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

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Explainable AI by Learning Mechanistic Models

- The Machine Learning field provides tools to analyze time series data and yield predictions.
  - Classical algorithms are Recurrent Neural Networks
  - While predictions can be accurate, they do not come with an explanation
  - Black box model
- **Mechanistic Model Learning** aims at achieving the same predictive power with an explainable learned model

Focus: Chemical Reaction Networks (CRN) Inference

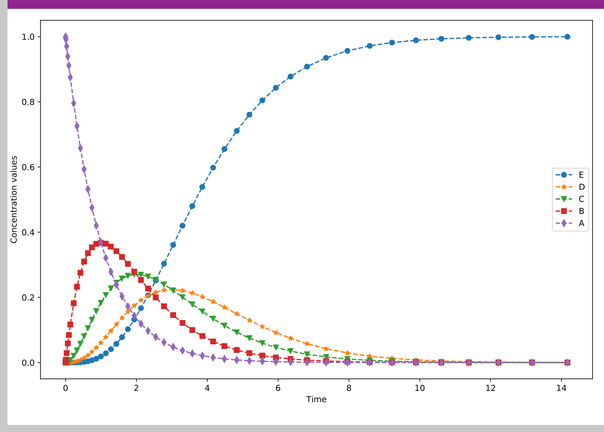
- Input : **time series data on molecular concentrations**
  - single trace (wild type)
  - multiple traces with perturbed conditions (gene knock outs)
- Output :
  - **CRN structure**: reactions with -1/0/1 stoichiometry
  - **CRN kinetics**: mass action law, Michaelis-Menten or Hill functions

The learned CRN provides a mechanistic explanation of the observations and allows predictions

Learning parameters: well-understood

Learning structure: hard without prior knowledge (see DREAM challenge)

Chain CRN Example

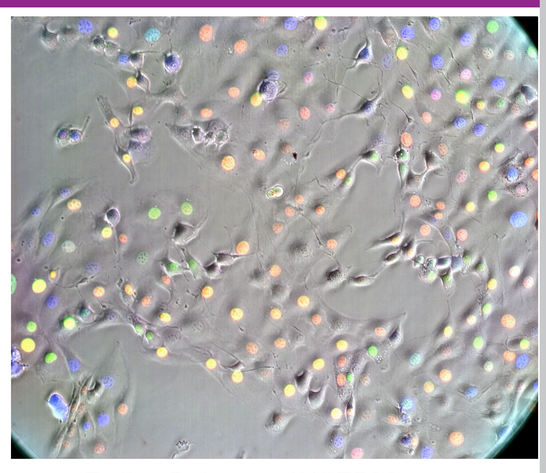


Learning from a single simulation trace

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 to Time Lapse Videomicroscopy Data

- NIH3T3 embryonic mouse fibroblasts
- Time lapse of 15 min during 72 hours
- Cell tracking (through cell divisions)
- 3 fluorescent markers of
  - cell cycle (***G1*** and ***S-G2-M***)
  - circadian clock (*Reverb-*α)



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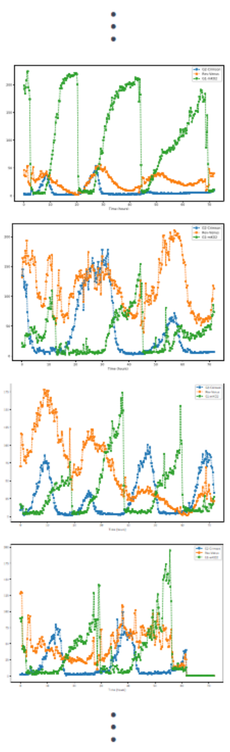


Algorithm

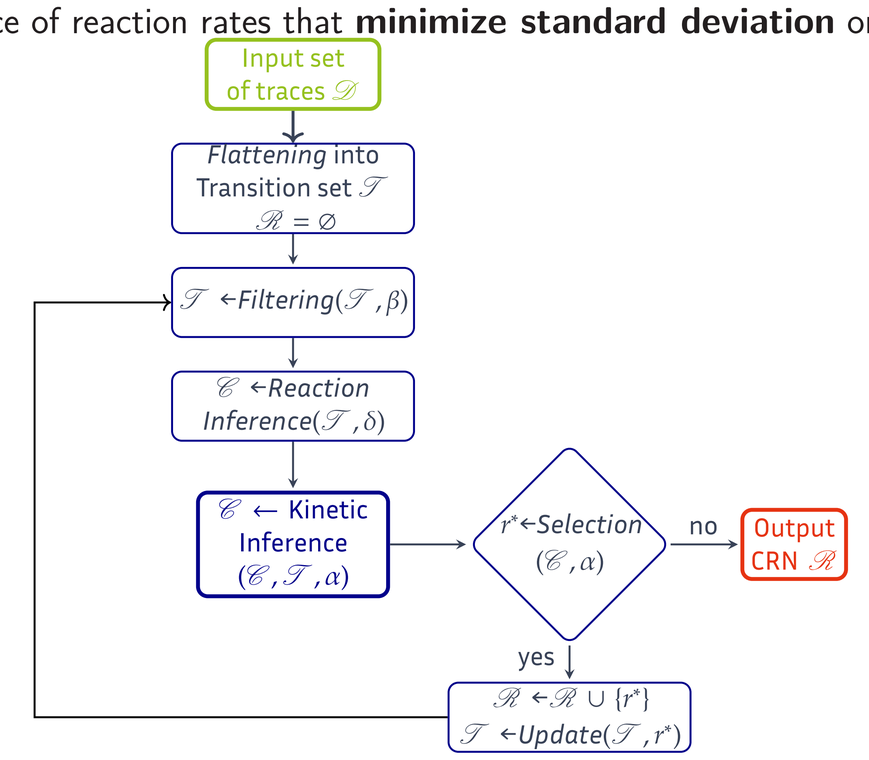
Learned CRN	Rate Functions
$G1 \Longrightarrow G2$	$7.1\frac{G1}{G1+3.68}$
$RevErb\alpha \Longrightarrow G1$	$22.56\frac{RevErb\alpha}{RevErb\alpha+71.45}$
$G1 \Longrightarrow \emptyset$	$5.96\frac{G1}{G1+5.0}$
$G2 \Longrightarrow \emptyset$	$54.84\frac{G2}{G2+176.23}$

