Algo Epi Reading Group

Systems biology informed deep learning for inferring parameters and hidden dynamics

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Introduction

Background

- Traditionally, systems biological processes are modelled using a system of Ordinary Differential Equations (ODEs).
- With data available, the actual challenge lies in computing the estimated values of the parameters of the ODEs.
- In biological reaction networks, experimental data are insufficient considering the size of the model, which results in parameters that are non-identifiable or only identifiable within confidence intervals.
- Some models are highly sensitive to slight change in parameter values.

Contributions

- It uses a Neural Network Model to infer the hidden dynamics of experimentally unobserved species as well as the unknown parameters in the system of equations.
- The model adds constraints to the optimization algorithm, which makes the method robust to measurement noise and few scattered observations.
- The algorithm is computationally scalable and feasible, and its output is interpretable even though it depends on a high-dimensional parameter space.

Problem

Preliminaries

- Systems biological processes can be modeled by a system of ODEs of the form:

$$\frac{d\mathbf{x}}{dt} = \boldsymbol{f}(\mathbf{x}, t; \mathbf{p}), \tag{1a}$$

$$\mathbf{x}(T_0) = \mathbf{x}_0, \tag{1b}$$

$$\mathbf{y} = \boldsymbol{h}(\mathbf{x}) + \boldsymbol{\epsilon}(t), \quad \boldsymbol{\epsilon}(t) \sim \mathcal{N}(0, \sigma^2), \tag{1c}$$

$x = (x_1, x_2, \ldots, x_S)$ is the concentration of S species.

$p = (p_1, p_2, \ldots, p_K)$ are the K parameters of the model.

$y = (y_1, y_2, \ldots, y_M)$ are the M measurable signals. ($M \le S$)

h() could be any function (in this case, is considered linear).

Preliminaries cont.

- Є is just Gaussian noise.

If h() is a linear function, the system could look like:

$$\begin{pmatrix} y_1 \\ y_2 \\ \cdots \\ y_M \end{pmatrix} = \begin{pmatrix} x_{s_1} \\ x_{s_2} \\ \cdots \\ x_{s_M} \end{pmatrix} + \begin{pmatrix} \epsilon_{s_1} \\ \epsilon_{s_2} \\ \cdots \\ \epsilon_{s_M} \end{pmatrix}, \tag{2}$$

The SIR System of ODEs

Considering the system of ODEs of the simple SIR model, the equations can be written as:

- 3 states (Susceptible (S), Infected (I) and Recovered (R)). So, here S= 3
- So, β and γ are the parameters of the ODE. p= (β, γ).

$$\frac{dS}{dt} = -\frac{\beta S I}{N}$$

$$\frac{dI}{dt} = \frac{\beta S I}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

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Cont.

- If β = 0.6 and γ = 0.4, then x may look something like this:

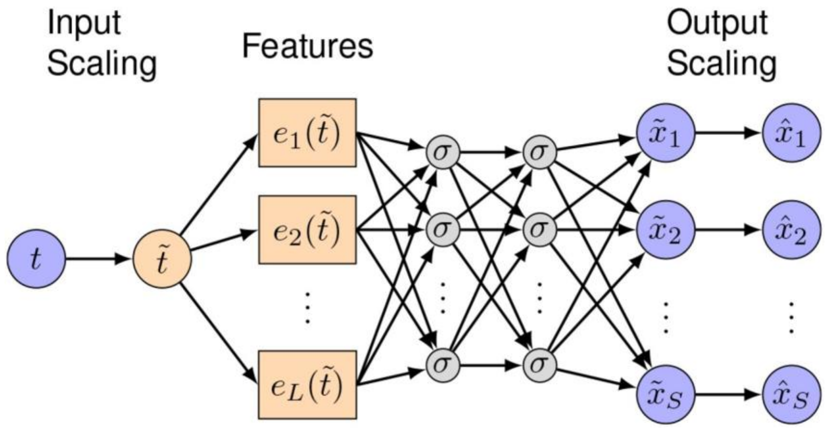
Given a population of 100 people,

Time Period	Susceptible	Infected	Recovered
0	999	1	0
1	999	1	0
2	998	2	0
3	996	2	1

The Model

Neural Network Structure

- **Input:** time t, **Output:** Vector of state variables $\hat{x}(t,\theta)$
- **Input Scaling Layer:** $\bar{t} = \frac{t}{T}$.
- **Feature layer:** $\bar{t}\ == \left(e_1(\bar{t}), e_2(\bar{t}), \dots, e_\mathrm{L}(\bar{t})\right)$.
- **Output Scaling Layer:** Similar to input scaling.



