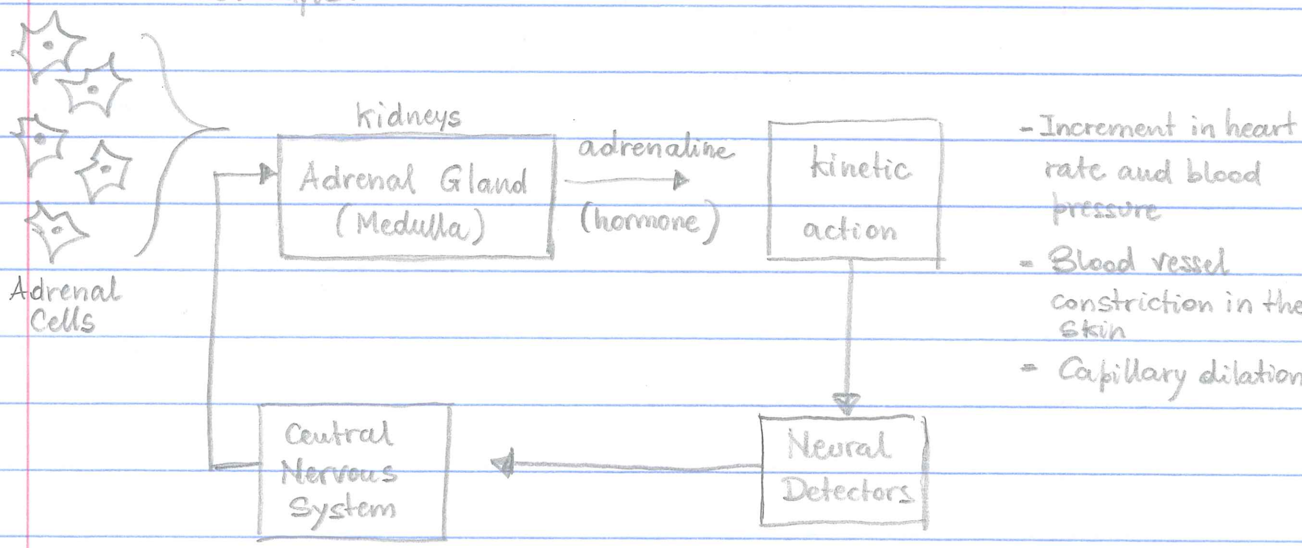
- Nonholonomic constraints

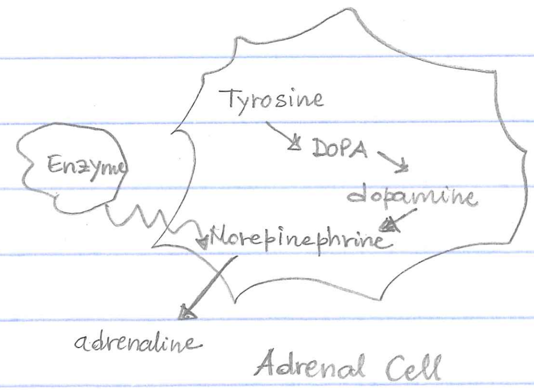
  (the behavior of the system under a given set of conditions and inputs depends on the path taken up to that point)

Example:
Fatigue affects ligaments
and muscles involved in repeating
a movement over and over

- <u>Hierarchy</u>. A physiological system may be organized as a cascade of feedback loops (positive and negative) aiming at controlling one specific function. Each subsystem along these loops can itself aggregate several more elementary physiological systems, each one implementing regulatory feedback loops

Example:





- **Redundancy**. A physiological system may duplicate the mechanisms used to implement a given function.

  Alternatively, more than one physiological system may provide the same function

It provides reliable fine regulation of the function

⇓

Example: While insulin is the hormone specific for glucose-level regulation in the blood, glucagon, adrenaline and steroids can all provide non-specific compensation in case of low-glucose level

It provides robustness against non-nominal conditions and facilitates the implementation of more sophisticated functions

⇓

Examples:

- Two eyes allow binocular vision
- Numerous nervous cells carry the same bit of information to avoid losses

* How do we conceive a model for a physiological system?

