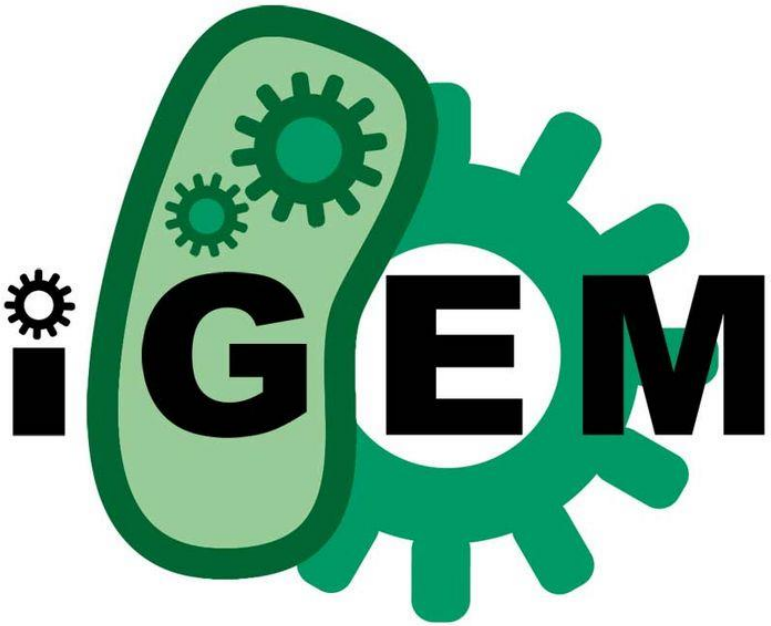
Deterministic model

iGEM2013



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

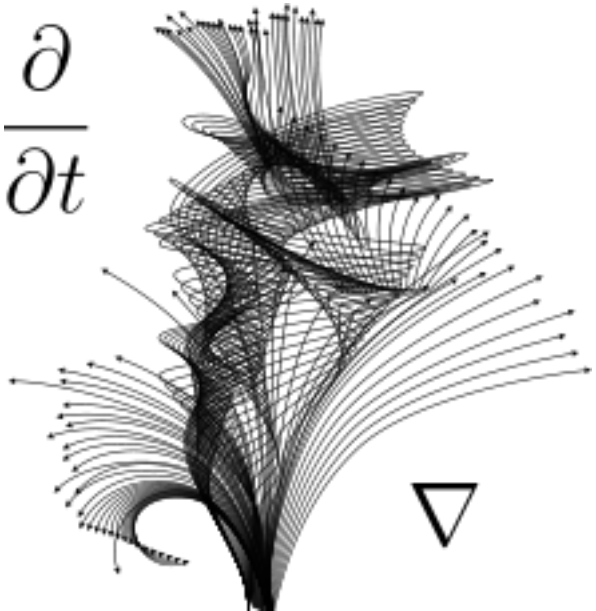
Sensibility analysis

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:

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C} + \mathrm{D}$$

Reaction rate

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

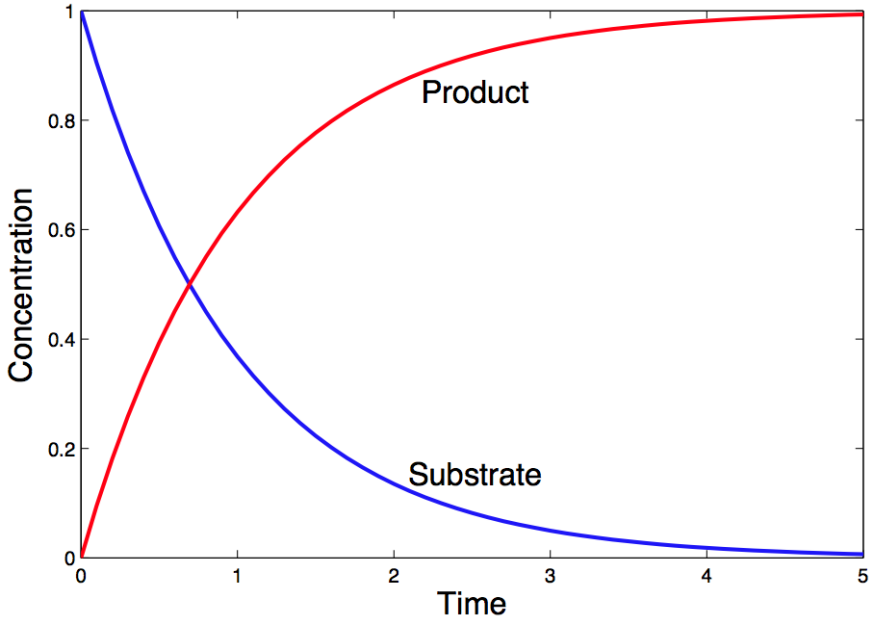
How do we do it?

