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# Dynamical modeling of reaction networks 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

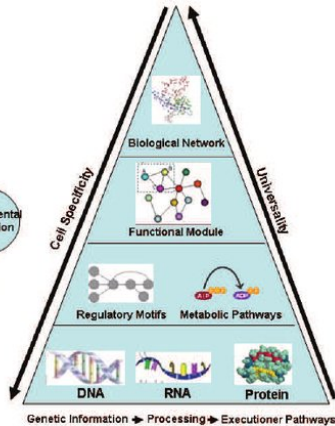
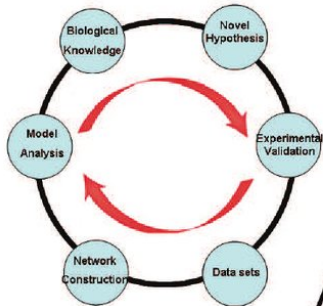
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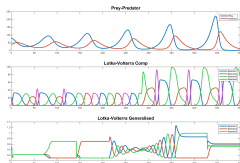
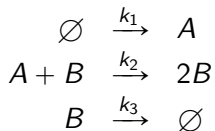


Oltvai and Barabasi, Science 25 :763-764, 2002.

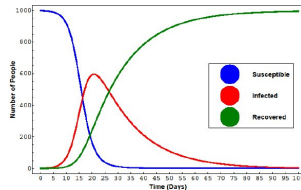
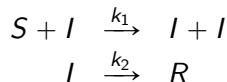
## Small networks in Population dynamics

(Interactions between populations, Epidemiology)

### Lotka-Volterra model



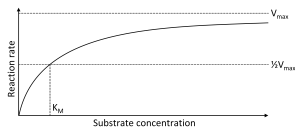
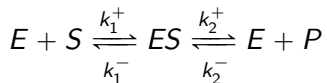
### S.I.R model



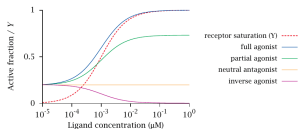
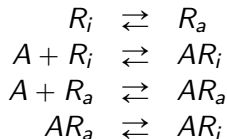
## Small networks in molecular biology

('Toy' molecular models with isolated components)

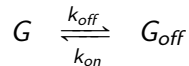
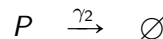
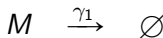
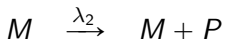
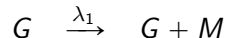
### Enzymatic kinetics



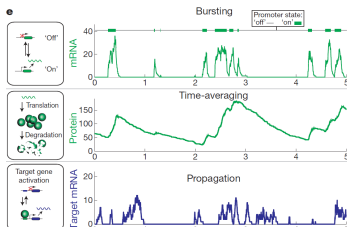
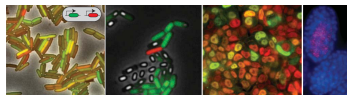
### Pharmacology model



## (Single) Gene Expression



Eldar and Elowitz (*Nature* 2010)





