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Dynamical modeling of reaction networks and biased signaling. Mathematics of system biology

Romain Yvinec

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Dynamical modeling of reaction networks

Mathematics of system biology

Romain Yvinec

Systems Biology and Networks

Motivations and Objectives

Chemical reaction network formalism

Parameter estimation

Applications

Outline

Systems Biology and Networks

Motivations and Objectives

Chemical reaction network formalism

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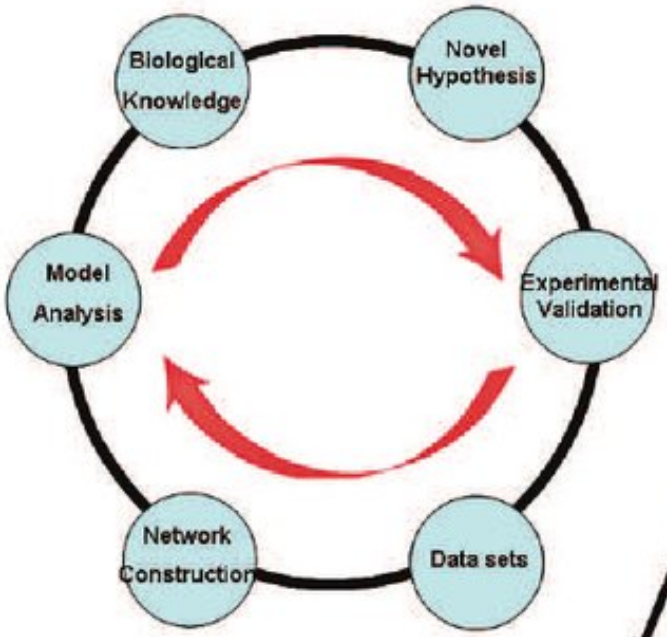
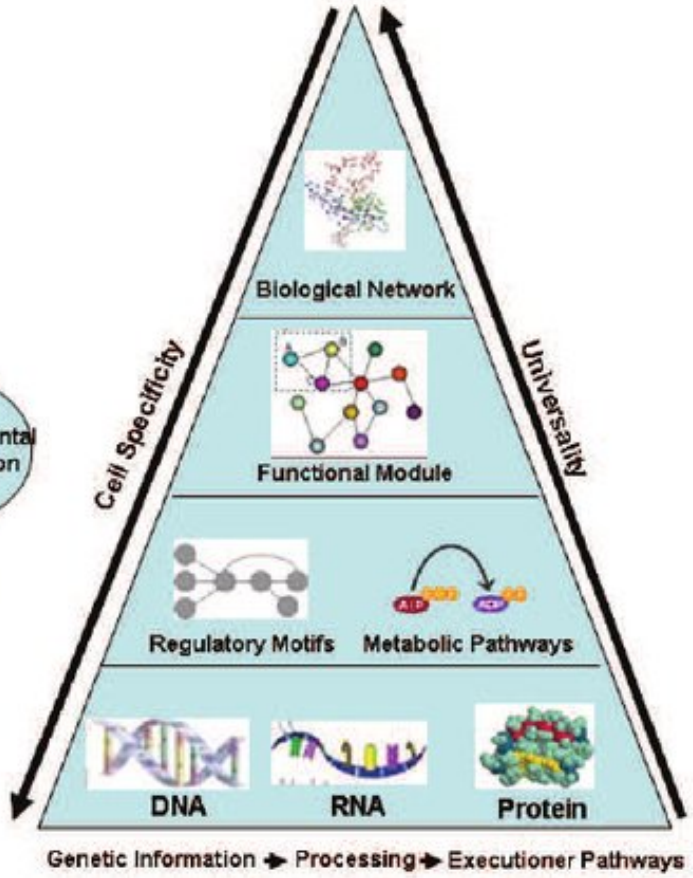




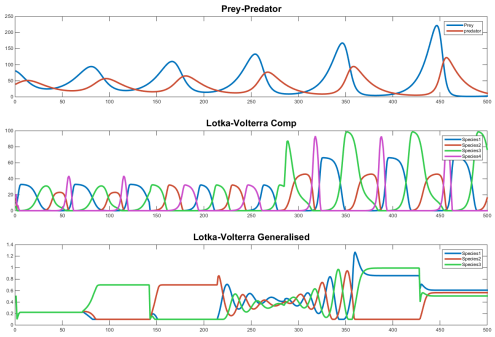
Oltvai and Barabasi, Science 25 :763-764, 2002.

Small networks in Population dynamics

(Interactions between populations, Epidemiology)

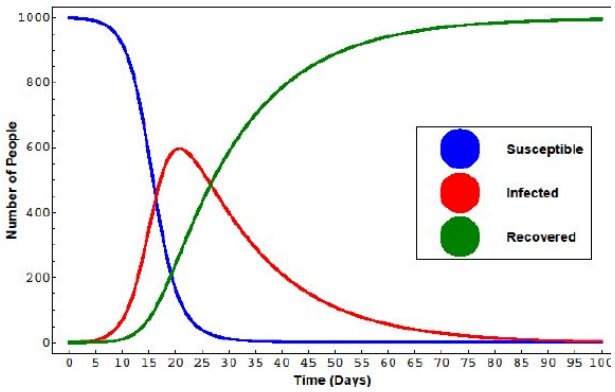
Lotka-Volterra model

$$\begin{aligned} \varnothing &\xrightarrow{k_1} A \\ A + B &\xrightarrow{k_2} 2B \\ B &\xrightarrow{k_3} \varnothing \end{aligned}$$



S.I.R model

$$\begin{aligned} S + I &\xrightarrow{k_1} I + I \\ I &\xrightarrow{k_2} R \end{aligned}$$

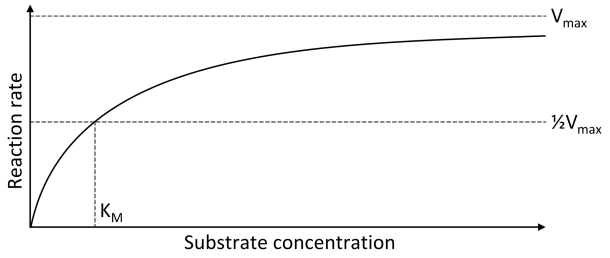


Small networks in molecular biology

('Toy' molecular models with isolated components)

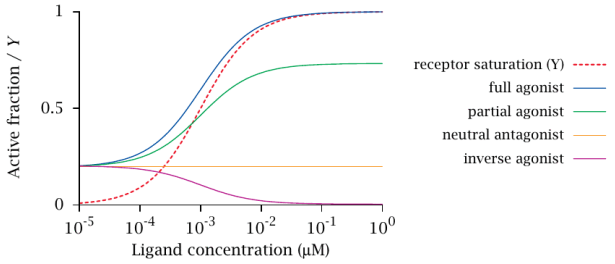
Enzymatic kinetics

$$E + S \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} E + P$$



Pharmacology model

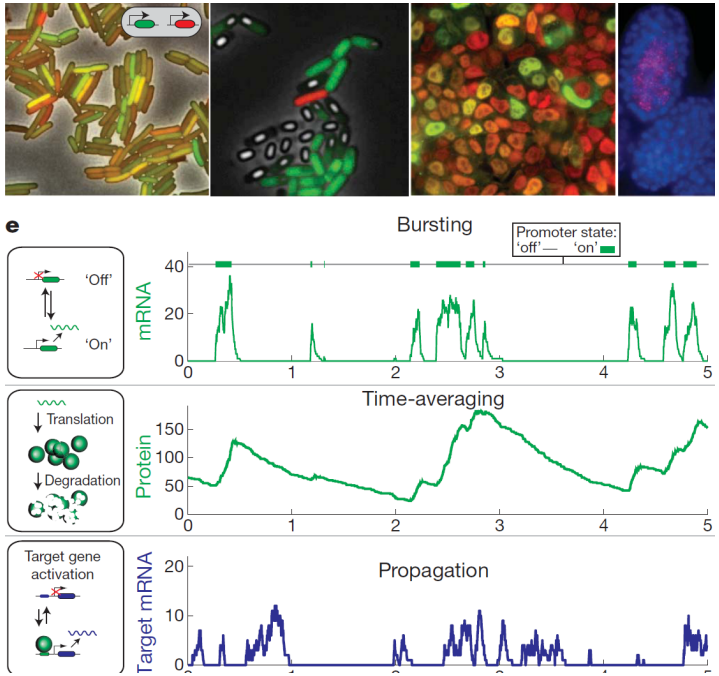
$$\begin{aligned} R_i &\rightleftarrows R_a \\ A + R_i &\rightleftarrows AR_i \\ A + R_a &\rightleftarrows AR_a \\ AR_a &\rightleftarrows AR_i \end{aligned}$$



(Single) Gene Expression

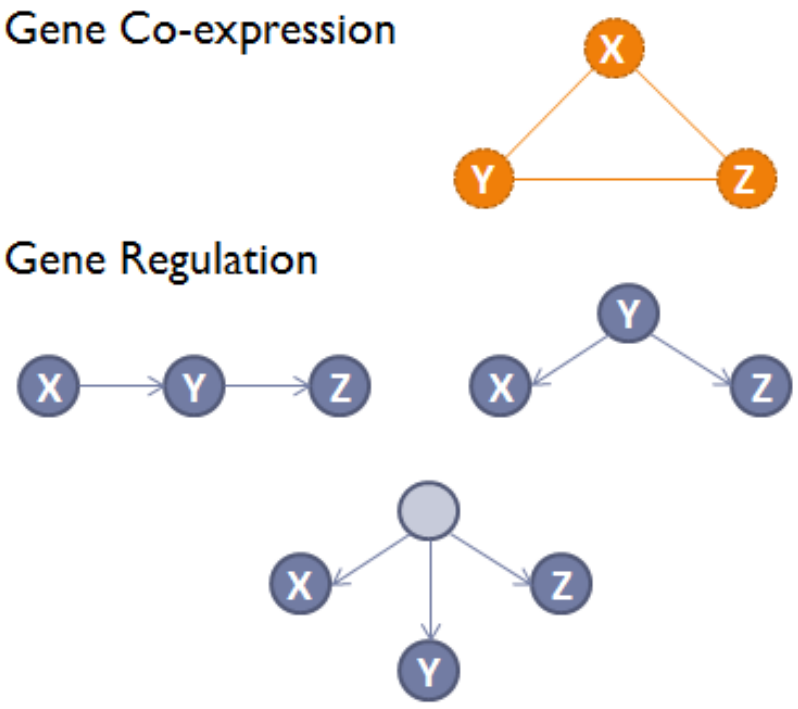
$$G \xrightarrow{\lambda_1} G + M$$
$$M \xrightarrow{\lambda_2} M + P$$
$$M \xrightarrow{\gamma_1} \emptyset$$
$$P \xrightarrow{\gamma_2} \emptyset$$
$$G \underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} G_{off}$$

Eldar and Elowitz (Nature 2010)

