# Deterministic model

iGEM2014

# Why do we need it?

- To see how the mean of the population will act.
- To understand how the system behaves.
- To find out what need to be changed.
- To improve the circuit.
- To find the parameters.
- ....
- ....

# How do we do it?

- Before learning how a deterministic model is done is important to understand a few concepts…

Optimization

Screening

Assumptions

Michaelis Menten

Reaction rate

Hill's equation

Equilibrium

Cooperation

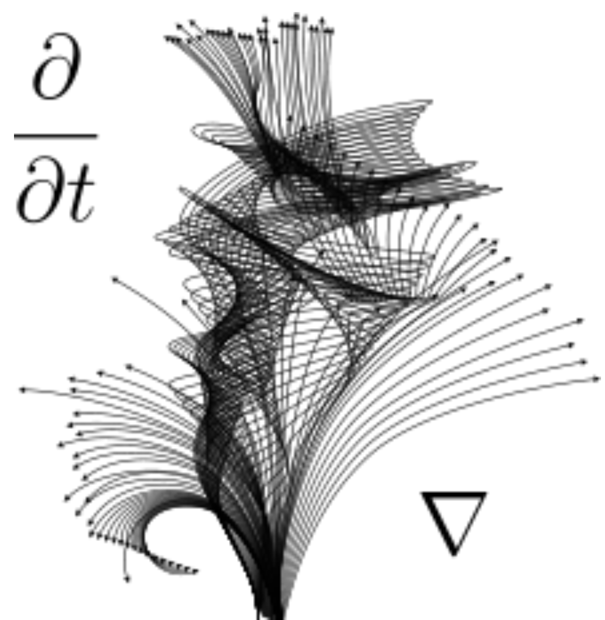
Sensibility analysis

Hysteresis

Mass action law

# How do we do it?

- Finding a expression in terms  of time and concentration usually is not easy.
- Expressions that define the change in time of the substances are easier to find.



# How do we do it?

Change in time of the concentration of the molecules:

$$A + B \rightarrow C + D$$

**Reaction rate**

$$\frac{dA}{dt}, \frac{dB}{dt}, \frac{dC}{dt}$$

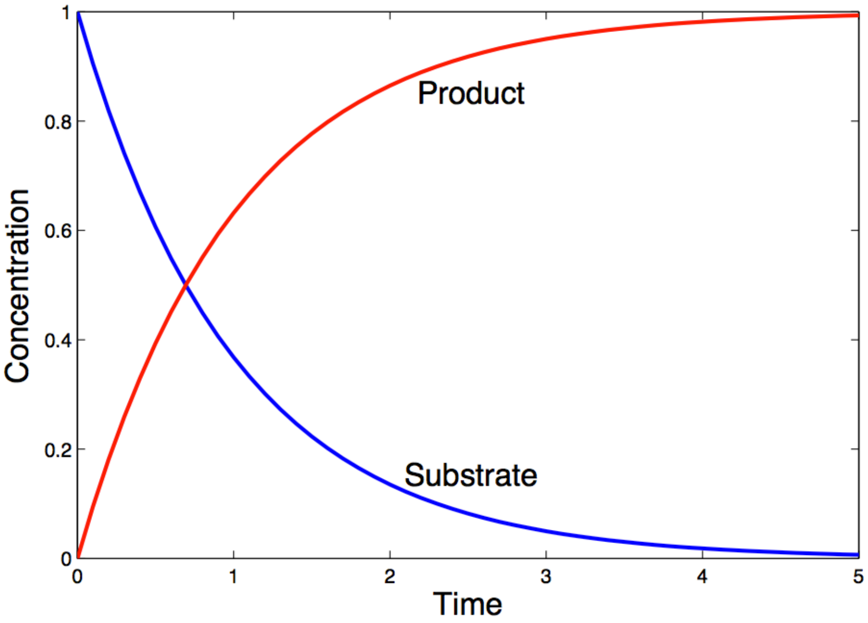
# How do we do it?

## Mass action law

$$A + B \xrightarrow{k} C + D$$

$$\frac{dA}{dt} = \frac{dB}{dt} = -kAB$$

$$\frac{dC}{dt} = \frac{dD}{dt} = kAB$$



# How do we do it?

## Mass action law

More than one reaction…

EXAMPLES!

