A Statistical Learning Algorithm for Inferring Reaction Systems from Data Time Series

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Mechanistic Model Learning for explainable AI

The Machine Learning field provides tools to analyze time series data and yield predictions. Classical examples are Recurrent Neural Networks.

- While these predictions can be accurate, they do not come with an interpretation
- We say that the model is **Black Box**

On the contrary, Mechanistic Model Learning aims at achieving the same predictive results while being **explainable**

(XAI : Explainable Artificial Intelligence)

Focus : chemical reaction network (CRN) inference

Input : time series data from multiple traces describing evolution of molecular species

Output :

- CRN structure
- CRN kinetics

The learned model provides an understanding of the underlying processes involving the species while allowing predictions

Some attempts at Mechanistic Model Learning

- DREAM3 (2008) - Network Inference Challenge
- Logic programming
  - Prior knowledge on network's structure
  - Learn boolean function acting on species

  Boolean Network Identification from Perturbation Time Series Data combining Dynamics Abstraction and Logic Programming. L. Pauleve et al.
- Evolutionary Algorithms
  - Given number of reactions
  - Fitness to observed transitions

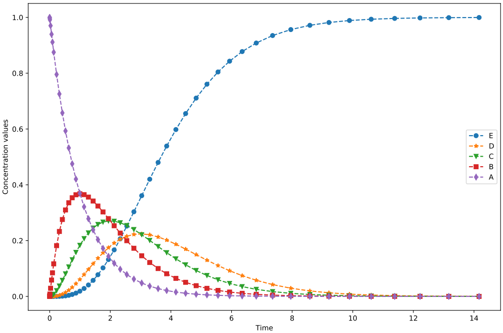
  Inferring Reaction Networks using Perturbation Data. H. Sauro et al.
- TimeDelay-ARACNE: Reverse engineering of gene networks from time-course data by an information theoretic approach
  - Information theory framework
  - Detect dependencies between genes at different time delays

  P. Zoppoli et al.

Learning parameters : well-understood
Learning the structure : remains difficult without prior knowledge.

Chain CRN learning example

On a chain of 4 reactions with mass action law kinetics, our algorithm is able to reconstruct the CRN from a single simulation trace.



Hidden CRN	Learned CRN
$A \xrightarrow{1} B$	$A \xrightarrow{1.07} B$
$B \xrightarrow{1} C$	$B \xrightarrow{1.09} C$
$C \xrightarrow{1} D$	$C \xrightarrow{1.04} D$
$D \xrightarrow{1} E$	$D \xrightarrow{0.99} E$

Application on Real data

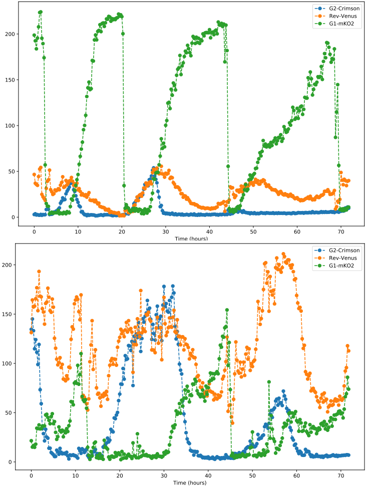
We apply the algorithm to real data and search for mechanistic models.

- NIH3T3 embryonic mouse fibroblasts left to proliferate in regular medium supplemented with 20% FBS concentration
- Time lapse videomicroscopy, one image taken every 15 minutes during 72 hours
- *Cell tracking* using three different fluorescent markers of the circadian clock and the cell cycle :
  - *Reverb-*α clock gene reporter
  - Fluorescence Ubiquitination Cell Cycle Indicators, *Cdt1* and *Geminin*, two cell cycle proteins which accumulate during the G1 and S/G2/M phases respectively.

