Inferring parameters in genetic regulatory networks

Camilo La Rota\textsuperscript{1}  Fabien Tarissan\textsuperscript{2}  Leo Liberti\textsuperscript{2}

\textsuperscript{1}Complex Systems Institute (IXXI)
Ecole Normale Superieure - CNRS, Lyon, France

\textsuperscript{2}LIX (Computer science laboratory)
Ecole Polytechnique, Palaiseau, France

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Outline

1. Introduction
   - Inverse Problems in Biological Complex Systems
   - Biological Context

2. Modelling the Biological Problem
   - Gene Expression, regions and tissues
   - Gene Interaction Network
   - Gene Regulatory Network models

3. GRN Inference
   - Modelling the inverse problem
     - Defining the GRN
     - Defining the inverse problem
   - Mathematical Programming Formulation
     - Definitions
     - Objective Function and Constraints
     - Reformulation and linearization

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European Morphex Project

Biological Problem Solving:
Gene regulatory networks and cell interactions in morphogenesis.
Models and protocols for parameter inference.

Complex Systems:
Meta-model and associated concepts for designing tools and protocols.

Simulation Platform:
Generic pre and post simulation tools and generic protocols.

WP2
Data

WP3
Model

WP4
Simulation

How to propose a first possible model
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Inferring parameters in genetic regulatory networks
Genetic regulatory networks (GRN) and morphogenesis
Developmental stages of Arabidopsis Thaliana

**Arabidopsis Flower Development**

- GRN dynamics + other factors: morphogenesis, structure, tissue diversity
- Continuous development
- Discrete stages

**Genetic Control of Morphogenesis**
GRN Subnetworks’ Stability

Mutants stable states \(\sim\) Unstable states at wild-type stages.

Wild type stages (unstable states)

Unstable states stage 2 \(\sim\) (ag, pi) mutant stable states

(Pelaz, 2000)

stage 2 = at least 4 stable states (sepals (1) + meristem (3))
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Gene Expression, regions and tissues

Expression data
- mRNA
- Spatiotemporal distribution
  - Qualitative
  - Imprecise
  - Time-discrete

Exploiting the data
- Superposition of expression patterns reveals regions.
- Data is difficult to analyze, multiple interpretations are possible.
- Tentative subdivisions in homogeneous regions are proposed.
Cell or tissue lineage

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Gene Interaction Network

Interaction data
- Molecular evidence
- Genetic evidence

Exploiting the Data
- Uncertain
- Conflicting interpretations
- Error prone
- Prior Interaction Network
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Inferring parameters in genetic regulatory networks
Quantitative activity of gene $i$

$$\frac{d([x_i](t))}{dt} = f_i([P], [x_1], \ldots, [x_m]) - \lambda_i [x_i]$$

$$f_i([P], [x_1], \ldots, [x_m]) = \sum_{s \in S_i} v(s) \mathbb{P}(s_i = s)$$

$$\mathbb{P}(s_i = s) = \frac{K_B(s)[P]^{\alpha_s} [x_1]^{\alpha_1^s} \cdots [x_m]^{\alpha_m^s}}{1 + \sum_{z \in S_i} K_B(z)[P]^{\alpha_z} [x_1]^{\alpha_z^1} \cdots [x_m]^{\alpha_z^m}}$$

Exemples of regulatory phenomena

Activation

$$f_i([P], [x_a]) = \frac{[P](v_P K_P + v_{ap} K_{ap}[x_a])}{1 + K_p[P] + K_a[x_a] + K_{ap}[x_a][P]}$$
Gene Regulatory Network models

Gene transcription mechanisms, mass action kinetics: the Shea-Ackers model

Quantitative activity of gene i

\[
\frac{d([x_i](t))}{dt} = f_i([P], [x_1], \ldots, [x_m]) - \lambda_i [x_i]
\]

\[
f_i([P], [x_1], \ldots, [x_m]) = \sum_{s \in S_i} \nu(s) \mathbb{P}(s_i = s)
\]

\[
\mathbb{P}(s_i = s) = \frac{K_B(s)[P]^{\alpha_s} [x_1]^{\alpha_1} \ldots [x_m]^{\alpha_m}}{1 + \sum_{z \in S_i} K_B(z)[P]^{\alpha_z} [x_1]^{\alpha_1} \ldots [x_m]^{\alpha_m}}
\]