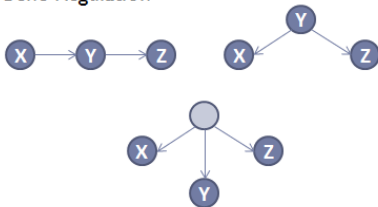
## Co-expression genes network

### Small motifs

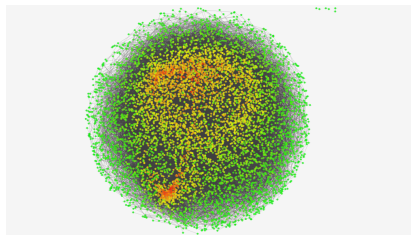
Gene Co-expression



Gene Regulation

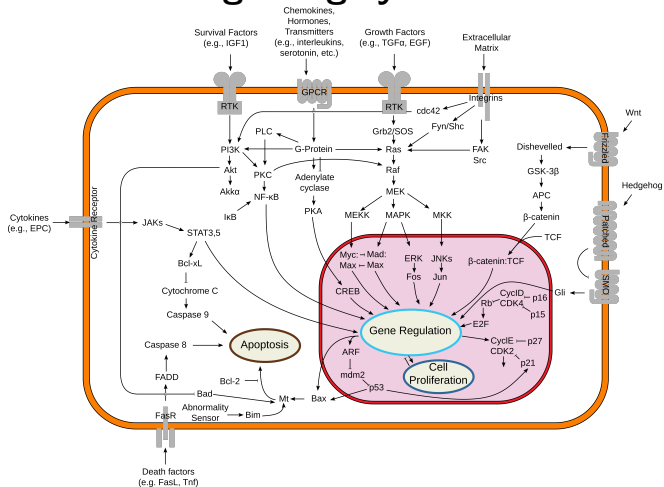


### Large networks



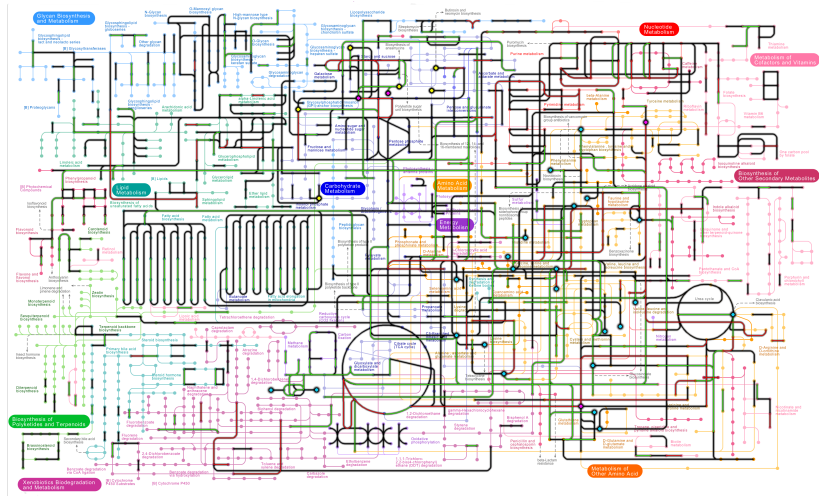
# Systems Biology and Networks at different scales

## Signaling system



# Systems Biology and Networks at different scales

## Metabolomic Network



# Outline

Systems Biology and Networks

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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

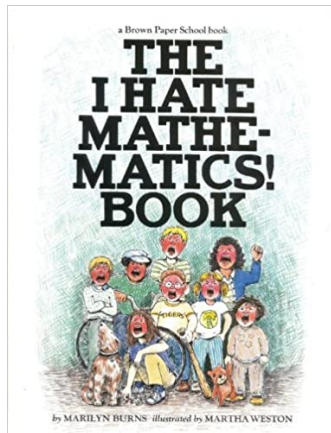
**Today :** Understand the mathematical formalism of dynamical reactions network

# 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!

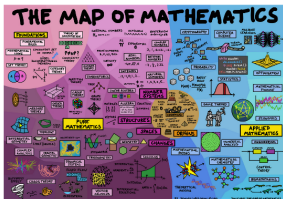


#Ihatemathematics

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



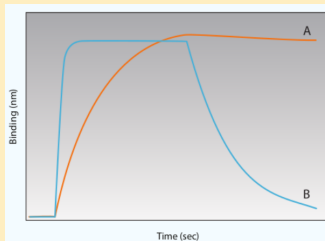
# Maths is about structures...and is generic !



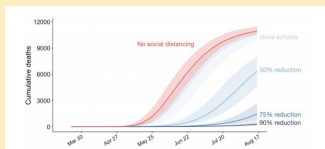
Reactions networks applications range from

- ▶ Chemistry
- ▶ molecular biology
- ▶ epidemiology
- ▶ and beyond !

## Binding experiments



## Covid-19 models



# Outline

Systems Biology and Networks

Motivations and Objectives

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# Chemical Reaction Network, vocabulary

## Definition

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

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

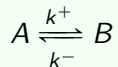
# Chemical Reaction Network, vocabulary

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

## Example



Species  $\mathcal{E} := \{A, B\}$

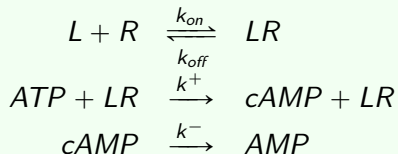
R / P  $\mathcal{C} := \{A, B\}$

Reaction  $\mathcal{R} := \{A \rightarrow B, B \rightarrow A\}$

Rate  $\{k^+, k^-\}$

# Chemical Reaction Network, vocabulary

Example (minimal cAMP production model)