Plot of two traces from the dataset

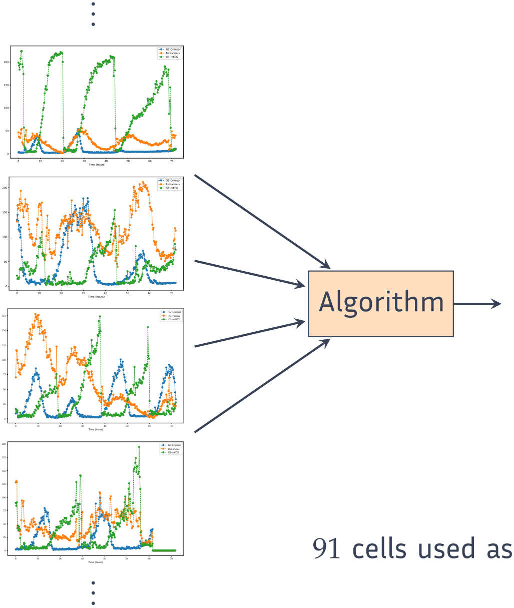
Videomicroscopy

Feillet Delaunay INSERM 2013



The cells display a high variability

Results



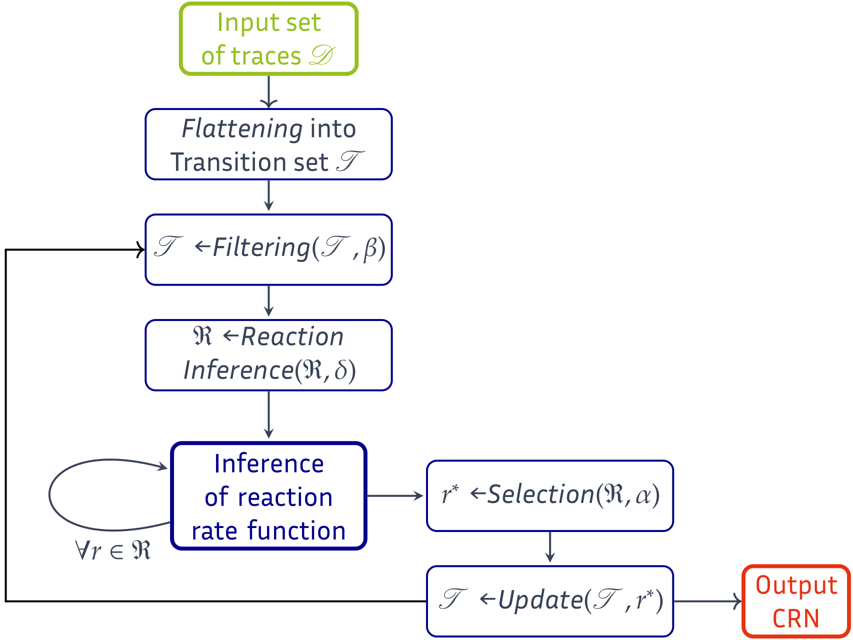
Learned CRN	Rate Functions
$G1 \implies G2$	$7.1 \dfrac{G1}{G1 + 3.68}$
$RevErb\alpha \implies G1$	$22.56 \dfrac{RevErb\alpha}{RevErb\alpha + 71.45}$
$G1 \implies \varnothing$	$5.96 \dfrac{G1}{G1 + 5.0}$
$G2 \implies \varnothing$	$54.84 \dfrac{G2}{G2 + 176.23}$

91 cells used as input $\implies \approx 18000$ data points

Contributions

- A statistical learning algorithm to iteratively infer reactions from time series data
- Infer reaction structures that maximise the pairing between reactant consumption and product formation
- Infer reaction rates that minimize the standard deviation between the observed kinetics and the inferred kinetics

Flowchart of the algorithm



Input set of traces $\mathscr{D}$
Flattening into Transition set $\mathscr{T}$
$\mathscr{T} \leftarrow$ *Filtering*$(\mathscr{T}, \beta)$
$\Re \leftarrow$ *Reaction Inference*$(\Re, \delta)$
Inference of reaction rate function
$\forall r \in \Re$
$r^* \leftarrow$ *Selection*$(\Re, \alpha)$
$\mathscr{T} \leftarrow$ *Update*$(\mathscr{T}, r^*)$
Output CRN

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Chemical Reaction Networks

Let $S = \{1, \dots, n\}$ be the set of n molecular species. Species can also be noted with simple capital letters like A, B, C instead of by their index.