Exemples of regulatory phenomena

**Activation**

\[
f_i([P], [x_a]) = \frac{[P](\nu_p K_p + \nu_{ap} K_{ap}[x_a])}{1 + K_p[P] + K_a[x_a] + K_{ap}[x_a][P]}
\]

**Repression**

\[
f_i([P], [x_r]) = \frac{[P] \nu_p K_p}{1 + K_p[P] + K_r[x_r] + K_{rp}[x_r][P]}
\]
Gene Regulatory Network models
Gene transcription mechanisms, mass action kinetics: the Shea-Ackers model

Quantitative activity of gene $i$

$$\frac{d([x_i](t))}{dt} = f_i([P], [x_1], \ldots, [x_m]) - \lambda_i [x_i]$$

$$f_i([P], [x_1], \ldots, [x_m]) = \sum_{s \in S_i} v(s) [P](s_i = s)$$

$$[P](s_i = s) = \frac{K_B(s)[P]^{\alpha_s}[x_1]^{\alpha_s^1} \cdots [x_m]^{\alpha_s^m}}{1 + \sum_{z \in S_i} K_B(z)[P]^{\alpha_z}[x_1]^{\alpha_z^1} \cdots [x_m]^{\alpha_z^m}}$$

Exemples of regulatory phenomena

**Activation**

$$f_i([P], [x_a]) = \frac{[P](v_p K_p + v_a p K_a p[x_a])}{1 + K_p[P] + K_a[x_a] + K_a p[x_a][P]}$$

**Repression**

$$f_i([P], [x_r]) = \frac{[P] v_p K_p}{1 + K_p[P] + K_r[x_r] + K_r p[x_r][P]}$$

**Competition/Synergy**

$$f_i([P], [x_1], \ldots, [x_m]) = \frac{[P](v_p K_p + \sum_{i=1}^{m} v_i p K_i p[x_i])}{1 + K_p[P] + \sum_{i=1}^{m} K_i[x_i] + K_i p[x_i][P]}$$
Gene Regulatory Network models
Quantitative Piecewise Differential and Qualitative Generalized Logical models

Quantitative activity of gene i

\[
\frac{d(x_i(t))}{dt} = f_i(x_1, \ldots, x_m) - \lambda_i x_i(t)
\]

\[
f_i(\vec{x}(t)) = \sum_{j \in 1, \ldots, m} (\nu_{0i} + \nu_{ji} H^{\alpha_{ji}}(x_j(t), \sigma_{ji}))
\]

\[
x_i(t) = \frac{F_i(\vec{x}^0)}{\lambda_i} - \left( \frac{F_i(\vec{x}^0)}{\lambda_i} - x_i^0 \right) e^{-\lambda_i t}
\]

- \(\sigma_{ji}\): threshold of interaction.
- \(\nu_{ji}\): induced transcription rate.
- \(\alpha_{ij}\): Kind of interaction (-1, +1)

Remarks

Lost: transitory dynamics, interaction crosstalk (constant thresholds).
Gene Regulatory Network models
Quantitative Piecewise Differential and Qualitative Generalized Logical models

### Quantitative activity of gene i

\[
\frac{d(x_i(t))}{dt} = f_i(x_1, \ldots, x_m) - \lambda_i x_i(t) \\
f_i(\tilde{x}(t)) = \sum_{j \in 1, \ldots, m} (v_{0i} + v_{ji} H^{\alpha_{ji}}(x_j(t), \sigma_{ji})) \\
x_i(t) = \frac{F_i(\tilde{x}^0)}{\lambda_i} - (\frac{F_i(\tilde{x}^0)}{\lambda_i} - x_i^0) e^{-\lambda_i t}
\]

- \(\sigma_{ji}\): threshold of interaction.
- \(v_{ji}\): induced transcription rate.
- \(\alpha_{ij}\): Kind of interaction (-1, +1)

### Qualitative activity of gene i

\[
q_i(n) = \Delta(x_i(t_n), \{\sigma_{ji}\}_j) \\
\psi_i(n) = \Delta(f_i(\tilde{x}(t_n))/\lambda_i, \{\sigma_{ji}\}_j) \\
\psi_i(n) = F_L(q_1(n), \ldots, q_m(n)) \\
q_i(n+1) \rightarrow \psi_i(n)
\]

- \(\Delta\): Discretization operator.
- \(\psi\): Image of state \(\tilde{q}\).
- \(F_L\): Multivalued function.

