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

Romain Yvinec

Dynamical modeling of reaction networks

Mathematics of system biology

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Systems Biology and Networks

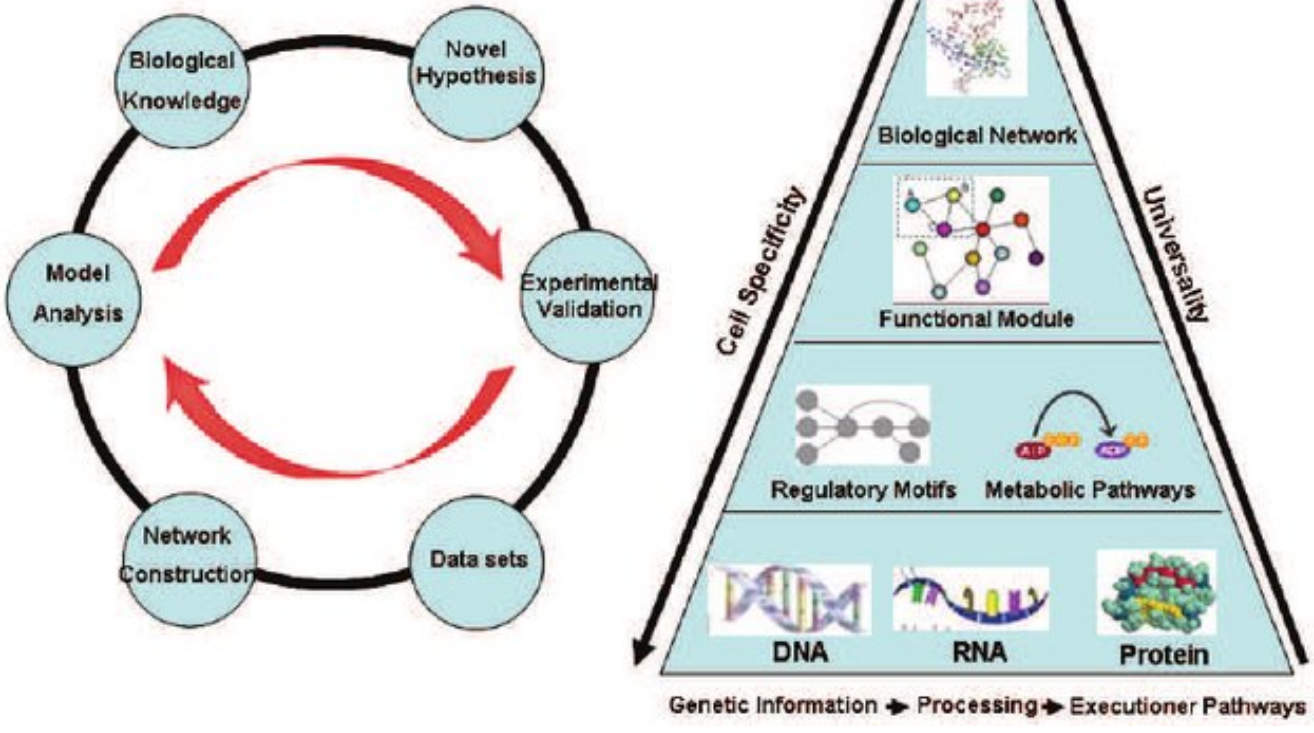
Motivations and Objectives

Chemical reaction network formalism

Parameter estimation

Applications

Outline



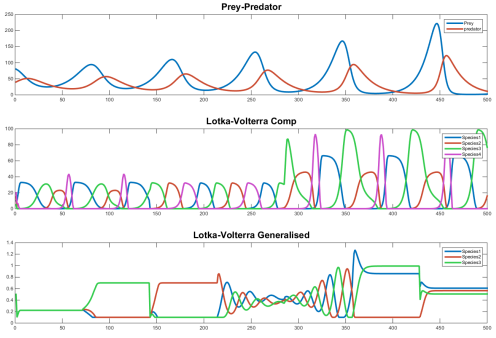
Oltvai and Barabasi, Science 25 :763-764, 2002.

Small networks in Population dynamics

(Interactions between populations, Epidemiology)

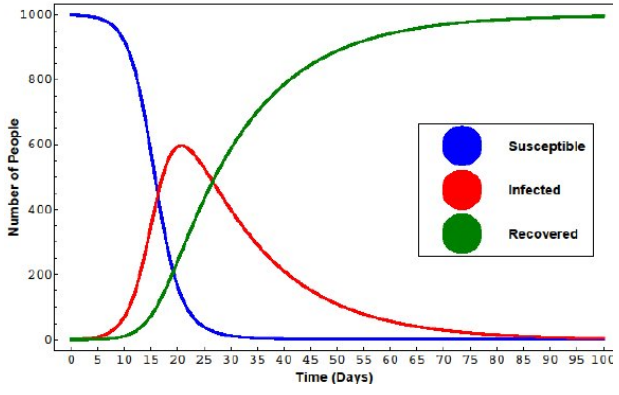
Lotka-Volterra model

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



S.I.R model

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

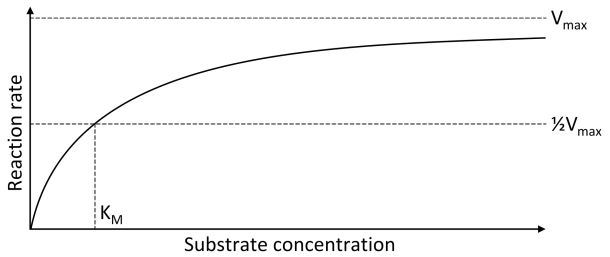


Small networks in molecular biology

('Toy' molecular models with isolated components)

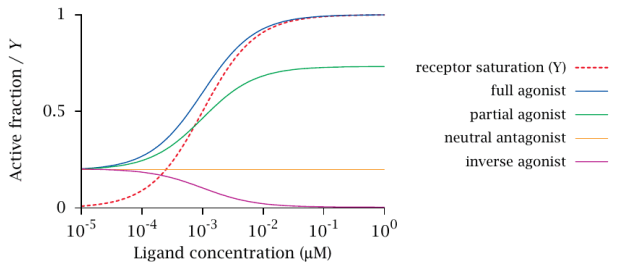
Enzymatic kinetics

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



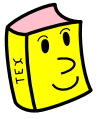
Pharmacology model

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

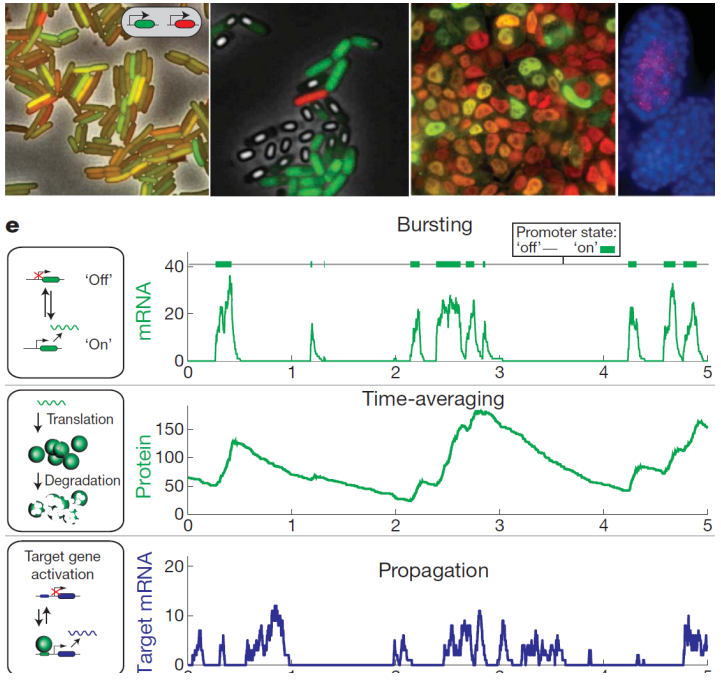


(Single) Gene Expression

$$
\begin{aligned}
G &\xrightarrow{\lambda_1} G + M \\
M &\xrightarrow{\lambda_2} M + P \\
M &\xrightarrow{\gamma_1} \varnothing \\
P &\xrightarrow{\gamma_2} \varnothing \\
G &\underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} G_{off}
\end{aligned}
$$



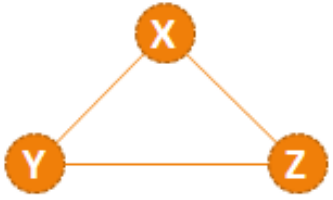
Eldar and Elowitz (Nature 2010)