# How do we do it?

## Michaelis Menten

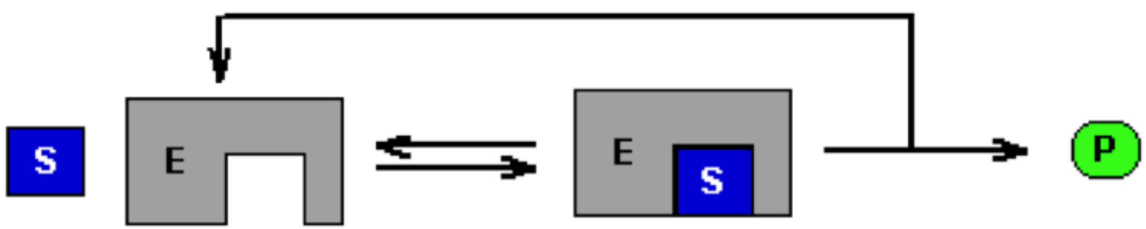



Figure 8: Michaelis-Menten mechanism.

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

# How do we do it?

## Michaelis Menten

$$\begin{cases} \dfrac{dS}{dt} = -k_1 ES + k_{-1} C \\ \dfrac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C \\ \dfrac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C \\ \dfrac{dP}{dt} = k_2 C \end{cases}$$

# How do we do it?

## Assumptions...

1. $k_1, k_{-1} >> k_2$
2. Steady state
3. Et= Efree + Ecomplex

$$\begin{cases} \dfrac{dS}{dt} = -k_1 ES + k_{-1} C \\ \dfrac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C \\ \dfrac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C \\ \dfrac{dP}{dt} = k_2 C \end{cases}$$

# How do we do it?

## Assumptions...

$$C = \frac{E_T S}{\frac{k_{-1}}{k_1} + S}$$

$$\begin{cases} \frac{dS}{dt} = -k_1 ES + k_{-1} C \\ \frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C \\ \frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C \\ \frac{dP}{dt} = k_2 C \end{cases}$$

# How do we do it?

## Michaelis Menten

$$\frac{dP}{dt} = k_2 C = V_{max} \frac{S}{K_S + S}$$

# Hill's equation

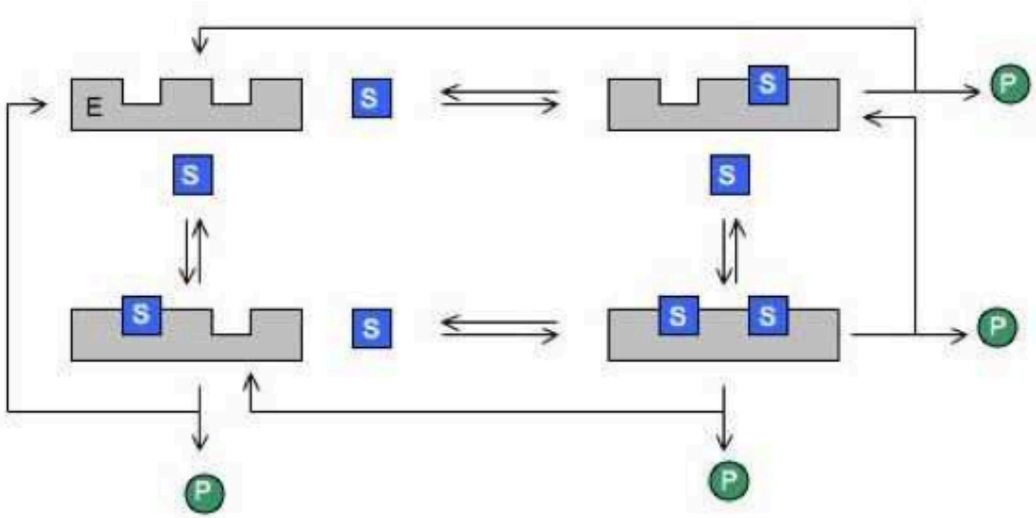



Figure 20: Enzyme with two binding sites: mechanism.

$$2 \times \left[ S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightarrow} E + P \right]$$

$$2 \times \left[ S + C_1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \overset{k_4}{\rightarrow} C_1 + P \right]$$

## Cooperation

# Hill's equation

$$2 \times \left[ \mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C}_1 \overset{k_2}{\rightarrow} \mathrm{E} + \mathrm{P} \right]$$
$$2 \times \left[ \mathrm{S} + \mathrm{C}_1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{C}_2 \overset{k_4}{\rightarrow} \mathrm{C}_1 + \mathrm{P} \right]$$

$$\begin{cases} \dfrac{dS}{dt} = 2(-k_1 SE + k_{-1} C_1 - k_3 S C_1 + k_{-3} C_2) \\ \dfrac{dC_1}{dt} = 2(k_1 SE - (k_{-1} + k_2) C_1 - k_3 S C_1 + (k_{-3} + k_4) C_2) \\ \dfrac{dC_2}{dt} = 2(k_3 S C_1 - (k_{-3} + k_4) C_2) \end{cases}$$

**Cooperation**

# How do we do it?

## Assumptions…

1. $k_1, k_{-1} >> k_2$
2. Steady state $\frac{dC_1}{dt} = \frac{dC_2}{dt} = 0$
3. Et= Efree + Ec1+ Ec2

# How do we do it?

## Assumptions...

4. $k_1 = k_3 = k_+$
   $k_{-1} = k_{-3} = k_-$
   $k_2 = k_4 = k_p$

   Binding sites independent.