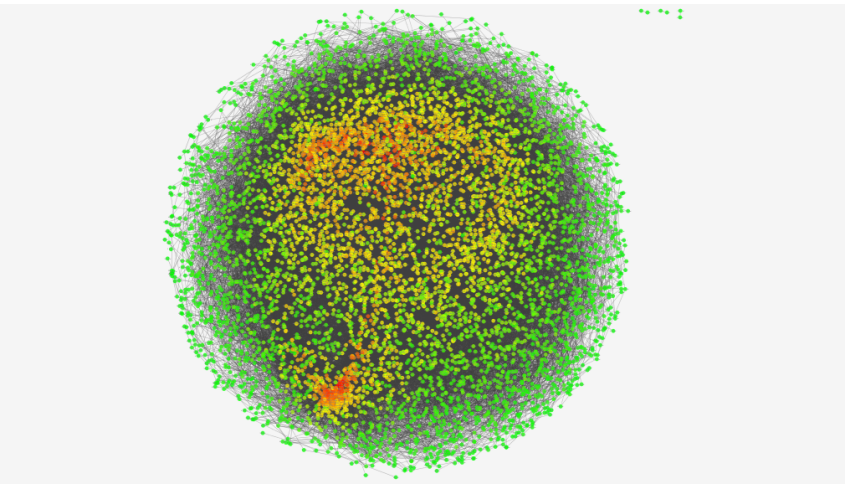


Co-expression genes network

Small motifs

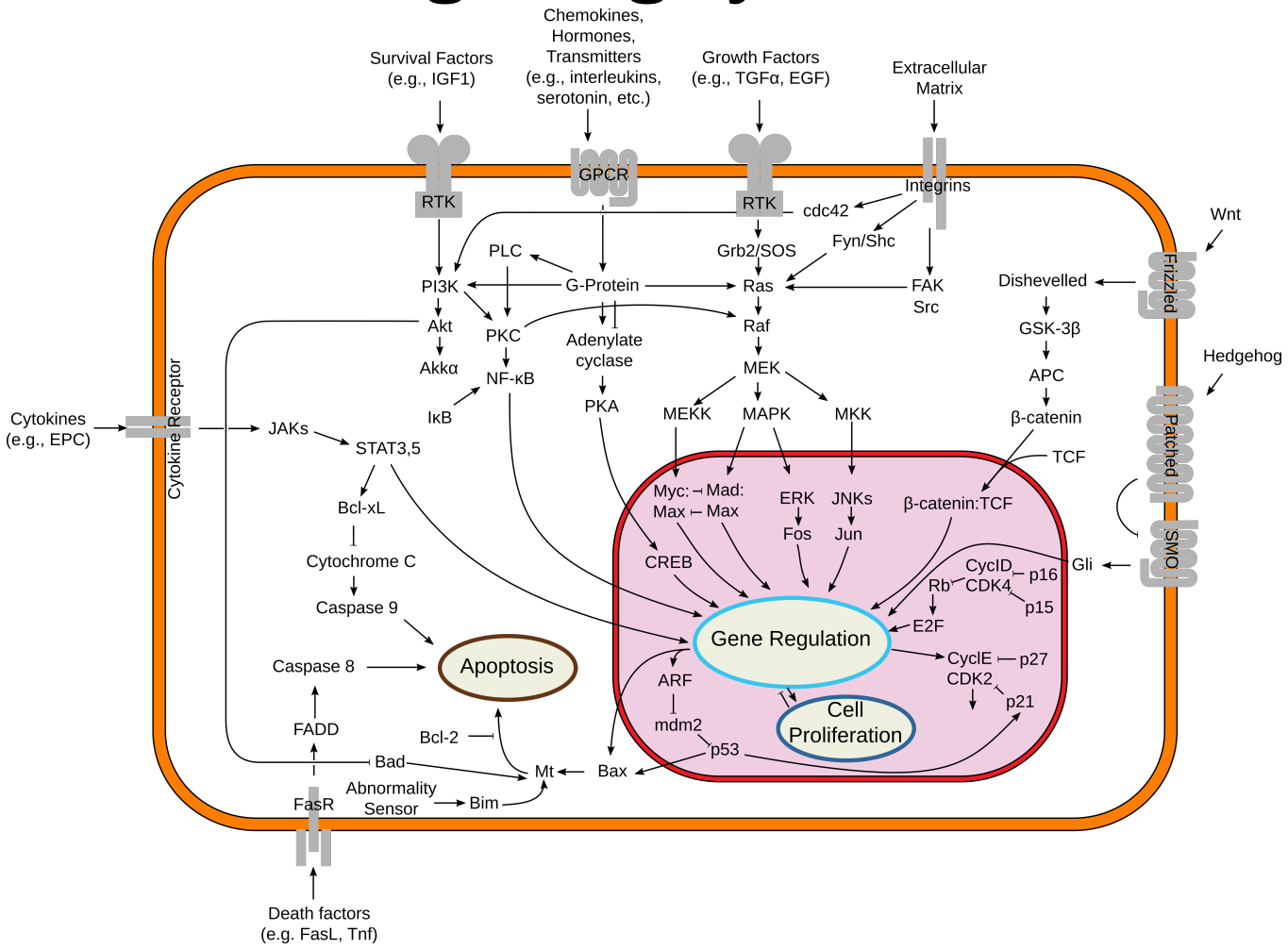


Large networks



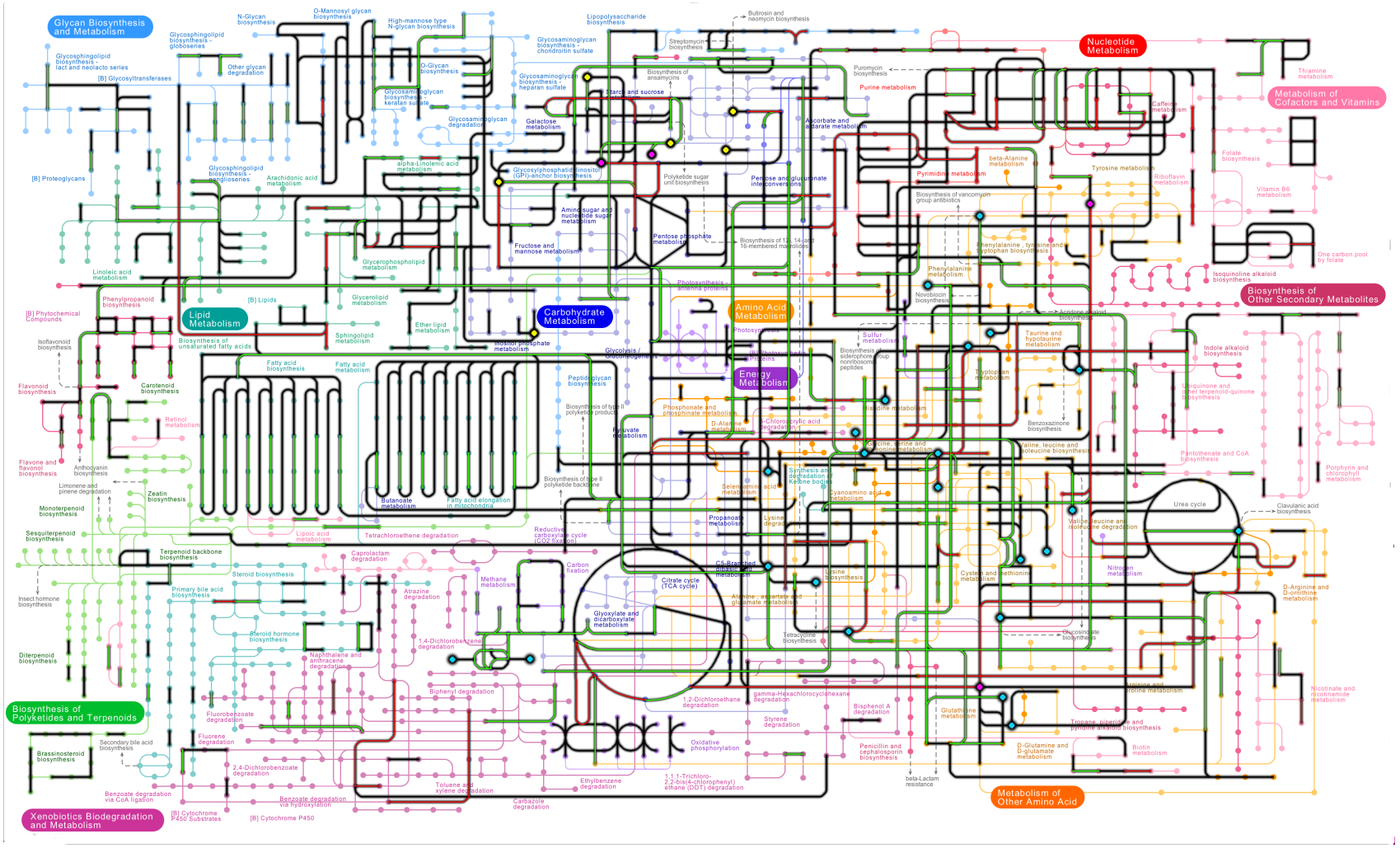
Systems Biology and Networks at different scales

Signaling system



Systems Biology and Networks at different scales

Metabolomic Network



Outline

Systems Biology and Networks

Motivations and Objectives

Chemical reaction network formalism

Parameter estimation

Applications

Possible applications of mathematical modelling

- Understand non-trivial behavior of a biological system (by reproducing this behavior with an understandable model, starting from 'first principles')
- Help to identify key regulatory process in signaling cascades
- Quantify some non-observables quantities, in particular : molecules concentrations, reaction rates.

Possible applications of mathematical modelling

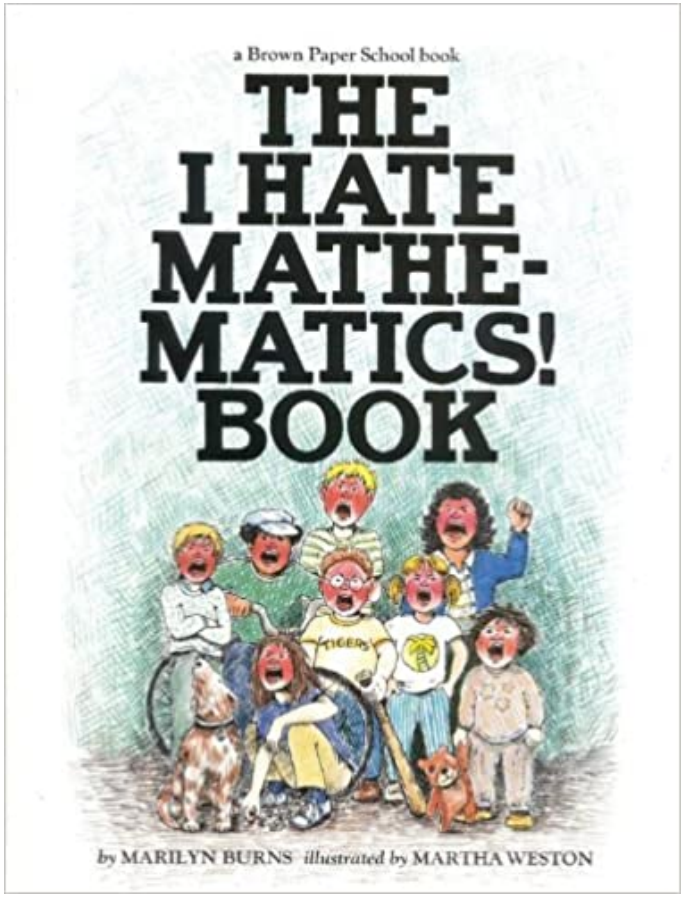
Today : Understand the mathematical formalism of dynamical reactions network

Possible applications of mathematical modelling

Today : Understand the mathematical formalism of dynamical reactions network

- Build a model from a network of interactions [Cell Designer]
- Parameter calibration with kinetic data [GraphPad Prism / Copasi]

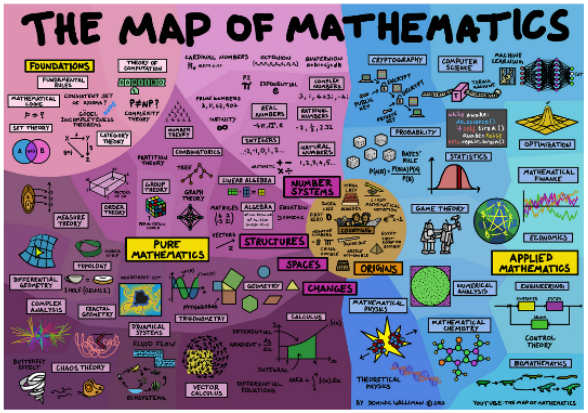
Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...
Why that ?

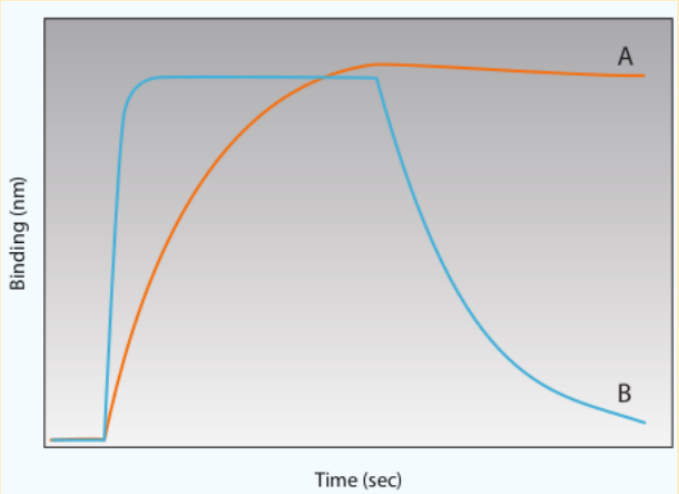
Maths is about structures...and is generic !