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

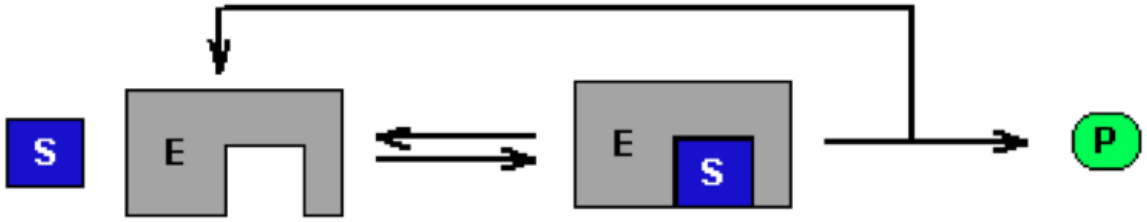


Figure 8: Michaelis-Menten mechanism.

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

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...

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

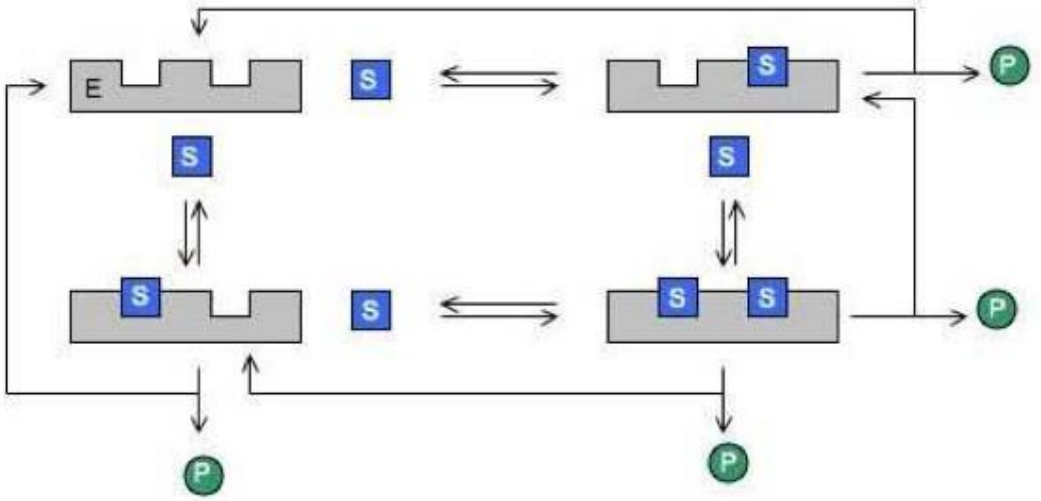
$$\begin{cases} \frac{dS}{dt} = -k_1 ES + k_{-1} C \\ \frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C \\ \frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C \\ \frac{dP}{dt} = k_2 C \end{cases}$$

How do we do it?

Michaelis Menten

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

Hill's equation



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

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

Figure 20: Enzyme with two binding sites: mechanism.