Constrain NN to satisfy ODE

- If we have measurements $y_1, y_2, \ldots, y_M$ at $t_1, t_2, \ldots, t_{Ndata}$ and we enforce the NN to satisfy the ODE system at time points $\tau_1, \tau_2, \ldots, \tau_{N_{ode}}$, then the total loss is defined as follows:

$$\mathcal{L}(\boldsymbol{\theta}, \mathbf{p}) = \mathcal{L}^{data}(\boldsymbol{\theta}) + \mathcal{L}^{ode}(\boldsymbol{\theta}, \mathbf{p}) + \mathcal{L}^{aux}(\boldsymbol{\theta}),$$

- The loss function is minimized by the Adam optimizer, given by:

$$\boldsymbol{\theta}^*, \mathbf{p}^* = \arg\min_{\boldsymbol{\theta}, \mathbf{p}} \mathcal{L}(\boldsymbol{\theta}, \mathbf{p}).$$

Parts of the Loss Function

- **First Part:**

$$\mathcal{L}^{data}(\boldsymbol{\theta}) = \sum_{m=1}^{M} w_m^{data} \mathcal{L}_m^{data} = \sum_{m=1}^{M} w_m^{data} \left[\frac{1}{N^{data}} \sum_{n=1}^{N^{data}} \left(y_m(t_n) - \hat{x}_{s_m}(t_n; \boldsymbol{\theta}) \right)^2 \right], \quad (4)$$

It is associated with M sets of observations **y** given in equation 1(c).

It is a supervised loss function.

Cont..

- **Second Part:**

$$\mathcal{L}^{ode}(\boldsymbol{\theta}, \mathbf{p}) = \sum_{s=1}^{S} w_s^{ode} \mathcal{L}_s^{ode} = \sum_{s=1}^{S} w_s^{ode} \left[\frac{1}{N^{ode}} \sum_{n=1}^{N^{ode}} \left(\frac{d\hat{x}_s}{dt}|_{\tau_n} - f_s\left(\hat{x}_s(\tau_n;\boldsymbol{\theta}), \tau_n; \mathbf{p}\right) \right)^2 \right], \tag{5}$$

This loss enforces the structure imposed by the system of ODEs given in equation 1(a).

This is an unsupervised loss function.

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- **Third Part:**

$$\mathcal{L}^{aux}(\boldsymbol{\theta}) = \sum_{s=1}^{S} w_s^{aux} \mathcal{L}_s^{aux} = \sum_{s=1}^{S} w_s^{aux} \frac{(x_s(T_0) - \hat{x}_s(T_0; \boldsymbol{\theta}))^2 + (x_s(T_1) - \hat{x}_s(T_1; \boldsymbol{\theta}))^2}{2}. \quad (6)$$

This is an additional source of information for the system identification and involves 2 time instants T0 and T1.

It is essentially a component of the data loss; however, we prefer to separate this loss from the data loss, as in the auxiliary loss data are given for all state variables at these 2 time instants.

This is also supervised loss.

Training

Step 1 Considering that supervised training is usually easier than unsupervised training, we first train the network using the two supervised losses $\mathcal{L}^{data}$ and $\mathcal{L}^{aux}$ for some iterations, such that the network can quickly match the observed data points.

Step 2 We further train the network using all the three losses.