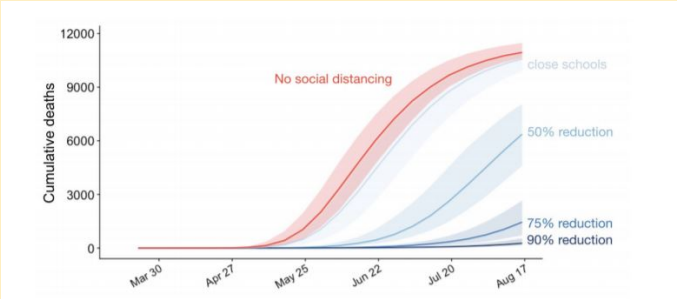
Reactions networks applications range from

- Chemistry
- molecular biology
- epidemiology
- and beyond !

Binding experiments



Covid-19 models



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Chemical Reaction Network, vocabulary

Definition

A chemical reaction network is given by thee sets $(\mathcal{S}, \mathcal{C}, \mathcal{R})$:

- Species, $\mathcal{S} := \{S_1, \cdots, S_d\}$: molecules that undergo a serie of chemical reactions.
- Reactant / Product, $\mathcal{C} := \{y^1, \cdots y^n\}$: Linear combination of species, that represent either 'what is consumed', or 'what is produced', in any reaction.
- Reaction, $\mathcal{R} := \{y^k \to y^{k'}, y^k, y^{k'} \in \mathcal{C}\}$: ensemble of reactions between species or combination of species (directed graph between Reactant / Product).

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- Mass-action law, κ : a list of positive parameter (kinetic rate) for each reaction in $\mathcal{R}$

Chemical Reaction Network, vocabulary

Example

$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B$$

Species	$\mathcal{E} := \{A, B\}$
R / P	$\mathcal{C} := \{A, B\}$
Reaction	$\mathcal{R} := \{A \to B, B \to A\}$
Rate	$\{k^+, k^-\}$

Chemical Reaction Network, vocabulary

Example (minimal cAMP production model)

$$
\begin{aligned}
L + R &\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR \\
ATP + LR &\xrightarrow{k^+} cAMP + LR \\
cAMP &\xrightarrow{k^-} AMP
\end{aligned}
$$

Species $\mathcal{E} := \{L, R, LR, ATP, cAMP, AMP\}$

R / P $\mathcal{C} := \{L + R, LR, ATP + LR, cAMP + LR, cAMP, AMP\}$

Reaction $\mathcal{R} := \{L + R \to LR, LR \to L + R, ATP + LR \to cAMP + LR, cAMP \to AMP\}$

Rate $\{k_{on}, k_{off}, k^+, k^-\}$

Chemical Reaction Network, FSHR-induced cAMP signals

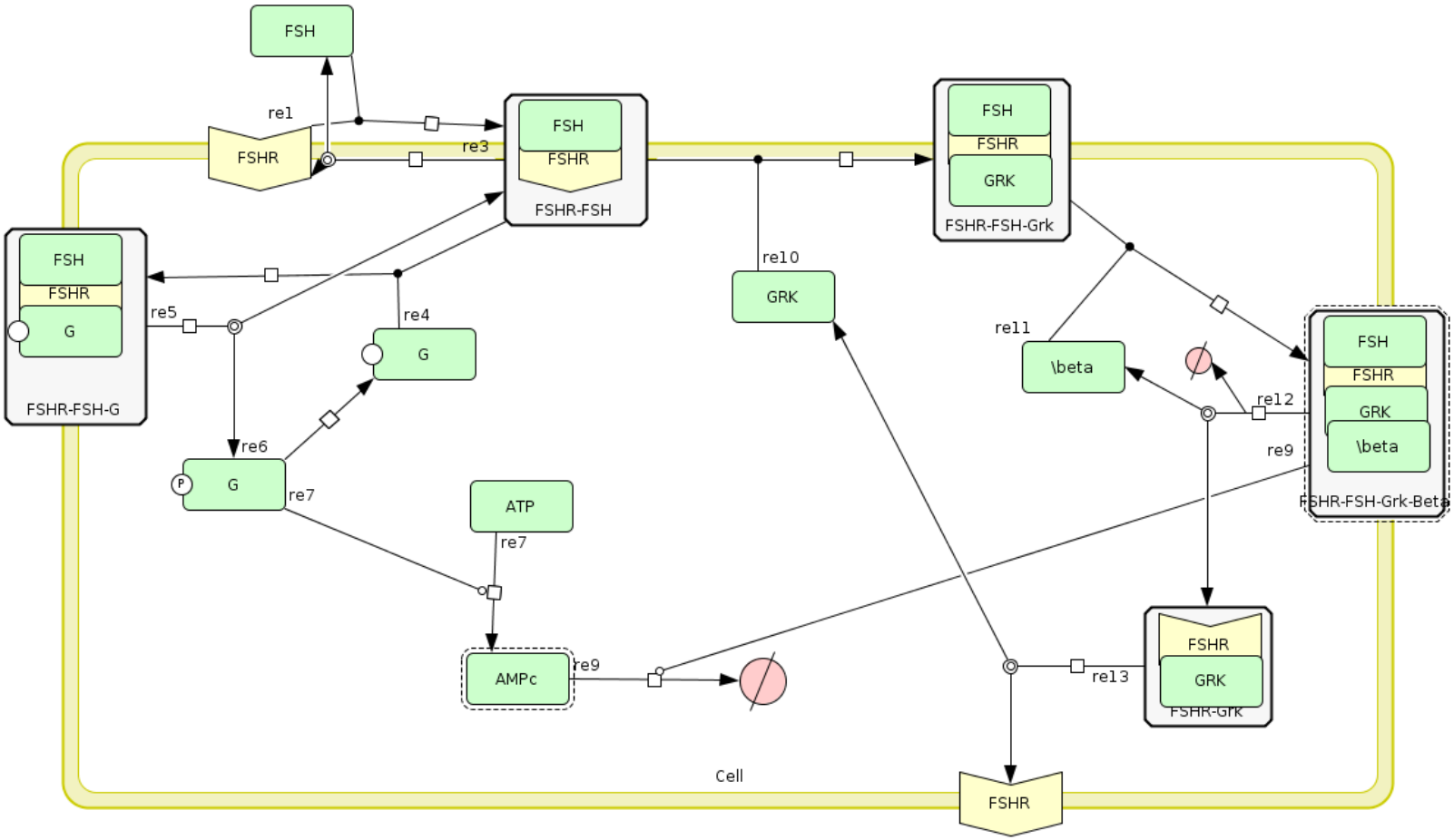
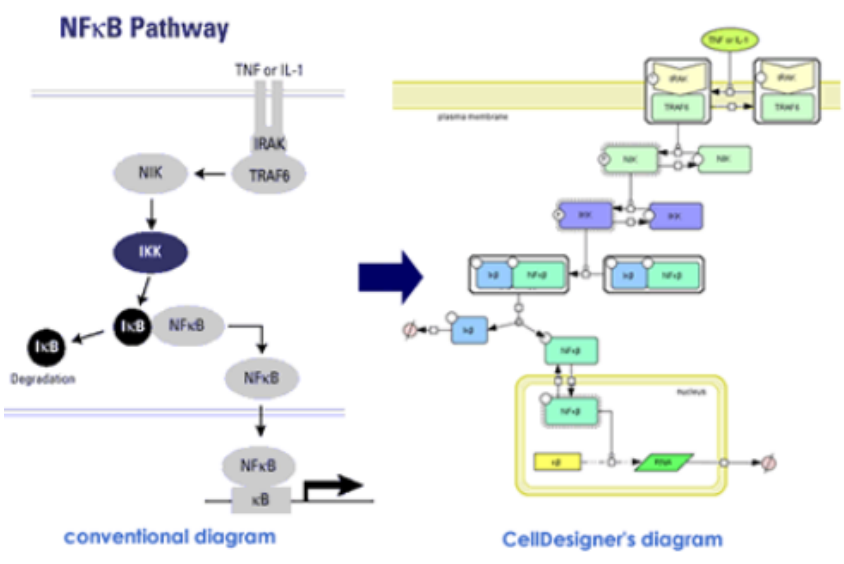


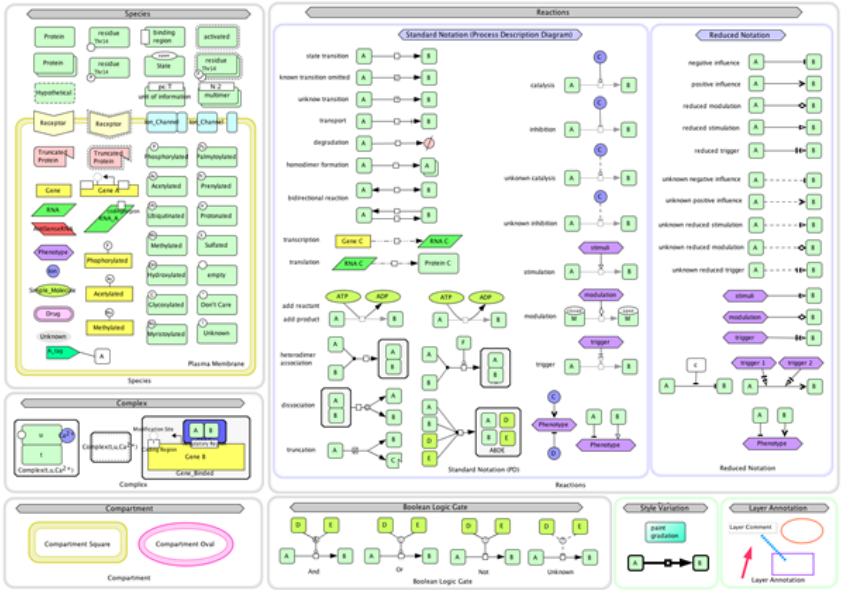
Figure – FSHR (Gαs-coupled GPCR) models build on CellDesigner

Cell Designer

About diagrams and layout...



...with well-defined conventions



Funahashi, A., Tanimura, N., Morohashi, M., and Kitano, H., CellDesigner : a process diagram editor for gene-regulatory and biochemical networks, BIOSILICO, 1 :159-162, 2003

Chemical Reaction Network, "real" example

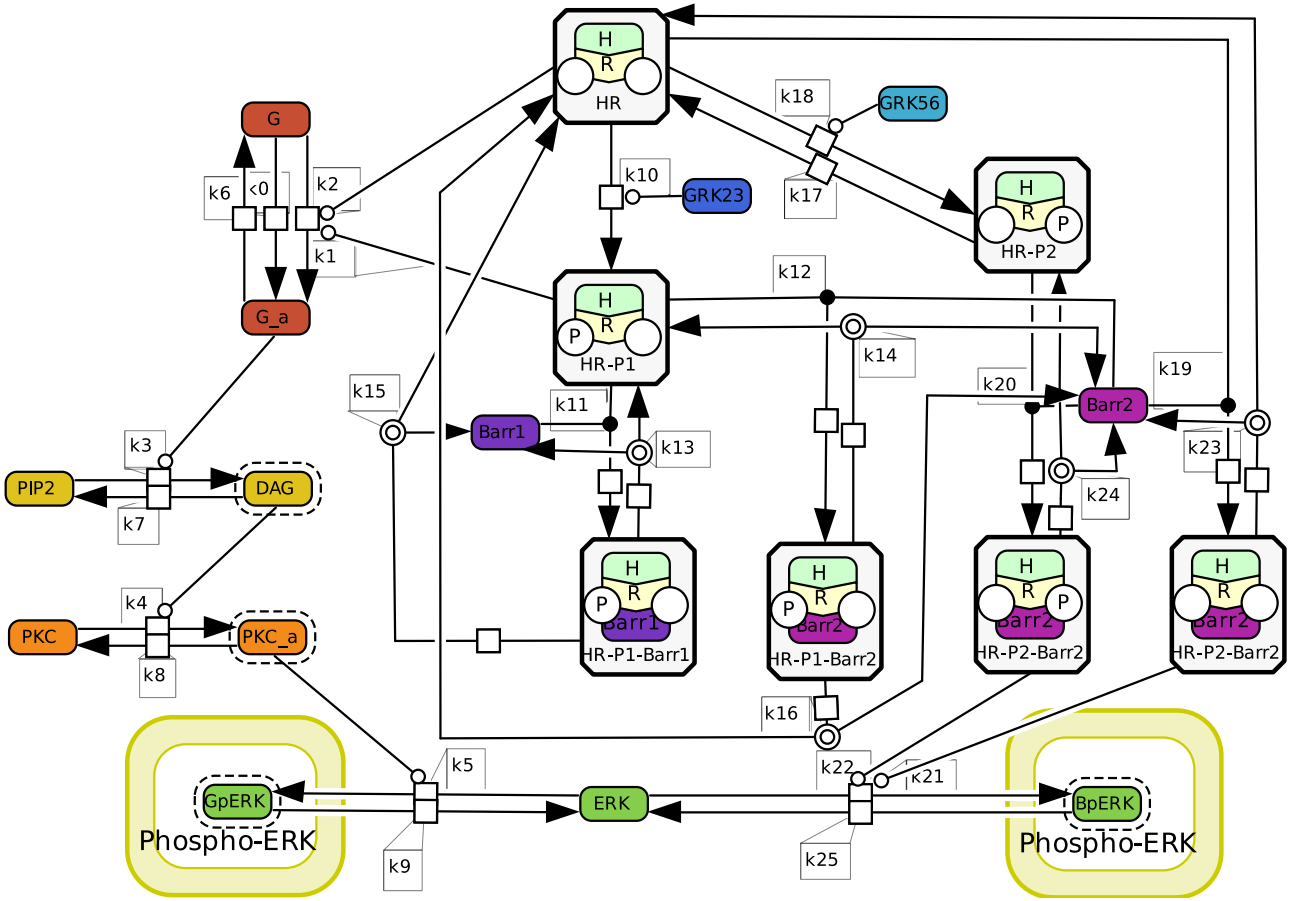


Figure – ERK Phosphorylation pathways build on CellDesigner, Heitzler et al. MSB 2012

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

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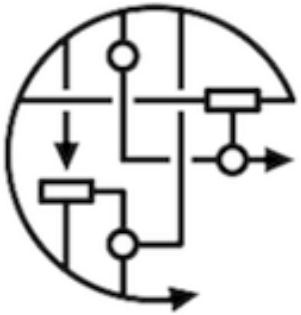
NB : there exists public databases of reaction network models.