- Remember that a "model" is a representation of a piece of reality involving some degree of approximation

We need to decide which aspects are captured in our model and which ones are neglected

⇓

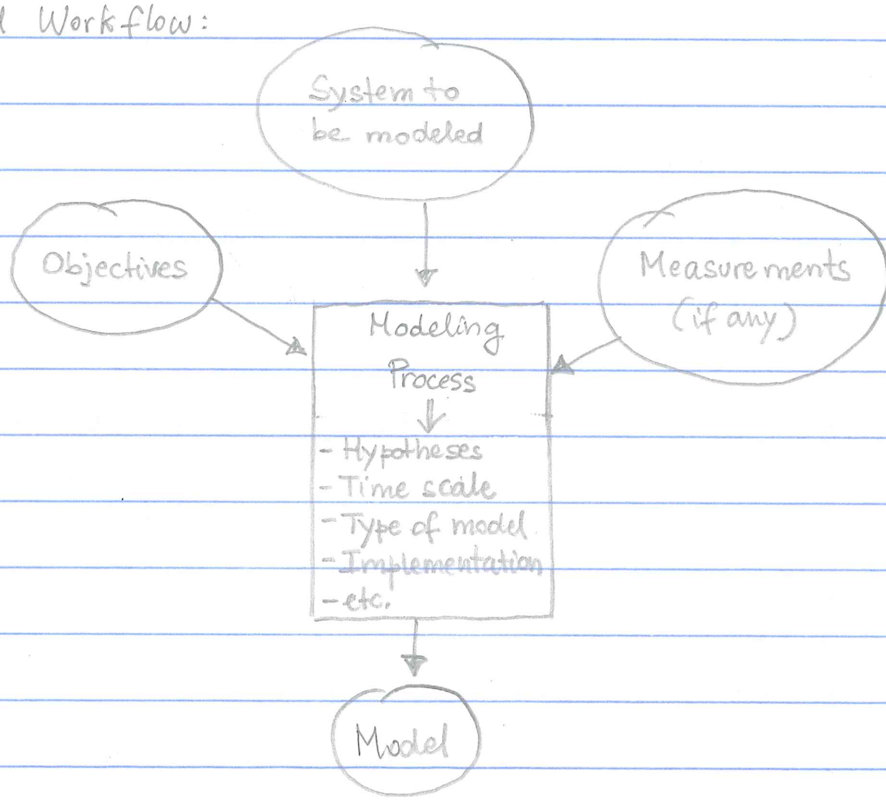
OBJECTIVES

We need to decide how the aspects of interest are modeled and under what conditions

⇓

HYPOTHESES

- Conceptual Workflow:



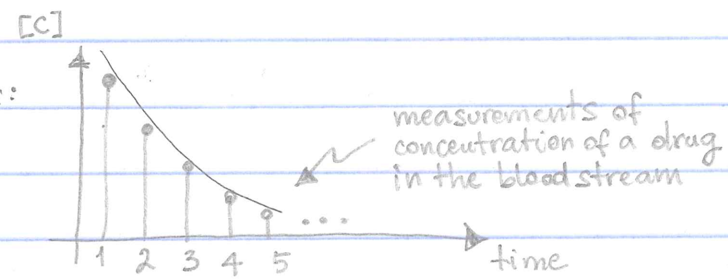
- With regard to the objective, a model may be necessary for:

- ANALYSIS: A model may provide a mathematical (⇒ quantitative) relationship between two or more variables that explains how the system works

Ex: Fluidodynamics can be used to model the relationship between blood flow rate and vessel anatomy ⇒ The model aids understanding the differences in flow rate between large vessels and capillaries

- INTERPRETATION OF EXPERIMENTAL RESULTS: A model may interprete series of measurements collected during an experiment and facilitate inferences on the system's own dynamics

Ex:

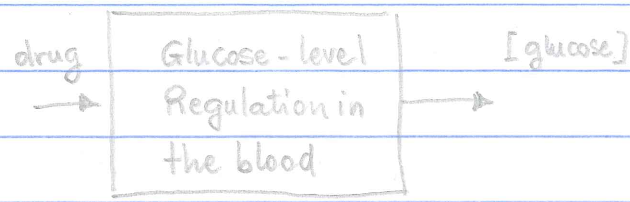


$[C]_t = [C]_0 e^{-t/\tau}$ ⇒ The parameter "τ" is fitted on the data and it provides information on the rate of clearance of the drug from the blood stream