Cooperation

Hill's equation

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

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

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

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

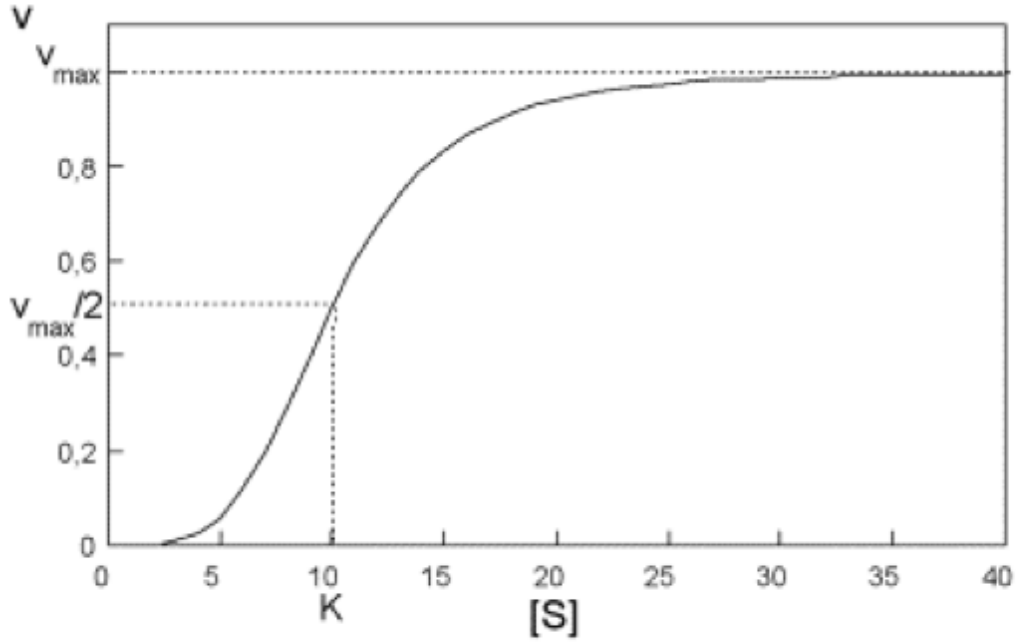


Figure 22: Hill kinetics.

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

How do we do it?

Hill's equation

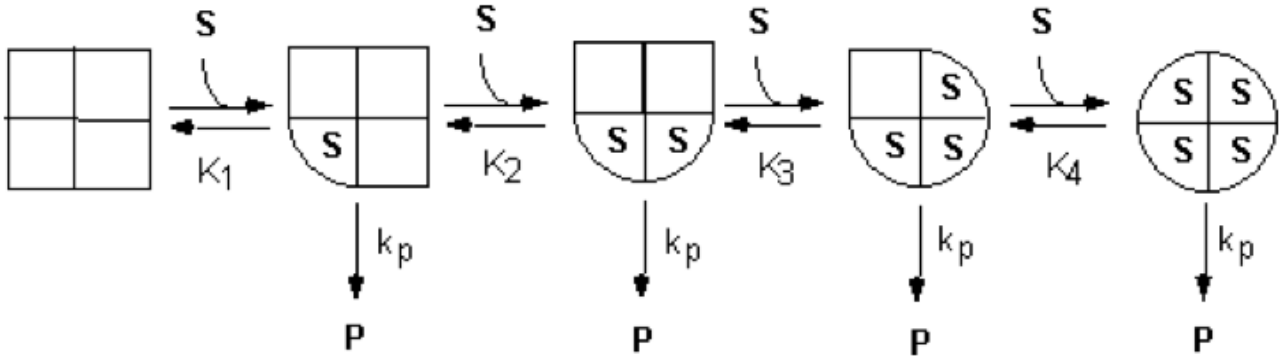
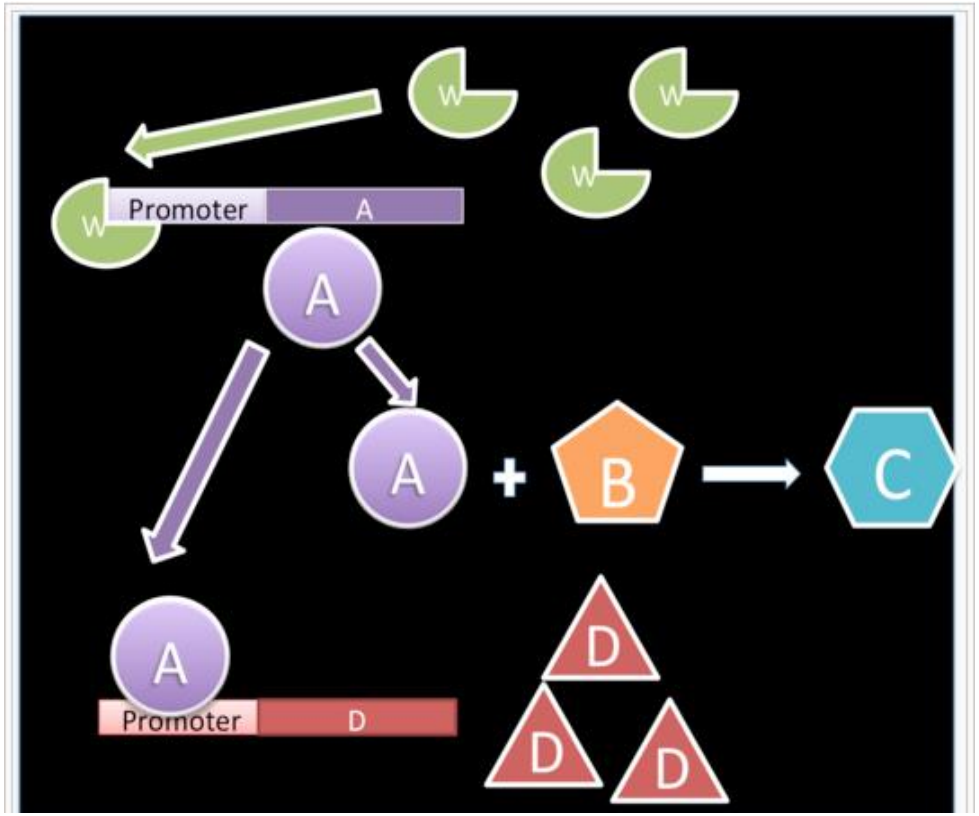