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

$\Longrightarrow$ CRN learned in 5 minutes CPU time

Statistical Learning Algorithm

- **Greedy algorithm** that iteratively infers reactions
- Reaction structures that maximise the pairing between reactant consumption and product formation in the observed transitions $\mathcal{F}$
- Choice of reaction rates that **minimize standard deviation** on $\mathcal{F}$



Proposition

Time complexity in $\mathcal{O}(t.n^2)$ where

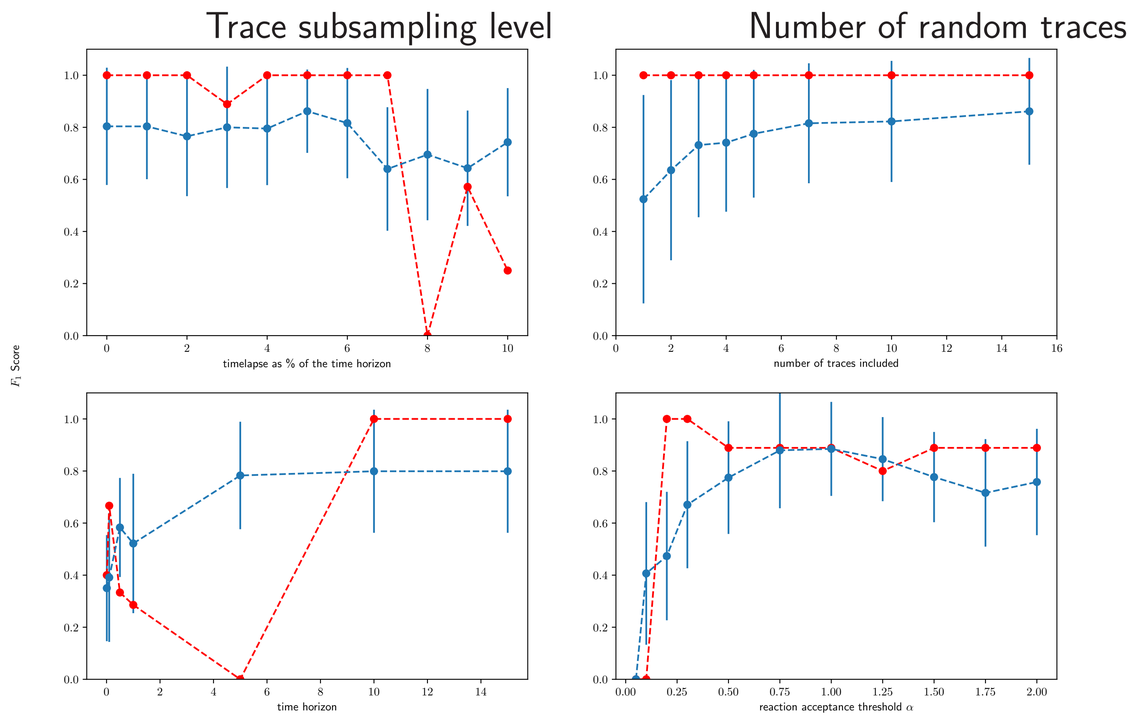
- t is the number of observed transitions in the traces
- and n the number of observed molecular species

F-score on Simulation Traces from a Hidden Model

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

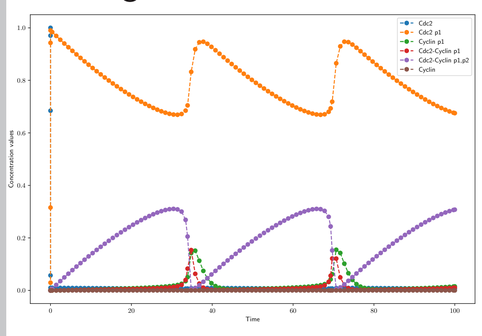
$\Longrightarrow$ **Sensitivity of the F-score** w.r.t. algorithmic parameters

Chain CRN example red: single trace (wild type)
blue: multiple traces (from perturbed initial states with random zeroes)



Results on the Yeast Cell Cycle Model [Tyson 1991]

Single simulation trace



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

Slow/fast multiple time scales make fast reactions unobservable.
The slow dynamics is inferred.