Data-Driven Governing Equations of Glycolytic Oscillator Using Deep Neural Network

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Introduction

Recently, the rate of data collection at an ever-increasing pace and advanced computing power have led to the huge interest on data-driven system. And the invaluable features of deep neural network, which is composed of multiple layers, allow the computational models to learn representations of data. In this work, we will present deep neural networks with different architecture to approximate the unknown governing equations by suing observed data. In addition, we use the glycolytic oscillator as the main example.

Setup

Let 's consider nonlinear dynamical system

$$\frac{d}{dt}\boldsymbol{x}(t) = \boldsymbol{f}\left(\boldsymbol{x}(t)\right),$$

where $\boldsymbol{x}(t) \in \mathbb{R}^D$ are the state of system at time t and the governing function f describes the evolution of system. The goal is to create a neural network model for governing function by utilizing data of the solution trajectories. We used the ode solver, which is python odeint(), to collect the data by given initial conditions. Here, a general form of a linear multistep method with M steps to ode is applied.

$$\sum_{m=0}^{M}\left[\alpha_m \boldsymbol{x}_{n-m} + \Delta t \beta_m \boldsymbol{f}(\boldsymbol{x}_{n-m})\right] = 0, \quad n = M, \ldots, N.$$

Different alpha and beta will result in different schemes. In the neural network , we could use this equation to learn the parameters by minimizing the mean squared error loss function.

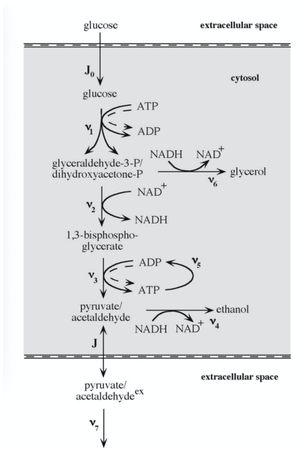
$$MSE := \frac{1}{N-M+1}\sum_{n=M}^{N}|\boldsymbol{y}_n|^2,$$

where

$$\boldsymbol{y}_n := \sum_{m=0}^{M}\left[\alpha_m \boldsymbol{x}_{n-m} + \Delta t \beta_m \boldsymbol{f}(\boldsymbol{x}_{n-m})\right], \quad n = M, \ldots, N,$$

Glycolytic Oscillator

Fuel processes are necessary for cells to grow, reproduce and respond to environment. In cells, the energy-rich molecule adenosine triphosphate (ATP) is used as a direct energy source and the purpose of energy metabolism is to produce ATP through the conversion of an indirect energy source such as a glucose molecule.
The first part of energy metabolism is called glycolysis and in this process glucose molecules are converted into pyruvate through a number of enzymatic reactions. For each glucose molecule converted, two adenosine diphosphate (ADP) molecules are phosphorylated to two ATP molecules and two nicotinamide adenine dinucleotide (NAD+) molecules are reduced to two NADH molecules. the simplified schematic of energy metabolism in yeast. If yeast cells are exposed to certain concentrations of glucose and cyanide, the concentration of metabolites in glycolysis starts to oscillate.



The Model

Reaction scheme for the glycolytic model showing the main reactions of anaerobic glycolysis in a yeast cell together with the influx and outflux of glucose and pyruvateyacetaldehyde, respectively.

- J_0 is input of glucose via the cellular membrane
- J is the membrane transport of the coupling substance, which is is the net flux of pyruvatey/acetaldehyde out of the cell
- v_1 is the reaction velocity of the combined reactions of hexokinase, phosphoglucoisomerase and PFK
- v_2 is the velocity of the glyceraldehyde-3-phosphate dehydrogenase reaction
- v_3 is the velocity of the combined reaction of phosphoglycerate kinase, phosphoglycerate mutase, enolase and pyruvate kinase
- v_4 is the velocity of the alcohol dehydrogenase reaction
- v_5 is the velocity of nonglycolytic ATP-consumption
- v_6 is the velocity for forming glycerol from triose phosphates
- v_7 is the degradation of extracellular pyruvatey/acetaldehyde
- A_3 and A_2 denote the concentrations of ATP and ADP
- N_1 and N_2 denote the concentrations of NAD^+ and NADH

Because several glycolytic reactions are omitted and that other reactions are lumped, the model variables denote, in some cases, the concectrations of pools of intermediates rather than concentrations of individual compunds.