### Remarks

Lost: transitory dynamics, interaction crosstalk (constant thresholds).
Gene Regulatory Network model
Weighted sum and threshold boolean network paradigm

Qualitative activity of gene i

\[ q_i(n) = H(x_i(t_n), \sigma_i) \]
\[ \psi_i(n) = H\left( \frac{f_i(x(t_n))}{\lambda_i} \right), \sigma_i \]
\[ q_i(n+1) = \psi_i(n) \]
\[ f_i(x(t_n)) = \sum_{j=1}^{m} \left( \frac{v_{0i}}{\lambda_i} + \frac{v_{ji}}{\lambda_i} H^{\alpha_{ji}}(x_j(t), \sigma_j) \right) \]
\[ q_i^{n+1} = H \left( \sum_{j=1}^{m} \alpha_{ij} w_{ij} q_j^n - \theta_i \right) \]

- \( \theta_i \): threshold of activation.
- \( w_{ij} \): interaction strength \( \left( \frac{\text{induced production}}{\text{decay}} \right) \).
- \( \alpha_{ij} \): Kind of the interaction \( (-1, +1) \)

Remarks

No explicit update scheduling (transitory parameters lost).
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     • Reformulation and linearization
Gene Regulatory Network (GRN): \((G, T, \alpha, w, x, \theta)\)

- **Sets and Graph:**
  - \(V\): vertexes (genes)
  - \(A\): arcs (interactions)
  - \(G = (V, A)\)

- **Evolution rules**
  \[ y(v) = \begin{cases} 
  1 & \text{if } \sum_{u \in \delta^-(v)} \alpha(u, v)w(u, v)x(u) \geq \theta(v) \\
  0 & \text{otherwise}, 
\end{cases} \]

  where \(\delta^-(v) = \{u \in V \mid (u, v) \in A\}\) for all \(v \in V\).

- **Functions:**
  - \(\alpha : A \rightarrow \{+1, -1\}\) \text{ arc sign;}
  - \(w : A \rightarrow \mathbb{R}_+\) \text{ arc weight;}
  - \(x : V \rightarrow \{0, 1\}\) \text{ gene state;}
  - \(y : V \rightarrow \{0, 1\}\) \text{ state image;}
  - \(\theta : V \rightarrow \mathbb{R}\) \text{ threshold,}
**Modelling the inverse problem: defining the problem**
Finding network parameters for simultaneous stable subnetworks

**Given**
- \((G, \alpha)\)
- \(S := \{1..S_{\text{max}}\}\): set of stages and/or mutants.
- \(U = \{U_s\}_{s \in S}; U_s \subseteq V\): nodes of \(G_s\), the (induced) subnetworks of \(G\).
- \(R = \{R_s\}_{s \in S}; R_s := \{1..R_{\text{max}_s}\}\): regions of homogeneous expression.
- \(\Phi = \{\phi_{s,r,u}\}_{s \in S, r \in R_s, u \in U_s}; \phi_{s,r,u} : V \rightarrow \{0, 1\}\): expression data.

**Find**
- \(w, \theta\) such that all \((G_s, \alpha, w, \tilde{x}_{s,r}, \theta)\) satisfy the steadiness constraints and collectively minimize the total \(D_H(\tilde{x}, \phi)\).

\(D_H\): hamming distance from steady state (fixed point) to data.
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Inferring parameters in genetic regulatory networks
Mathematical Programming Formulation

\[
\begin{align*}
\min_{x} & \quad f(x) \\
\text{subject to} & \quad g(x) \leq 0,
\end{align*}
\]

x: decision variables, f: objective function, g: constraints

Sets V, A, S, R (genes, interactions, stages, regions)

Variables \( x : V \times R \rightarrow \{0, 1\} \), \( w : A \rightarrow \mathbb{R}^+ \), \( \theta : A \rightarrow \mathbb{R} \)

Parameters \( \alpha : A \rightarrow \{-1, +1\} \), bounds: \( \theta^L, \theta^U, w^L, w^U \)
\( \phi_{v,r} \), (observed gene expression.)