5. S+ E → C1 and S+ C1 → C2

# How do we do it?

## Hill's equation

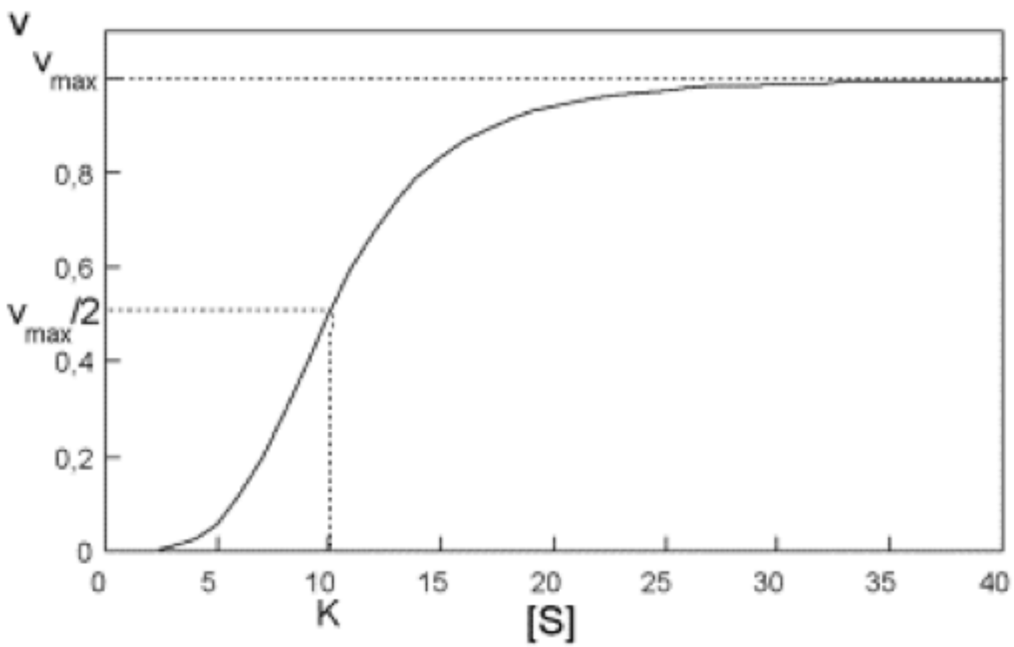



Figure 22: Hill kinetics.