- S_1: concentration of glucose
- S_2: concentrations of pool of the triose phosphates, glyceraldehyde 3-phosphate and dihydroxyacetone phosphate
- S_3: concentrations of 1,3-bisphosphoglycerate
- S_4: concentrations of pool of pyruvate and acetaldehyde
- S_4^{ex}: concentrations of the coupling substance in the external solution

The model is based on the following set of rate equations:

$$\frac{dS_1}{dt} = J_0 - v_1$$
$$\frac{dS_2}{dt} = 2v_1 - v_2 - v_6$$
$$\frac{dS_3}{dt} = v_2 - v_3$$
$$\frac{dS_4}{dt} = v_3 - v_4 - J$$
$$\frac{dN_2}{dt} = v_2 - v_4 - v_6$$
$$\frac{dA_3}{dt} = -2v_1 + 2v_3 - v_5$$
$$\frac{dS_4^{ex}}{dt} = \varphi J - v_7$$

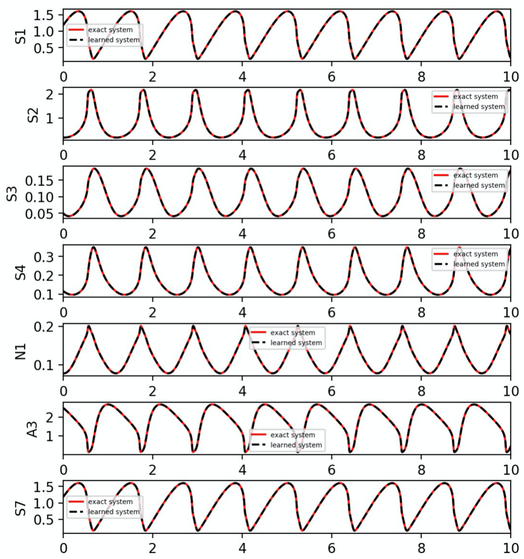
$$v_1 = k_1 S_1 A_3 [1 + \frac{A_3}{K_1}^q]^{-1}$$
$$v_2 = k_2 S_2 N_1$$
$$v_3 = k_3 S_3 A_2$$
$$v_4 = k_4 s_4 N_2$$
$$v_5 = k_5 A_3$$
$$v_6 = k_6 S_2 N_2$$
$$v_7 = k S_4^{ex}$$

The differential equation for N_1 and A_2 are omitted, because these concentrations follow the conservation conditions:

$$N_1 + N_2 = N = constant$$
$$A_2 + A_3 = A = constant$$

Results

Here, the data are collected from t=0 to t=25 with a time-step size 0.01. And we used a neural network with one hidden layer and 256 neurons to represent the nonlinear system.



Exact dynamics versus learned dynamics the given initial conditions from the following two tables. The parameter values in table 1 have been selected in such a way that the metabolite concentrations are in a realistic range for yeast cells.

Table 1 Parameter values of the reference state

Parameter	Value
J_0	3.0 mM · min^{-1}
k_1	100.0 mM^{-1} · min^{-1}
k_2	6.0 mM^{-1} · min^{-1}
k_3	16.0 mM^{-1} · min^{-1}
k_4	100.0 mM^{-1} · min^{-1}
k_5	1.28 min^{-1}
k_6	12.0 mM^{-1} · min^{-1}
k	1.3 min^{-1}
κ	13.0 min^{-1}
q	4.0
K_1	0.52 mM
N	1.0 mM
A	4.0 mM
φ	0.1

Table 2
Initial concentrations for reference state oscillations

Compound	Concentration (mM)
Glucose	1.187
Glyceraldehyde-3-P/dihydroxyacetone-P	0.193
1,3-Bisphosphoglycerate	0.050
Pyruvate/acetaldehyde	0.115
External pyruvate/acetaldehyde	0.077
ADP	1.525
ATP	2.475
NAD^+	0.923
NADH	0.077

Reference

1: Qin Tong, Wu Kailiang, Xiu Dongbin "Data driven governing equations approximation using deep neural networks" Journal of Computational Physics 395(2019):620-635.

2: Maziar Raissi, Paris Perdikaris, George Em Karniadakis "Multistep Neural Networks for Data-driven Discovery of Nonlinear Dynamical Systems" Mathematics, Physics, ArXiv 2018

3: Jana Wolf, Jutta Passarge, Oscar J.G. Somsen, Jacky L. Snoep, Reinhart Heinrich, Hans V. Westerhoff "Transduction of Intracellular and Intercellular Dynamics in Yeast Glycolytic Oscillations" Biophysical Journal Volume 78 March 2000 1145-1153

4: Peter Ruoff, Melinda K. Christensen, Jana Wolf, Reinhart Heinrich "Temperature dependency and temperature compensation in a model of yeast glycolytic oscillations" Biophysical Chemistry 106(2003) 179-192

5: Jana Wolf, Reinhart Heinrich "Effect of cellular interaction on glycolytic oscillations in yeast: a theoretical investigation" Biochemical Journal 2020