- PREDICTION: A model may be simulated numerically to predict the response of the system to a change of input or model parameters

The simulation precedes or replaces time-consuming expensive experiments

Ex:



The response of the system to a new input is predicted

Ex: $\frac{d[C]}{dt} = f(\ldots) - \alpha[C]$

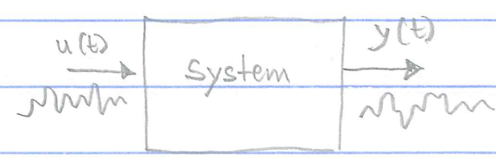
It captures the kidneys' function

The concentration of creatinine in the blood decreases because of the filtering action of the kidneys

By lowering the value of "α" one may simulate the effects of kidneys' disfunction on the concentration of creatinine in the bloodstream

- There are two distinct approaches to model development:

• DATA-DRIVEN (black-box)

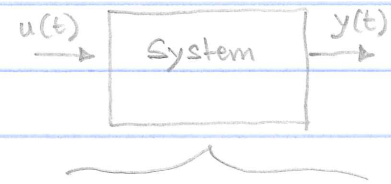


The model needs experimentals measurements of the input signals to the system and the corresponding output values $\{u(t), y(t)\}$ $t=0,1,\ldots$

The model provides a quantitative description of how $y(t)$ is determined by $u(t)$ - Ex: $y(t+1) = a_1 y(t) + a_2 y(t-1) + b_1 u(t) + b_2 u(t-1)$

There is no explicit description of the physiology underneath

- KNOWLEDGE - DRIVEN
  (gray - box)



- a priori knowledge from physical laws
- known relationships between physiological variables
- constraints on variables' values
- assumptions

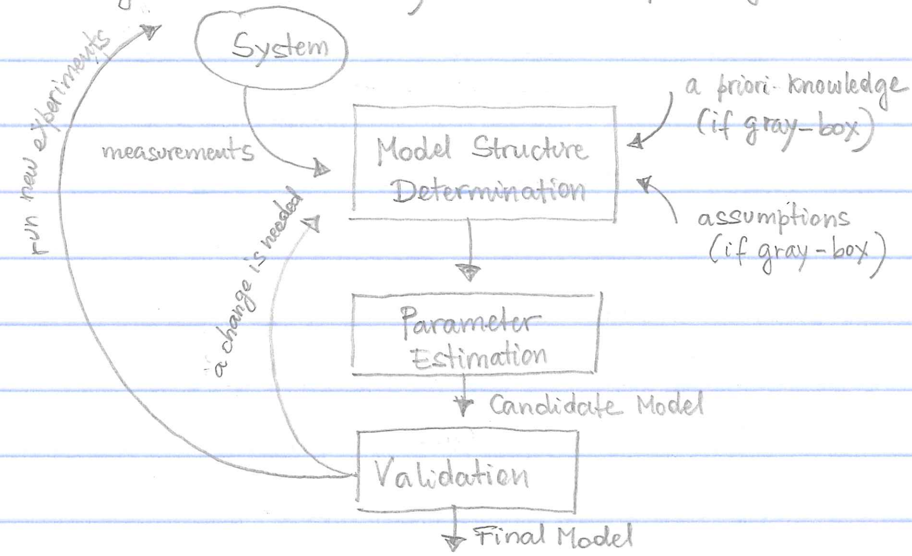
The model is constructed from basic physical laws, well-known physiological relationships between variables, and constraints on the physiological range of one or more variables

⇓

The result may be a model with a few unknown parameters that need to be estimated from experimental data

NOTE : Both approaches use data at some point for parameter estimation
The difference is in how the physiology is represented (i.e., implicitly vs. explicitly)

- The Modeling Process ultimately follows this paradigm:



The validation is the phase when we assess whether the model is adequate to the objectives it was developed for

The model has to be credible, i.e., the model behavior should be close to the system outputs and the parameters should be physiologically plausible

If there are many alternative models, the final model must be chosen as the "best" one under some criteria