Definition

A *reaction* over S is a triple (R, P, f), where R is a multiset of *reactants* in S, P is a multiset of *products* in S and $f : \mathbb{R}^n \longrightarrow \mathbb{R}$ is a *rate function* over molecular concentrations.

A *catalyst* of the reaction is a species $i \in R \bigcap P$.

A *Chemical Reaction Network* (CRN) is a finite set of reactions.

Example

$(\{A\}, \{B\}, k \cdot [A])$ also written $A \overset{k}{\Longrightarrow} B$ is the case of mass action law.

CRN classification

Definition

A *reactant-parallel* CRN is a CRN in which any two reactions do not share the same reactant (catalysts aside).

A *product-parallel* CRN is a CRN in which any two reactions do not share the same product (catalysts aside).

A *parallel* CRN is a CRN in which any two reactions do not share the same species (catalysts aside).

The chain CRN $A \implies B \implies C \implies D \implies E$ is both reactant-parallel and product-parallel but not parallel.

Differential semantics

A CRN can be interpreted in different manners, in a hierarchy of continuous differential, stochastic, discrete and Boolean semantics.

Here we consider the continuous interpretation by ordinary differential equations

$$\forall s \in S, \frac{ds}{dt} = \sum_{(R,P,f)\in\mathscr{R}} f.(P(s) - R(s))$$

Traces

Definition

A state vector is a vector $x \in \mathbb{R}^{n+1}$ where x_0 represents the real time, and x_i the concentration of species i

A *trace*, or time-series data is a finite sequence $(x(1), \dots, x(d))$ of state vectors at increasing times, i.e. $x_0(1) < \cdots < x_0(d)$.

Such traces can be :

- simulation traces, e.g. numerical integration or stochastic simulation
- experimental traces, e.g. time lapse videomicroscopy

Hypotheses

- We only study reactions with stoichiometry at most 1 : the multisets R and P are actually sets of $\mathscr{P}(S)$.

- We also restrict ourselves to the following common rate functions
  - mass action law kinetics
  - Michaelis-Menten kinetics
  - Hill of order 4 kinetics.

Flattening and Filtering

The set of traces $\mathscr{D}$ is flattened into a set of transitions $\mathscr{T}$:

$$\mathscr{T} \leftarrow \{(x^j(t), x^j(t+1) - x^j(t), j) \mid 1 \leqslant j \leqslant l,\ 1 \leqslant t \leqslant d_j - 1\}$$

A filterering step is applied on $\mathscr{T}$. For each species $i \in S$ and $\forall (x, d, j) \in \mathscr{T}$

$$\text{if } \left|\frac{d_i}{d_0}\right| < \beta . \max_{1 \leqslant t < d_j} \left|\frac{x_i^j(t+1) - x_i^j(t)}{x_0^j(t+1) - x_0^j(t)}\right| \text{ then } d_i \leftarrow 0$$

Collecting possible reactions

For $(x, d, j) \in \mathscr{T}$, let $s^* = \underset{s}{\operatorname{argmax}} |d_s|$.

Let $I := \{i \in S \text{ s.t. } |d_{s^*}| \leqslant (1+\delta)|d_i|\}$. $\forall j \in I$

- $d_j < 0 \implies j$ is a reactant of the reaction.
- $d_j > 0 \implies j$ is a product of the reaction.

Example

$I = \{u, v, s^*\}$ with $d_{s^*} > 0, d_u > 0$ and $d_v < 0$ gives $\mathbf{v} \implies \mathbf{s}^* + \mathbf{u}$

This is done $\forall (x, d, j) \in \mathscr{T}$ and leads to a set of reactions $\mathscr{R}$

Mass action law kinetics rate function inference

Once a reaction $r = (R, P)$ has been inferred :