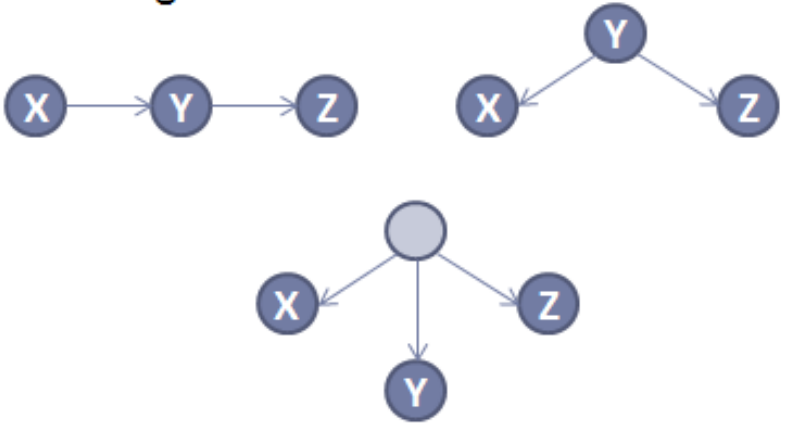
Co-expression genes network

Small motifs

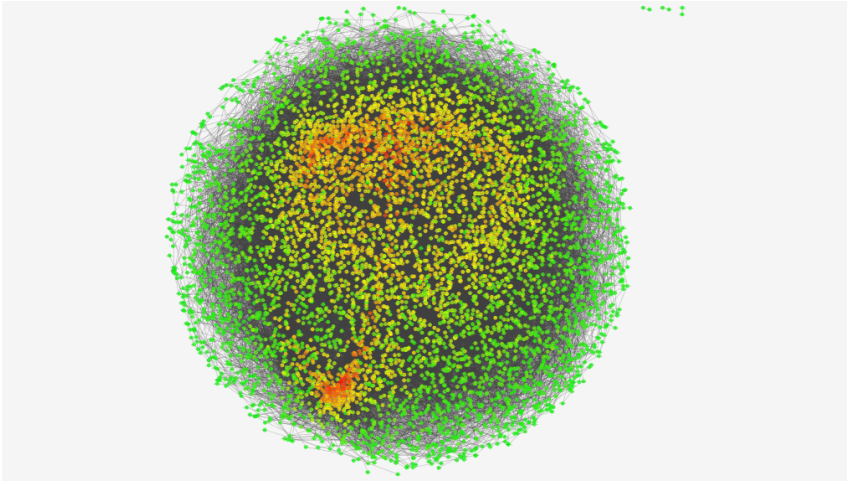
Gene Co-expression



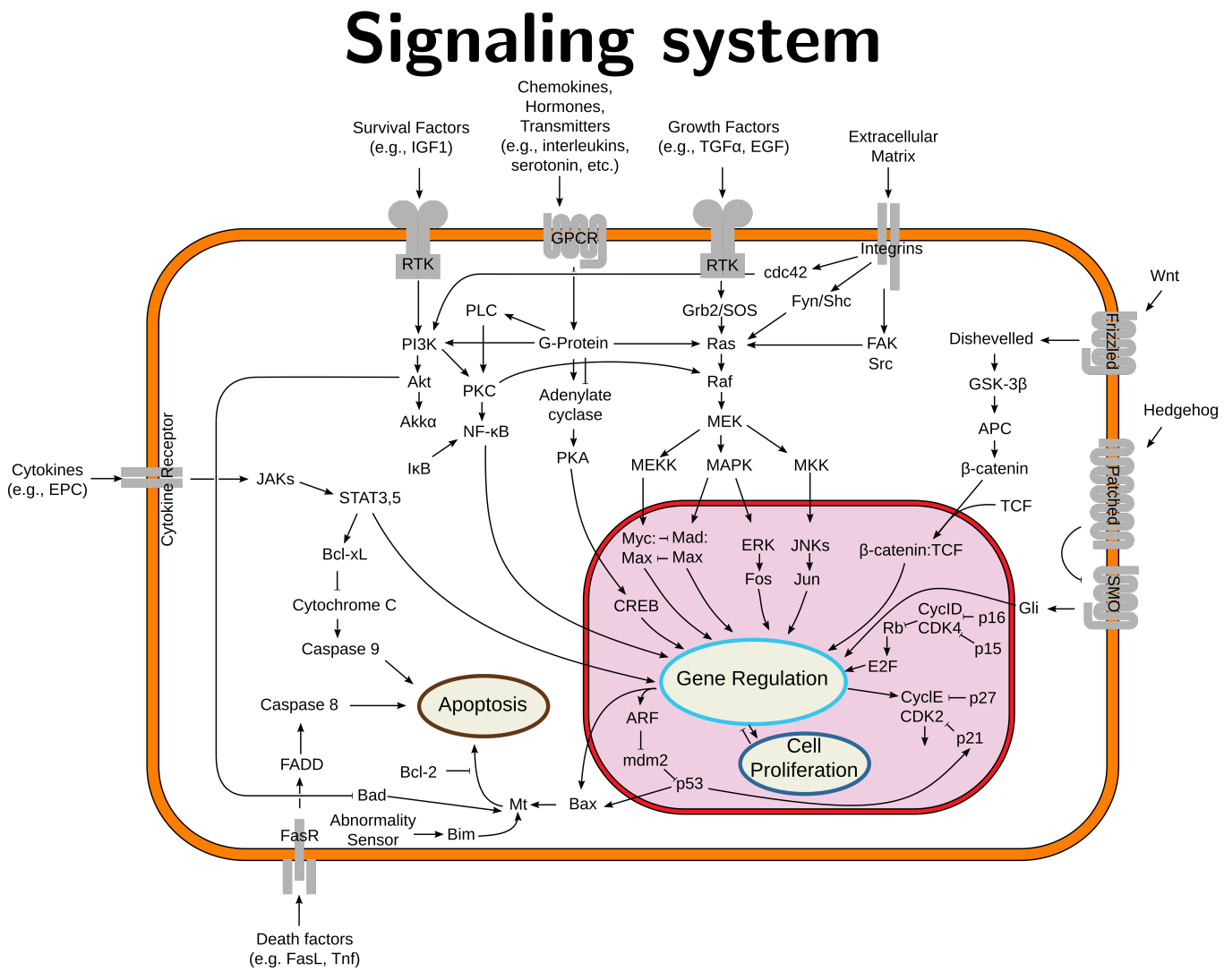
Gene Regulation



Large networks

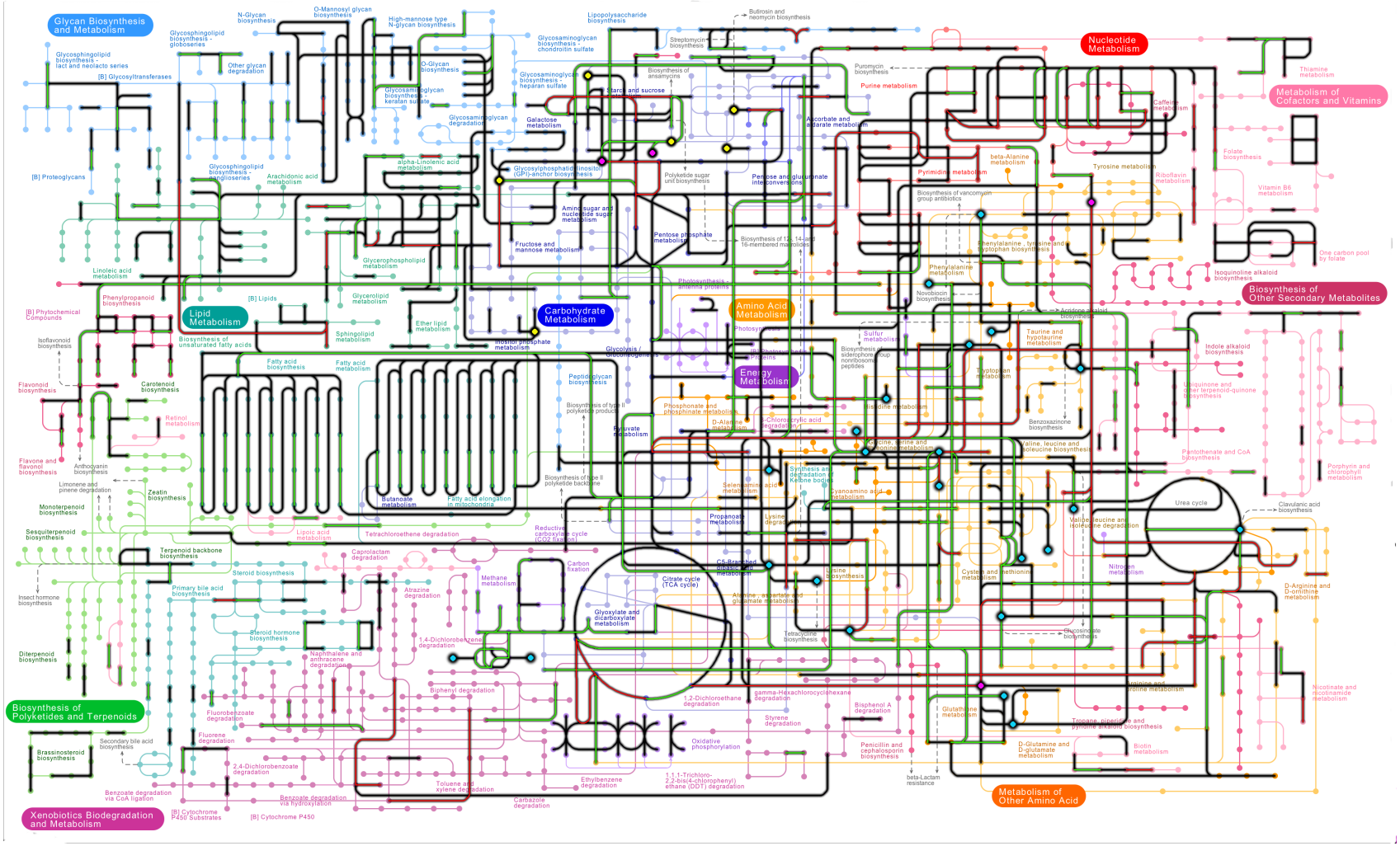


Systems Biology and Networks at different scales



Systems Biology and Networks at different scales

Metabolomic Network



Outline

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

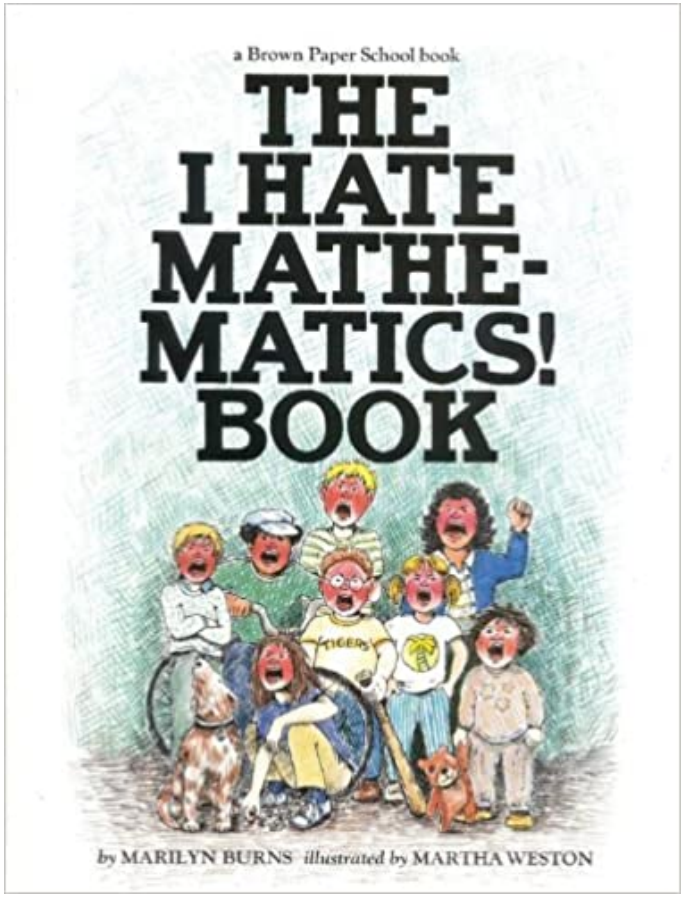
Today : Understand the mathematical formalism of dynamical reactions network

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]

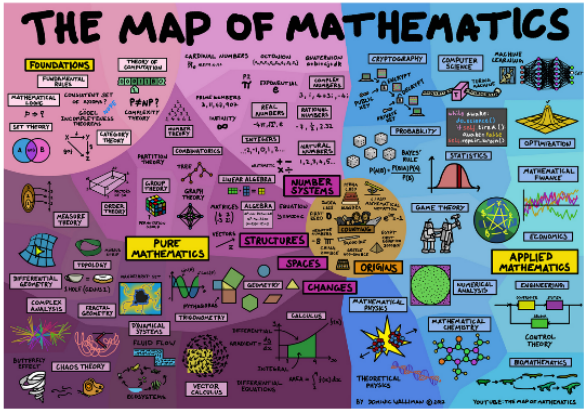
Warning !



#Ihatemathematics

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

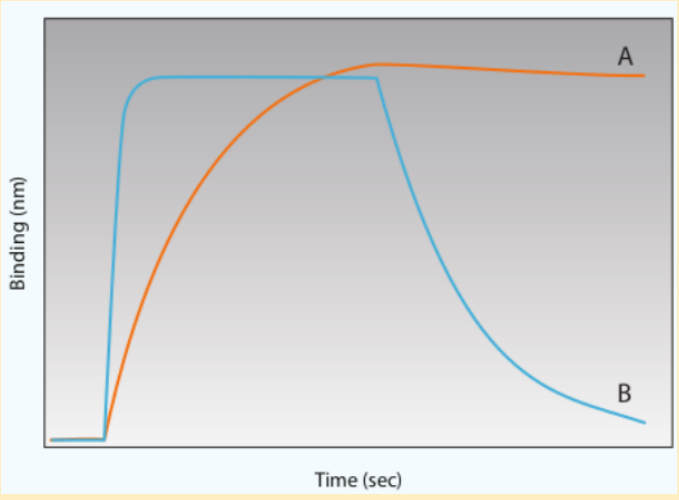
Maths is about structures...and is generic !