Figure 21: Cooperativity: mechanism.

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

How do we do it?

Genetic Circuits



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

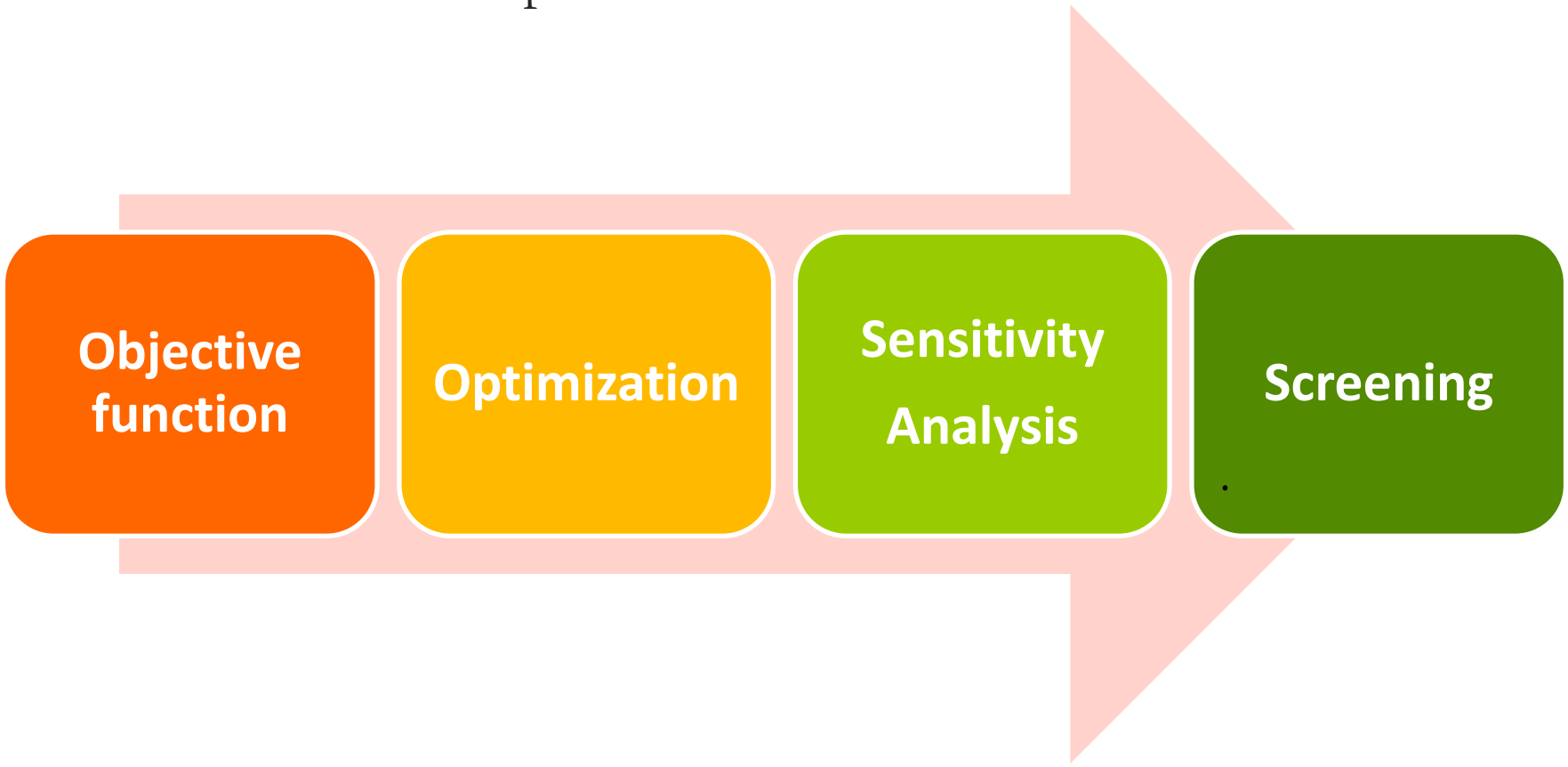
How do we do it?