BioModels

Pathguide » the pathway resource list

KEGG NETWORK Database

From gene variation to network variation

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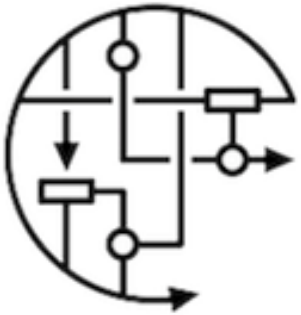

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KEGG NETWORK Database

From gene variation to network variation

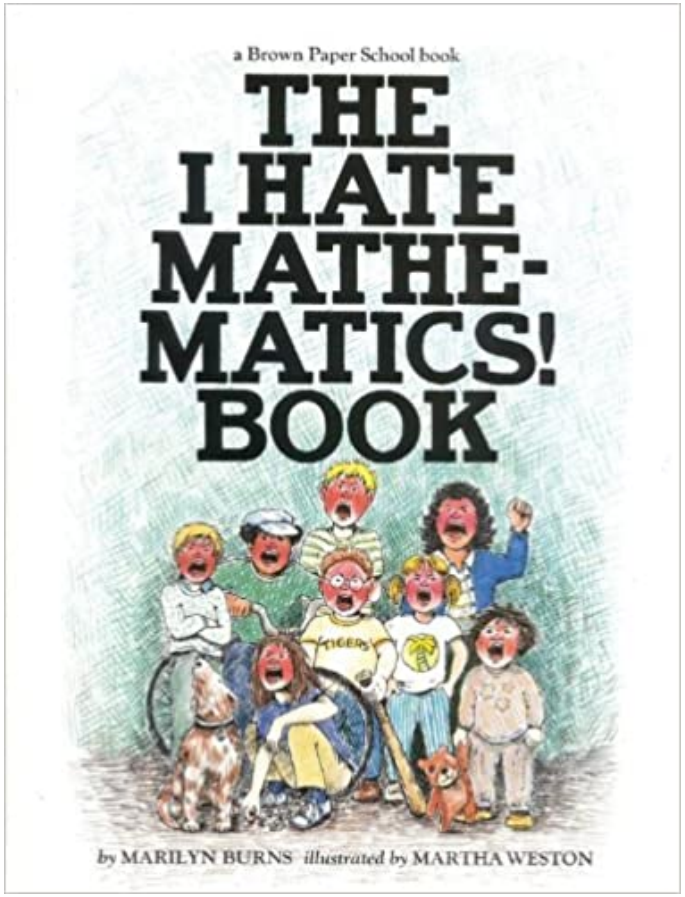
NB (bis) : A reaction network is a network... but a network is **NOT** a reaction network !

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer
- **What about dynamics ?**

Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...let's try to catch the meaning !

Chemical Reaction Network and Dynamical models

We build a model that

- Keep track of concentration of species along time.
- Satisfy Law of Mass action : The velocity of a reaction is proportional to the concentrations of its reactants.
- Is a system of Ordinary Differential Equations, in which reactions are "added" on top of each other, e.g. they happens continuously and simultaneously.

Chemical Reaction Network and Dynamical models

Example

$$A \underset{0.1}{\overset{2}{\rightleftharpoons}} B$$

$$\begin{aligned} \frac{dx_A}{dt}(t) &= -0.1x_A(t) + 2x_B(t)\,, \quad x_A(t=0) = A_{tot} \\ \frac{dx_B}{dt} &= +0.1x_A(t) - 2x_B(t)\,, \quad x_B(t=0) = 0 \end{aligned}$$

$x_A(t) =$ time dependent concentration of species A

Chemical Reaction Network and Dynamical models

Example

$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR$$

$$\begin{aligned}
\frac{dx_L}{dt}(t) &= -k_{on}x_L(t)x_R(t) + k_{off}x_{LR}(t)\,, \quad x_L(0) = Dose \\
\frac{dx_R}{dt}(t) &= -k_{on}x_L(t)x_R(t) + k_{off}x_{LR}(t)\,, \quad x_R(0) = R_{tot} \\
\frac{dx_{LR}}{dt}(t) &= k_{on}x_L(t)x_R(t) - k_{off}x_{LR}(t)\,, \quad x_{LR}(0) = 0.
\end{aligned}$$

Chemical Reaction Network and Dynamical models

Example (minimal cAMP production model)

$$
\begin{aligned}
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\frac{dx_{LR}}{dt} &= k_{on}x_L x_R - k_{off}x_{LR}\,, \quad x_{LR}(0) = 0 \\
\frac{dx_{cAMP}}{dt} &= k^+ x_{ATP}x_{LR} - k^- x_{cAMP}\,, \quad x_{cAMP}(0) = 0 \\
\frac{dx_{ATP}}{dt} &= -k^+ x_{ATP}x_{LR} \quad x_{ATP}(0) = ATP_{tot}\,.
\end{aligned}
$$

But what is an "Ordinary Differential Equation"? A math theory in one slide !

The equation

$$\frac{dx}{dt} = v(x)\,,$$

is numerically solved by successive time-step iteration, of small length $\Delta t \ll 1$:

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2) To calculate the value of x at the first time step, remember that *(assuming constant speed)*

$$\text{Final Position} = \text{Initial Position} + \text{velocity} * \text{Time}\,,$$

which becomes, in mathematical notations,

$$x(\Delta t) = x_0 + v(x_0) * \Delta t\,,$$

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$$x(\Delta t) = x_0 + v(x_0) * \Delta t\,,$$

Iterate : To calculate the value of x at the next time step, use

$$x((i+1) * \Delta t) = x(i * \Delta t) + v\left(x(i * \Delta t)\right) * \Delta t\,,$$

But what is an "Ordinary Differential Equation"? A math theory in one slide...and a figure!