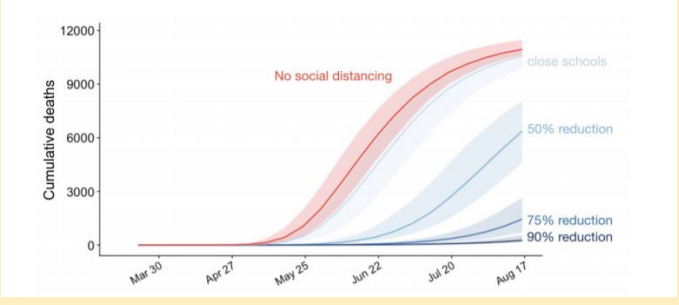
Reactions networks applications range from

- Chemistry
- molecular biology
- epidemiology
- and beyond !

Binding experiments



Covid-19 models



Outline

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

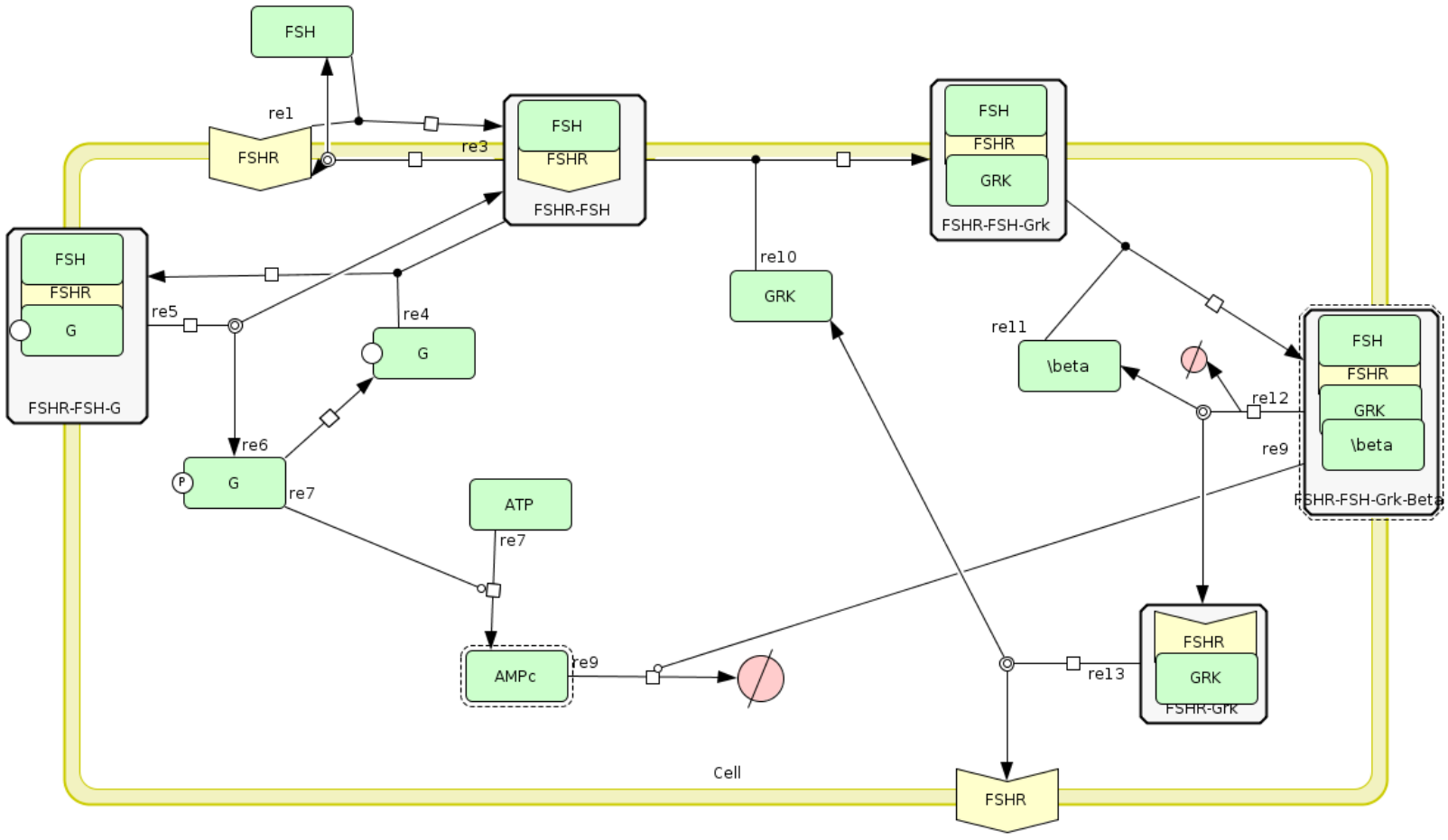
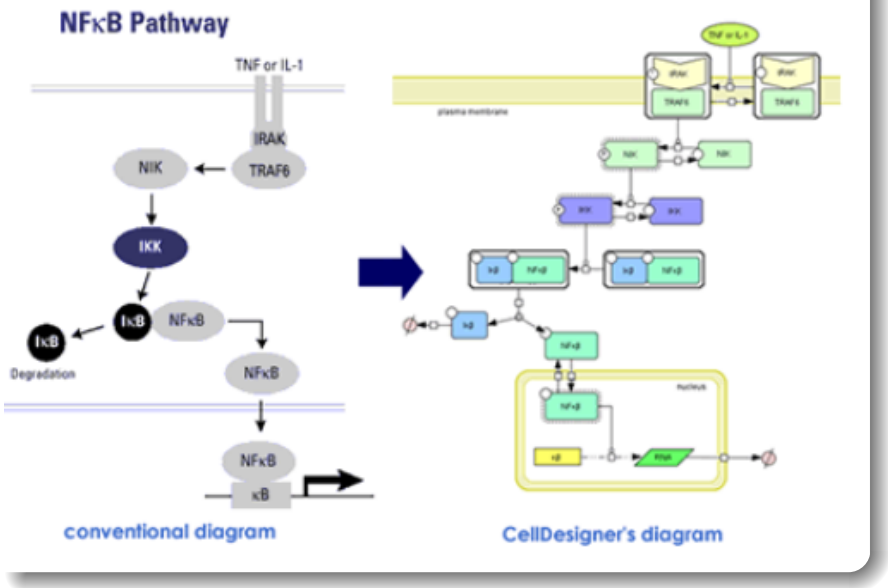


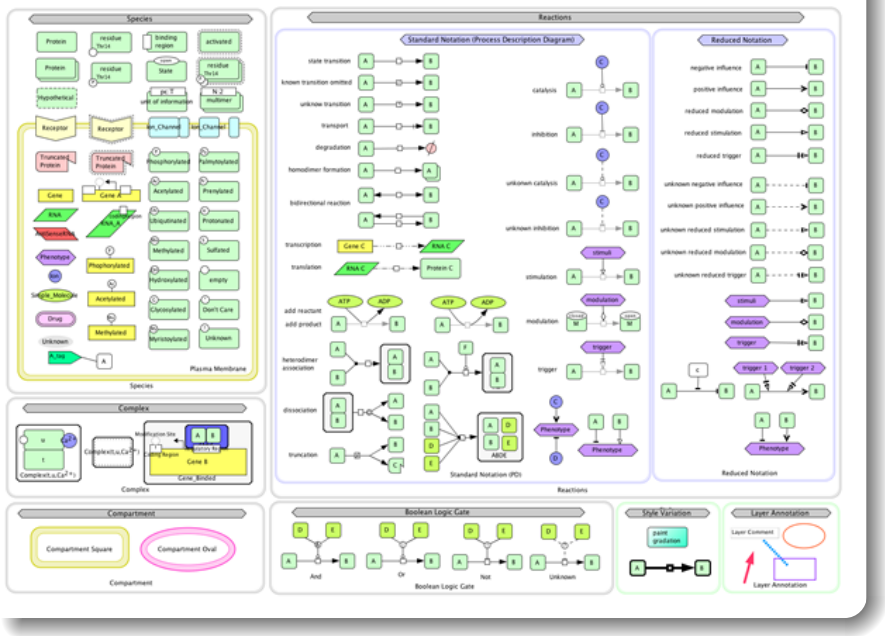
Figure – FSHR (Gαs-coupled GPCR) models build on CellDesigner

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

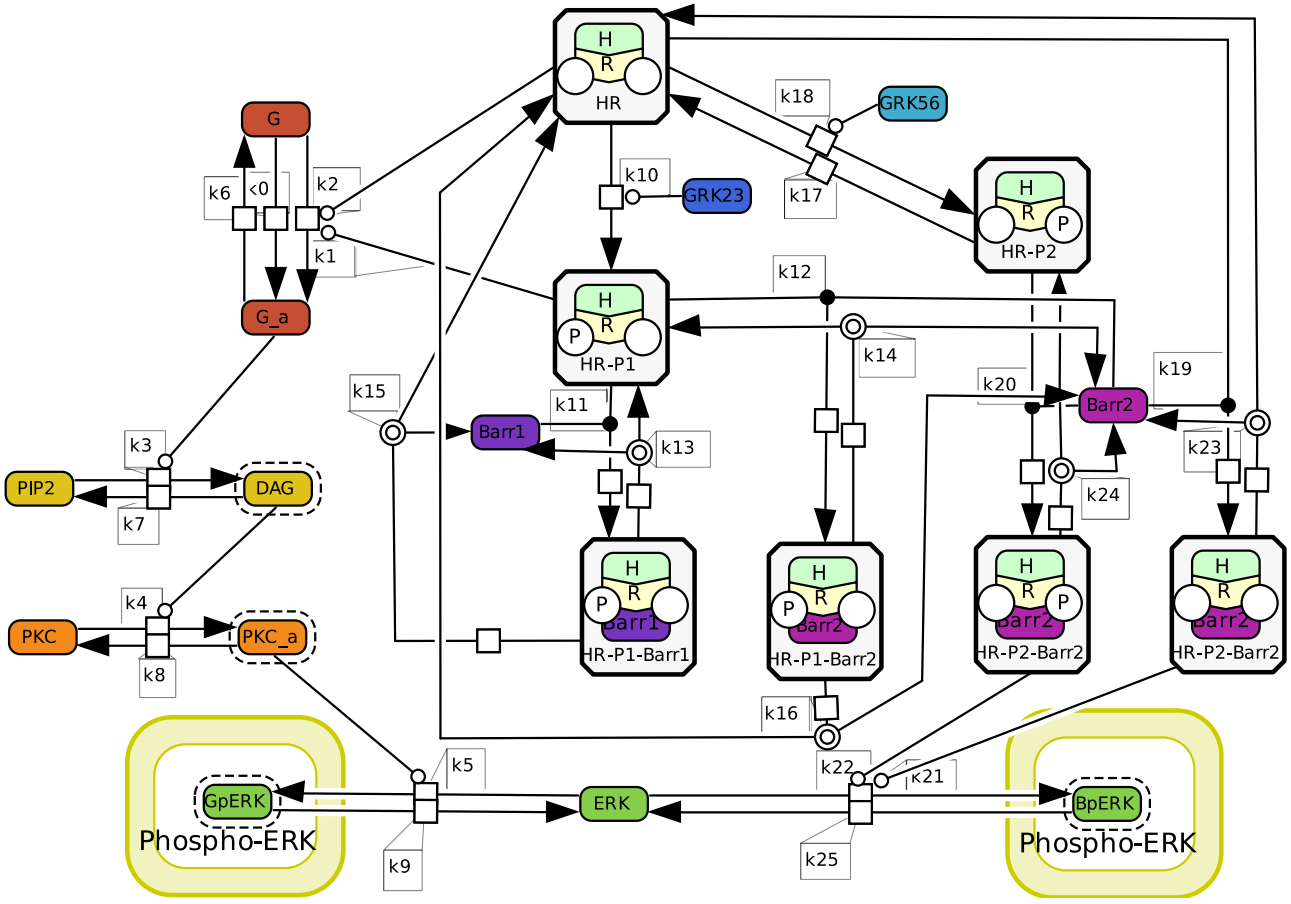


Figure – ERK Phosphorylation pathways build on CellDesigner, Heitzler et al. MSB 2012

Summary so far

We have seen

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- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

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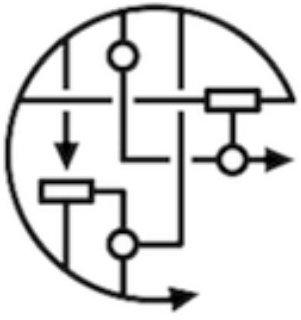
NB : there exists public databases of reaction network models.