Experiments

The Yeast Glycolysis Model

The System of ODEs

$$\frac{dS_1}{dt} = J_0 - \frac{k_1 S_1 S_6}{1 + (S_6/K_1)^q}, \tag{S4a}$$

$$\frac{dS_2}{dt} = 2\frac{k_1 S_1 S_6}{1 + (S_6/K_1)^q} - k_2 S_2 (N - S_5) - k_6 S_2 S_5, \tag{S4b}$$

$$\frac{dS_3}{dt} = k_2 S_2 (N - S_5) - k_3 S_3 (A - S_6), \tag{S4c}$$

$$\frac{dS_4}{dt} = k_3 S_3 (A - S_6) - k_4 S_4 S_5 - \kappa (S_4 - S_7), \tag{S4d}$$

$$\frac{dS_5}{dt} = k_2 S_2 (N - S_5) - k_4 S_4 S_5 - k_6 S_2 S_5, \tag{S4e}$$

$$\frac{dS_6}{dt} = -2\frac{k_1 S_1 S_6}{1 + (S_6/K_1)^q} + 2k_3 S_3 (A - S_6) - k_5 S_6, \tag{S4f}$$

$$\frac{dS_7}{dt} = \psi \kappa (S_4 - S_7) - k S_7, \tag{S4g}$$

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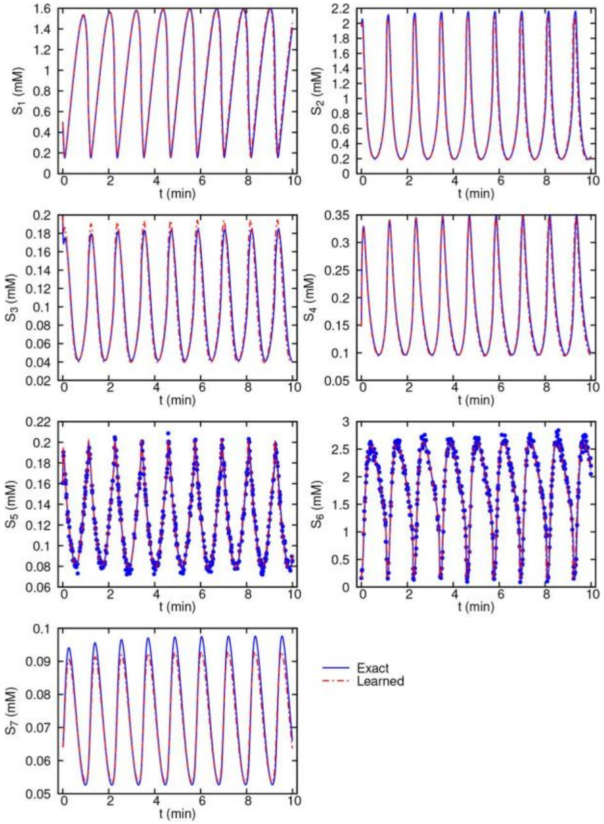
Steps

- Observation data is corrupted with Gaussian noise.
- Initially, dynamics are inferred using noiseless observations on 2 species S6 and S5 only.
- Sampling of data points between 1-10 mins at random is used to train the NN.
- Then, inferred dynamics of S5 and S6 is compared with noisy data.
- The parameters p of the ODE are inferred by backpropagation to estimate NN parameters θ.

Results



Parameter	Target value	Inferred value (Noiseless observations)	Inferred value (Noisy observations)	Standard deviation
J_0	2.5	2.50	2.49	0.18
k_1	100	99.9	86.1	62.0
k_2	6	6.01	4.55	21.3
k_3	16	15.9	14.0	21.9
k_4	100	100.1	97.1	103.6
k_5	1.28	1.28	1.24	0.25
k_6	12	12.0	12.7	5.1
k	1.8	1.79	1.55	4.34
κ	13	13.0	13.4	25.9
q	4	4.00	4.07	0.27
K_1	0.52	0.520	0.550	0.091
ψ	0.1	0.0994	0.0823	0.317
N	1	0.999	1.29	2.94
A	4	4.01	4.25	2.28

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Discussions

Points to be Noted

- We are able to infer the unknown parameters of the system of ODEs once the neural network is trained
- In this model we can use a minimalistic amount of data on a few observables to infer the dynamics and the unknown parameters.
- The goal in this work was not to do systematic identifiability analysis, but rather to use identifiability analysis to explain some of their findings.

Thank You

→ https://github.com/alirezayazdani1/SBINNs