Constructing Data-Driven Network Models of Cell Dynamics with Perturbation Experiments

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Abstract

Systematic perturbation of cells followed by comprehensive measurements of molecular and phenotypic responses provides informative data resources for constructing computational models of cell biology. Existing machine learning models of cell dynamics have limited effectiveness to find global optima in a high-dimensional space and/or lack interpretability in terms of cellular mechanisms. Here we introduce a hybrid approach that combines explicit protein-protein and protein-phenotype interaction models of cell dynamics with automatic differentiation. We tested the modeling framework on a perturbation-response dataset of a melanoma cell line with drug treatments. These machine learning models can be efficiently trained to describe cellular behavior with good accuracy but also can provide direct mechanistic interpretation. The predictions and inference of interactions are robust against simulated experimental noise. The approach is readily applicable to a broad range of kinetic models of cell biology and provides encouragement for the collection of large-scale perturbation-response datasets.

1 Introduction

Resistance to single drug treatment emerged as a new bottleneck for therapeutics in cancer [1–4]. However, experimental screening of all possible pairwise or higher-order combinations of anticancer agents is practically unrealistic. The ability to model cell biology at a larger scale and to infer potential effects of unobserved drug combos is critical in facilitating the search for combinatorial, potentially therapeutic candidates.

Perturbation screens In order to address the challenge of understanding cell behavior, a large variety of experimental screening approaches has been used to profile cellular responses under different perturbations. Phenotypic screening collects high-throughput information on whole-cell responses with univariate readouts such as cell viability or growth rate [5–9]. In order to resolve intracellular interactions and provide mechanistic insights, molecular screenings have been developed to profile post-perturbational systematic responses, e.g., changes in transcript [10–12] and protein levels [13, 14]. These rich datasets challenge computational methods to describe mechanisms more comprehensively and to model cell responses to unseen perturbations quantitatively, e.g. in order to propose potential drug combinations.

Computational methods To efficiently narrow down the search space and nominate promising sets of experimentally testable candidates, computational biology models have been used to predict cellular responses based on sets of perturbation experiments, but the majority are limited by scope. A more detailed review of existing computational models can be found in Section 4. Recently, a promising alternative emerges from the field of machine learning, that is to use deep neural networks to train a

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black-box predictor of drug effects. Deep learning has been successfully applied to many domains of biomedical research, from pathology image classification [15, 16] to sequence motif detection [17]. While predictive power of deep learning models is often impressive, their interpretation, which is crucial for providing understandable and, therefore, more trustable predictions in biomedical research, remains challenging. One of the main reasons is that the complex multi-layer network architecture of most deep learning models lacks explicit representations and consequent direct interpretation [18].

CellBox: a hybrid approach To address the problem of both accuracy and interpretability, we apply a deep learning optimization approach to learn a data-driven network model, which incorporates a dynamic differential equations system of an explicitly interpretable interaction network of cellular components [19]. We performed proof-of-concept model training with experimental data from a cancer cell line (Section 2), achieved a high level of learning performance (Section 3.1), and demonstrated the robustness of the approach (Section 3.2). We named this scientific machine learning framework CellBox, in contrast to a 'black-box' neural network. We also provided a detailed review of related modeling approaches (Section 4).

2 Proposed models

Model construction A set of ordinary differential equations (ODE) is used to link the measurements of the system upon perturbations:

$$\frac{\partial x_i^{\mu}(t)}{\partial t} = \epsilon_i \Phi(\sum_{j \neq i} w_{ij} x_j^{\mu}(t) + u_i^{\mu}(t)) - \alpha_i x_i^{\mu}(t) \tag{1}$$

where each $x_i^{\mu}(t)$ represents a log-normalized change of a molecular or phenotypic measurement relative to control measurement under a particular perturbation condition μ. $u_i^{\mu}(t)$ quantifies the strength of the perturbation on its downstream target i. α_i characterizes the effect of natural decay, which is the tendency of an entity to return to its steady state level before perturbation. The interaction parameter w_{ij} quantifies the directional interaction from network node j to network node i. The interaction parameters w_{ij} are constrained such that there are no i) ingoing connections for direct downstream nodes of perturbations, ii) out-going connections for phenotpyic nodes, or iii) self-interactions. A sigmoid envelope function $\Phi(x) = tanh(x)$ is used to introduce a saturation effect of the interaction term so that it is bounded by ϵ_i.