BioModels

Pathguide the pathway resource list

KEGG NETWORK Database

From gene variation to network variation

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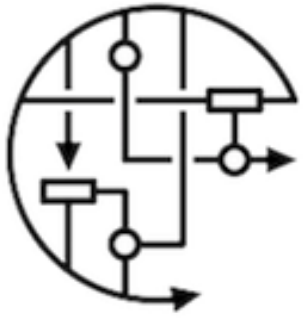

BioModels

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KEGG NETWORK Database

From gene variation to network variation

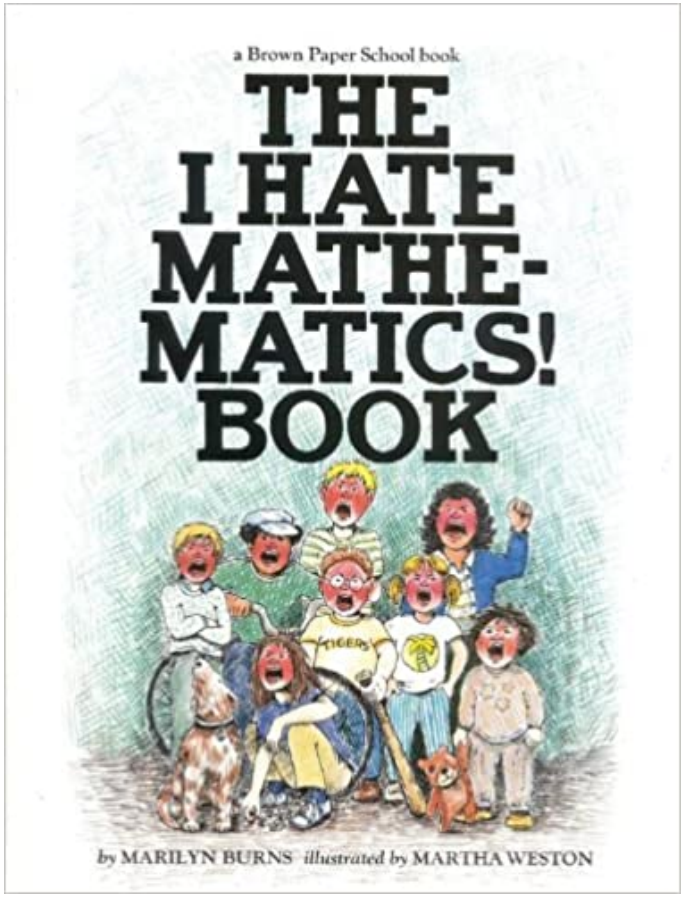
NB (bis) : A reaction network is a network... but a network is **NOT** a reaction network !

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)

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

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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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!

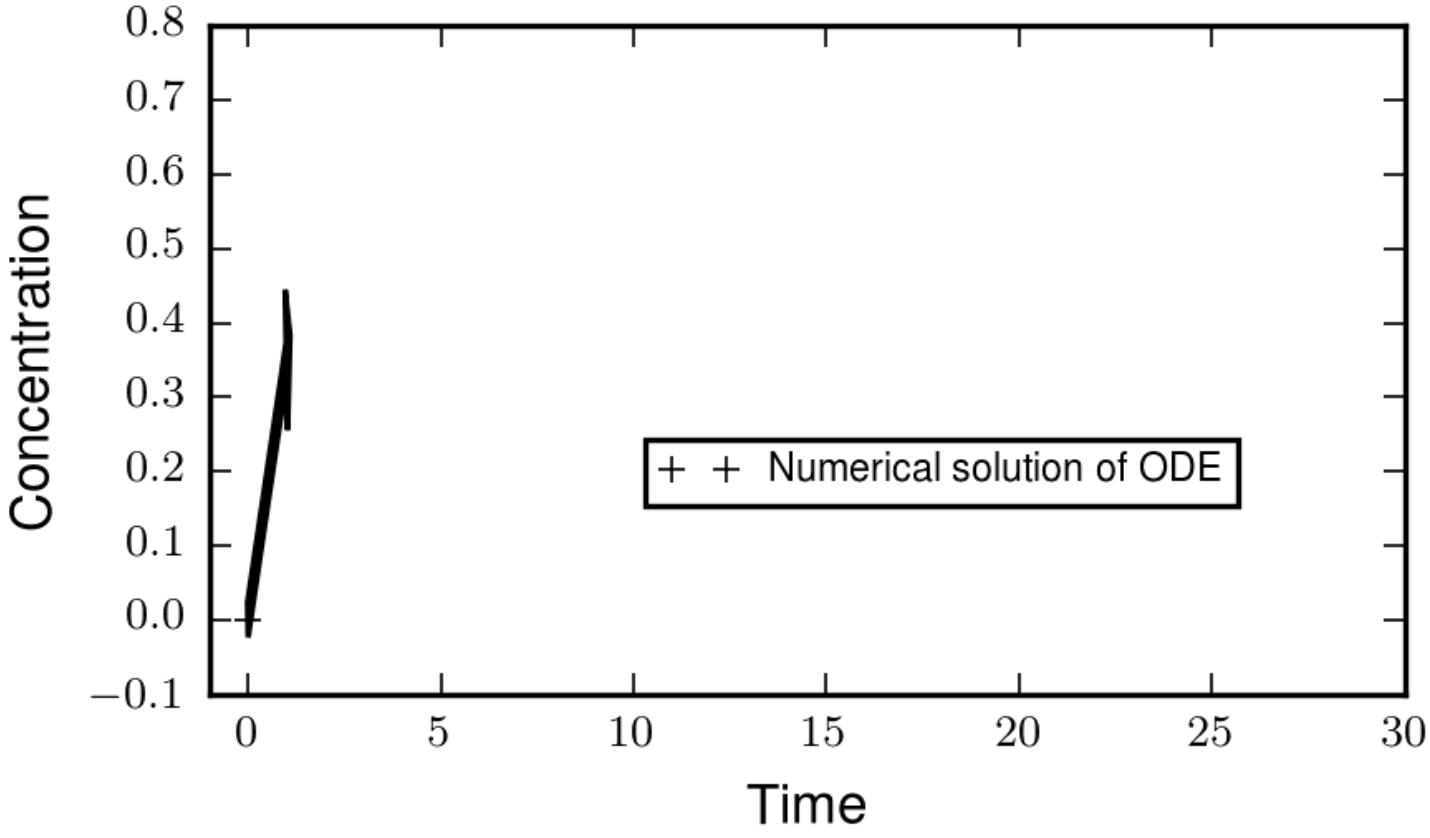

Figure – Solving an ODE

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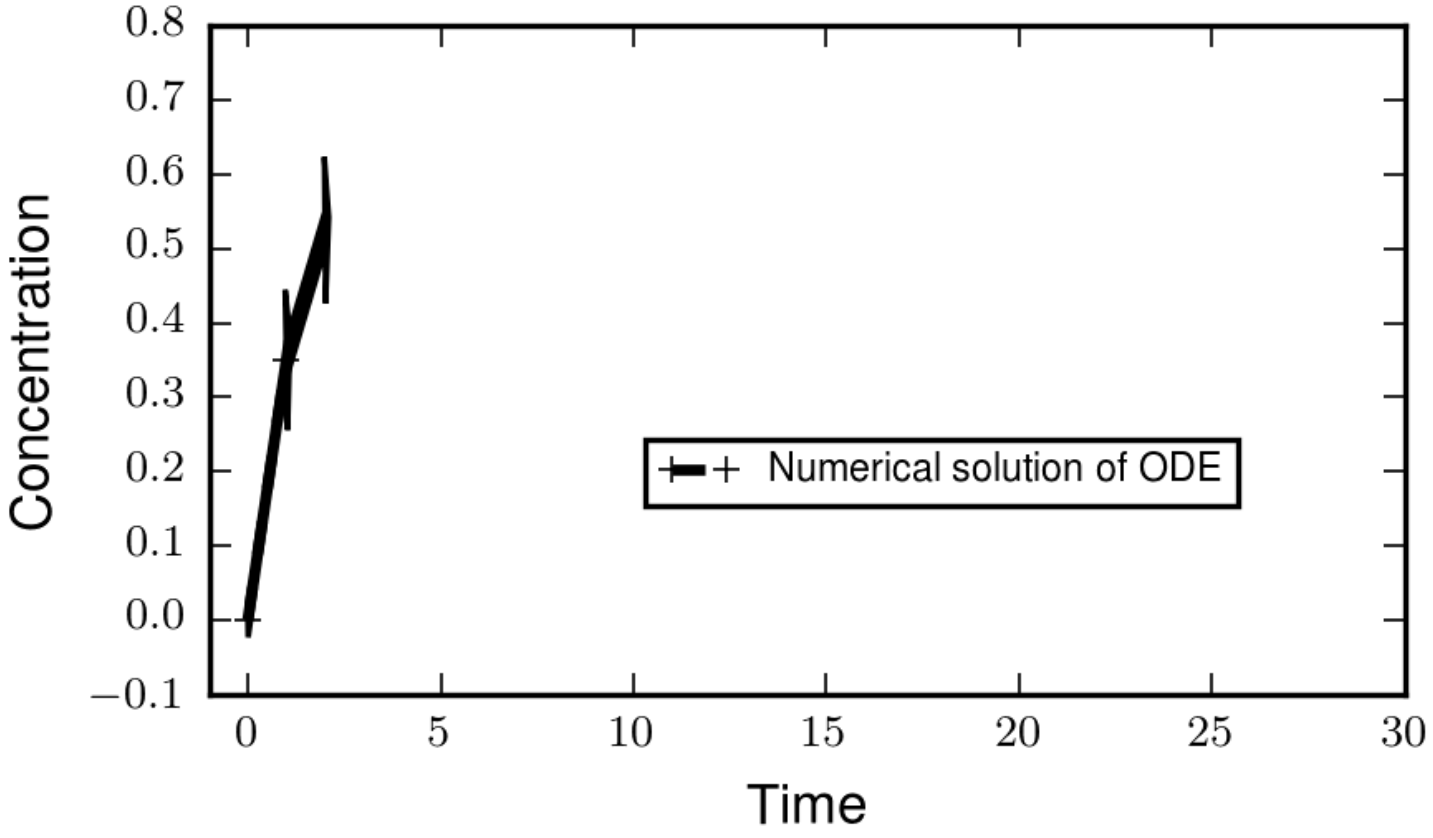