THE PROBLEM:

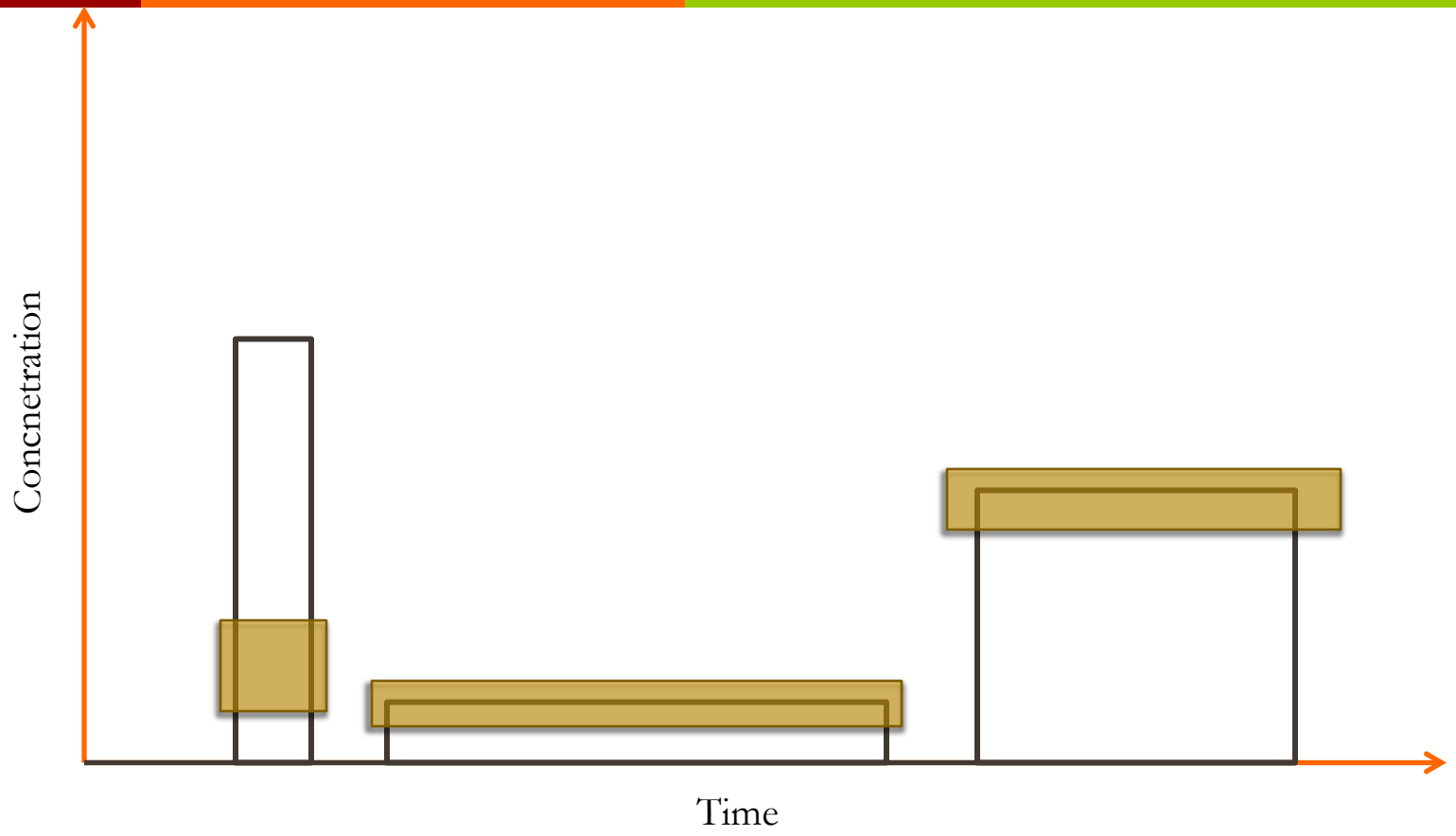
THE PARAMETERS!!!!