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

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

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

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

# Chemical Reaction Network, FSHR-induced cAMP signals

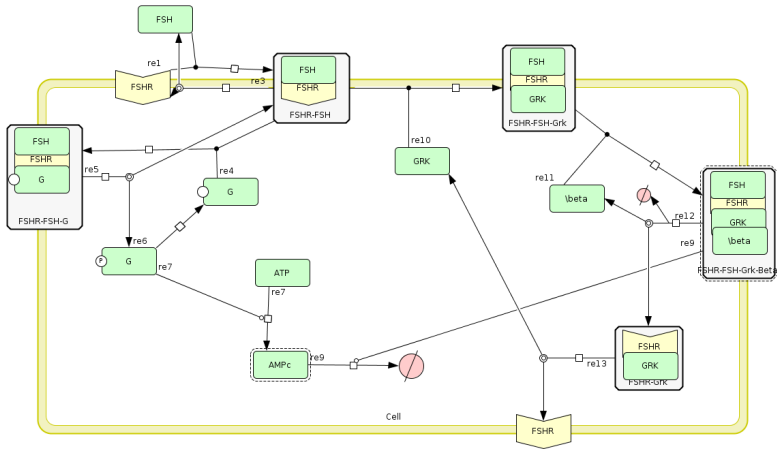
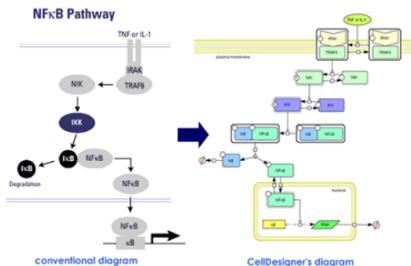
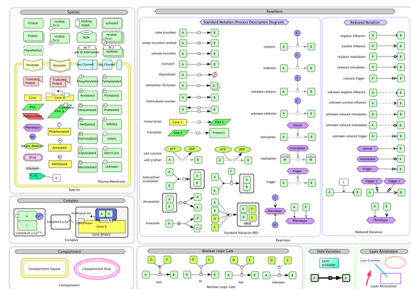


Figure – FSHR ( $G\alpha_s$ -coupled GPCR) models build on CellDesigner

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

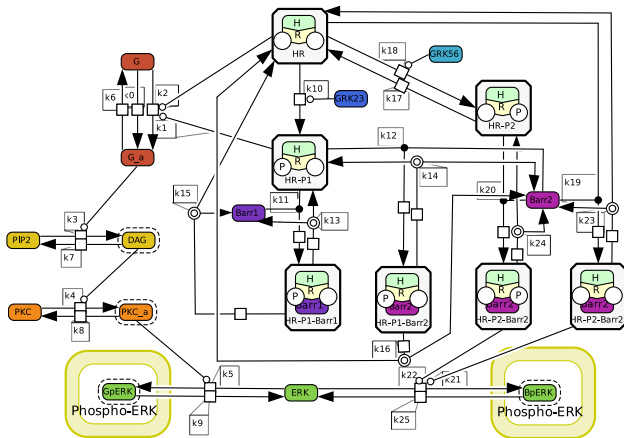


Figure – ERK Phosphorylation pathways build on CellDesigner, Heitzler et al. MSB 2012

# Summary so far

We have seen

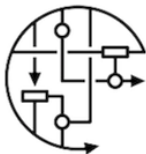
- ▶ Many examples of dynamical system biology models
- ▶ The formalism of *reaction network* models
- ▶ How to *build* a reaction network within Cell Designer

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NB : there exists public databases of reaction network models.



Pathguide) the pathway resource list



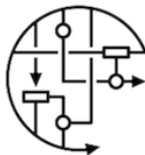
KEGG NETWORK Database  
From gene variation to network variation

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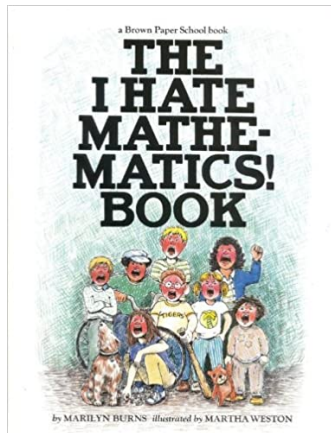
KEGG NETWORK Database  
From gene variation to network variation

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

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

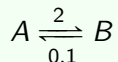
The following couples of slides contain some abstract notions...let's try to catch the meaning!