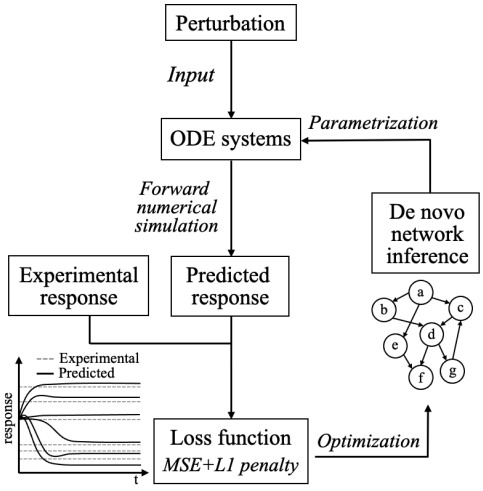

Figure 1: The CellBox pipeline.

Inference As described in Figure 1, the ODE system is numerically solved using Heun's method [20]:

$$x_i(t+h) = x_i(t) + \frac{h}{2}[f(t, x_i(t)) + f(t+h, \hat{x}_i(t+h))] \tag{2}$$

where $\hat{x}_i(t+h) = x_i(t) + hf(t, x_i(t))$, $x_i(t_0) = 0$. The loss function $L(w)$ is defined as a weighted sum of prediction error, represented as mean squared error, and complexity penalty of the network, represented as L1 regularization:

$$L(w) = \sum_{\mu} \sum_{i} \|\hat{x}_i(w_{ij}, t) - x_i^{\mu *}(t)\|_2 + \lambda_1 \|w_{ij}\|_1 \tag{3}$$

where $\hat{x}_i(w_{ij}, t)$ is calculated as the converged value of the numerical simulation of the ODE with the inferred interaction parameters w_{ij} and defined simulation time t, and $x_i^{\mu *}(t)$ represents the experimental measurement. During model training, the parameters would be optimized iteratively via back propagation and automatic differentiation on the total loss using Adam optimizer [21].

The implementation is under the TensorFlow framework [22] and is publicly available at https://github.com/dfci/CellBox.

Bias-variance tradeoff Optimizing parameters to model a biological system is hard in part because of the huge parameter space. We are interested in examining the bias-variance tradeoff of CellBox models. *Bias* error, or approximation error, is the error resulting from the model choice, e.g. oversimplification or wrong assumptions. We denoted the bias error as $||f^*(\mathbf{w}) - \hat{f}(\mathbf{w})||$, which is lower bound of the total error. *Variance*, or estimation error, in contrast, indicates the parameter inference errors resulting from numerical optimization, denoted as $||\hat{f}(\mathbf{w}) - \hat{f}(\hat{\mathbf{w}})||$. The total model error is therefore upper bounded by,

$$||f^*(\mathbf{w}) - \hat{f}(\hat{\mathbf{w}})|| \leq ||f^*(\mathbf{w}) - \hat{f}(\mathbf{w})|| + ||\hat{f}(\mathbf{w}) - \hat{f}(\hat{\mathbf{w}})|| \tag{4}$$

The bias-variance tradeoff describes that, in general, the simpler the proposed model, the larger the approximation error and the smaller estimation error. In the CellBox training objective function (4), we included an L1 loss term, which rewards model with sparser interactions by a factor λ_1, in addition to the reconstruction loss $\sum_\mu \sum_i \|\hat{x}_i(\mathbf{w}, t) - x_i^{\mu*}(t)\|_2$. We also adapted the stability selection tests [23] to evaluate the stability of out inferred interactions.

3 Results

3.1 CellBox models accurately predict cell response to unseen perturbations and the inferred networks are stable

Training We first evaluated the efficiency of training CellBox models to predict cell response. As the training progresses, the predicted response converge to measured experimental response in both the training and test set (Figure 2A). At the end of the training, the predicted values highly correlate with the experimental values, independent of how the data was randomly partitioned into the training and test set.