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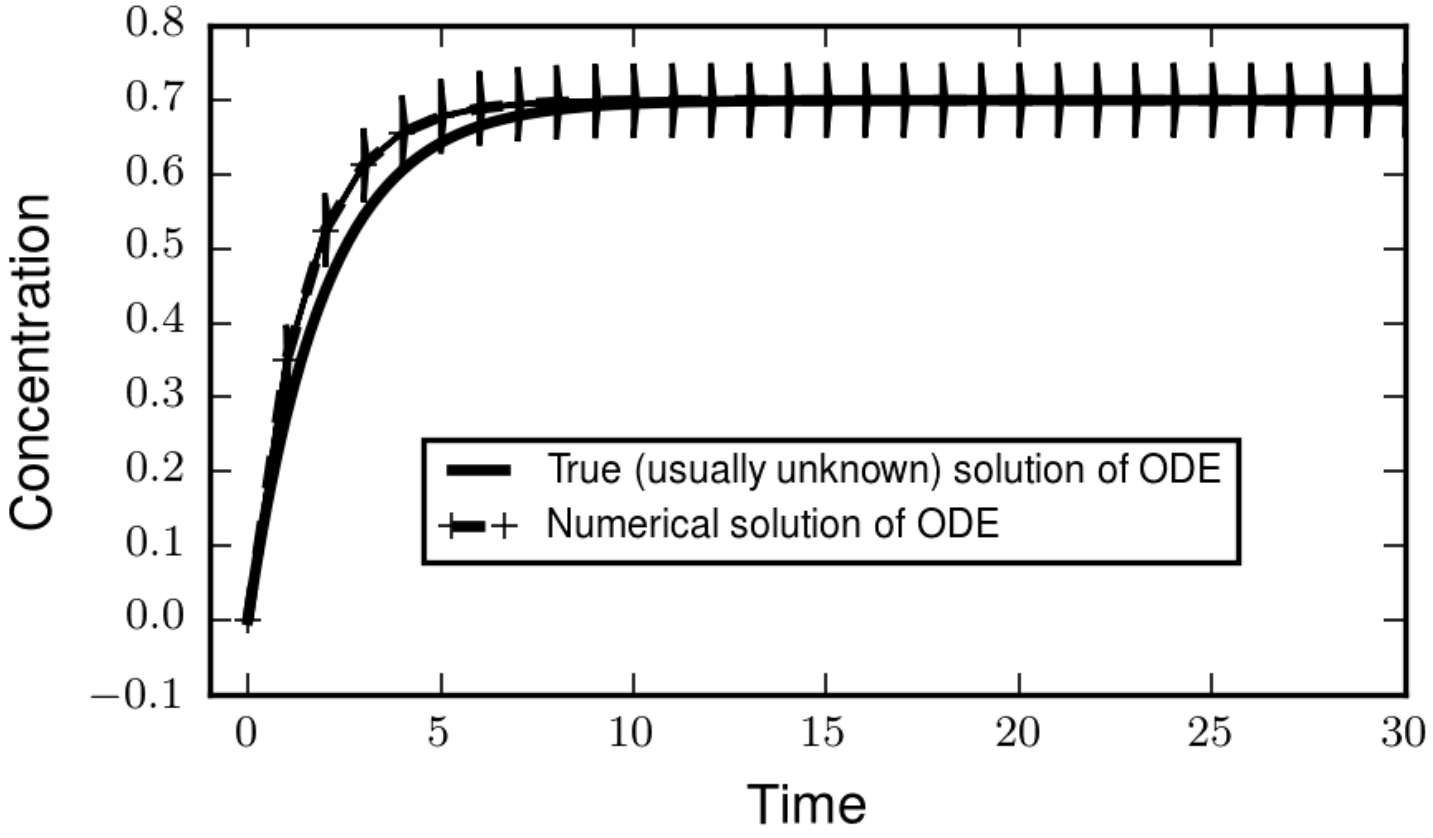
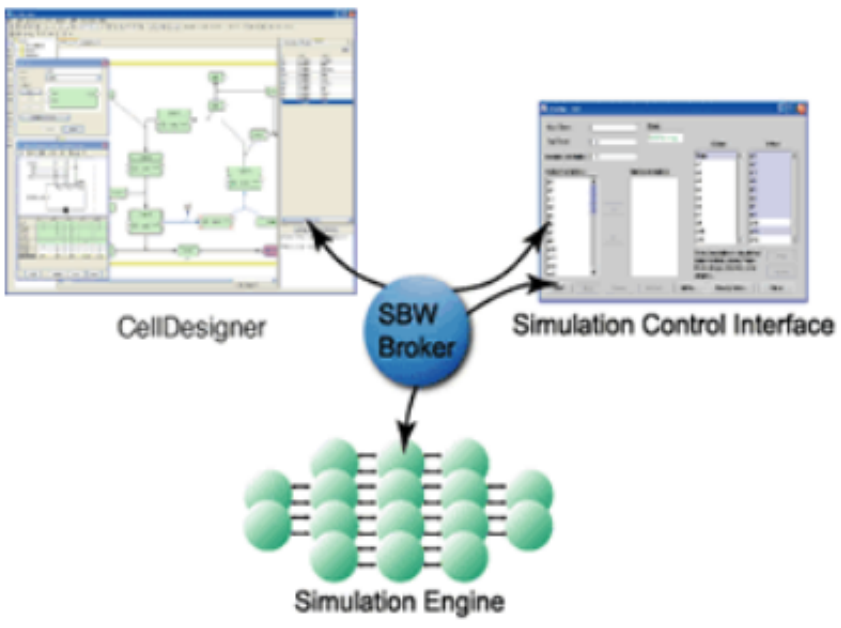
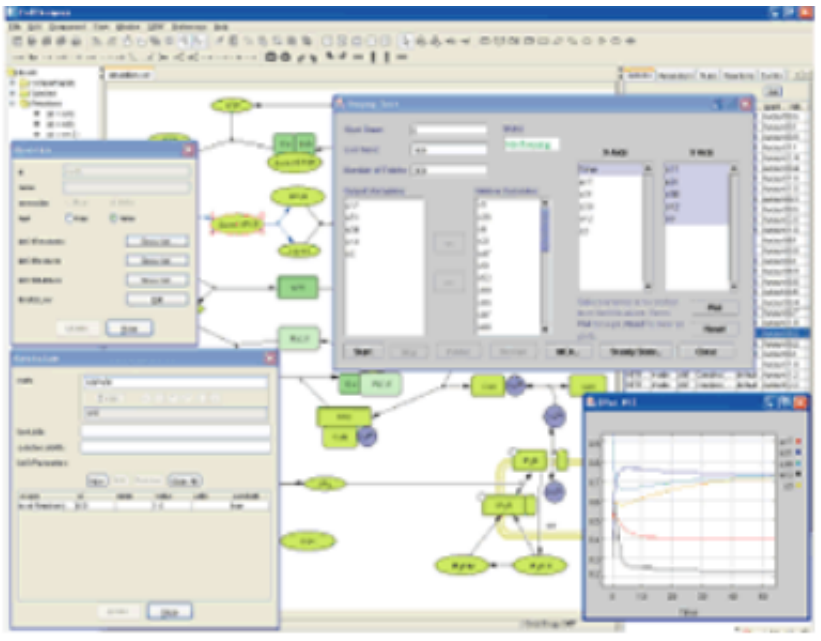


Figure – Solving an ODE

Solving an ODE in practice : no need to code !

ODE solver within Cell Designer





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NB : You don't need to code, but you need to specify kinetic rate and initial condition values to simulate a reaction network.

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 ?

Outline

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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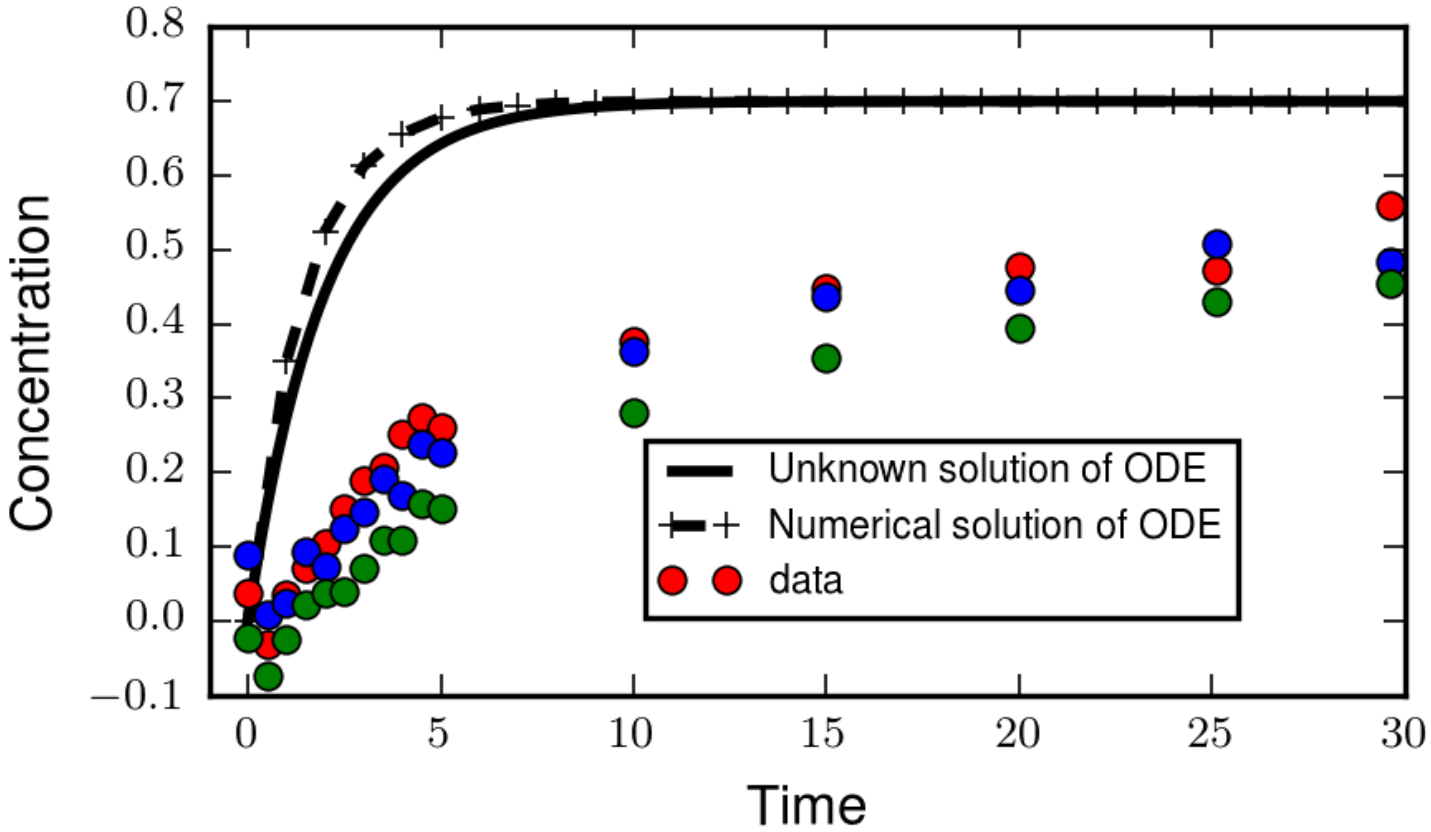