# 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**.

## Example



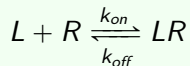
$$\frac{dx_A}{dt}(t) = -0.1x_A(t) + 2x_B(t), \quad x_A(t=0) = A_{tot}$$

$$\frac{dx_B}{dt} = +0.1x_A(t) - 2x_B(t), \quad x_B(t=0) = 0$$

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



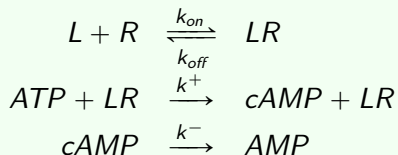
## Example



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

# Chemical Reaction Network and Dynamical models

Example (minimal cAMP production model)



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

# 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*)

Final Position = Initial Position + velocity \* Time ,

which becomes, in mathematical notations,

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

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which becomes, in mathematical notations,

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

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

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

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

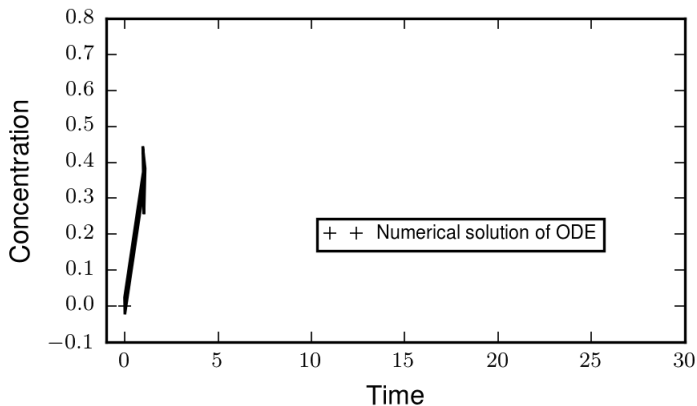


Figure – Solving an ODE

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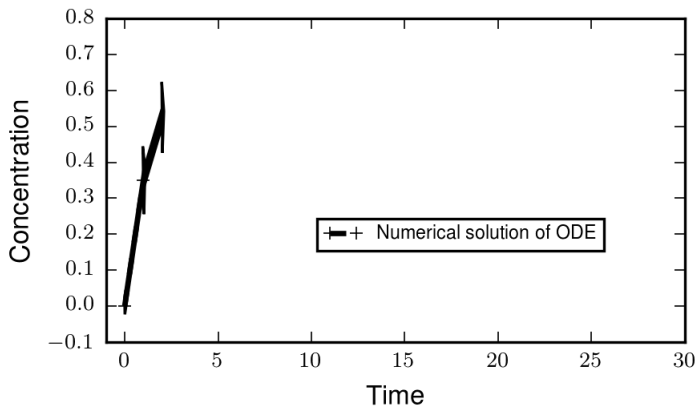


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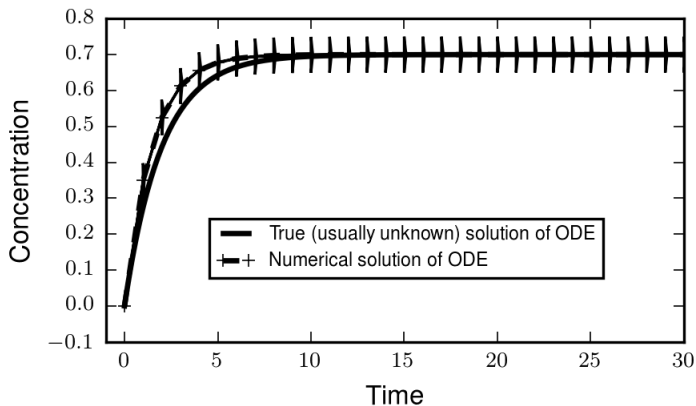
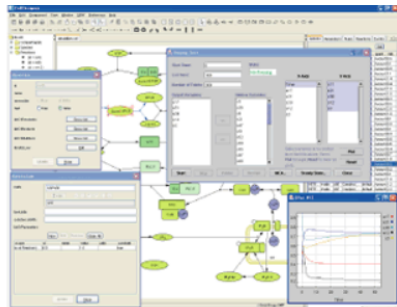
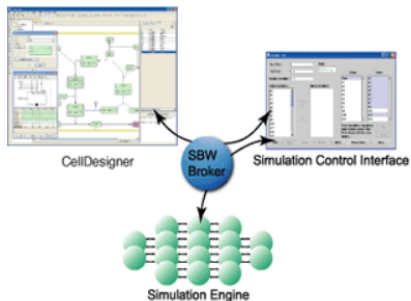