$$v = V_{max} \frac{S^2}{K + S^2}$$

# How do we do it?

## Hill's equation

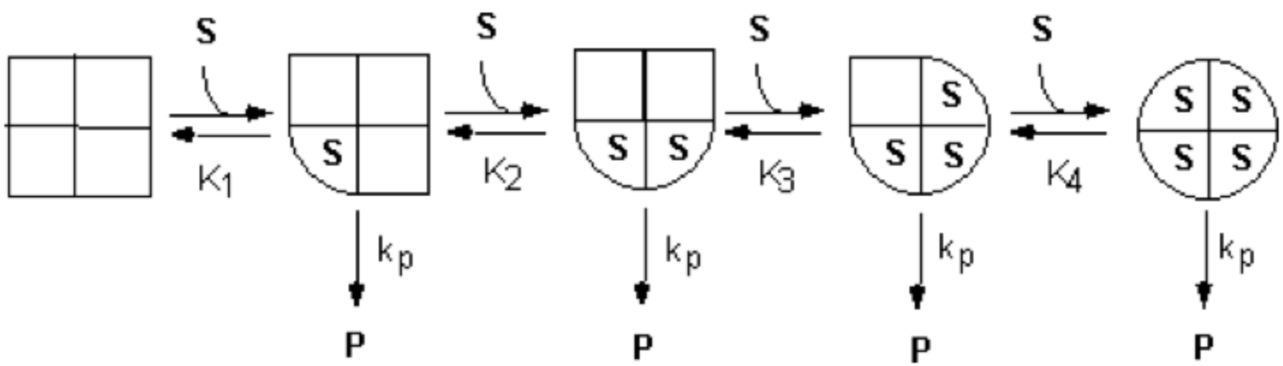
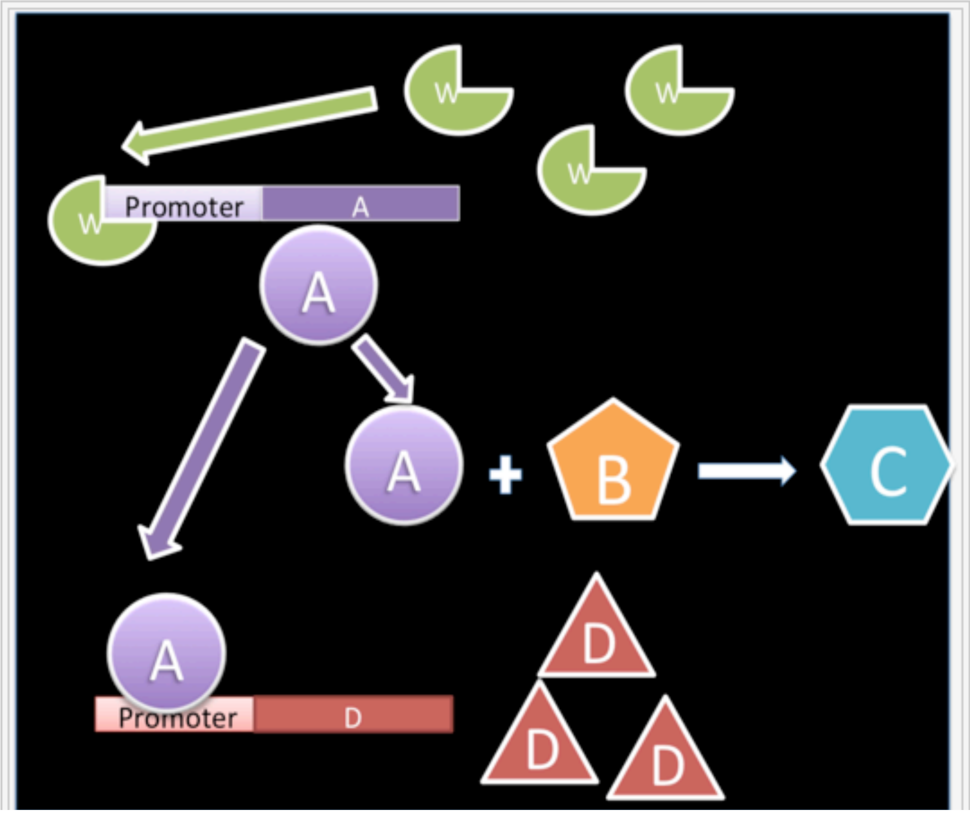



Figure 21: Cooperativity: mechanism.