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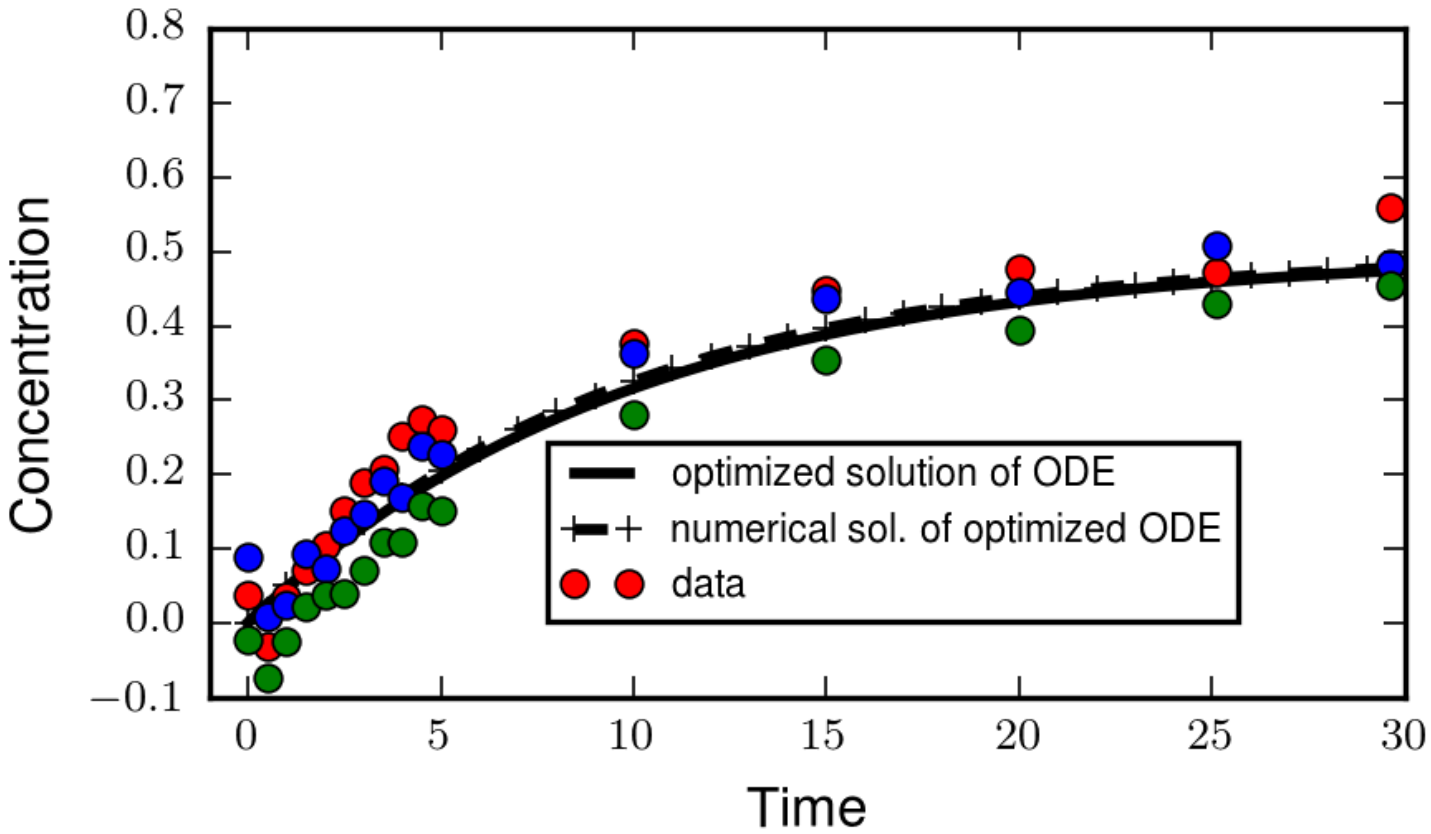


Regression analysis and Parameter estimation with time series : What is difficult ?

- 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.

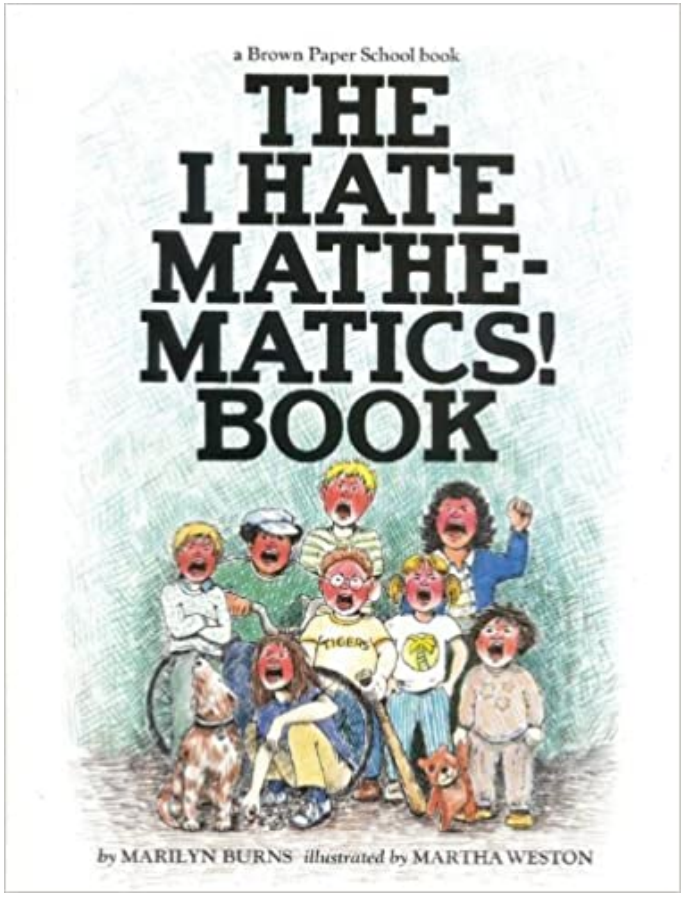
Regression analysis and Parameter estimation with time series : What is difficult ?

- 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 !



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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).

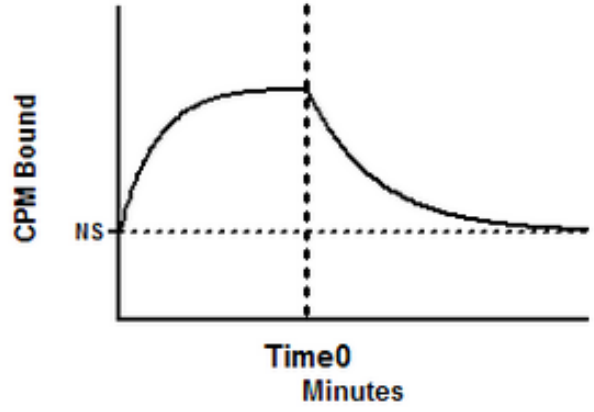
Parameter estimation in

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

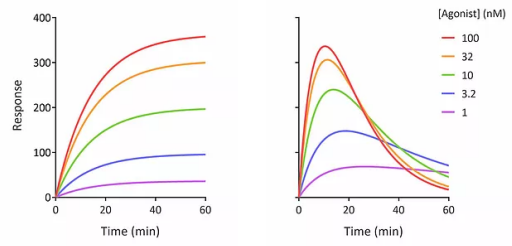
GraphPad

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

Pharmechanics

Pharmacology Data Analysis and Consulting

HOME DATA ANALYSIS CURVE FITTING CONSULTING ABOUT CONTACT



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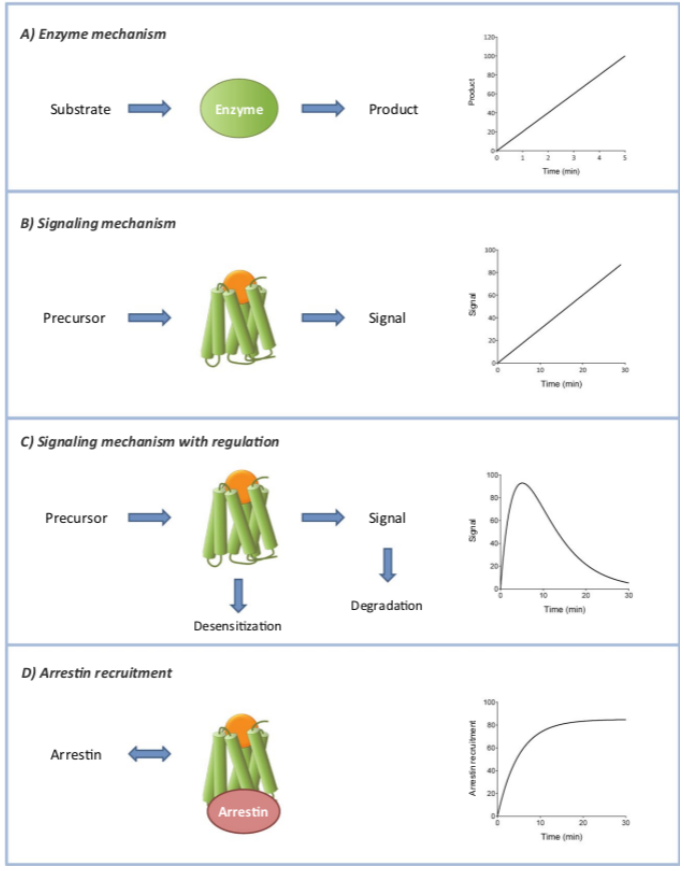
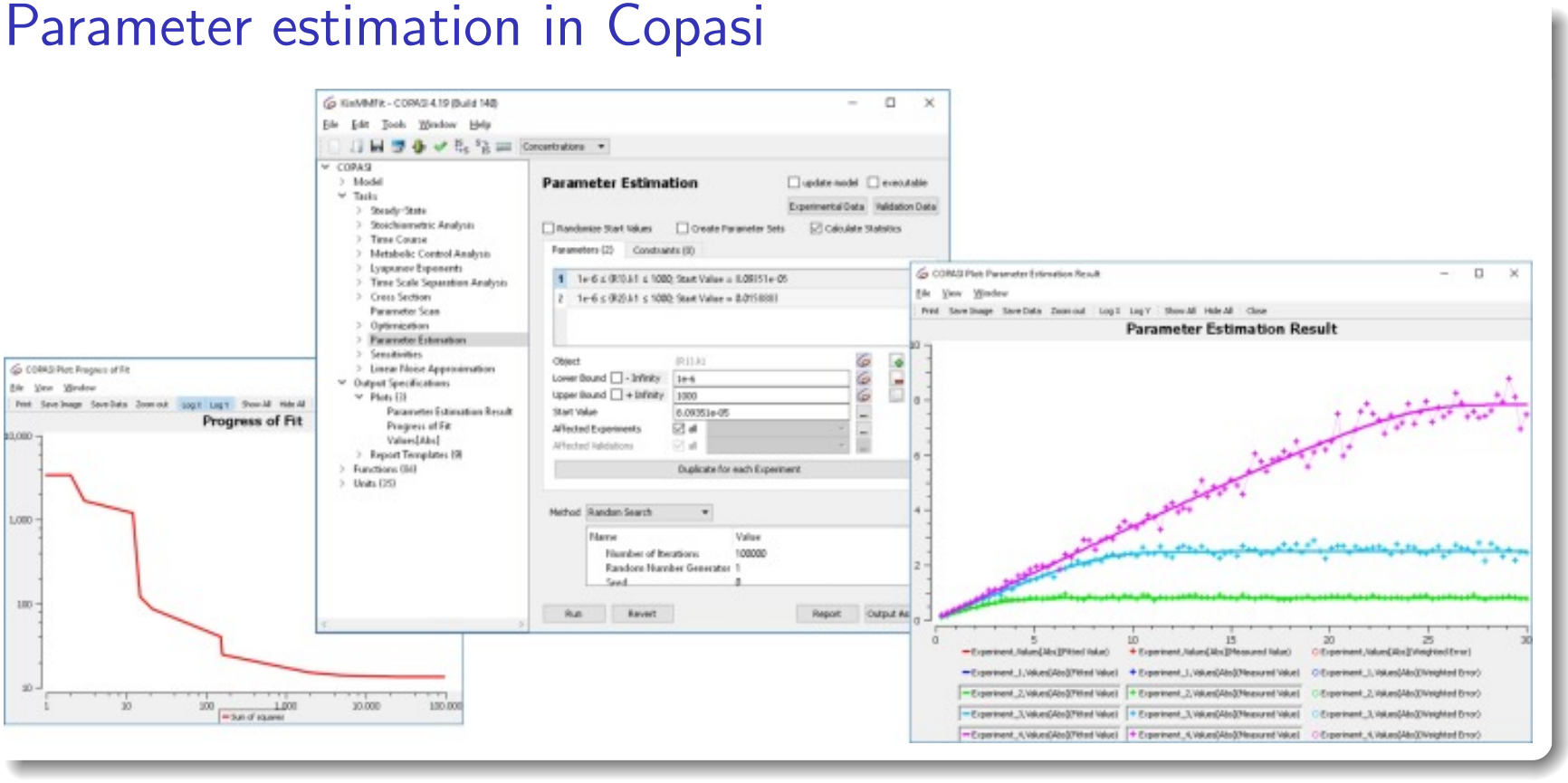


