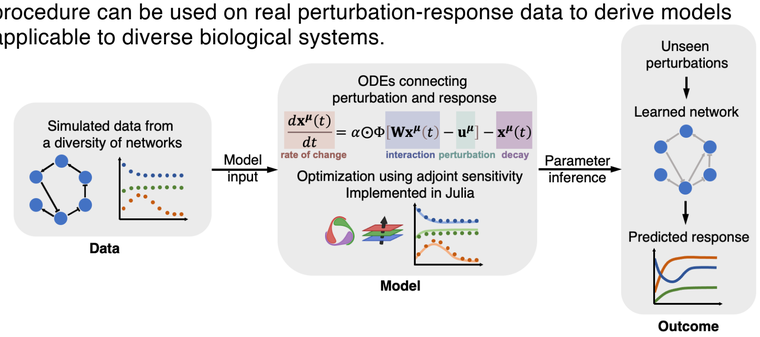
Inference of Cell Dynamics on Perturbation Data Using Adjoint Sensitivity

Weiqi Ji[1], Bo Yuan[2,3], Ciyue Shen[2,3], Aviv Regev[3,4], Chris Sander[2,3], Sili Deng[1]

[1] Department of Mechanical Engineering, Massachusetts Institute of Technology
[2] Department of Cell Biology, Cell Biology, Harvard Medical School
[3] Broad Institute of MIT and Harvard
[4] Department of Biology, Massachusetts Institute of Technology

Abstract

Data-driven dynamic models of cell biology can be used to predict cell response to unseen perturbations. Recent work (CellBox) had demonstrated the derivation of interpretable models with explicit interaction terms, in which the parameters were optimized using machine learning techniques. While the previous work was tested only in a single biological setting, this work aims to extend the range of applicability to a diversity of biological systems. Here we adapted CellBox in Julia differential programming and augmented the method with adjoint algorithms, which has recently been used in the context of neural ODEs. We trained the models using simulated data from both abstract and biology-inspired networks. The accuracy of prediction by these models is high both in terms of low error against data and excellent agreement with the network structure used for the simulated training data. This work demonstrates the ability to construct and parameterize a considerable diversity of network models with high predictive ability. The expectation is that this kind of procedure can be used on real perturbation-response data to derive models applicable to diverse biological systems.



Background and motivation

We have previously developed a hybrid approach, CellBox, that combines explicit ODE models of cellular interactions with an automatic differentiation framework implemented in TensorFlow. CellBox had some key limitations including, only tested in one specific system and on steady-state data, potential trucation errors due to the use of non-stiff solvers, and arbitrary choice of fixed time step due to the static computational graph in Tensorflow. To move beyond these limitations, we implemented the CellBox algorithm in Julia, where we replaced back propagation through time with adjoint sensitivity and changed Heun's ODE solver with fixed time steps to high-order ODE solvers with adaptive time steps.

Method

A set of ODEs was used to describe the time development of the system variables upon perturbation:

$$\frac{d\mathbf{x}^\mu(t)}{dt} = \boldsymbol{\alpha} \odot \Phi\left[\mathbf{W}\mathbf{x}^\mu(t) - \mathbf{u}^\mu\right] - \mathbf{x}^\mu(t)$$

where the n dimensional vector $\mathbf{x}^\mu(t)$ represents the change in molecular or phenotypic measurement, e.g., log ratios of molecular concentration after and before perturbation $\mathbf{u}$. The initial condition is $\mathbf{x}(0) = 0$. $\mathbf{W} \in \mathbb{R}^{n\times n}$ quantifies the directional interaction among molecules. The scaling factor $\boldsymbol{\alpha}$ quantifies the strength of the natural decay term $-\mathbf{x}^\mu(t)$. A hyperbolic tangent envelope function is used to introduce a saturation effect. $\odot$ denotes element wise multiplication.

We re-implemented CellBox to learn the model parameters in the framework of neural ODEs. For instance, one can view the above equation as a neural network with single hidden layer where both the dimension of input and output is equal to n. We denote the model predictions as

$$\hat{\mathbf{x}}^\mu(t) = ODESolve(\frac{d\mathbf{x}^\mu(t)}{dt}; \mathbf{x}^\mu(t=0), \mathbf{W}, \boldsymbol{\alpha})$$