$$v = V_{max} \frac{S^n}{K^n + S^n}$$

# How do we do it?

## Genetic Circuits




$$Accumulation = Input - Output + Production - Consumption$$

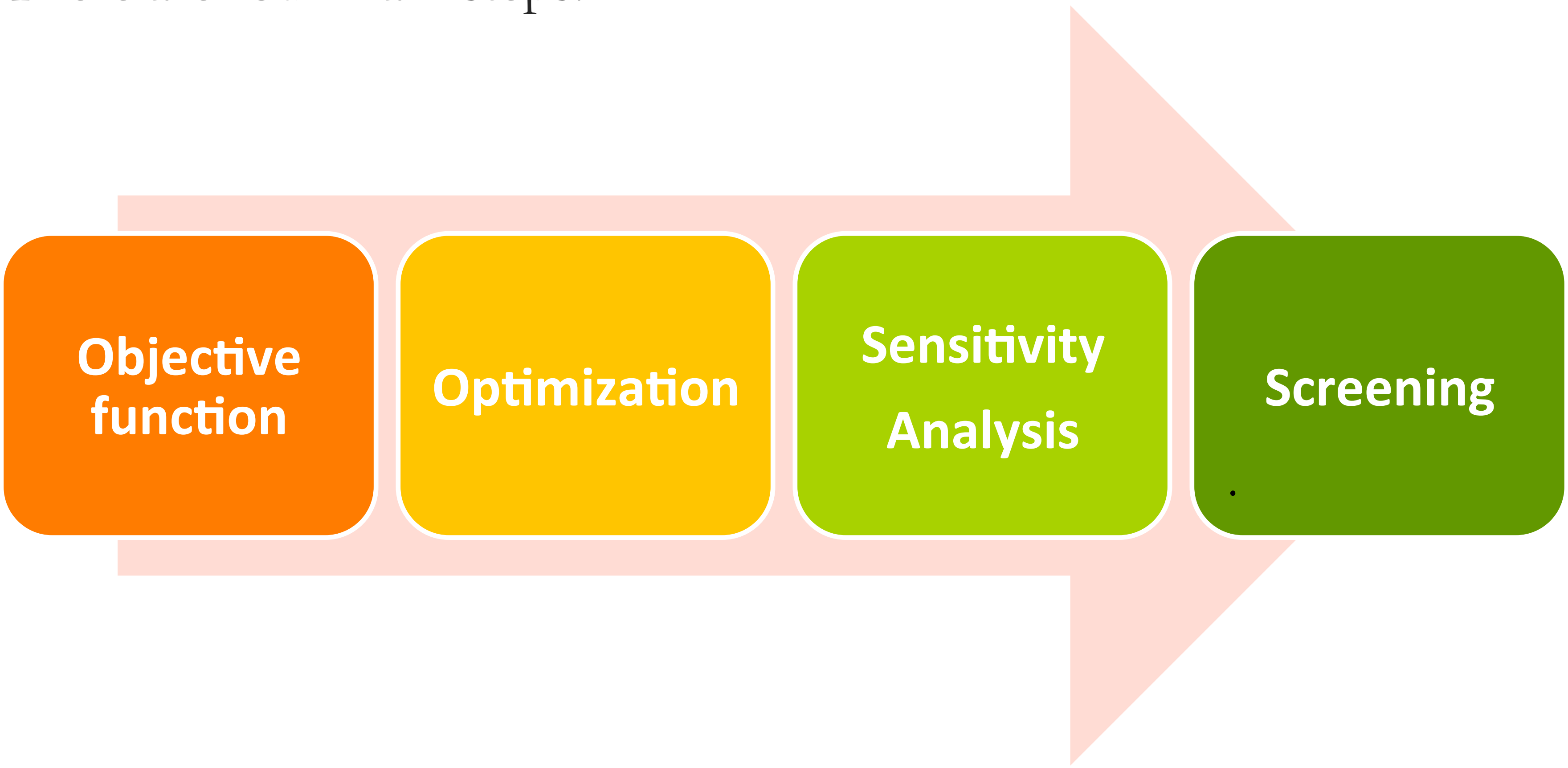
# How do we do it?

