Building GPCR signalisation networks. Example of the FSH receptor
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Mathematics of system biology

Romain Yvinec
Systems Biology

Motivation

(Bio)chemical reaction network formalism

Practice!
Systems Biology

Motivation

(Bio)chemical reaction network formalism

Practice!
Systems Biology

- Describe the behaviors and functions of a system (cell, individual, ecosystem) by studying interactions between its constituents (molecules, tissue, individuals): holistic approach, complex system.

- "Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" (Denis Noble).
Describe the behaviors and functions of a system (cell, individual, ecosystem) by studying interactions between its constituents (molecules, tissue, individuals): holistic approach, complex system.

"Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" (Denis Noble).

Computer science and Mathematical modeling of complex system biology.

Theory of dynamical systems applied to molecular biology.
Population dynamics
(Birth and death processes)

\[ \emptyset \Leftrightarrow A \]

Goal: Understand when a population goes to extinct, survive, invades...
**Small networks**
(Interaction between population, ’toy’ molecular models)

**Logistique model**

\[
\begin{align*}
\emptyset & \rightarrow A \\
A + A & \rightarrow \emptyset
\end{align*}
\]

**Lotka-Volterra model**

\[
\begin{align*}
\emptyset & \rightarrow A \\
A + B & \rightarrow 2B \\
B & \rightarrow \emptyset
\end{align*}
\]

Goal: gives simple description/explanation of yet complex behaviors (oscillation, multi-stability...)

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*Systems Biology and reaction network*
Small networks
(Interaction between population, 'toy' molecular models)

Enzymatic kinetics

\[
E + S \rightleftharpoons ES \rightleftharpoons E + P
\]

Pharmacology model

\[
\begin{align*}
R_i & \rightleftharpoons R_a \\
A + R_i & \rightleftharpoons AR_i \\
A + R_a & \rightleftharpoons AR_a \\
AR_a & \rightleftharpoons AR_i
\end{align*}
\]

Goal: gives simple description/explanation of yet complex behaviors (oscillation, multi-stability...)
(Single) Gene Expression

\[
\begin{align*}
  G & \rightarrow G + M \\
  M & \rightarrow M + P \\
  M & \rightarrow \emptyset \\
  P & \rightarrow \emptyset \\
  G + P & \rightarrow G_{off}
\end{align*}
\]

Goal: Understand the variability of level of expression between cells
Systems Biology and reaction network

Co-expression genes network

Small motifs

Gene Co-expression

Gene Regulation

Large networks

Goal: characterize network topology (and dynamics) associated to certain conditions, diseases, etc.)
Goal: Understand cell response to external stimuli (to control it)
Goal: Understand regulations of key metabolites, explain toxicity or determine phenotype...
Outline

Systems Biology

Motivation

(Bio)chemical reaction network formalism

Practice!
Possible applications of mathematical modelling

- Understand non-trivial behavior of a biological system (by reproducing this behavior with an understandable model)
- Help to identify intermediate molecules and/or give some evidence for direct interactions between molecules
- Quantify some non-observables quantities, in particular: molecules concentrations, reaction rates.
Possible applications of mathematical modelling

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- Quantify some non-observables quantities, in particular: molecules concentrations, reaction rates.

Today: Compare quantitatively the effect of two Ligands on two signalling pathways: bias signalling
Outline

Systems Biology

Motivation

(Bio)chemical reaction network formalism

Practice!
Definition

A chemical reaction network is given by the sets \((S, C, R)\):

- **Species**, \(S := \{S_1, \cdots, S_d\}\): molecules that undergo a series of chemical reactions.

- **Reactant / Product**, \(C := \{y^1, \cdots, y^n\}\): Linear combination of species, that represent either 'what is consumed', or 'what is produced', in any reaction.

- **Reaction**, \(R := \{y^k \rightarrow y^{k'}, y^k, y^{k'} \in C\}\): 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**, a function $\kappa : R \rightarrow \mathbb{R}_+^*$ that gives to any reaction a positive parameter (kinetic rate).
Chemical Reaction Network, vocabulary

Exemple

\[ \emptyset \rightleftharpoons A \]

Species  \( \mathcal{E} := \{ A \} \)

R / P  \( \mathcal{C} := \{ \emptyset, A \} \)

Reaction  \( \mathcal{R} := \{ \emptyset \rightarrow A, A \rightarrow \emptyset \} \)
**Exemple**

\[
\begin{align*}
A & \iff 2B \\
A + C & \iff D \\
B + E & \\
\end{align*}
\]

**Species** \( \mathcal{E} := \{A, B, C, D, E\} \)

**R / P** \( \mathcal{C} := \{A, 2B, A + C, D, B + E\} \)

**Reaction** \( \mathcal{R} := \{A \rightarrow 2B, 2B \rightarrow A, A + C \rightarrow D, D \rightarrow A + C, D \rightarrow B + E, B + E \rightarrow A + C\} \)
Exemple (the one we will consider later on)

\[
FSH + FSHR \quad \rightleftharpoons \quad FSH/FSHR \\
ATP + FSH/FSHR \quad \rightarrow \quad cAMP + FSH/FSHR \\
cAMP \quad \rightarrow \quad AMP \\
\ldots \quad \rightarrow \quad \ldots
\]