In this course we will focus on how to develop and validate gray-box models of physiological systems ranging from single cells to ensembles of organs. For each problem, we will assume that parameters are given to us by someone in charge with designing and running experiments to estimate parameters

REFERENCE:

Cobelli – Carson "Introduction to Modeling in Physiology and Medicine" Academic Press, 2008 - chapter 2-3

A copy of these two chapters is available on Husky CT. Please download it

* Computational tools we need in this course

- ODE Solver in MATLAB:

We will develop mathematical models in one of three forms:

- EXPLICIT $y' = f(t, y)$ or $y' = f(t, y, u)$

dependent variable (it could be a vector)

independent variable (usually time)

exogenous input variable (it is provided)

- LINEARLY IMPLICIT $M(t, y)\, y' = f(t, y)$

a function (scalar or matrix) of the variables t, y

- FULLY IMPLICIT $f(t, y, y') = 0$

the derivative y' cannot be separated from the rest and brought to the other side of the equation

Note that an ODE may involve derivatives of order higher than one. If so, the problem must formulated as a system of first order ODEs

Example: $y'' = 3(1 - y^2)y' - y$

We can increase the number of variables to be integrated by defining: $y_1 \triangleq y$; $y_2 \triangleq y'$ $\Rightarrow$

$$\Rightarrow \begin{cases} y_1' = y_2 \\ y_2' = 3(1 - y_1^2)\, y_2 - y_1 \end{cases}$$ - system of first order ODEs

In general, if an ODE involves derivatives up to the n^{th} order, it can be formulated equivalently as a system of n ODEs

$$y^{(n)} = f(t, y, y', y'', \dots, y^{(n-1)})$$

$$\Updownarrow$$

$$\begin{cases} y_1' = y_2 \\ y_2' = y_3 \\ y_3' = y_4 \\ \vdots \\ y_{n-1}' = y_n \\ y_n' = f(t, y_1, y_2, y_3, \dots, y_n) \end{cases}$$

where: $y_1 \triangleq y$; $y_2 \triangleq y'$

$y_3 \triangleq y''$; ....; $y_n \triangleq y^{(n-1)}$

To solve an ODE in explicit form by using the ODE Solver in MATLAB, we implement these steps:

a) Formulate the ODE as a system of first-order ODEs in explicit form

$$y'' - \mu(1-y^2)y' + y = 0$$

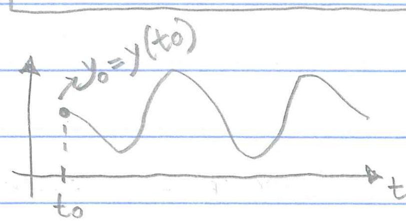
$$\Updownarrow$$

$$\begin{cases} y_1' = y_2 \\ y_2' = \mu(1-y_1^2)y_2 - y_1 \end{cases}$$

b) Implement the "right side" of your system of ODEs in a MATLAB m-function

```
function dydt = vanderpol (t,y)
  μ = 1;
  dydt (1,1) = y (2);
  dydt (2,1) = μ (1-y(1)*y(1))*y(2)-y(1);
```

c) Set an initial condition to begin the solution with



$$y_0 = \begin{bmatrix} 2 \\ 0 \end{bmatrix}$$

d) Set the time horizon over which the solution must be computed

start-time, end-time

timespan = [0 20];

or

timespan = 0:0.01:20;

the actually times where we want the solution evaluated are set upfront and equally spaced with step size 0.01

e) Choose the most appropriate method to integrate the ODEs and run it by passing as input parameters y_0, timespan and the name of the m-function

[t, y] = ode45(@vanderpol, ... timespan, y_0)

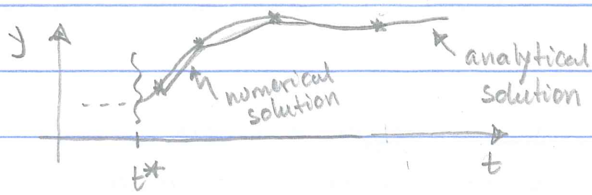
It is a N×2 vector (first column for y_1, second column for y_2) where N is the number of time points $t_1, t_2, \ldots,$ where the solution was computed

There are two classes of solvers in MATLAB for ODEs in explicit form. These classes are taylored to the nature of the ODEs to be solved and their initial conditions.

ode45 ode23 ode113	Solvers for NONSTIFF problems	ode15s ode23s ode23t ode23tb	Solvers for STIFF problems

A "problem" is the combination of ODEs to be solved, initial conditions, and time horizon.