Our strategy for choosing parameters

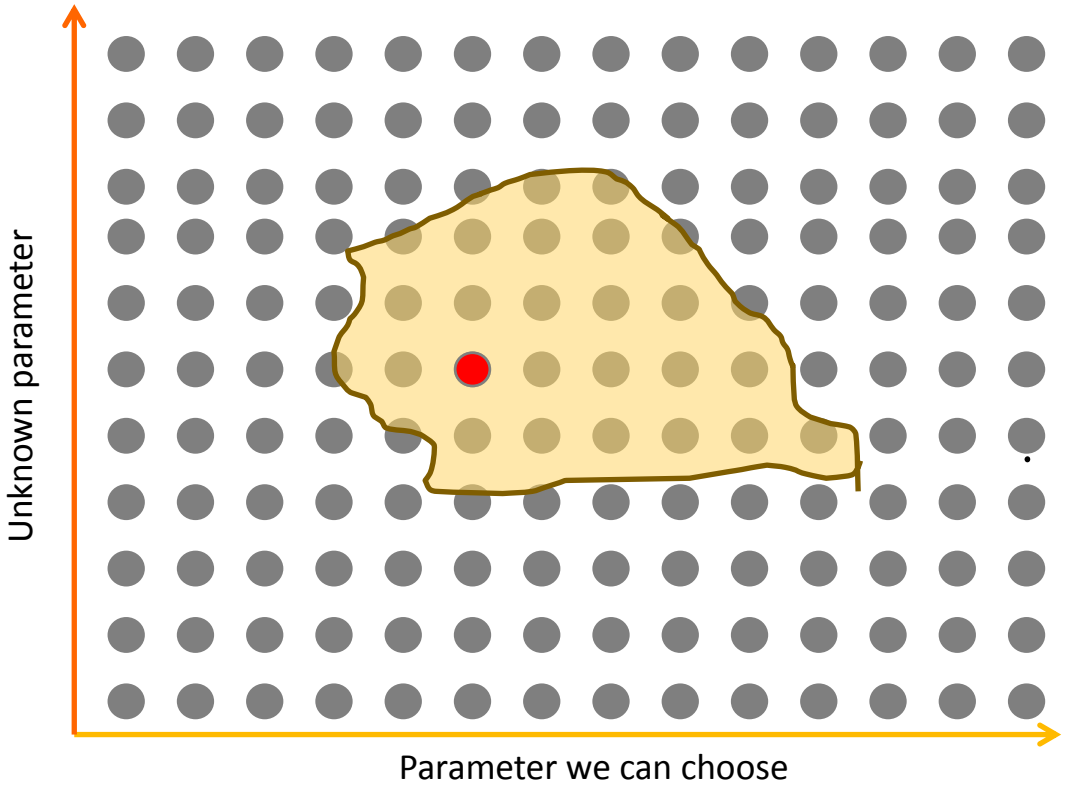
There are four main steps:



Which set of parameters do we choose?