Species \quad \mathcal{E} := \{FSH, FSHR, FSH \rightarrow FSHR, ATP, cAMP, AMP\}

R / P \quad \mathcal{C} := \{FSH + FSHR, FSH/FSHR, ATP + FSH \rightarrow FSHR, cAMP + FSH/FSHR, cAMP, AMP\}

Reaction \quad \mathcal{R} := \{FSH + FSHR \rightarrow FSH/FSHR, FSH/FSHR \rightarrow FSH + FSHR, ATP + FSH/FSHR \rightarrow \\
cAMP + FSH/FSHR, cAMP \rightarrow AMP\}
Chemical Reaction Network, "real" example

Figure – Classical GPCR models
Figure – ERK Phosphorylation pathways, Heitzler et al. MSB 2012
A (deterministic) dynamical model of a Chemical Reaction Network keep track of

- **concentration** of species: \( x_i \in \mathbb{R}_+, \ i = 1..d \).
- Reactions happen **continuously** and **simultaneously**
- [Law of Mass action] The velocity of a reaction is proportional to the concentrations of its reactants.
- Systems of Ordinary Differential Equations.
Exemple

\[ \emptyset \xrightarrow{2}{\text{0.1}} A \]

\[ \frac{dx_A}{dt} = 2 - 0.1x_A. \]
Exemple

\begin{align*}
A & \xrightarrow{0.8} 2B \\
A + C & \xrightarrow{100} 0.33 \rightarrow D \\
D & \xrightarrow{1.0} B + E
\end{align*}

\begin{align*}
\frac{dx_A}{dt} &= -0.8x_A + 100x_B^2 - 0.33x_Ax_C \\
\frac{dx_B}{dt} &= +0.8x_A - 2 \times 100x_B^2 + x_D \\
\frac{dx_C}{dt} &= -0.33x_Ax_C \\
\frac{dx_D}{dt} &= 0.33x_Ax_C - x_D \\
\frac{dx_E}{dt} &= x_D
\end{align*}
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 \( \Delta t \ll 1 \):

1) Start at a given initial condition \( x_0 \) at time \( t_0 = 0 \)
But what is an "Ordinary Differential Equation"? A math theory in one slide!

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1) Start at a given initial condition \( x_0 \) at time \( t_0 = 0 \)

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

\[
\text{Final Position} = \text{Initial Position} + \text{velocity} \times \text{Time},
\]

which becomes, in mathematical notations,

\[
x(\Delta t) = x_0 + v(x_0) \times \Delta t,
\]
But what is an "Ordinary Differential Equation"? A math theory in one slide!

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\[ x(\Delta t) = x_0 + v(x_0) \times \Delta t, \]

Iterate : To calculate the value of \( x \) at the next time step, use
\[ x((i + 1) \times \Delta t) = x(i \times \Delta t) + v(x(i \times \Delta t)) \times \Delta t, \]
But what is an "Ordinary Differential Equation"? A math theory in one slide...and a figure!

Figure – Solving an ODE
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Figure – Solving an ODE
**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.
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 $(S, C, R)$, 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.
Parameter and network optimization in Chemical Reaction Network

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2) Using **optimization** algorithms, find the best parameter values \(k, x_0\), to minimize the distance
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and compute a **distance** between the solution and the data.

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

3) If needed, change the reaction network (add or delete species/reactions)
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 resolve parameter non-identifiability (See Likelihood maximization or Bayesian statistics).
Outline

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(Bio)chemical reaction network formalism

Practice!
Let’s go to practice!
Dose-response curves and operational model

Figure – End-point Dose-response curves
Dose-response curves and operational model

Figure – 2 minutes Dose-response curves
Dose-response curves and operational model

Figure – 5 minutes Dose-response curves
Dose-response curves and operational model

Figure – 10 minutes Dose-response curves
Dose-response curves and operational model

Figure – 20 minutes Dose-response curves
Dose-response curves and operational model

Figure – 30 minutes Dose-response curves
All the analyses of dose-response curves at particular time points might not be consistent with respect to each other!

Dose-response curve and kinetic data

- All the analyses of dose-response curves at particular time points might not be consistent with respect to each other!
- Go for a dynamical model!
Reaction network model

Figure – One possible model
Time-dependent data

Figure – Dose 1
Time-dependent data

**Figure – Dose 2**

- **cAMP FSH**
- **Barr2 FSH**
- **cAMP 239**
- **Barr2 239**
Time-dependent data

Figure – Dose 3
Time-dependent data

Figure – Dose 4
Time-dependent data

Figure – All doses in one fitted model
Parameter identifiability

Figure – Cell parameters
Parameter identifiability

Figure – Ligand specific parameters
Reaction network model: bias between FSH and 239

Figure – One possible model for FSH
Reaction network model: bias between FSH and 239

Figure – One possible model for 239