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Inferring parameters in genetic regulatory networks
Objective Function and Constraints

**Objective function**

\[
\sum_{s \in S, r \in R_s} \sum_{u \in U_s} \left| x_{s,u,r} - \rho_{s,u,r} \right|
\]

**State image rules**

\[
\sum_{u \in U_s : (u,v) \in A} \alpha_{u,v} w_{u,v} x_{s,r,u} \geq \theta_v y_{s,r,v} - \| V \| (1 - y_{s,r,v})
\]

\[
\sum_{u \in U_s : (u,v) \in A} \alpha_{u,v} w_{u,v} x_{s,r,u} \leq (\theta_v - \varepsilon)(1 - y_{s,r,v}) + \| V \| y_{s,r,v}
\]

**Steadiness conditions**

\[
\forall s \in S, r \in R_s, u \in U_s \quad y_{s,u,r} = x_{s,u,r}
\]
Cell or tissue lineage:
Knowledge on steady states AND initial conditions

- Which transitory dynamics?
- Which update scheduling?
Modelling the inverse problem (II): defining the GRN

Find fixed points from initial conditions

Gene Regulatory Network (GRN): \((G, T, \alpha, w, x, \iota, \theta)\)

- **Sets and Graph:**
  - \(V\): vertexes (genes)
  - \(A\): arcs (interactions)
  - \(T: =\{1, 2, ..\} \subset \mathbb{N}\)
  - \(G = (V, A)\)

- **Evolution rules**
  - \(x(v, 1) = \iota(v)\)
  - \(x(v, t) = \begin{cases} 1 & \text{if } \sum_{u \in \delta^{-}(v)} \alpha(u, v)w(u, v)x(u, t-1) \geq \theta(v) \\ 0 & \text{otherwise,} \end{cases}\)

Where \(\delta^{-}(v) = \{u \in V \mid (u, v) \in A\}\) for all \(v \in V\)

- **Functions:**
  - \(\alpha: A \rightarrow \{+1, -1\}\) \textit{arc sign};
  - \(w: A \rightarrow \mathbb{R}_+\) \textit{arc weight};
  - \(x: V \times T \rightarrow \{0, 1\}\) \textit{gene activation};
  - \(\iota: V \rightarrow \{0, 1\}\) \textit{initial configuration};
  - \(\theta: V \rightarrow \mathbb{R}\) \textit{threshold},
Modelling the inverse problem: defining the problem
Finding network parameters for simultaneous stable subnetworks, using initial condition data

Given

- \((G, T, \alpha)\)
- \(S := \{1..S_{max}\}\): set of stages and/or mutants.
- \(U = \{U_s\}_{s \in S}; U_s \subseteq V\): nodes of \(G_s\), the (induced) subnetworks of \(G\).
- \(R = \{R_s\}_{s \in S}; R_s := \{1..R_{max_s}\}\): regions of homogeneous expression.
- \(I = \{i_{s,r,u}\}_{s \in S, r \in R_s, u \in U_s}; i_{s,r,u} : V \rightarrow \{0, 1\}\): initial conditions.
- \(\Phi = \{\phi_{s,r,u}\}_{s \in S, r \in R_s, u \in U_s}; \phi_{s,r,u} : V \rightarrow \{0, 1\}\): expression data.

Find

- \(w, \theta\) such that \(\forall i_{s,r}, (G_s, T, \alpha, w, \tilde{x}_{s,r}, i_{s,r}, \theta)\) satisfies the evolution constraints and have fixed points that collectively minimize \(D_H(\tilde{\rho}, \tilde{\phi})\).