Figure – Solving an ODE



# Solving an ODE in practice : no need to code !

## ODE solver within Cell Designer



Funahashi, A., Tanimura, N., Morohashi, M., and Kitano, H.,  
CellDesigner : a process diagram editor for gene-regulatory and  
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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.

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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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We have seen

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**What about inferring those values from data ?**

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Systems Biology and Networks

Motivations and Objectives

Chemical reaction network formalism

**Parameter estimation**

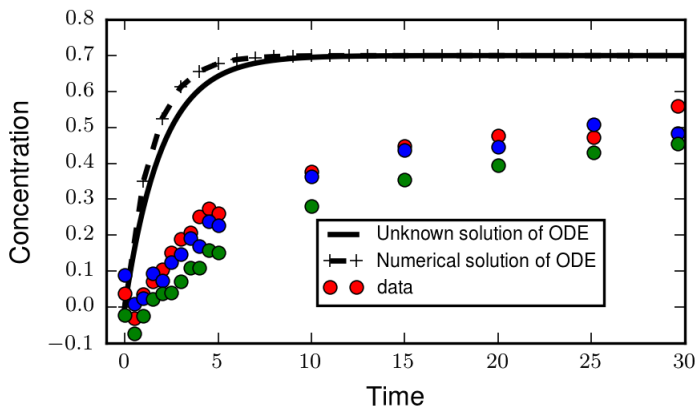
Applications

# 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.

# Parameter and network inference in Chemical Reaction Network

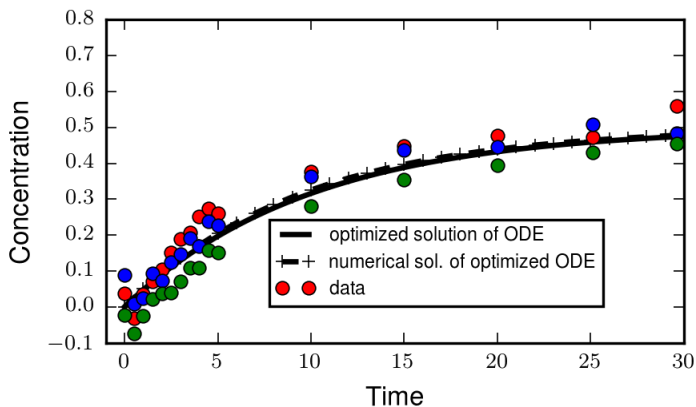
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# Parameter and network inference in Chemical Reaction Network

**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.

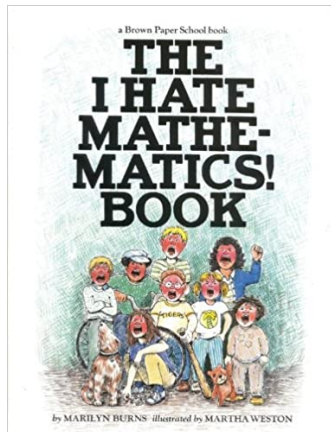
# Regression analysis and Parameter estimation with time series : What is difficult ?

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

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

**Strategy** 2) Using **optimization** algorithms, find the best parameter values  $k, x_0$ , to minimize the distance

# 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.

**Strategy** 2) Using **optimization** algorithms, find the best parameter values  $k, x_0$ , to minimize the distance

**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).

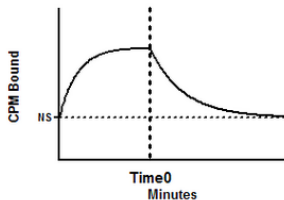
## Parameter estimation in



## 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

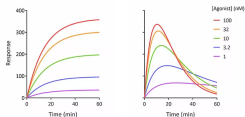


- ▶ Limited to *solvable* models
- ▶ Adapted to analyze one single output at a time, assuming excess of Ligand.