The concept of "stiffness" is related to the following intuition: if the solution of a problem is a smooth, slowly varying curve then the solver should be able to move fast by choosing large integration steps



A problem is "STIFF" if the intuition is disproved. More precisely, if a nonstiff solver is used to solve the problem and results in a step length that is excessively small in relation to the smoothness of the exact solution

NOTE: I am willingly "deceitful" here because I am saying: "take a problem and try to solve it by using one of the nonstiff solvers. If the integration rapidly slows down by taking smaller and smaller steps even though the solution varies little, then the problem is stiff!"
The reason is because the notion of "stiffness" requires a discussion on how numerical methods work, which is beyond the scope of the lecture

To understand stiffness, let us solve the following problem:

$y'' - 1000(1-y^2)y' + y = 0 \qquad y_0 = \begin{bmatrix} 2 \\ 0 \end{bmatrix} \qquad tspan = [0 \;\; 1500]$

by using ode45: 143 s*

by using ode15s: 0.15 s*

* time required to solve the problem with MATLAB 2015a on my laptop

Based on the solution of the example one can extrapolate conditions that are often present in a stiff problem:

- the steplength is constrained because of stability issues with the solver

  This can happen when the solution varies slowly over some interval and rapidly over another

- some components of the solution (if a system of ODEs) vary much more rapidly than others

Hence, a solver for STIFF problems is a solver that implements special algorithms that are designed for those conditions that lead to stiffness

To solve an ODE in fully implicit form by using the ODE Solver in MATLAB, we implement these steps:

a) Formulate the ODE as a system of fully implicit ODEs that only involve y and y'

$$y(y'')^3 - t(y'')^2 + y' - t^2 y = 0$$

$$\Updownarrow$$

$$\begin{cases} y_1' - y_2 = 0 \\ y_1(y_2')^3 - t(y_2')^2 + y_2 - t^2 y_1 = 0 \end{cases}$$

b) Implement the "left side" of your system of ODEs in a m-function

```
function res = fullyimp(t,y,yp)
res(1,1) = yp(1)-y(2);

res(2,1) = y(1)*yp(2)^3+...
           -t*yp(2)^2+y(2)+...
           -t^2*y(1);
```

c) Set an initial condition for y and y' to begin with. Set the time horizon over which the solution must be computed

$$y_0 = \begin{bmatrix} 3 \\ -2 \end{bmatrix}; \quad y_0' = \begin{bmatrix} 2 \\ 0 \end{bmatrix}$$

$$tspan = [\,1 \quad 30\,];$$

d) Solvers for fully implicit ODEs may be very sensitive to the choice of the initial conditions. In particular, we want:

$$f(t_0, y_0, y_0') = 0$$

$$\Downarrow$$

Because this is not guaranteed by y_0, y_0', and tspan(1) chosen above, we need to refine the initial conditions by using the MATLAB function "decic":

$$[\hat{y}_0, \hat{y}_0'] = decic(@fullyimp, tspan(1), y_0, 0, y_0', 0);$$

e) Invoke the ODE solver from MATLAB ("ode15i")

$$[t, y] = ode15i(@fullyimp, tspan, \hat{y}_0, \hat{y}_0');$$

y: It is a Nx2 vector as before

To solve an ODE in linearly implicit form by using MATLAB, we must formulate the ODE in explicit or fully implicit form first and then we must use the appropriate procedure as outlined above

- ODE Solver in Simulink:

It is used if: (1) a more intuitive graphical interface is needed

and/or

(2) the solution of the ODE must be interfaced with other Simulink blocks or code

and/or

(3) Fixed-step ODE Solvers are required (those seen before use a variable integration steplength)

AND

* (4) The ODE is already in explicit form

Check example in class.

REFERENCE:

A guide on how to solve fully implicit and explicit ODEs in MATLAB with examples is available on HuskyCT. It is taken from the MathWorks website.

Software implementing the examples shown in class is available on HuskyCT