\(D_H(\tilde{\rho}, \tilde{\phi})\): total hamming distance from model fixed points to data.
Modelling the inverse problem: illustrating the problem
Finding network parameters for simultaneous stable subnetworks
Modelling the inverse problem: illustrating the problem

Finding network parameters for simultaneous stable subnetworks
Modelling the inverse problem: illustrating the problem
Finding network parameters for simultaneous stable subnetworks
Modelling the inverse problem: illustrating the problem
Finding network parameters for simultaneous stable subnetworks
Mathematical Programming Formulation

\[
\min_x f(x) \\
\text{subject to} \quad g(x) \leq 0,
\]

\(x\): decision variables, \(f\): objective function, \(g\): constraints

Sets  \(V, A, T, S, R\) (genes, interactions, time steps, stages, regions)

Variables  \(x : V \times R \times T \rightarrow \{0, 1\}, \ w : A \rightarrow \mathbb{R}^+, \ \theta : A \rightarrow \mathbb{R}\)

Parameters  \(\alpha : A \rightarrow \{-1, +1\}\), bounds: \(\theta^L, \theta^U, w^L, w^U\)

\(\phi_{v,r}, l_{v,r}\) (observed gene expression and initial cond.)
Objective Function and Constraints

**Objective function**

\[
\sum_{s \in S, r \in R_s} \sum_{t \in T \setminus 1} \left( \sigma_{s,r}^{t-1} - \sigma_{s,r}^t \right) \sum_{u \in U_s} \left| x_{s,u,r}^t - \rho_{s,u,r} \right|
\]

**Evolution rules**

\[
\sum_{u \in U_s : (u, v) \in A} \alpha_{u,v} w_{u,v} x_{s,r,u}^{t-1} \geq \theta_v x_{s,r,v}^t - \| V \|(1 - x_{s,r,v}^t)
\]

\[
\sum_{u \in U_s : (u, v) \in A} \alpha_{u,v} w_{u,v} x_{s,r,u}^{t-1} \leq (\theta_v - \varepsilon)(1 - x_{s,r,v}^t) + \| V \| x_{s,r,v}^t
\]

**Fixed point conditions**

\[
\sum_{u \in U_s} \left| x_{s,u,r}^t - x_{s,u,r}^{t-1} \right| \leq \| U_s \| \sigma_{s,r}^t
\]

\[
\sum_{u \in U_s} \left| x_{s,u,r}^t - x_{s,u,r}^{t-1} \right| \geq \sigma_{s,r}^t
\]
Reformulation, Linearization and Solution

Nonconvex Mixed-Integer Nonlinear Program (MINLP). Reformulated exactly to a MILP.

\[
\begin{align*}
\theta x \text{ terms} \\
(\theta: \text{real}, x: \text{binary}) \\
\zeta \leq \theta + (|\theta^L| + |\theta^U|)(1 - x) \\
\zeta \geq \theta - (|\theta^L| + |\theta^U|)(1 - x)
\end{align*}
\]

\[
\begin{align*}
yx \text{ terms} \\
(y, x: \text{binary}) \\
z \geq 0 \\
z \leq y \\
z \leq x \\
z \geq x + y - 1
\end{align*}
\]

- Absolute values and distances.
- Auxiliary decision variables for fixed point conditions.

We use AMPL to write the model of the problem, and use CPLEX 11.0.1 to solve efficiently to optimality the MILP problem.
Ongoing work: transitory dynamics

- Deterministic vs Stochastic
- Deterministic: Asynchronouse vs synchronous
- Biological interpretation

**Asynchronous parameters**

\[ x_{i}^{(p_{i} \tau + q_{i} + 1)} = F_{i}(x_{i}^{(p_{i} \tau + q_{i})}) \]

- \( p_{i} \): period
- \( q_{i} \): delay

**Biologically based**

\[ \tau_{x_{i}^{0}} = \lambda_{i} \log \left( \frac{1}{1 - d_{i}(x_{i}^{0})/D_{i}(x_{i}^{0})} \right) \]

- \( \lambda_{i} \): gene product degradation
- \( D_{i} \): distance to state image
- \( d_{i} \): distance to threshold
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Inferring parameters in genetic regulatory networks
Summary

- **Static** modelling of a *dynamic* system.
- **Generic modeling approach** for the inference of biological regulatory networks.
- Easier to test different models than simulation approaches.

**Perspectives**
- “Flexibilize” the “hard” constraint on the prior network (find signs, new interactions)
- Introduce theoretical results on regulatory networks.
- Multiobjective problems ?
- Reintroduce transitory dynamics (Is it possible using mathematical programming ?).
- Study more complicated qualitative models of GRN.