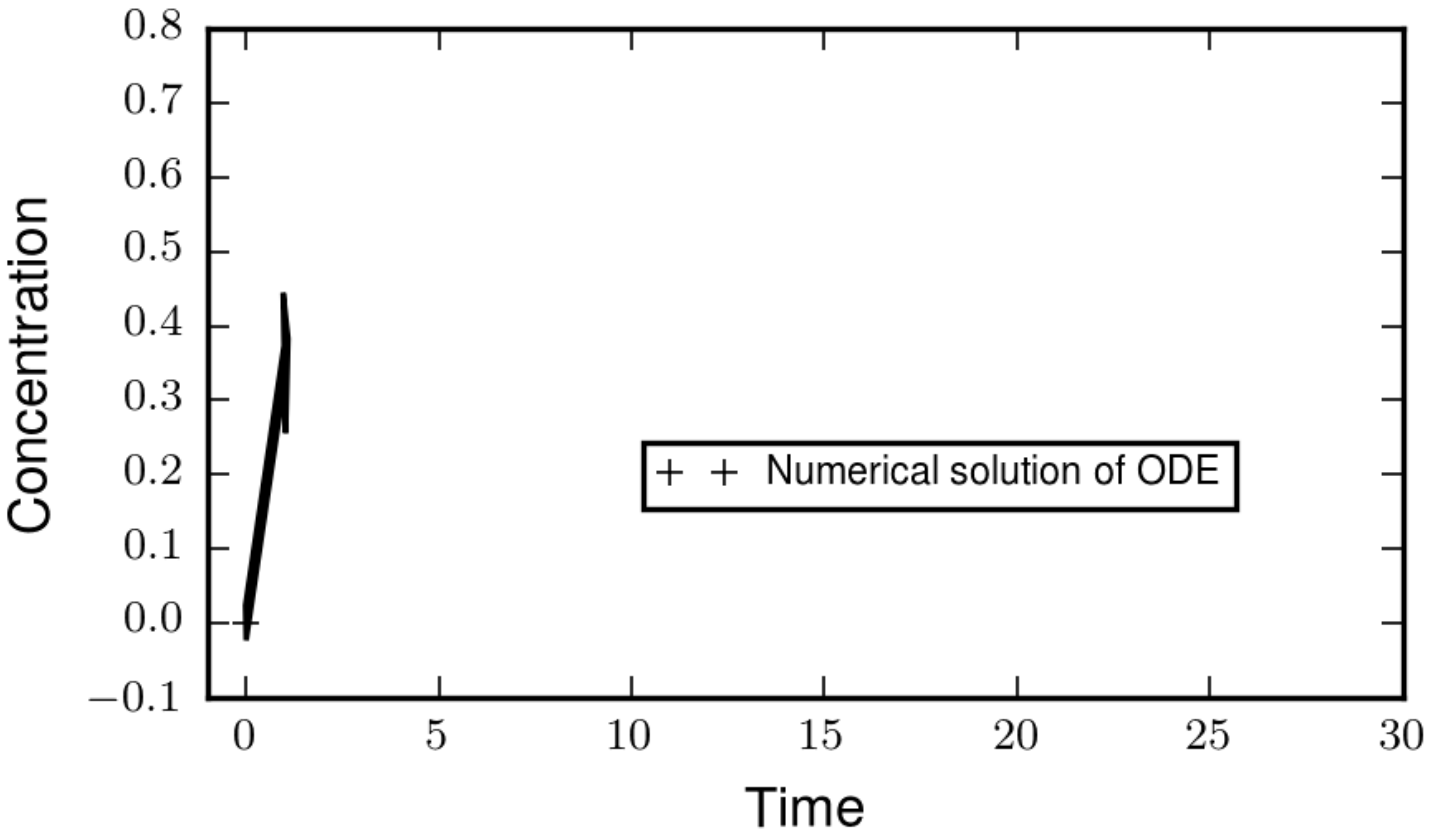

Figure – Solving an ODE

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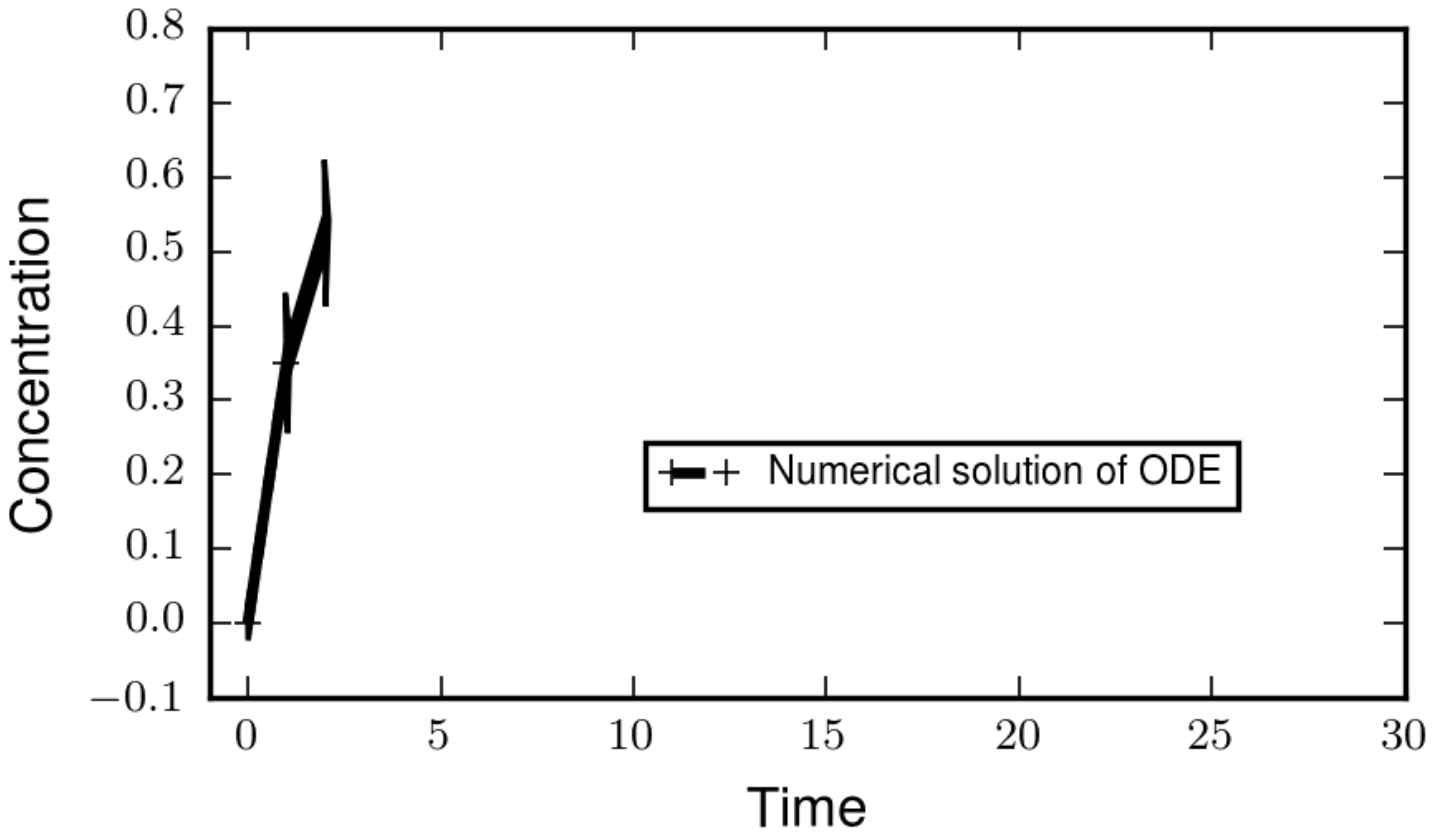

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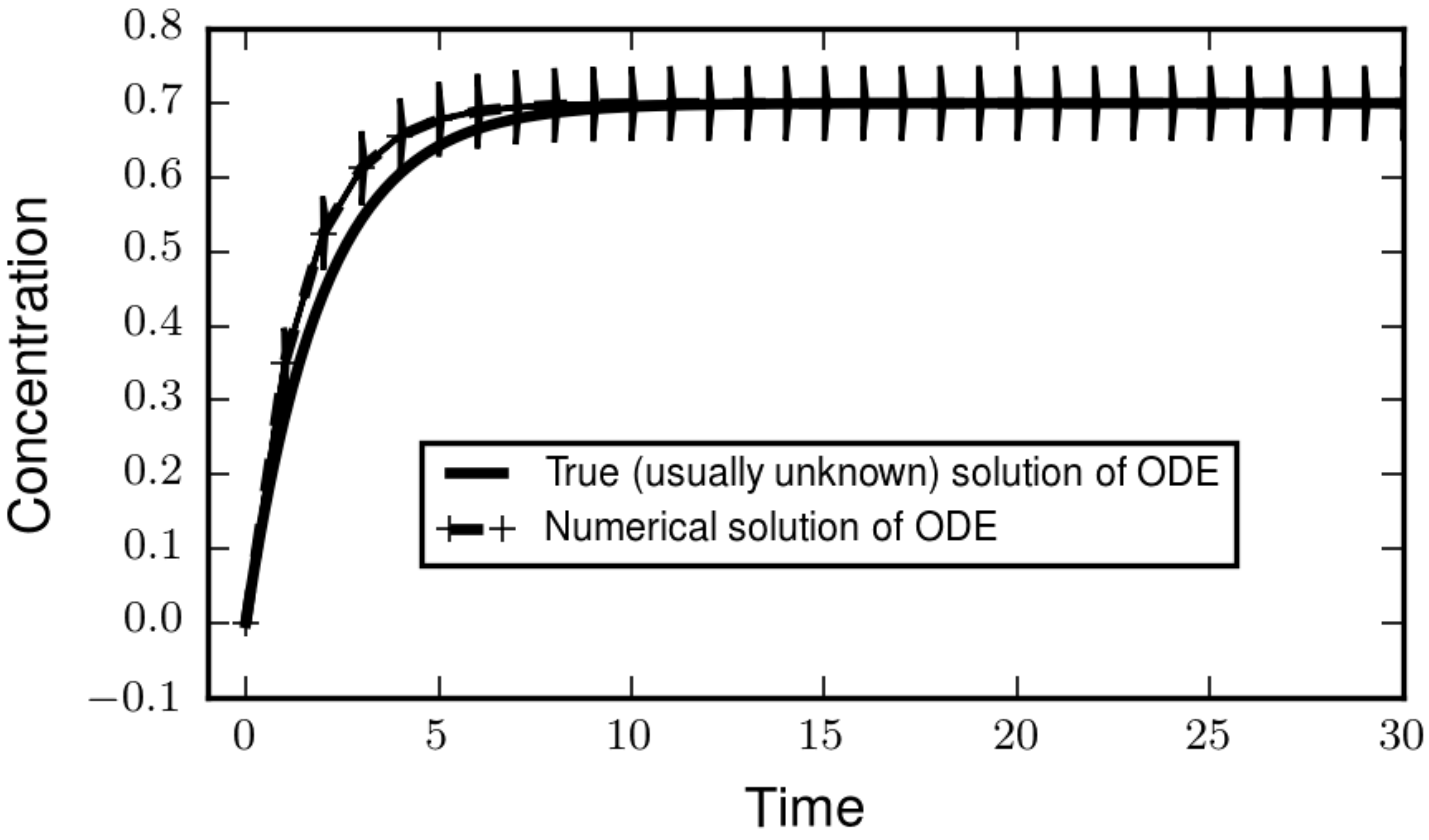
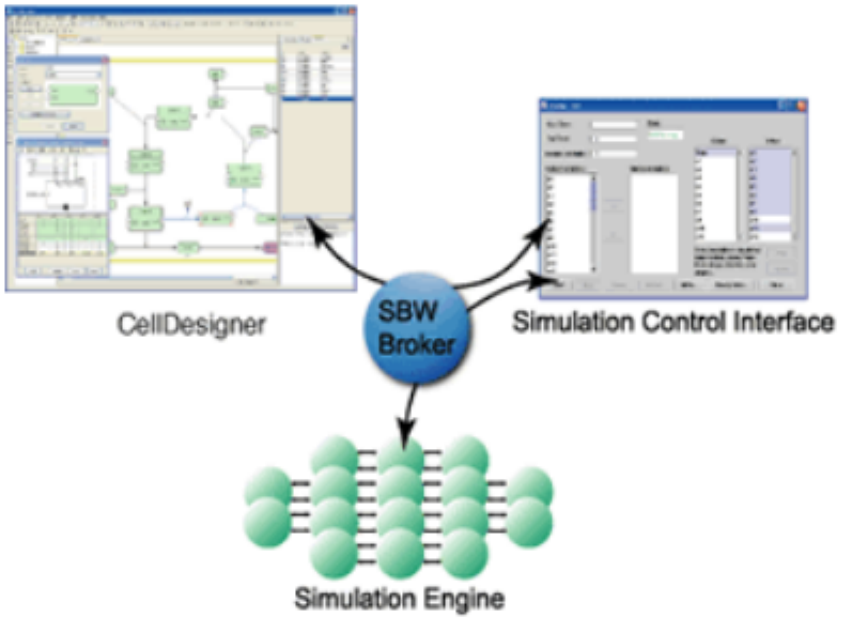
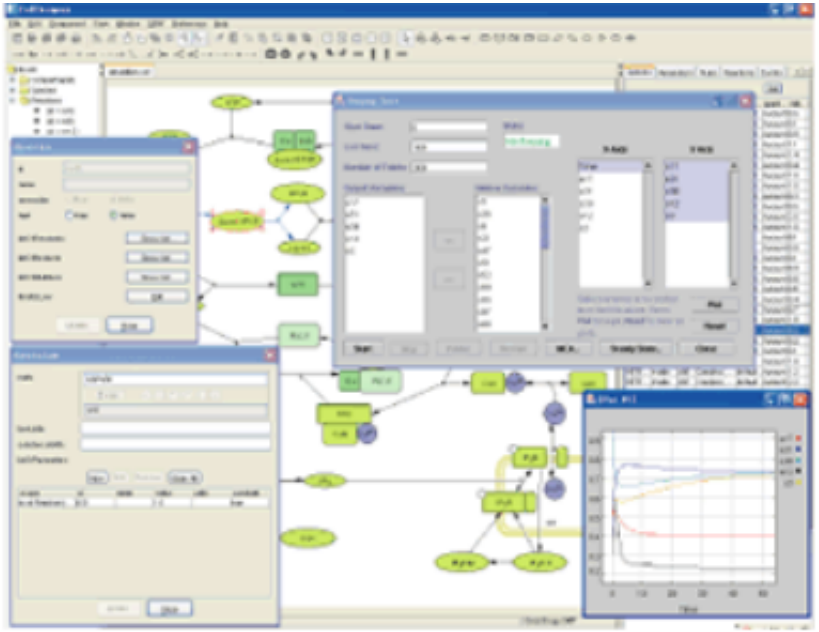


Figure – Solving an ODE

Solving an ODE in practice : no need to code !

ODE solver within Cell Designer





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NB (bis) : You can play with this tools to "explore" the behavior of a model. But that can be time consuming and inefficient...

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What about inferring those values from data ?

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Parameter and network inference in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