**THE PROBLEM:**

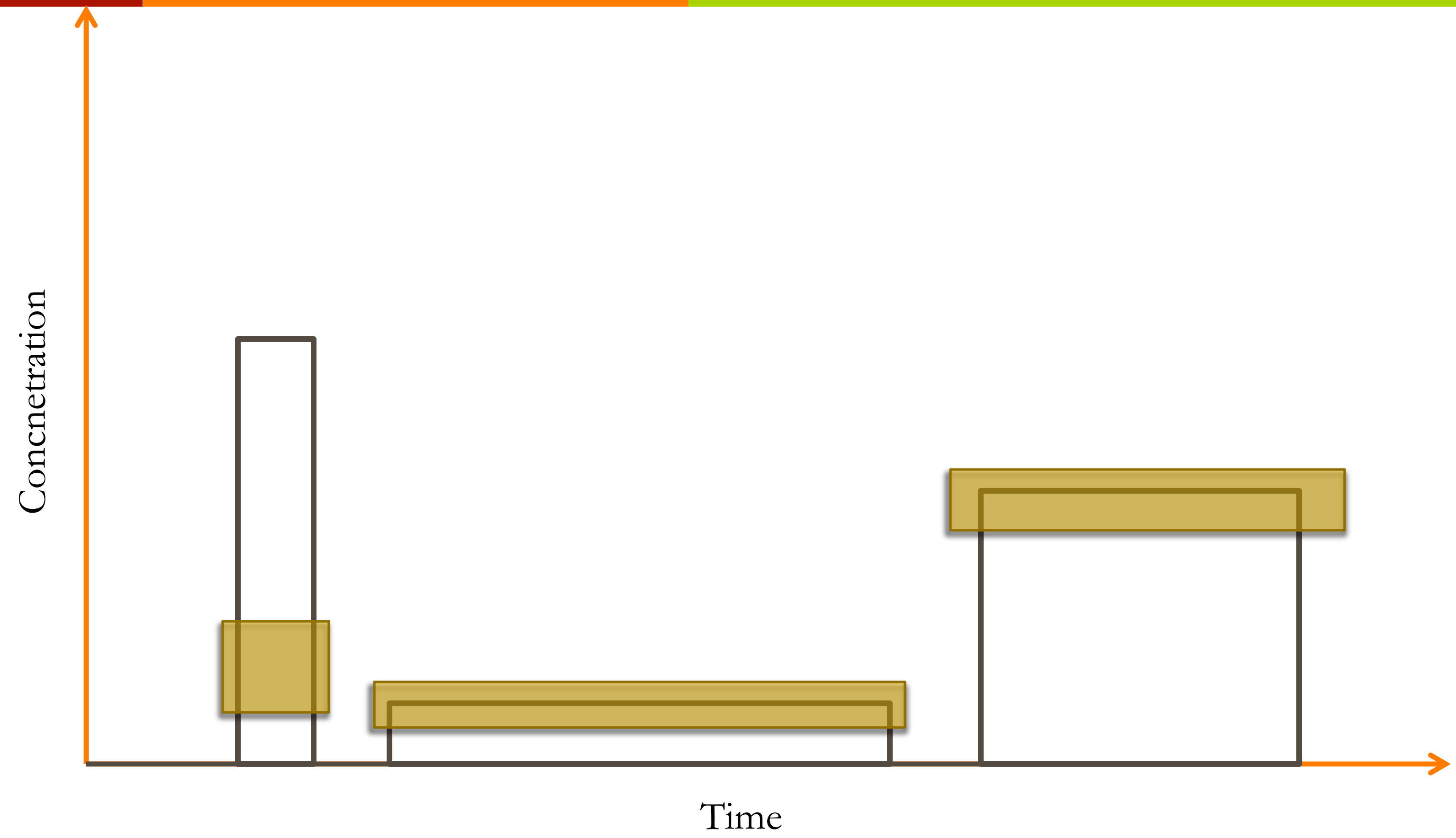
**THE PARAMETERS!!!!**

# Our strategy for choosing parameters

There are four main steps:



# Which set of parameters do we choose?

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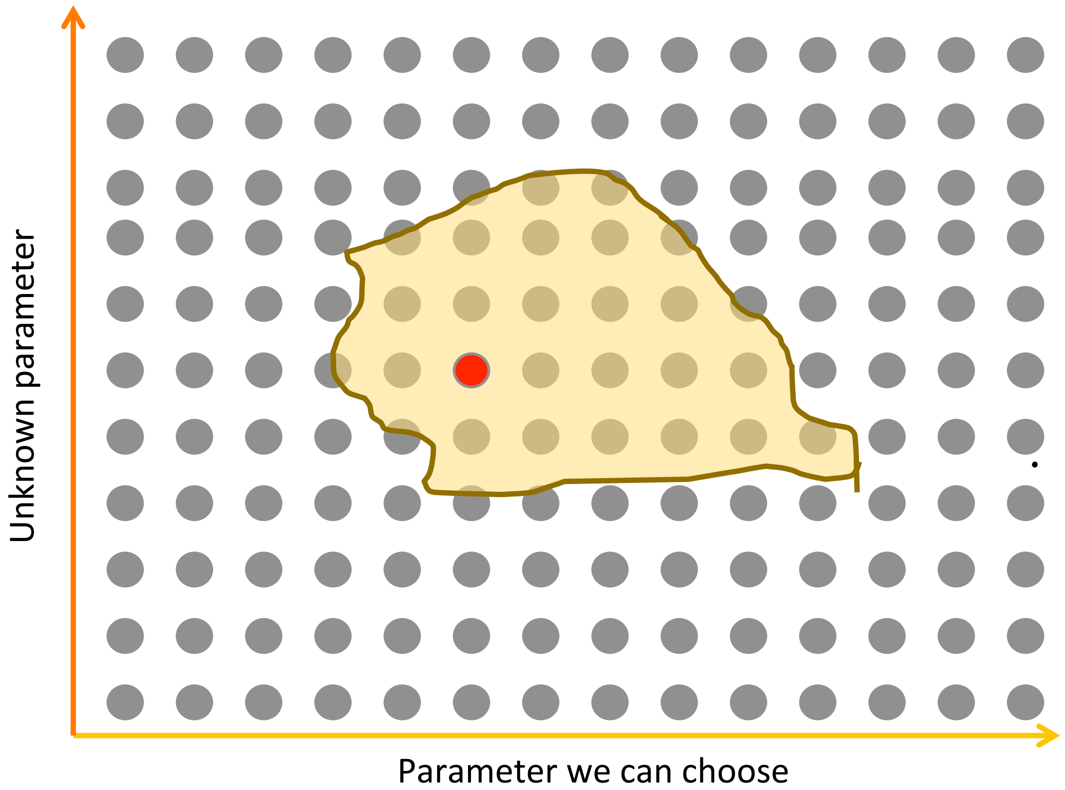
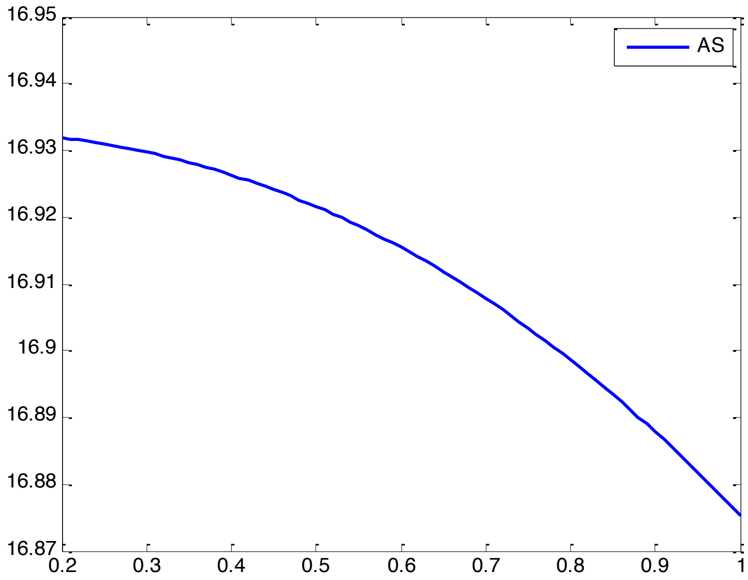
# A point within the area