Pharmechanics

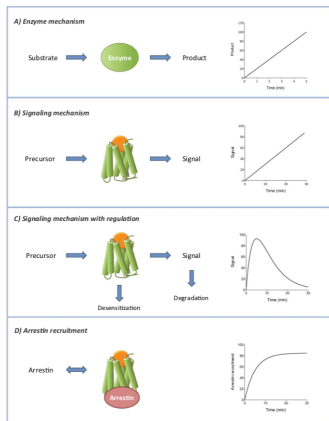
Pharmacology Data Analysis  
and Consulting

HOME DATA ANALYSIS CURVE FITTING CONSULTING ABOUT CONTACT

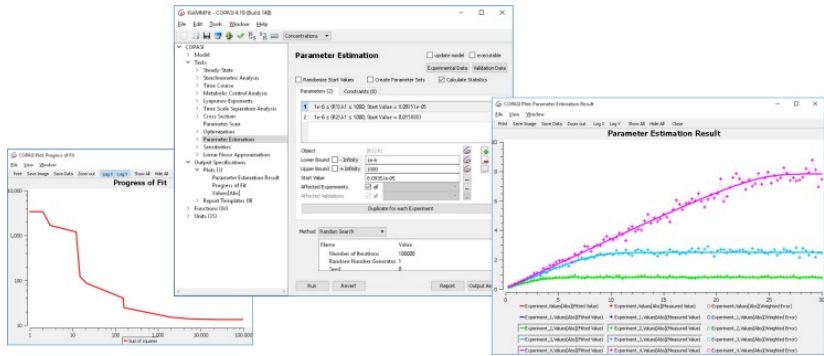


Hoare et al., Analyzing kinetic signaling data for G-protein-coupled receptors, Scientific Reports 10(1) :12263 2020

## Predefined or user-defined time-dependent equations



# Parameter estimation in Copasi



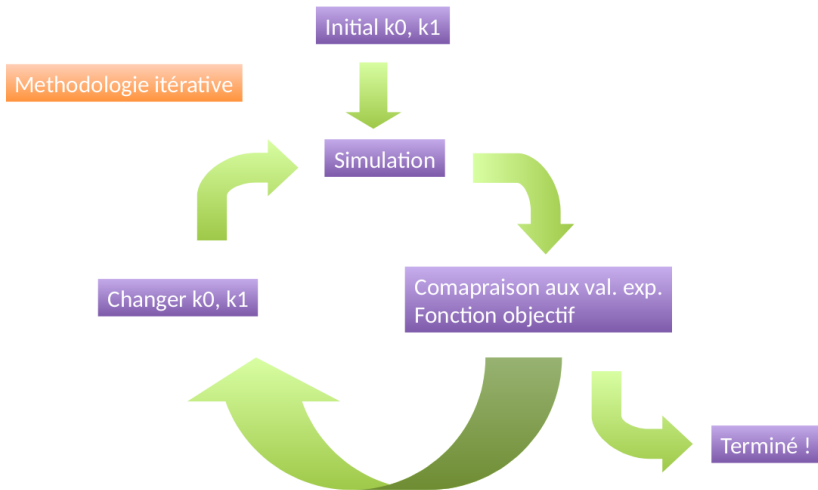
- ▶ Models can be imported from Cell Designer.
- ▶ Supports both graphical interface and command line.



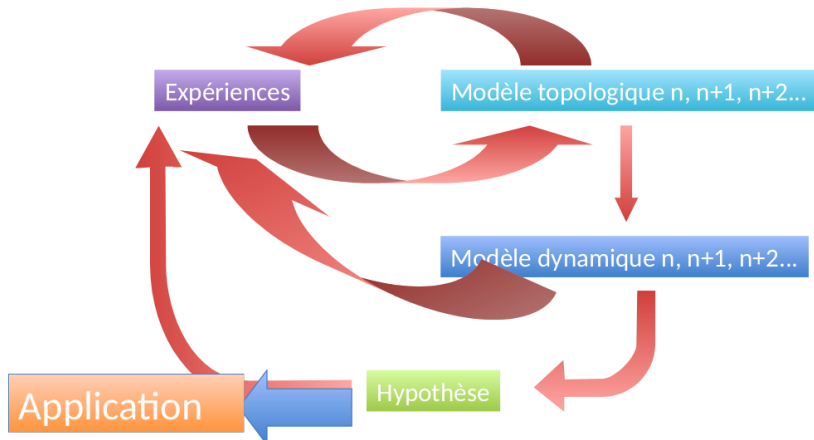
Bergman et al. COPASI and its applications in biotechnology, *Journal of Biotechnology* 261 :215-220, 2017.