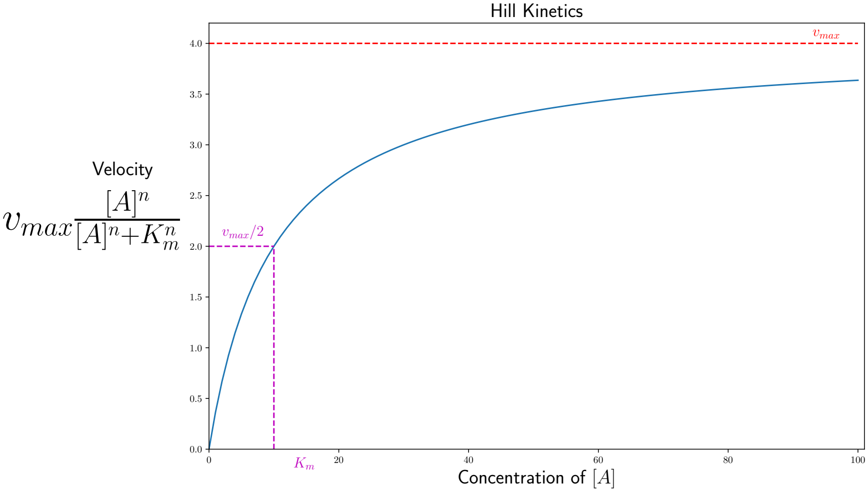
- Mass action law kinetics is computed as inferred kinetics
- the ratio between inferred kinetics and observed kinetics is measured $\forall (x, d, j) \in \mathscr{T}$ s.t. $x_i > 0, \forall i \in R$

For a reaction $A \overset{k}{\Longrightarrow} B$, this ratio reads $\epsilon = k\frac{[A]}{\frac{dA}{dt}} = k\frac{[A]}{\frac{dB}{dt}}$

$K = \left\{ \frac{x_A}{\frac{d_A}{d_0}}, (x, d, j) \in \mathscr{T} \text{ s.t. } x_A > 0 \right\}$ and $k = \left| \frac{1}{mean(K)} \right|$ so that $\epsilon = 1$.

Moreover, we set $\sigma = std(K)$ to be the error criterion on the reaction

Hill rate function computation



$$\frac{dA}{dt} = v_{max}\frac{[A]^n}{[A]^n + K_m^n} \xrightarrow{[A]\to+\infty} v_{max}$$

Then, setting $K_m = [A]^n$ yields $\frac{dA}{dt} = \frac{v_{max}}{2}$

Search for a catalyst molecule

Let's assume reaction $\mathbf{A} \implies \mathbf{B}$ produced an error $\sigma > \alpha$ for any of the rate function described above.

$\forall C \in S \backslash \{A, B\}$

- Reaction $\mathbf{A} + \mathbf{C} \implies \mathbf{B} + \mathbf{C}$ is considered
- Its inferred dynamics $k[A][C]$ are compared to $k[A]$

$$C^* = \underset{C \in S \backslash \{A,B\}}{\operatorname{argmin}} \sigma_C$$

If $\sigma_{C^*} < \sigma$, reaction $\mathbf{A} + \mathbf{C}^* \implies \mathbf{B} + \mathbf{C}^*$ is selected.

Selection and Update

Reaction $(R, P, f) = r^* = \underset{r \in \mathscr{R}}{\operatorname{argmin}}\, \sigma_r$ is selected.

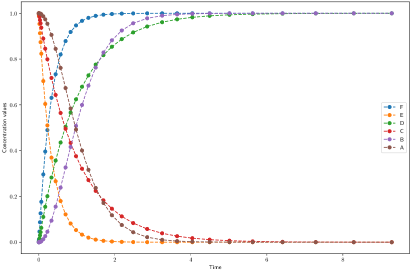
Its effect on the transitions removed.

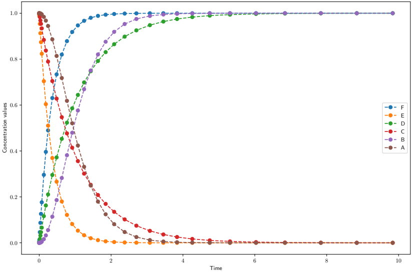
$\forall (x, d, j) \in \mathscr{T}$ s.t. $x_i > 0 \ \forall i \in R$

- $\forall i \in P, d_i \leftarrow d_i - d_0 f(x)$
- $\forall i \in R, d_i \leftarrow d_i + d_0 f(x)$