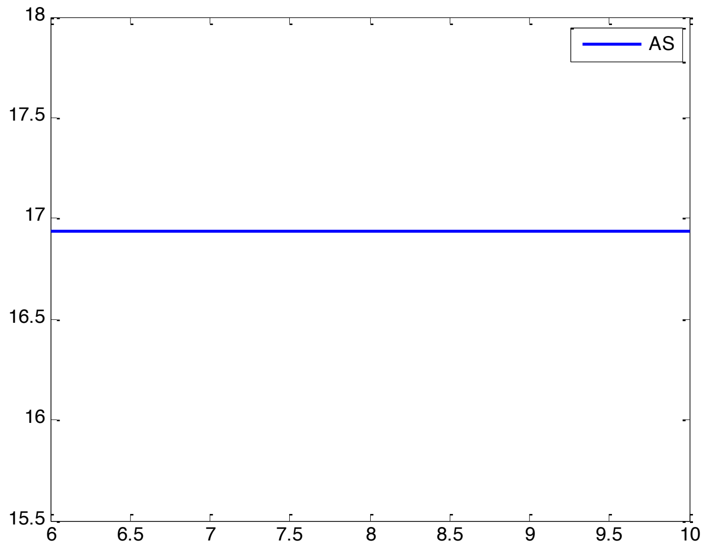


# Sensitivity analysis

How does each parameter affect the model?