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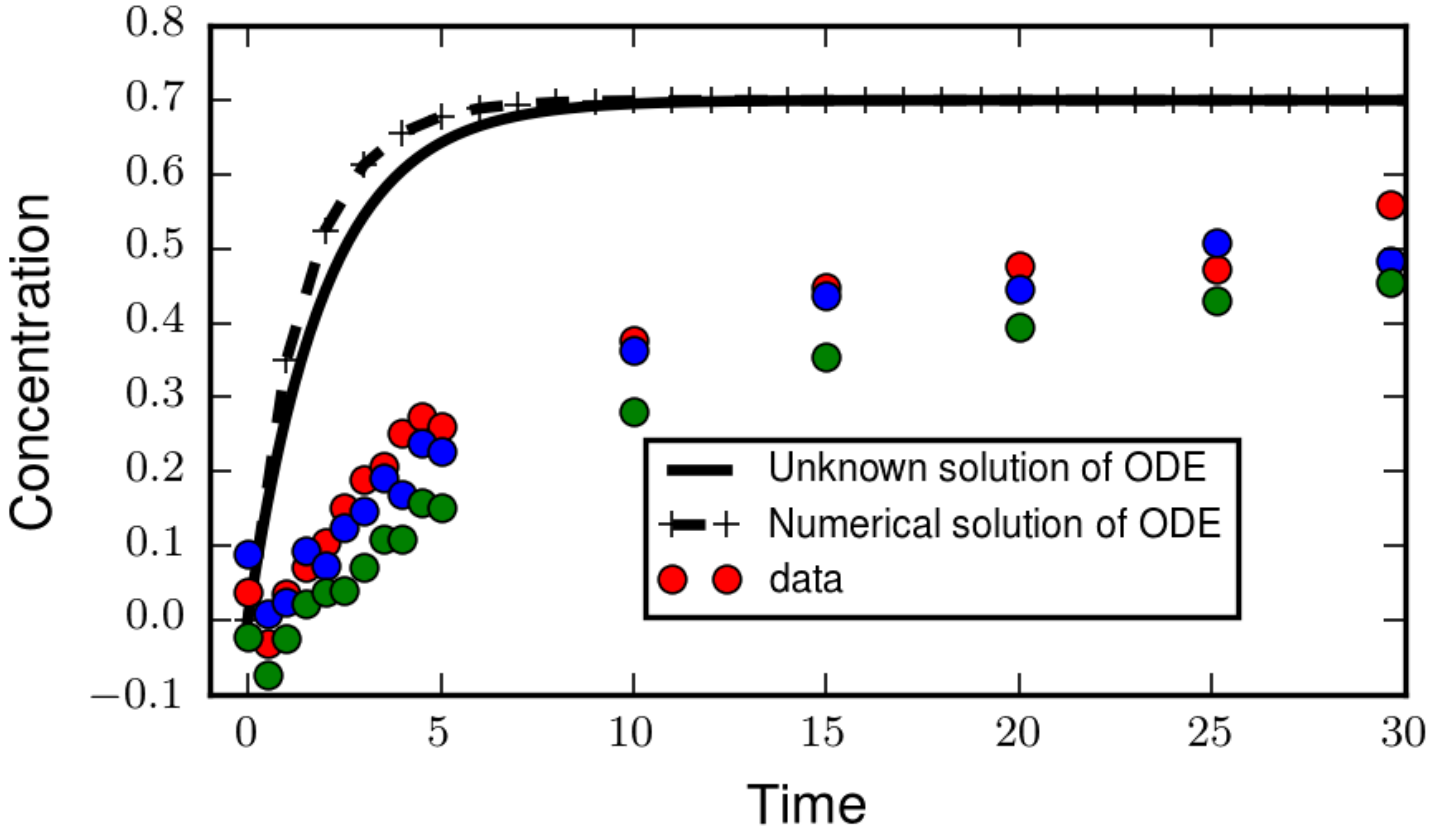
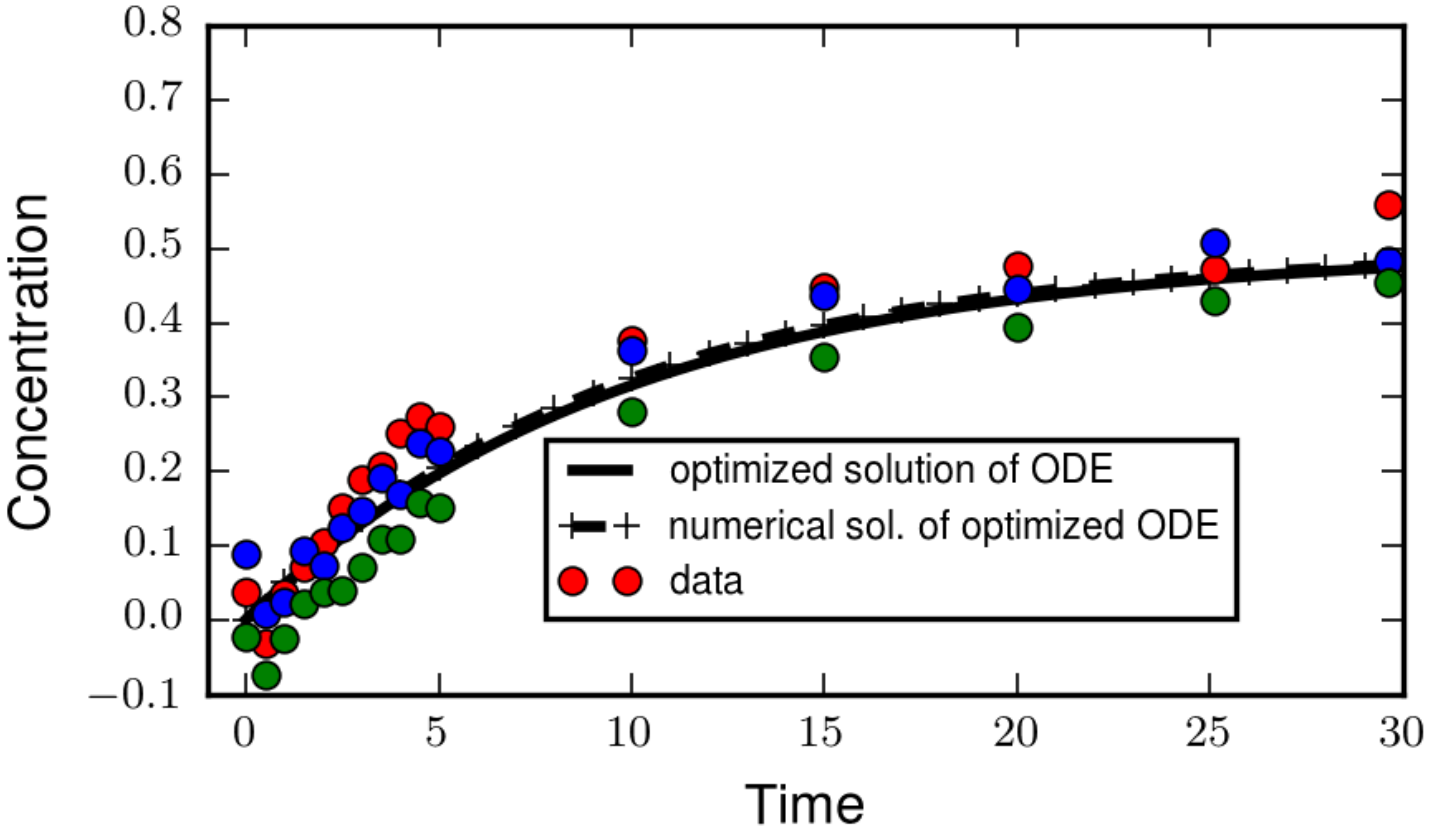


Parameter and network inference in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.



Regression analysis and Parameter estimation with time series : What is difficult ?

- In linear models, there exists a *unique optimal* solution
- Yet in practice, (generalized) linear models do not perform well on biochemical data due to Heteroscedasticity and highly dependent time point data.

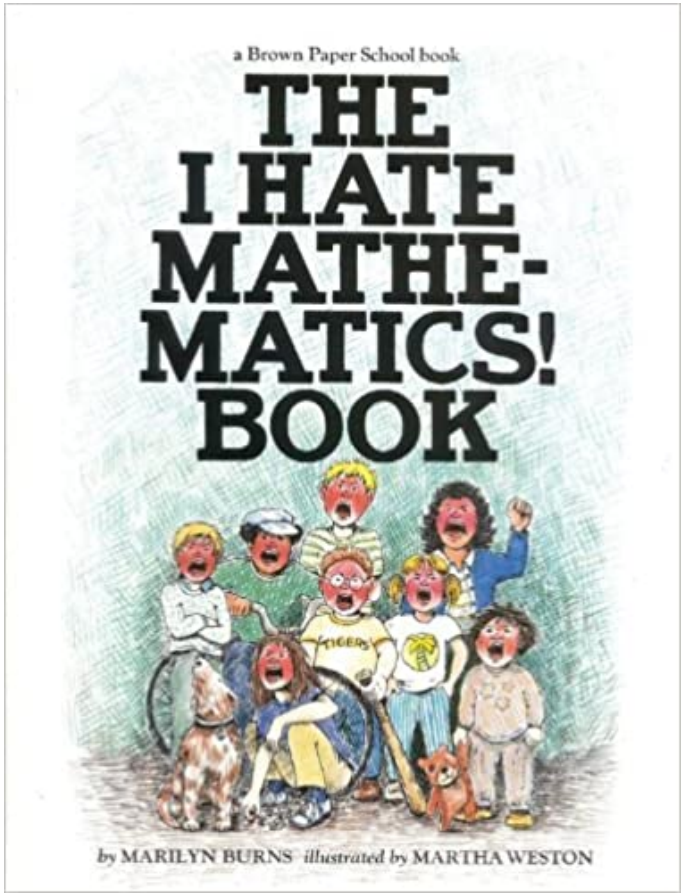
Regression analysis and Parameter estimation with time series : What is difficult ?

- For most of (nonlinear) reaction network, there is no guarantee to find a unique optimal solution.
- Reaction network models allows to perform multifactorial analysis ("Anova-like")

Regression analysis and Parameter estimation with time series : What is difficult ?

- For most of (nonlinear) reaction network, there is no guarantee to find a unique optimal solution.
- Reaction network models allows to perform multifactorial analysis ("Anova-like")
- Many other tools exists from the statistical field of *time series analysis*.

Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...*but that the last ones !*

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Strategy 1) From a given network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, with given parameter values, solve the ODEs,

$$\frac{dx}{dt} = v(x, k)\,, \quad x(0) = x_0\,,$$

and compute a **distance** between the solution and the data.

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Strategy 3) If needed, change the reaction network (add or delete species/reactions)

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Statistics There exists a well developed statistical theory to assess the **quality of a fit** and to give **confidence interval** on parameter values (-> See Likelihood maximization or Bayesian statistics).

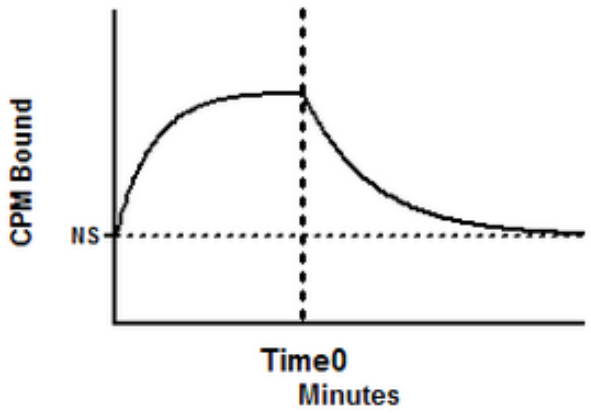
Parameter estimation in

GraphPad

Predefined or user-defined time-dependent equations

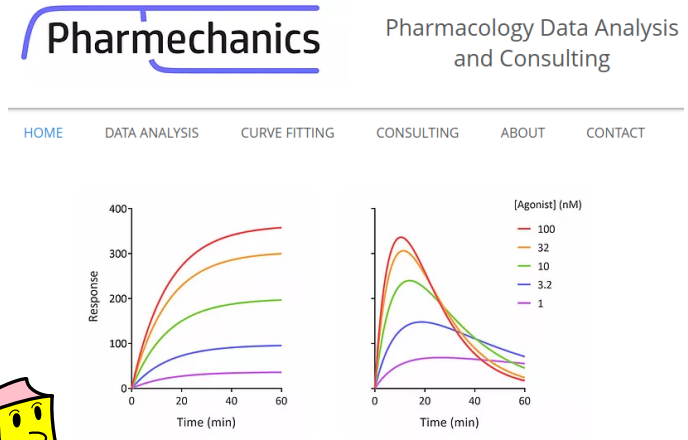
Model

```
Radioligand=HotNM*1e-9
Kob=[Radioligand]*Kon+Koff
Kd=Koff/Kon
Eq=Bmax*radioligand/(radioligand + Kd)
Association=Eq*(1-exp(-1*Kob*X))
YatTime0 = Eq*(1-exp(-1*Kob*Time0))
Dissociation= YatTime0*exp(-1*Koff*(X-Time0))
Y=IF(X<Time0, Association, Dissociation) + NS
```

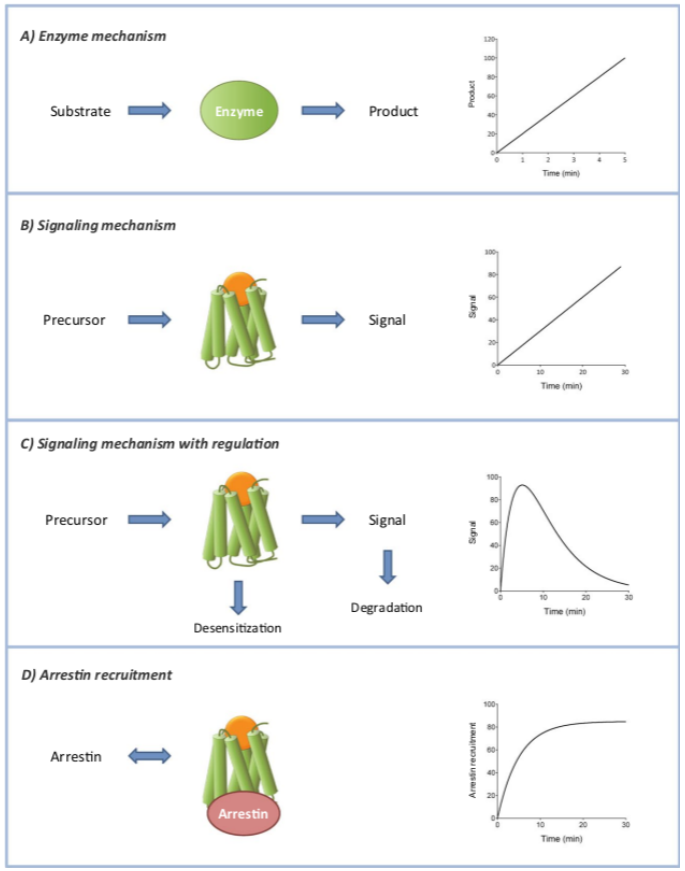


Parameter estimation in GraphPad

- Limited to *solvable* models
- Adapted to analyze one single output at a time, assuming excess of Ligand.