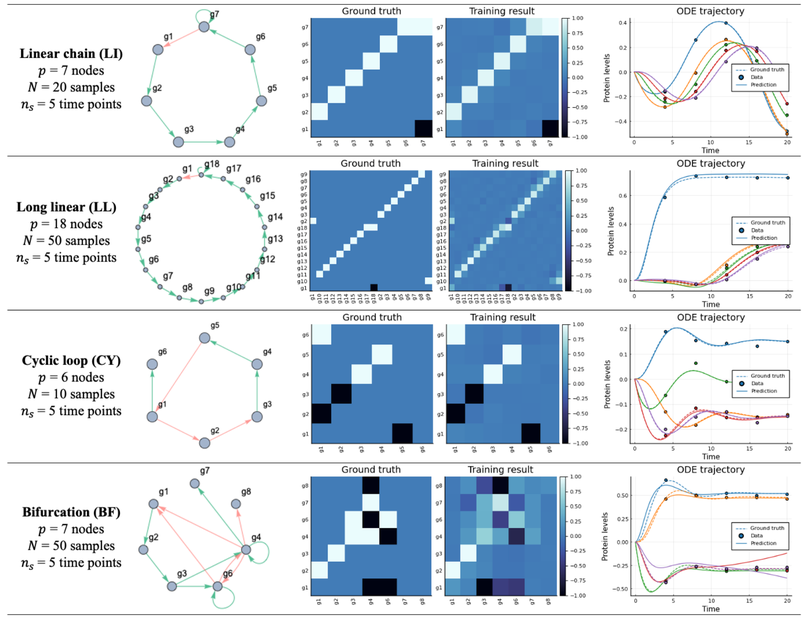
And we use the loss function of mean absolute error (MAE), i.e.,

$$Loss(\mathbf{W}, \alpha) = \underset{\mu,t}{MAE}(\hat{\mathbf{x}}^\mu(t), \mathbf{x}^\mu(t))$$

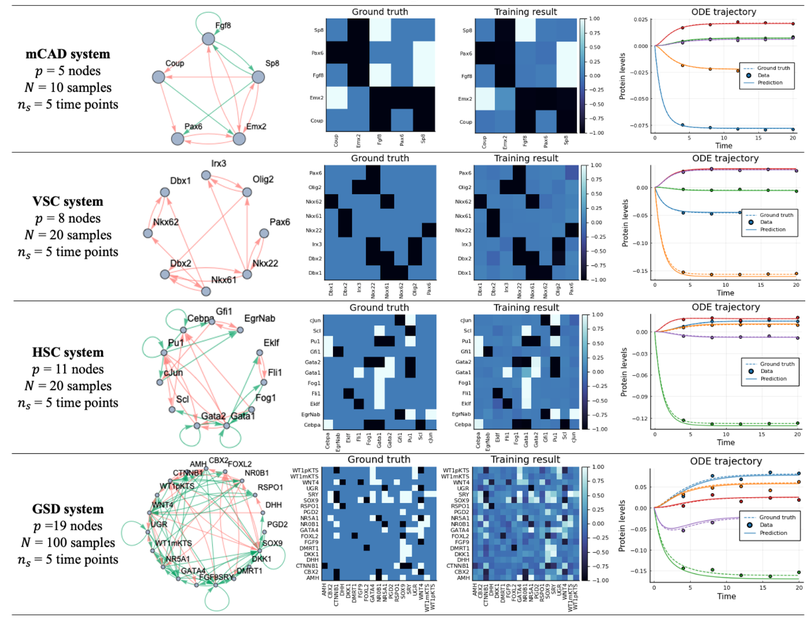
where $\hat{\mathbf{x}}^\mu(t)$ and $\mathbf{x}^\mu(t)$ correspond to simulated and measured molecular profiles. We use the ODE solver of the Tsitouras 5/4 Runge-Kutta method. The first-order optimizer Adam is adopted. Learning rate annealing is exploited. We employ weight decay to encourage sparsity in the interaction matrix, which is based on our understanding of interactions in biological networks. To accelerate training, the training proceeds with mini-batching, in which we sample $n_s = 5$ time points from each perturbation condition as a single batch and we iteratively loop over all conditions.

Results

Abstract synthetic systems We first conduct proof-of-concept experiments by applying the CellBox algorithm to several typical abstract networks presented in Pratapa et al. (2020), including linear (LI), cyclic (CY), and bifurcation (BI) networks.



We artificially introduce perturbations into the systems and use ODE equations to simulate pseudo-experimental response trajectories. We evaluated both the predictive accuracy of cell responses to these perturbations, as well as the accuracy of network inference. The models can predict system responses to external perturbations (average MAE < 10^{-3}), as well as capture the system structures by inferring the network interaction parameters (average Pearson's correlation > 0.9).



Biology-inspired synthetic systems We tested CellBox on synthetic analogs of four real biological systems adapted from Pratapa et al., including mammalian cortical area development (mCAD), ventral spinal cord (VSC) development, hematopoietic stem cell (HSC) differentiation and gonadal sex determination (GSD), which were human-curated from the research literature and have been repeatedly validated by experiments. Similar to the abstract systems, these models achieved the same level of prediction error (MAE: 10^{-4}-10^{-3}) and inference accuracy (Pearson's correlation: 0.9-0.99).

Conclusion and discussion

We have successfully adapted the CellBox method with adjoint sensitivity and demonstrated it can be effectively trained to predict responses and reconstruct the ground truth interaction networks in several abstract and biology-inspired networks. This suggests that the CellBox can potentially be applied to a wide variety of biological systems. The data requirement observed in this work might help with the design of future perturbation experiments needed to accurately simulate and predict the responses of a particular system.