Hoare et al., Analyzing kinetic signaling data for G-protein-coupled receptors, Scientific Reports 10(1) :12263 2020

Parameter estimation in Copasi

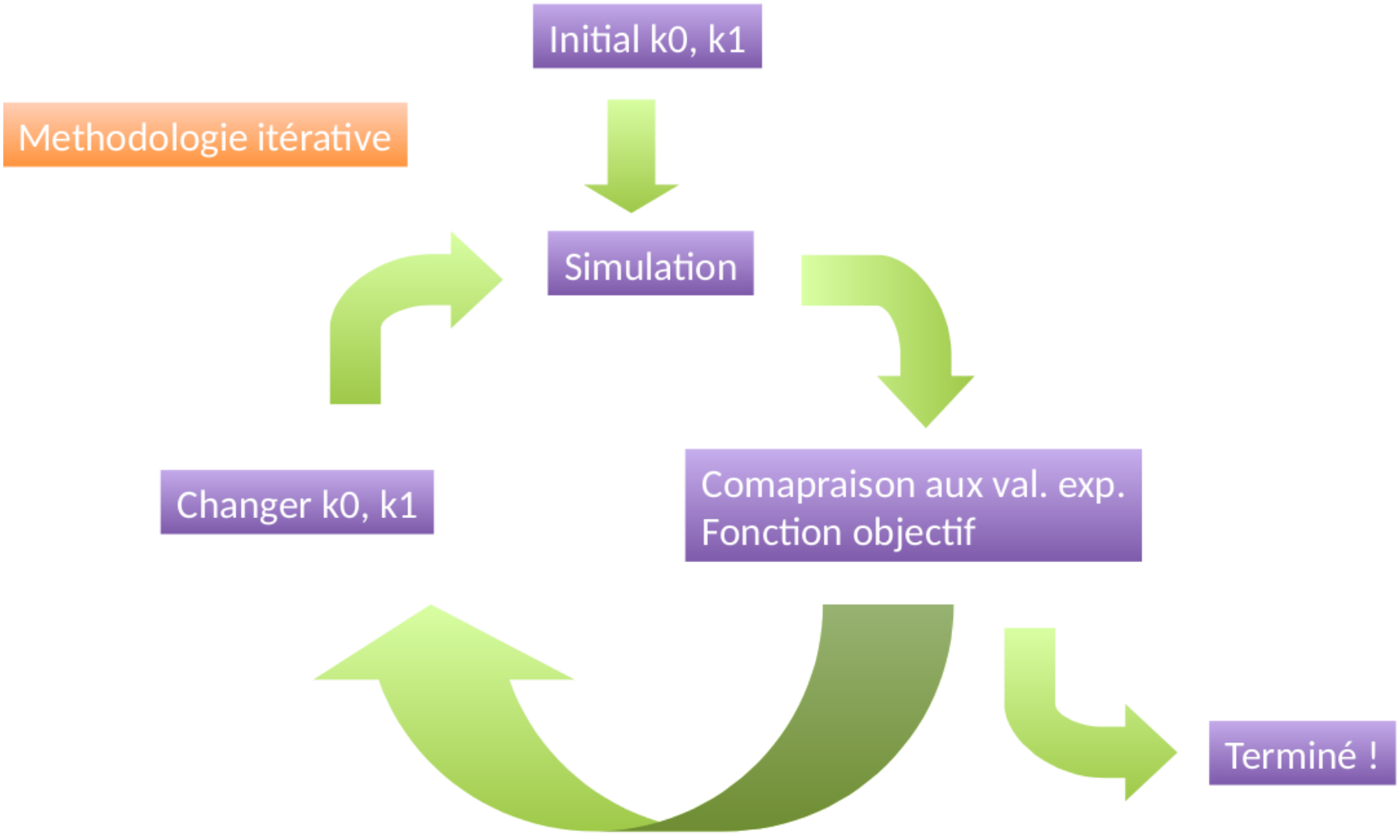


- Models can be imported from Cell Designer.
- Supports both graphical interface and command line.

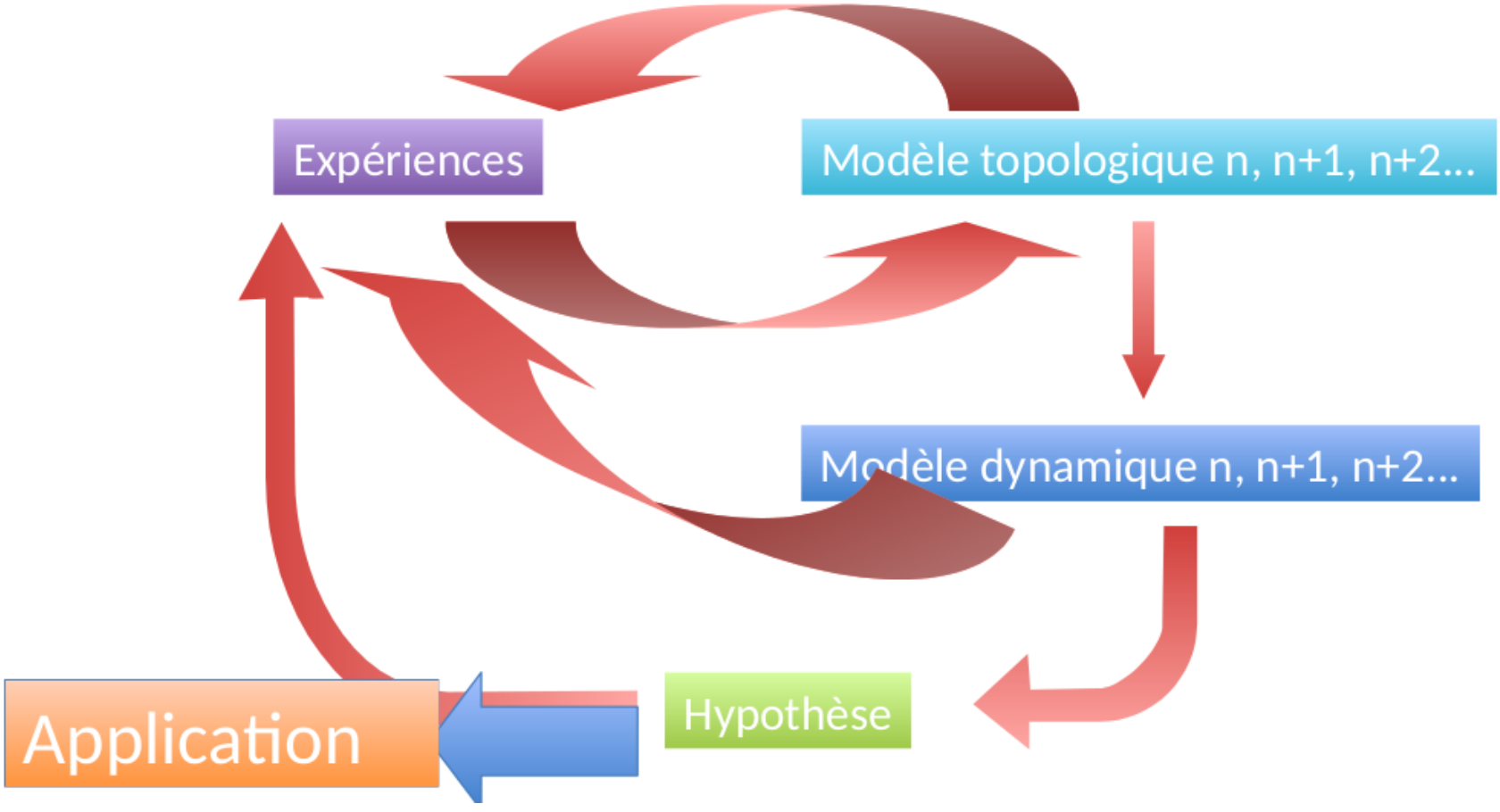
Bergman et al. COPASI and its applications in biotechnology, Journal of Biotechnology 261 :215-220, 2017.

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

Remember ! it's an iterative and interdisciplinary workflow !