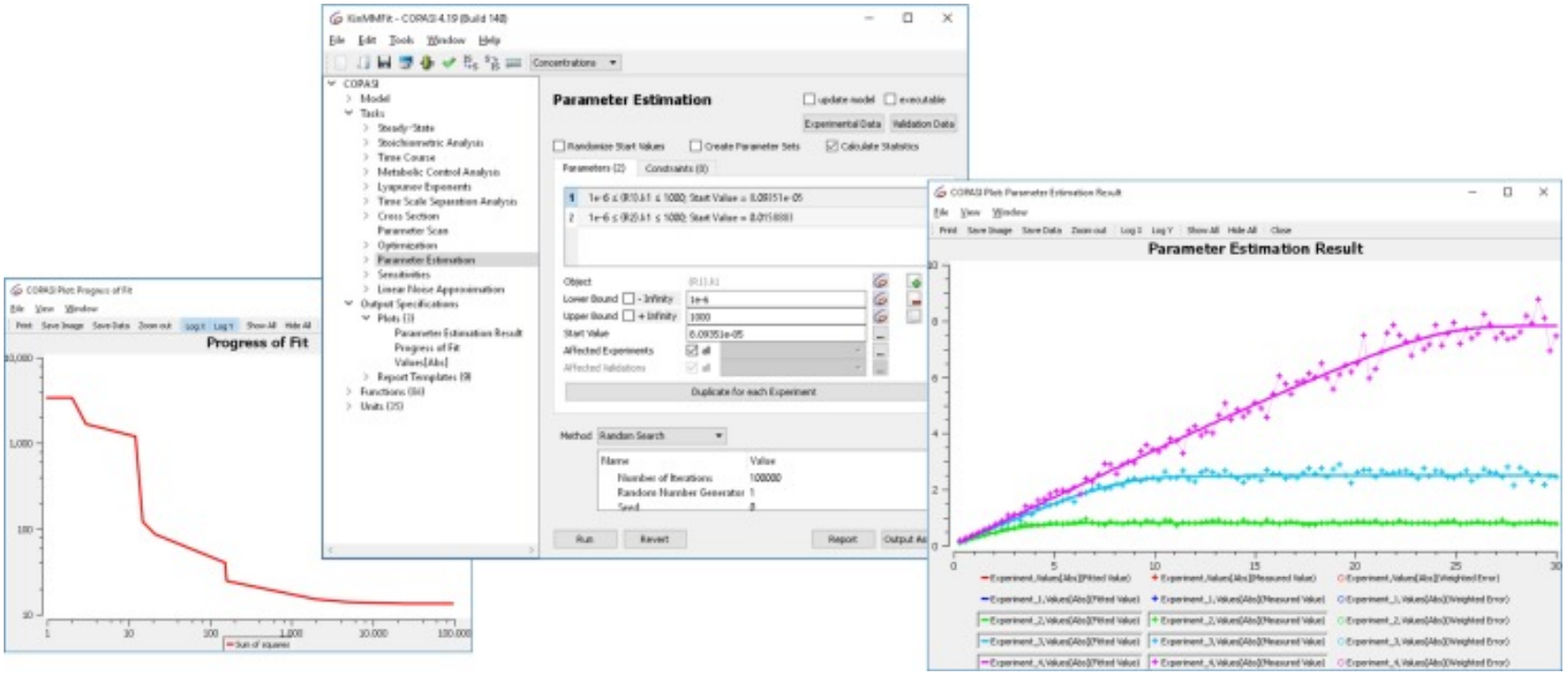


Predefined or user-defined time-dependent equations



Hoare et al., Analyzing kinetic signaling data for G-protein-coupled receptors, Scientific Reports 10(1) :12263 2020

Parameter estimation in Copasi

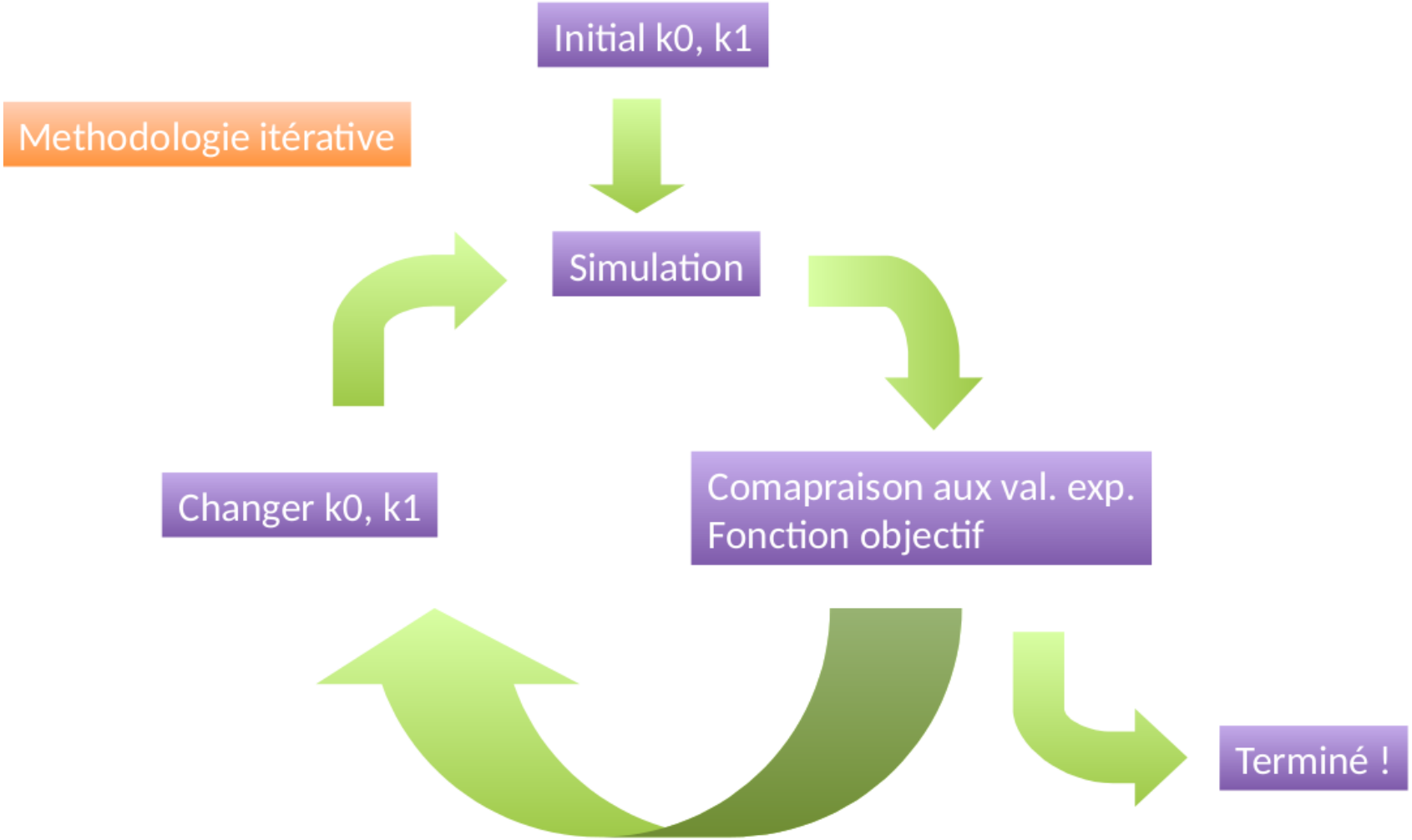


- Models can be imported from Cell Designer.
- Supports both graphical interface and command line.

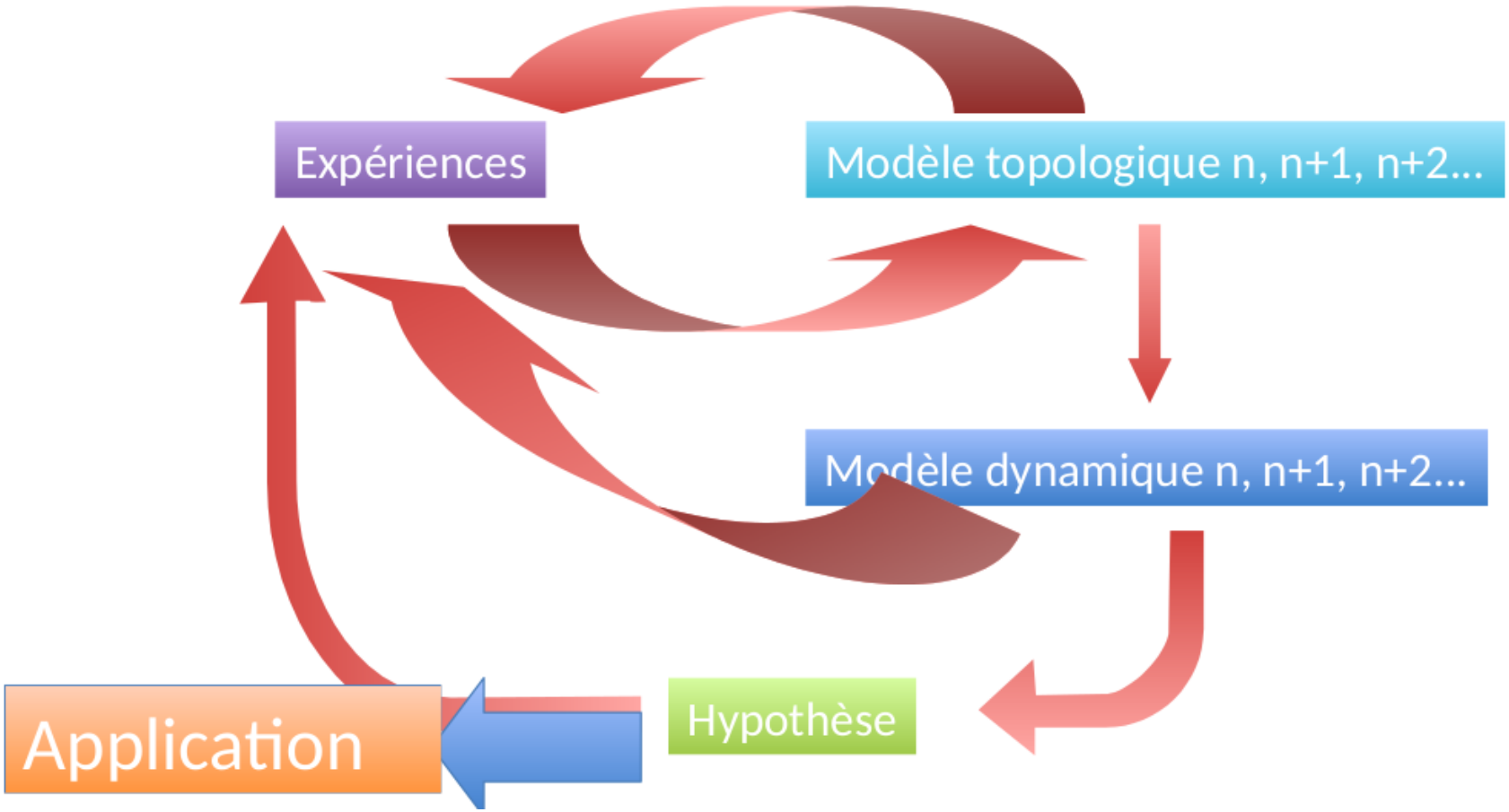
Bergman et al. COPASI and its applications in biotechnology, Journal of Biotechnology 261 :215-220, 2017.

Hoops et al. COPASI : a COmplex PAthway SImulator. Bioinformatics 22 :3067-74, 2006.

Remember ! it's an iterative and interdisciplinary workflow !