This update is followed by a new iteration of the algorithm. The main loop goes on while $\sigma_{r^*} < \alpha$

Results on parallel CRN



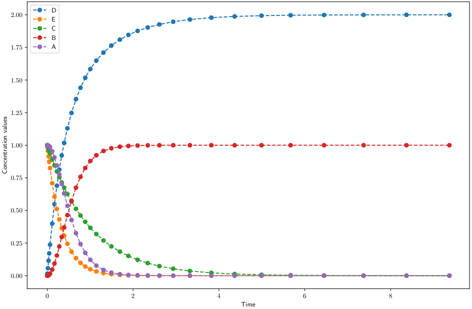


Hidden CRN
$A + D \xRightarrow{2} B + D$
$C \xRightarrow{1} D$
$E \xRightarrow{3} F$

Learned CRN
$A + D \xRightarrow{2.12} B + D$
$C \xRightarrow{0.96} D$
$E \xRightarrow{2.73} F$

It should be noticed that in this case, we have exactly $\forall (x, d, j) \in \mathscr{T}, |d_A| = |d_B|, |d_C| = |d_D|$ and $|d_E| = |d_F|$.

Reactant parallel CRN



Hidden CRN	Learned CRN
$A + D \xrightarrow{2} B + D$	$A + D \xrightarrow{2.2} B + D$
$C \xrightarrow{1} D$	$C \xrightarrow{0.98} D$
$E \xrightarrow{3} D$	$E \xrightarrow{2.78} D$

Here, $\nexists\, i \in S \backslash \{D\}$ s.t. $|d_D| \approx |d_i|$

- solution : find (i_1, i_2) s.t. $|d_D| \approx |d_{i_1}| + |d_{i_2}|$
- ensure $d_{i_1} d_{i_2} > 0$ and $d_{i_1} d_D < 0$

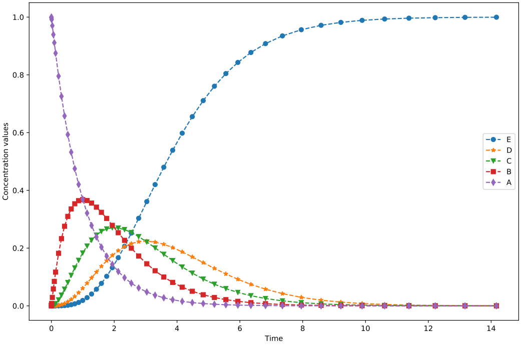
Promote reactions inferred on *sparse* transitions

Let $\mathscr{T}_r := \{(x, d, j) \in \mathscr{T} \mid r \in \text{ reaction\_inference}(d)\}$ be the *support* of reaction r :

Few species present $\implies$ more **informative** transitions $\implies$ inferred reaction more reliable

- Species s is considered *absent* of transition (x, d, j) if $x_s < \gamma \max_t x_s^j(t)$
- Let $m = mean(\#\{\text{absent species in } x \; \forall (x, d, j) \in \mathscr{T}_r\})$. $\sigma \leftarrow \frac{\sigma}{1+m}$

Back to the chain CRN



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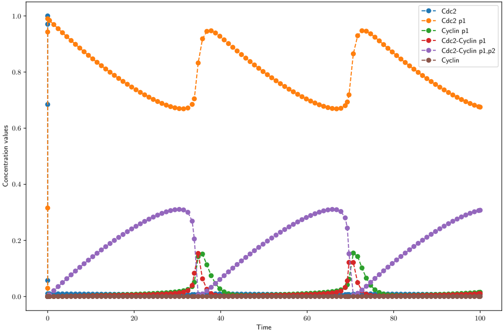
$D \xrightarrow{1} E$	$D \xrightarrow{0.99} E$

- At the end of the simulation only species D and E are showing non negligible concentrations values.
- Reaction $D \implies E$ will then benefit of this sparsity criterion.