Hoops et al. COPASI : a COmplex PATHway Simulator. *Bioinformatics* 22 :3067-74, 2006.

# Remember! it's an iterative and interdisciplinary workflow!

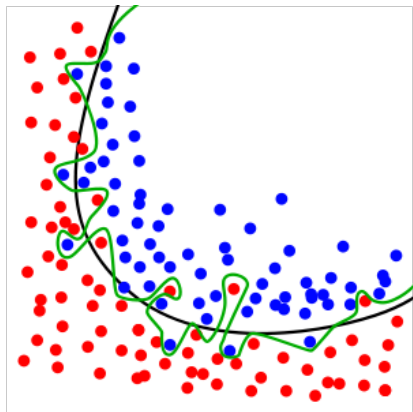


Remember! it's an iterative and interdisciplinary workflow!



# 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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We have seen

- ▶ 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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- ▶ The formalism of dynamical reaction network models
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NB bis : **What about applications?** Go to session 8 :  
Computational approaches !

# Outline

Systems Biology and Networks

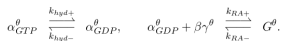
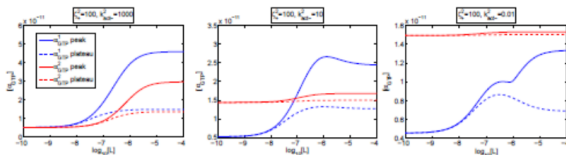
Motivations and Objectives

Chemical reaction network formalism

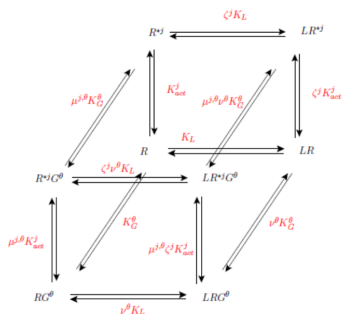
Parameter estimation

**Applications**

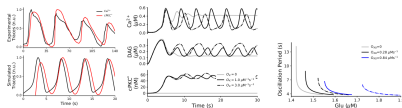
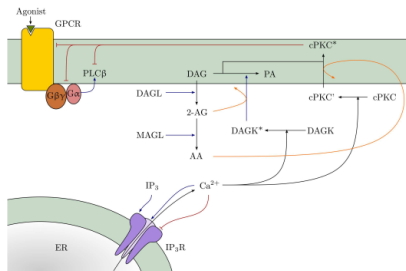
# Some applications : Understanding G protein activation cycle



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

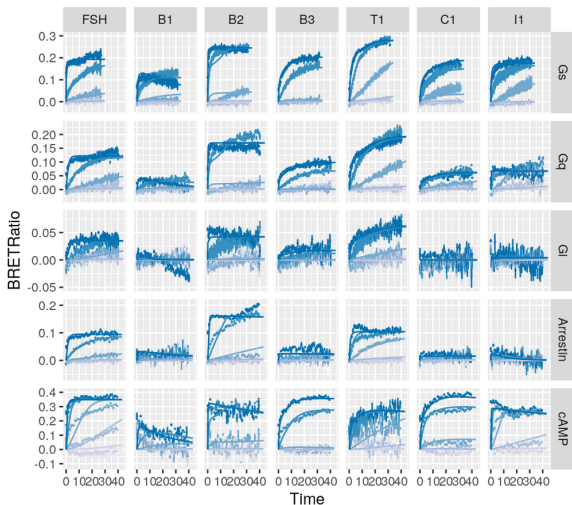


# Some applications : Shedding light on GPCR-induced Calcium oscillations in Astrocytes



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.