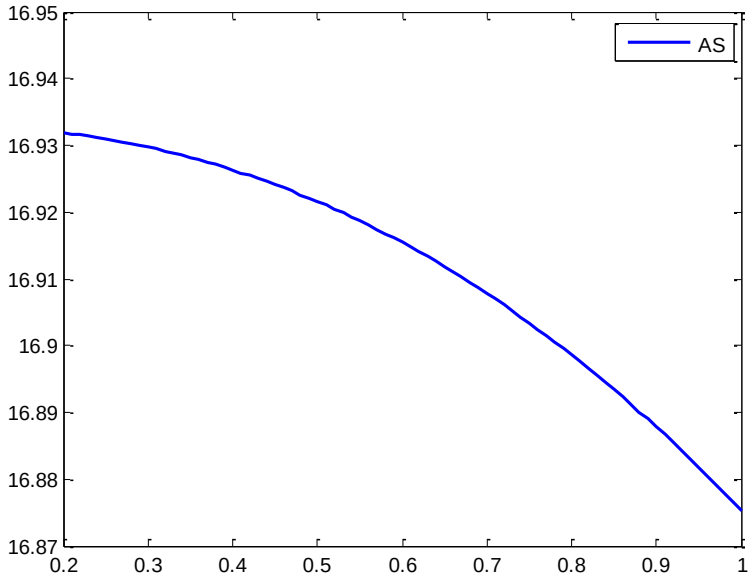


A point within the area



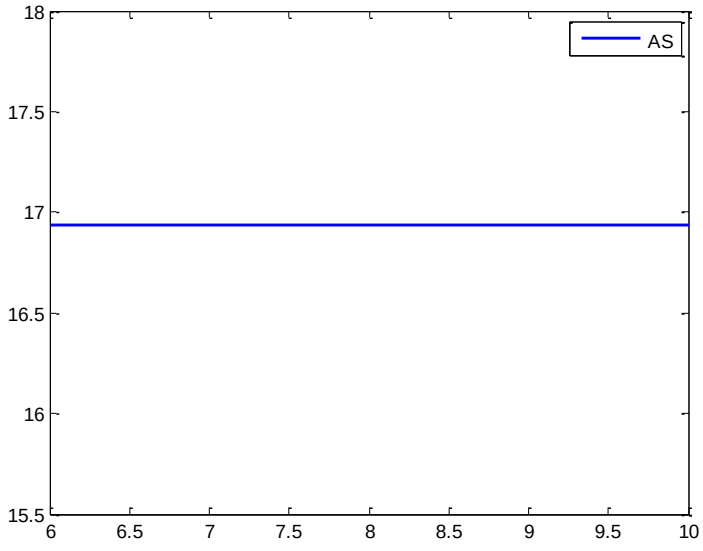
Sensitivity analysis

How does each parameter affect the model?



A sensitive parameter:

CI Hill constant

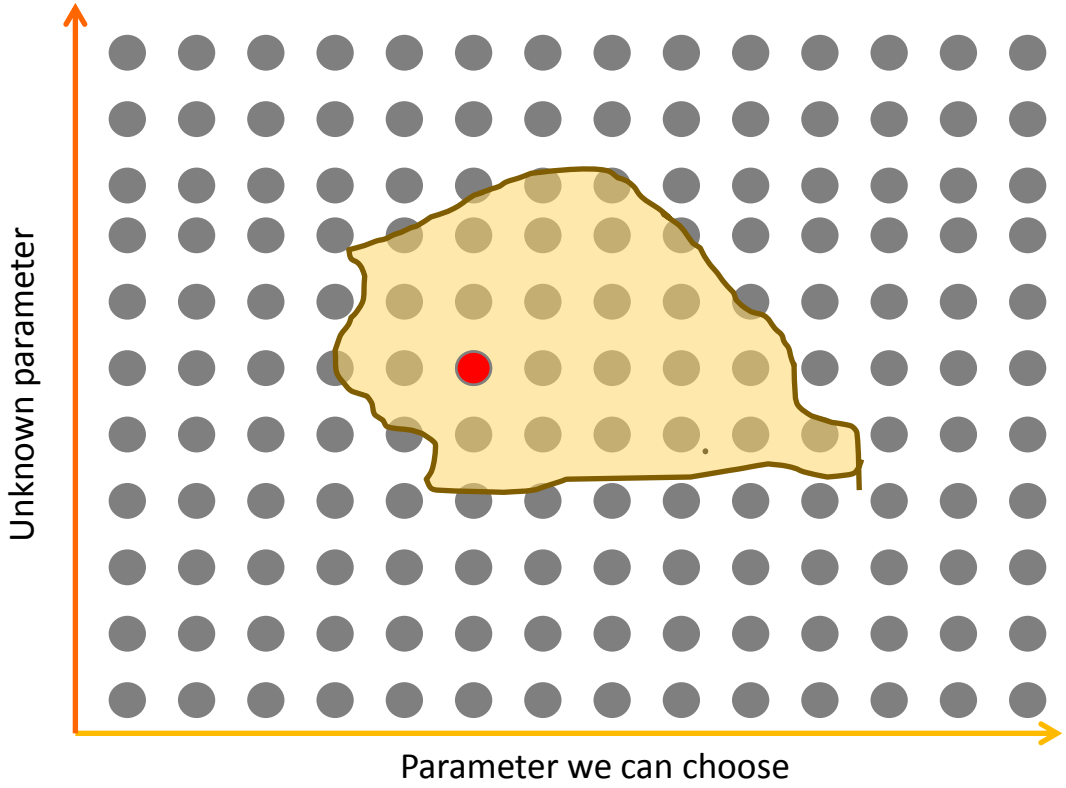


A non sensitive parameter:

Phoshporylation kinetic constant

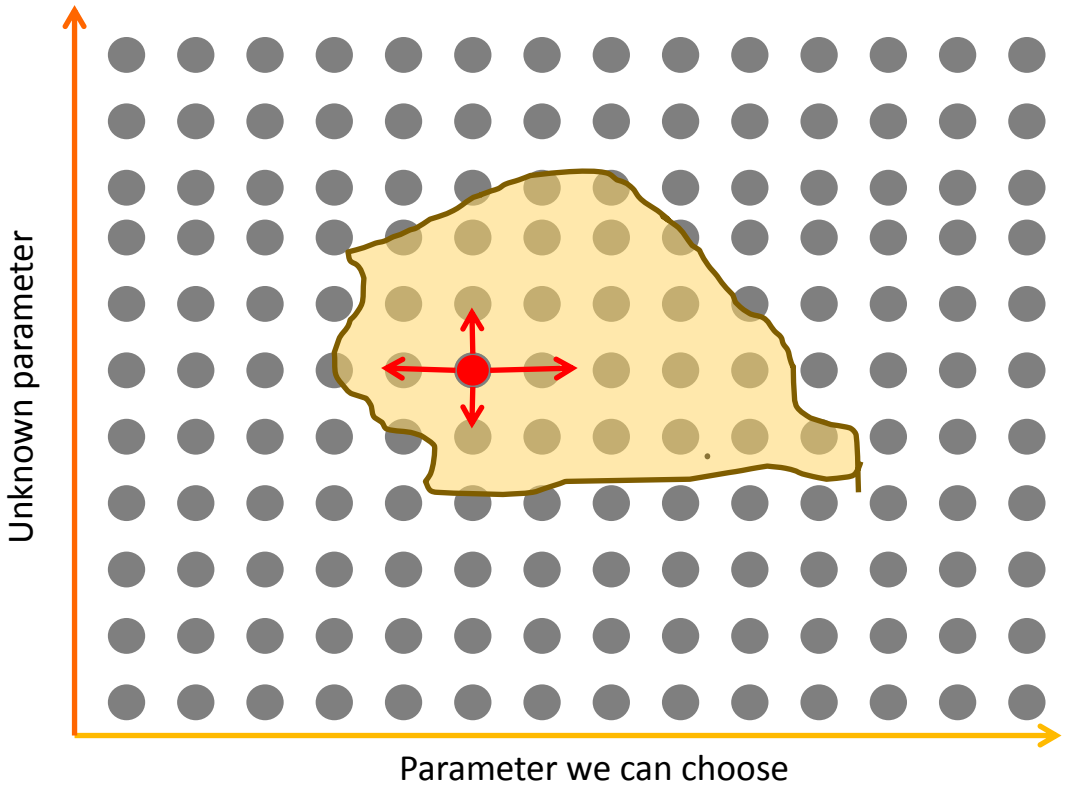
The screening

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