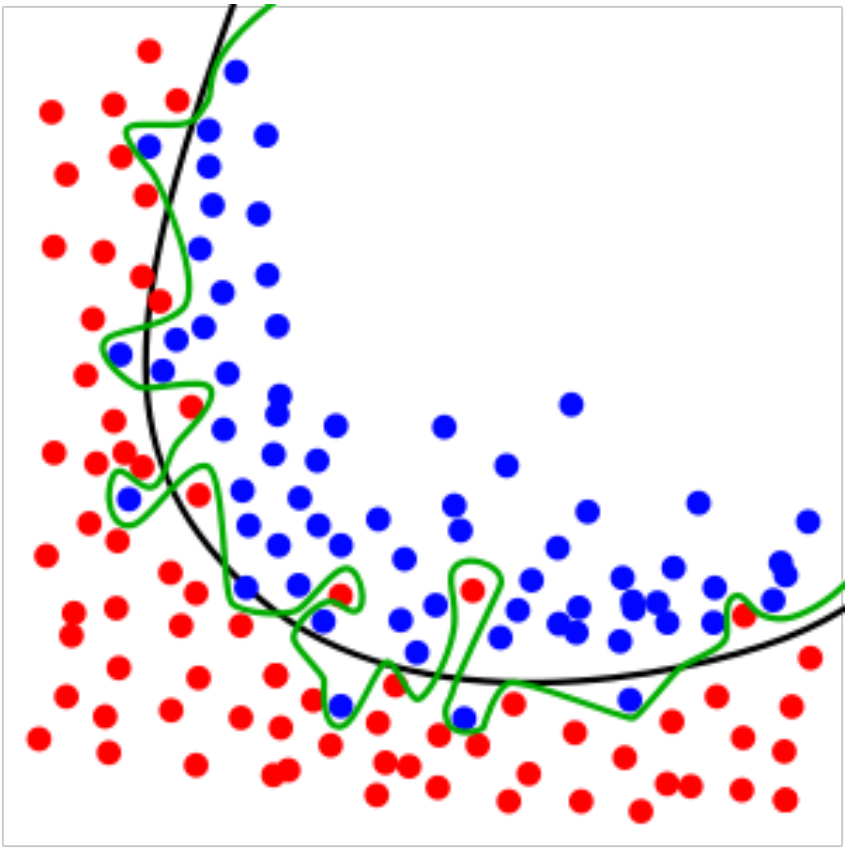


Remember ! it's an iterative and interdisciplinary workflow !



Is the monkey who typed Hamlet actually a good writer ?

Overfitting



- There is a trade-off between toy minimal models and detailed biochemistry pathways.
- Overfitting leads to unreliable prediction and meaningless model / parameter value.
- (Advanced) statistical tools exist to sort this out : model selection (especially for hierarchical models) and parameter identifiability.

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of dynamical reaction network models
- How to build and simulate a reaction network model within Cell Designer.
- How to calibrate parameters of a dynamical reaction network model with GraphPad Prism and/or Copasi.

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- Many examples of dynamical system biology models
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NB : The full workflow can be long and require collaboration with statistician / applied mathematician.

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We have seen

- Many examples of dynamical system biology models
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NB bis : **What about applications ?** Go to session 8 : Computational approaches !

Outline

Systems Biology and Networks

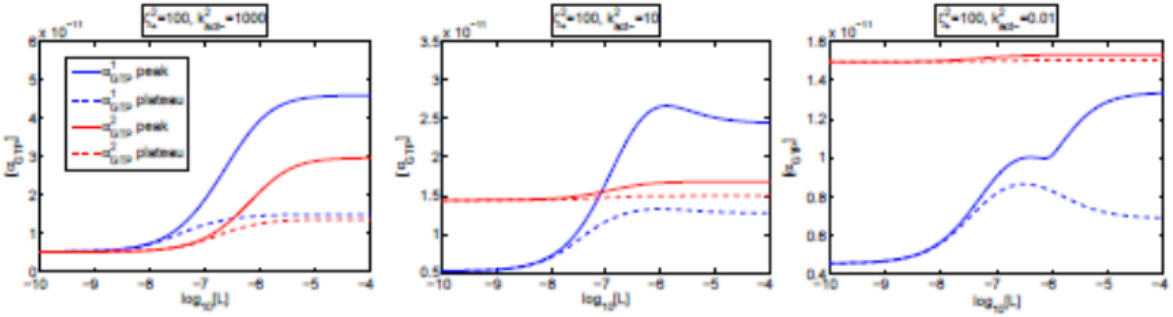
Motivations and Objectives

Chemical reaction network formalism

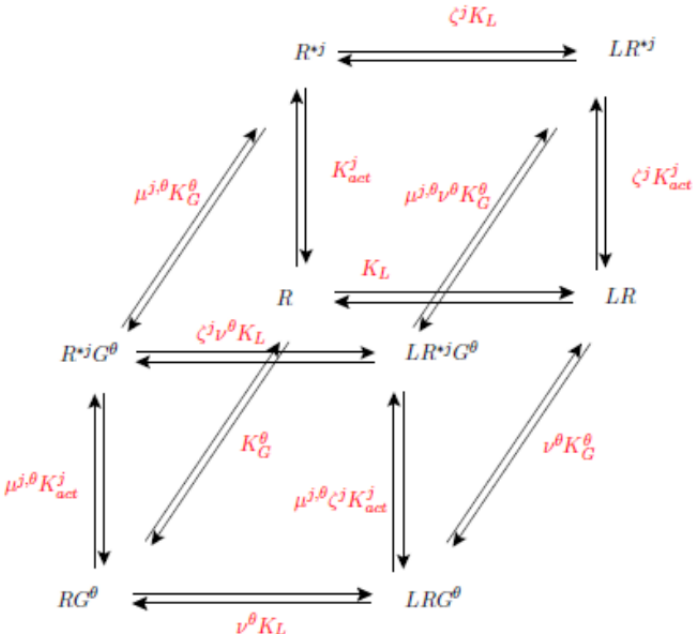
Parameter estimation

Applications

Some applications : Understanding G protein activation cycle

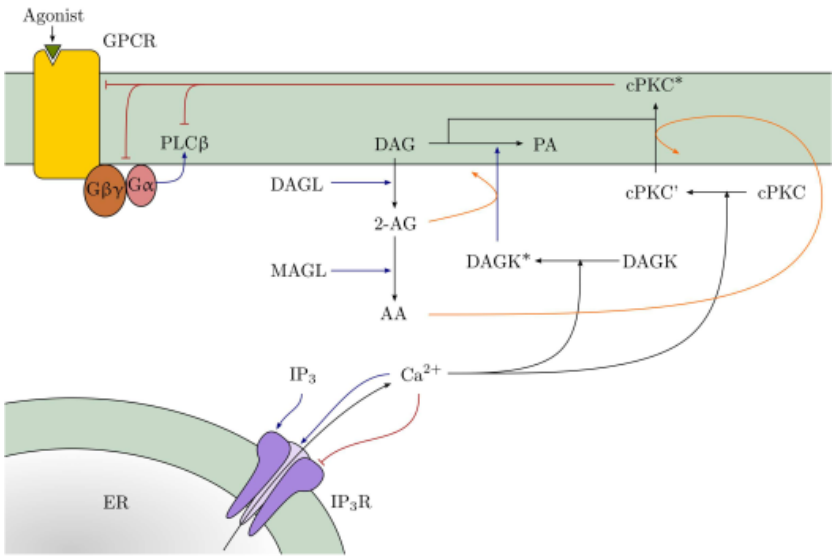


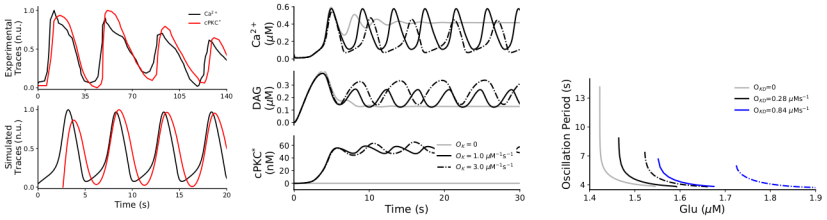
$$\alpha^{\theta}_{GTP} \underset{k_{hyd-}}{\overset{k_{hyd+}}{\rightleftharpoons}} \alpha^{\theta}_{GDP}, \qquad \alpha^{\theta}_{GDP} + \beta\gamma^{\theta} \underset{k_{RA-}}{\overset{k_{RA+}}{\rightleftharpoons}} G^{\theta}.$$



Bridge, Meads, Frattini, Winfield, Ladds, Modelling and simulation of biased agonism dynamics at a G protein-coupled receptor, J. Theoret. Biol. 442 :44–65, 2018

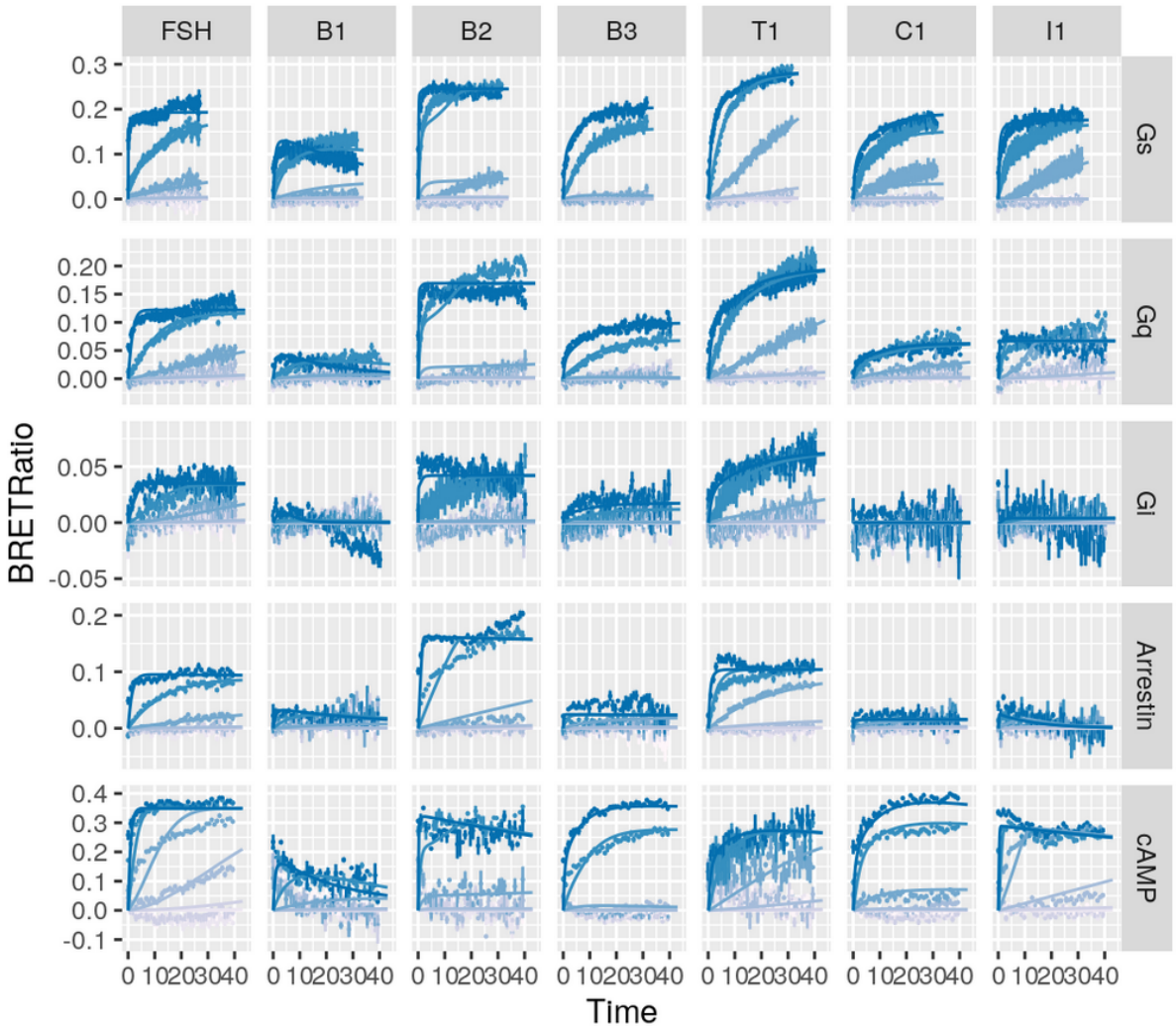
Some applications : Shedding light on GPCR-induced Calcium oscillations in Astrocytes





De Pittà, Ben-Jacob, Berry, G protein-coupled receptor-mediated calcium signaling in astrocytes, in Computational Glioscience, Springer 2019.

Some applications : Revisiting signaling bias using dynamical model



De Pascali, ..., R.Y,..., *in preparation*.

Conclusions

- Dynamical reaction network framework has many different applications.
- Its a powerful framework to reveal comprehensive spatio-temporal patterns behind GPCR signaling complexities.
- Its a powerful framework to analyze quantitatively time series data in GPCR signaling.
- Adequate tools foster necessary interdisciplinary collaborations by providing a common language.