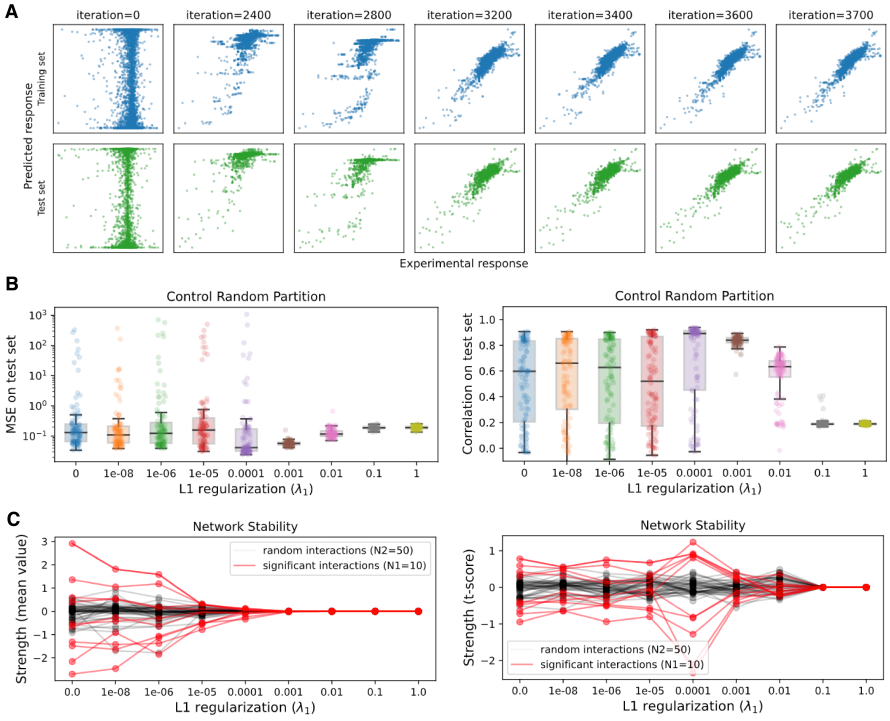

Figure 2: Model performance with different regularization strength

Bias-variance tradeoff We were interested in the effect of different network complexity upon prediction accuracy. By applying different regularization strength λ_1, the model performance changes as expected (Figure 2B). Using a smaller λ_1 results in increasing freedom for parameter choices, and therefore a higher upper bound of performance, but meanwhile there would be larger variances for parameter inference. To the opposite, when using smaller λ_1, the parameter estimation is more stable, i.e. smaller variances, but the upper bound of performance is limited. These results indicate the selection of kernel model for CellBox would affect the model training in a way that is consistent with the bias-variance tradeoff. In our proof-of-concept model training, $\lambda_1 = 1e-4$ appeared to be the sweet spot for regularization strength.

Network stability We also examine the stability of the resulting interactions in the network [23]. We found that the significant interactions inferred by the models are robust (Figure 2C). When the regularization strength λ_1 is strong, CellBox is not able to robustly identify significant interactions across models, because the objective function would be overwhelmed by the regularization term instead of the term of reconstruction accuracy.