Results on the Cell Cycle of Tyson (1991)



Hidden CRN	Learned CRN
$\emptyset \xRightarrow{0.015} cy$	$\emptyset \xRightarrow{0.66} cy1 + cdcy2$
$cy + cd1 \xRightarrow{200} cdcy2$	$\emptyset \xRightarrow{0.01} cdcy2$
$cdcy2 \xRightarrow{0.018} cdcy1$	$cdcy2 \xRightarrow{0.1152} cdcy1$
$cdcy2 + 2 * cdcy1 \xRightarrow{180} 3 * cdcy1$	$cdcy2 \xRightarrow{0.05} cy1$
$cdcy1 \xRightarrow{1} cy1 + cd$	$cdcy1 \xRightarrow{1.62} \emptyset$
$cy1 \xRightarrow{0.6} \emptyset$	$cy1 \xRightarrow{0.4} cdcy1$
$cd1 \xRightarrow{100} cd$	$cd1 \xRightarrow{11259} cd$
$cd \xRightarrow{10000} cd1$	$cd \xRightarrow{5912} cd1$

F-score on simulations traces from a hidden model

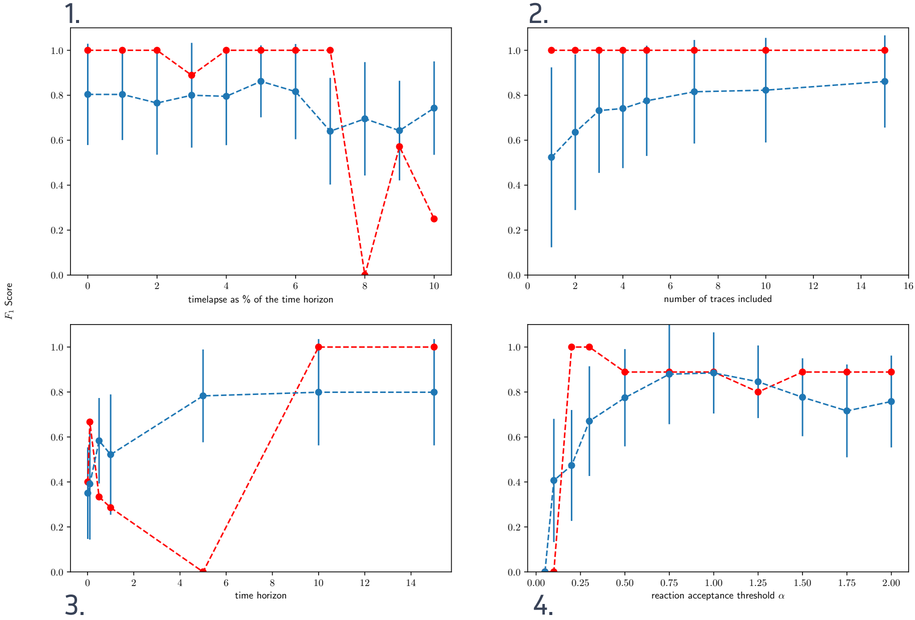
$$F = 2 \cdot \frac{\text{precision} \cdot \text{recall}}{\text{precision} + \text{recall}} \text{ where precision } = \frac{\text{tp}}{\text{tp+fp}} \text{ recall } = \frac{\text{tp}}{\text{tp+fn}}$$

(tp : true positive ; fp : false positive ; fn : false negatives)

Allows to assess sensibility of the algorithm to :

1. Level of trace subsampling
2. Number of traces with random initial conditions
3. Length of the traces
4. Reaction acceptance threshold α

Evaluation of the algorithm on the Chain CRN



Complexity

Proposition

The time complexity of the CRN learning algorithm for inferring one reaction is $\mathscr{O}(t.n^2)$ where t is the number of transitions in the traces and n the number of variables.

$\Longrightarrow$ 5 minutes on real data (91 cells and ≈ 18000 transitions, 3 variables)

Conclusion and Perspectives

- An unsupervised greedy algorithm able to infer meaningful reaction networks from time-series data.
- Reaction selection is driven by the analysis of the ratio between observed dynamics and inferred dynamics for each reaction
- Linear complexity in the number of data points and quadratic in the number of species

Perspectives :

- Relax the stoichiometry bounded to 1 constraint
- Add the kinetics in the F score of the learned model w.r.t. hidden model
- Infer hidden variables