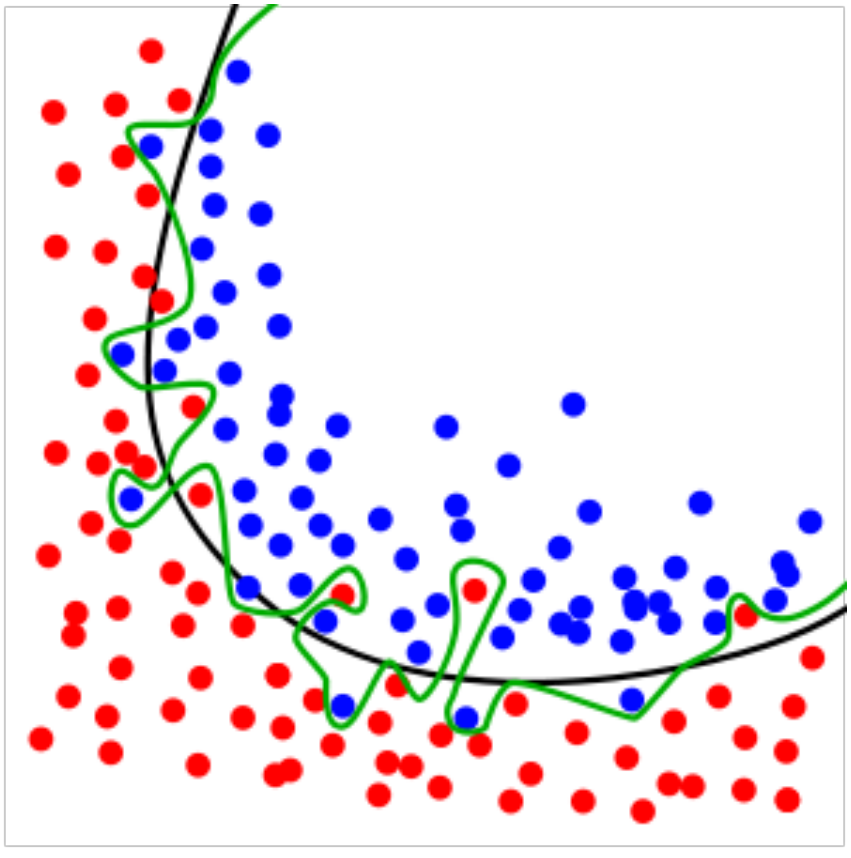


Remember ! it's an iterative and interdisciplinary workflow !



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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NB : The full workflow can be long and require collaboration with statistician / applied mathematician.

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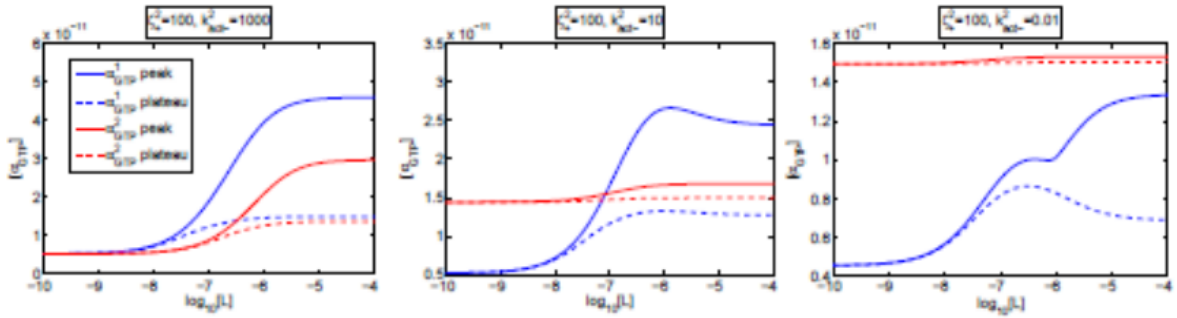
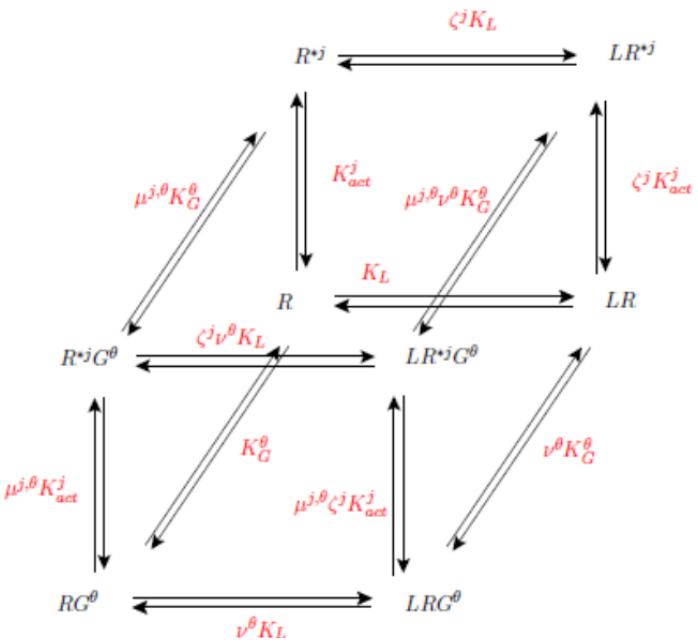
NB bis : **What about applications ?** Go to session 8 : Computational approaches !

Outline

Some applications : Understanding G protein activation cycle

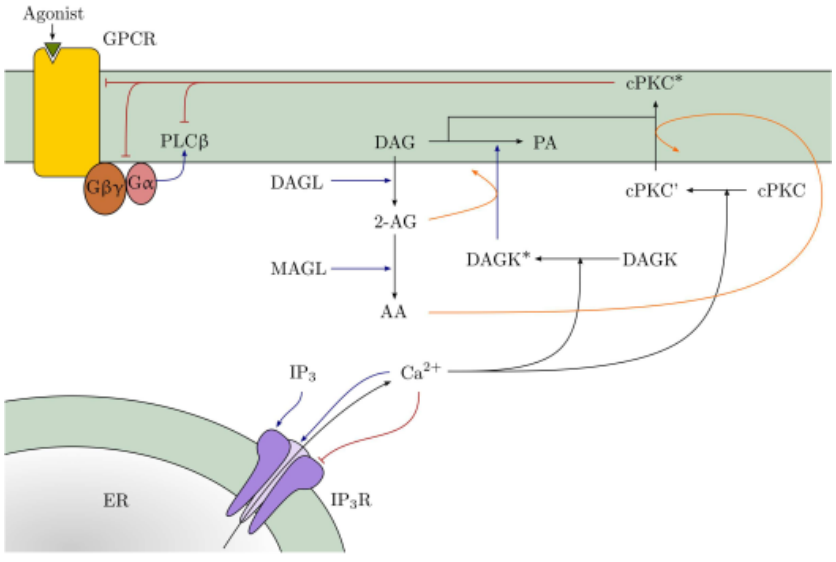


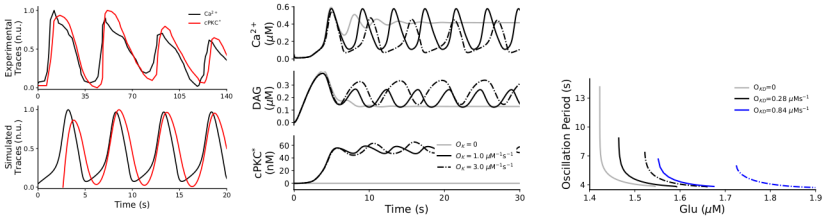
$$\alpha^{\theta}_{GTP} \underset{k_{hyd-}}{\overset{k_{hyd+}}{\rightleftharpoons}} \alpha^{\theta}_{GDP}, \qquad \alpha^{\theta}_{GDP} + \beta\gamma^{\theta} \underset{k_{RA-}}{\overset{k_{RA+}}{\rightleftharpoons}} G^{\theta}.$$



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

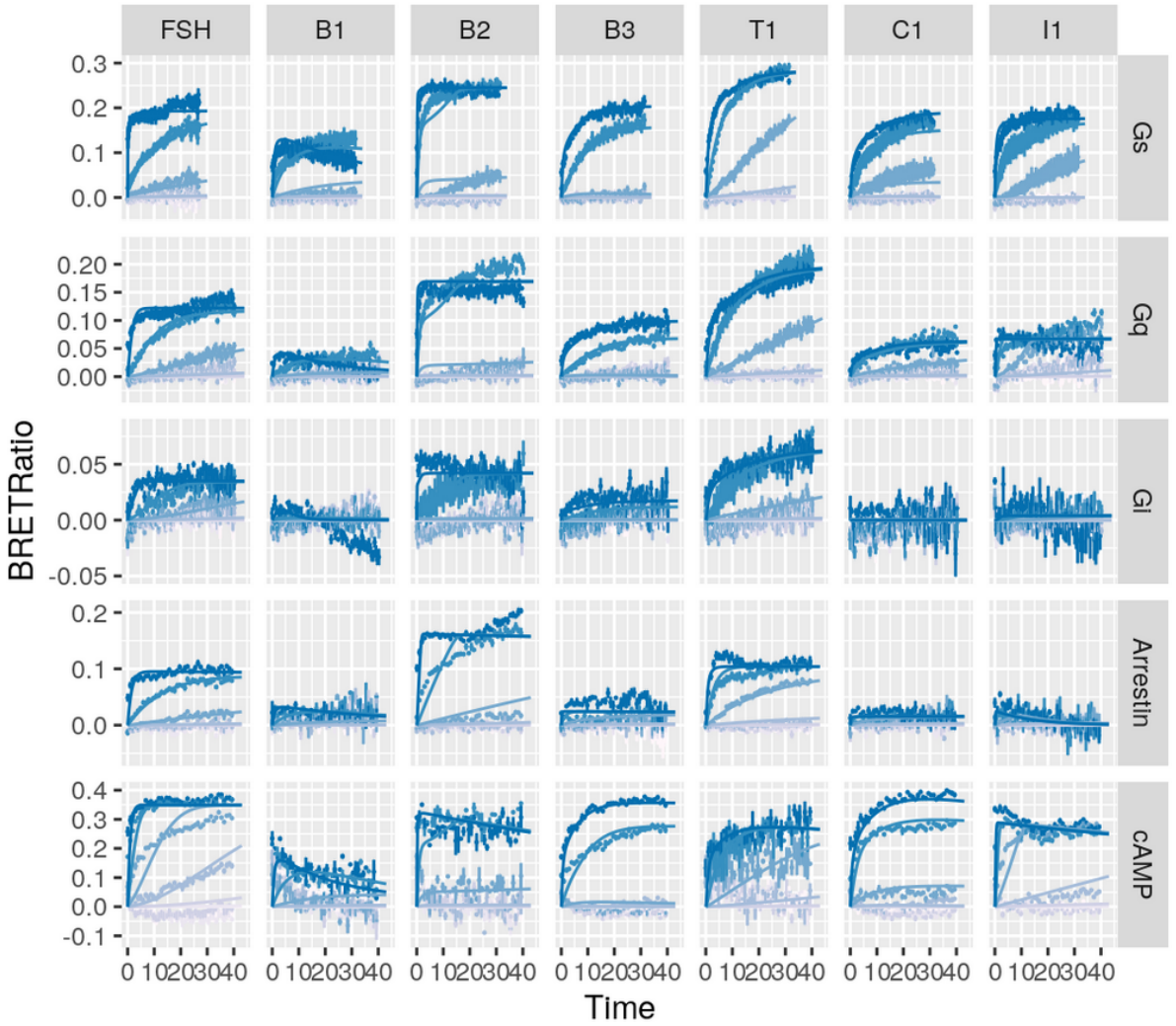
Some applications : Shedding light on GPCR-induced Calcium oscillations in Astrocytes





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.