3.2 Prediction accuracy and network stability are robust against common forms of experimental noise

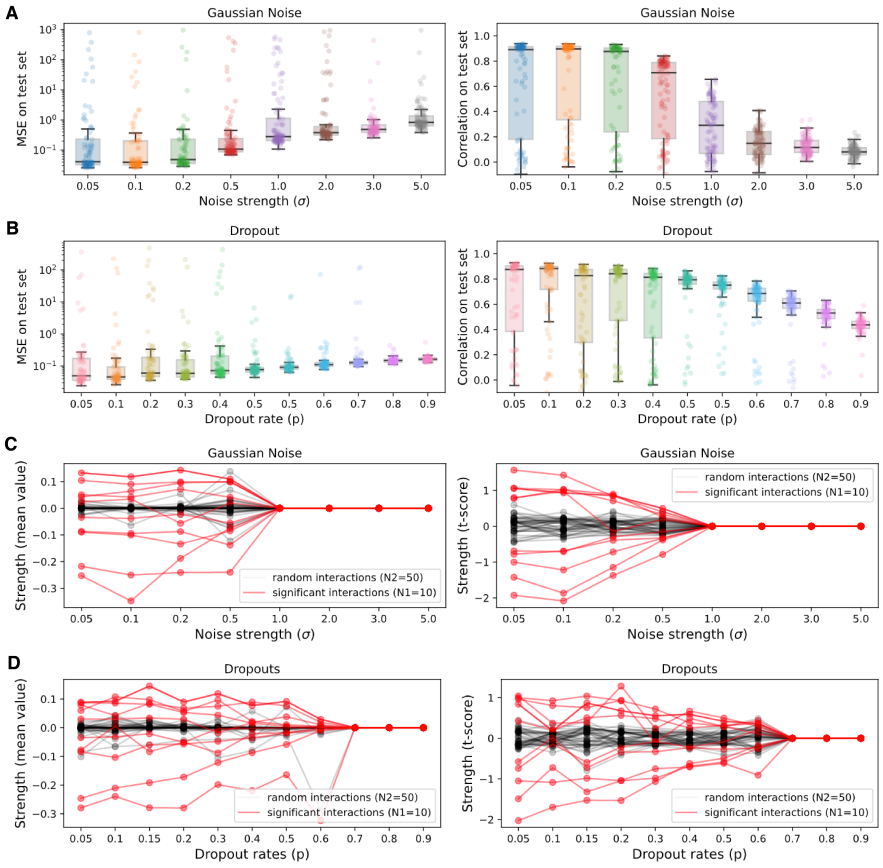

Figure 3: Model robustness against experimental noise

Multiple sources can give rise to uncertainty in data collection, and consequently in model optimization, especially in biomedicine. Common forms of experimental noise include inevitable measurement variances and dropout events, e.g., for single cell measurements. To test the robustness of our models against data precision and sparsity, we perform sensitivity analysis on the data with increasing additive noise and dropout rate. We introduced two noise forms, a Gaussian random noise

(5) and a simulated dropout event (6).

$$\tilde{x}_i(t) = x_i^*(t) + \mathcal{N}(0, \sigma) \tag{5}$$

$$\tilde{x}_i(t) = \{ \begin{array}{ll} 0 & (\texttt{with a probability of } p) \\ x_i^*(t) & (\texttt{otherwise}) \end{array} \tag{6}$$

With the best chosen regularization strength, the prediction accuracy of the models remain high for up to additive Gaussian noise of 0.2 standard deviation or 30% data dropout (Figure 3A-B). In addition, the inferred significant interactions are stable within the levels of data noise and dropout that the models can tolerate (Figure 3C-D). Such levels of data precision and sparsity are relevant for most experimental approaches in biological and biomedical studies, suggesting the potential of CellBox to generalize to various data sources.

4 Related work

Static regression models Co-expression models [24–26], maximum entropy networks [27, 28], or mutual information related methods [29, 30] construct network models of molecular interactions [31, 32] or use regression models to directly predict cellular responses based on molecular perturbation-response measurements [10, 12]. Such static regression models usually provide end-to-end predictions, while inevitably neglecting intermediate steps, and therefore leave prediction challenging for untested perturbations.

Dynamic models with prior knowledge Boolean network models [33], fuzzy logic models [34] , dynamic Bayesian networks [35] and ordinary differential equation (ODE) network models [36, 37] can provide mechanistic insight in terms of propagation of cellular signals to phenotypic response over time, but typically require prior knowledge of interaction parameters and thus currently only work for small systems [36, 38]. New algorithms to parametrize large-scale mechanistic models, while computationally efficient, require prior knowledge of a set of relevant interactions [39]. Insufficient prior knowledge is one of the major constraints for modeling large systems, e.g., in that prior information is not available for all components or is aggregated from disparate experimental sources and thus lacks uniform context.

Data-driven dynamic models Previous dynamic optimization approaches such as Monte CarloM-Cmethods and belief propagation (BP) algorithms have been used to construct data-driven network models [13, 38, 40–42] . Still, these may not efficiently scale to larger systems (e.g., MC) or may require excessive approximations for the chosen mathematical model to facilitate efficient exploration of solution space (e.g., independent row approximation in BP) [13, 40]. Models that integrate physics ODE system and neural networks uses simulated time-series datasets to look for data-driven physical laws using inductive bias methods [43, 44]. The numerical methods of ODE solver and training techniques, such as minibatching, have also been discussed [45, 46]. Recent work has highlighted mathematical analogies between recurrent neural networks (RNN) and ODEs [47], suggesting a potential merge of the two fields for scientific machine learning (SciML) models [48].

Therefore, we argue that the desired modeling methods requires four key features: 1) accuracy in describing both phenotypic and protein level changes; 2) efficiency in simulating dynamic cellular response; 3) interpretablity in terms of biological mechanisms; and 4) ability to be constructed without prior knowledge about the system of interest. And we designed CellBox as an attempt to meet such requirements.

5 Conclusion

We introduced a hybrid approach combining optimization of explicit dynamic models with automatic differentiation and named it CellBox, in contrast to black-box neural network models. We demonstrated that CellBox can be trained with experimental data to accurately predict cellular behavior in response to extracellular perturbations. Without compromising accuracy, CellBox models are directly interpretable by design, in terms of protein-protein interactions that can be compared to established

models of molecular biology, such as signaling pathways. Such accuracy and interpretability of CellBox models are robust against common forms of noise in experimental data. We therefore envision such scientific machine learning approach to be broadly applicable to other biological questions, such as developmental biology or synthetic biology, provided that suitable perturbation-response data becomes available.

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