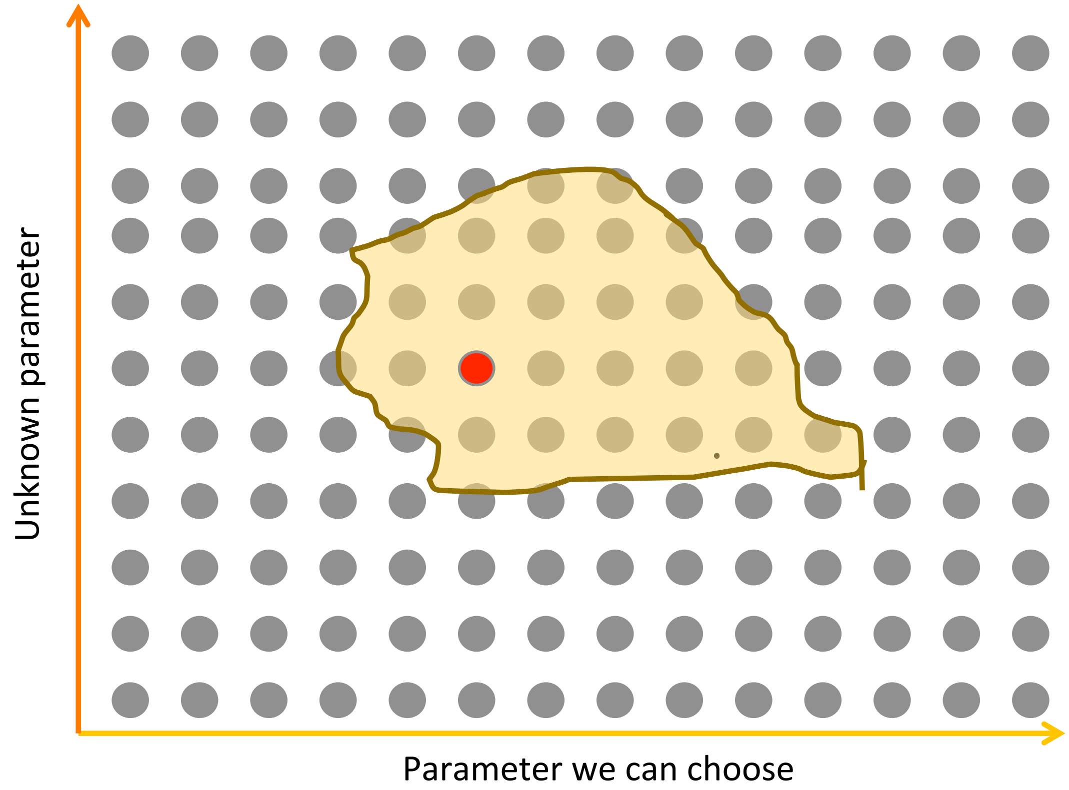

A sensitive parameter:
CI Hill constant




A non sensitive parameter:
Phoshporylation kinetic constant

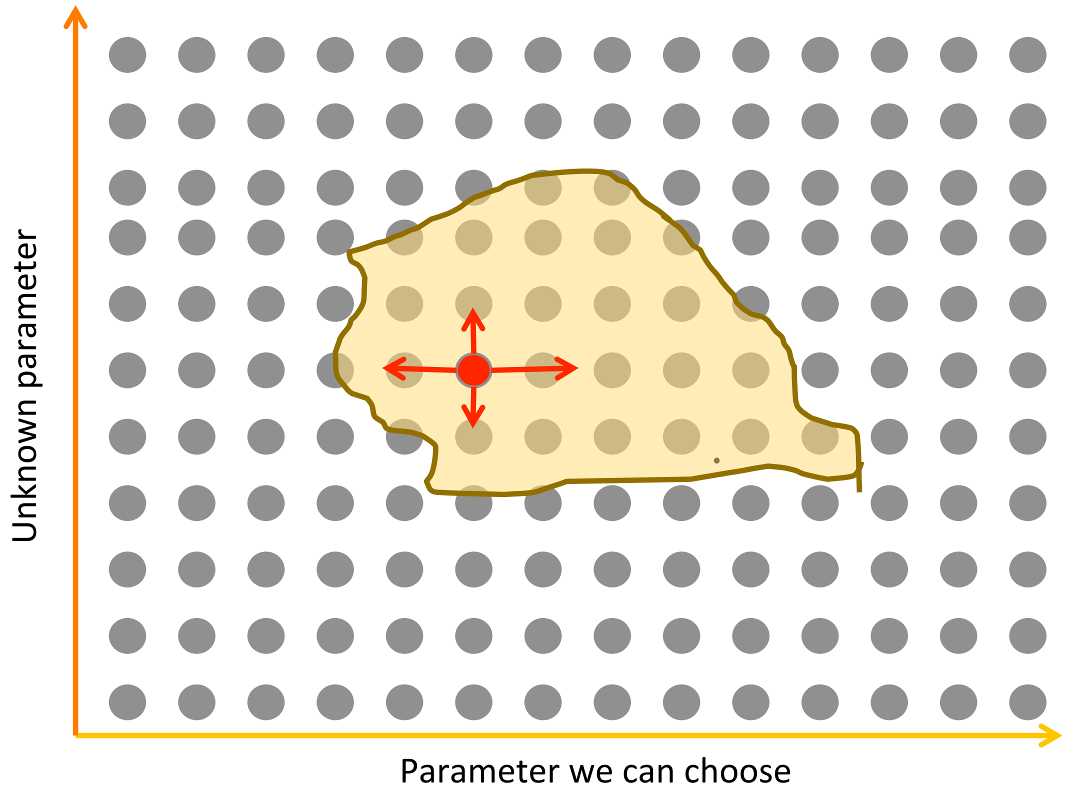
# The screening

Look for the area that represents the sets of parameters that have the expected response.



# The screening

Look for the area that represents the sets of parameters that have the expected response.



# The screening