Cancer Cell

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Previews

Biologically Informed Neural Networks Predict Drug Responses

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https://doi.org/10.1016/j.ccell.2020.10.014

Deep neural networks often achieve high predictive accuracy on biological problems, but it can be hard to contextualize how and explain why predictions are made. In this issue, Kuenzi et al. model the sensitivity of cancers to drugs using deep neural networks with a hierarchical structure derived from the Gene Ontology.

Deep neural networks have dramatically altered the methodological landscape of computational biology (Ching et al., 2018). This class of techniques often exhibits strong predictive performance. Deep neural networks are capable of both integrating relatively raw data into complex features that are useful for a target task and then also combining those features to make accurate predictions. For example, a neural network trained to compress and then reconstruct transcriptomic data groups direct gene interactions, as measured through protein-protein interactions, in the least complex network layer and disease-related genes in the more complex layers without being explicitly optimized to do so (Dwivedi et al., 2020). Two challenges with deep neural networks, or any approaches that aim to construct features and then build predictors, are that, first, they often require substantial training data, and second, the input data are transformed in such a way that makes interpretation of the predictions themselves difficult. Including information from outside the immediate context of the prediction task, which may be other types of data (Dincer et al., 2018), biological annotations (Taroni et al., 2019), or both, can satisfy the dual goals of more efficiently using limited amounts of training data and making models more interpretable.

In this issue of *Cancer Cell*, Kuenzi et al. introduce a method, DrugCell, that aims to split the difference between fully free-form neural networks and the imposition of strong structural, but biologically informed, model constraints to predict drug sensitivity and drug combinations in cancer (Kuenzi et al., 2020). They use cancer genotype and drug structures as inputs to a pair of neural network architectures. While the neural network for chemical structures is relatively straightforward, the structure of the neural network for genotype is defined by the Gene Ontology. These two neural networks are then combined to predict the sensitivity, defined by the area under the dose response curve, of an array of tumor-derived cell lines to certain compounds.

The approach that the authors use has substantial parallels to constrained machine-learning models such as capsule networks (Hinton et al., 2011), where hierarchical spatial information is encoded in the learning. That is, a typical deep neural network would treat a picture of a face and a Picasso-painted face as equally being faces, but a capsule network would constrain learning to ensure that two eyes of equal size are located above the nose, which is above the mouth, etc. The hierarchy of spatial structure of a face is analogous to the hierarchical structure of related biological processes in the Gene Ontology. For cell genotype, using such a structurally constrained neural network could plausibly reduce or increase performance. A standard neural network has more flexibility in how it models the data (Figure 1A), while the architecture proposed by the authors is tightly coupled to annotated biological processes and how these biological processes are connected (Figure 1B). To illustrate, a gene could be annotated as having a role in the process, GO:0006298; *mismatch repair*, which is a child of GO:0006281; *DNA repair*, which is a child of GO:00065281; *DNA metabolic process*, and so on to broader biological processes. In the end, the structure of this neural network is defined by 20 years of human curation of experiments described in the biomedical literature.

On the one hand, we might expect the architecture constrained by the Gene Ontology to have lower predictive performance because the neural network has less flexibility to fit the data. On the other hand, the performance could increase because the pre-specified neural network architecture represents a "correct" way to feed information through the learning model, and having the network pre-specified, by definition, means that training data are not required to discover the underlying network architecture. If this is the case, training the model for the prediction task would require less data because all relationships have already been defined. This is an exciting proposition because deep neural networks often require large amounts of data to properly learn the network architecture for the prediction task, thus limiting their application to the small number of biological scenarios with sufficient data. The results

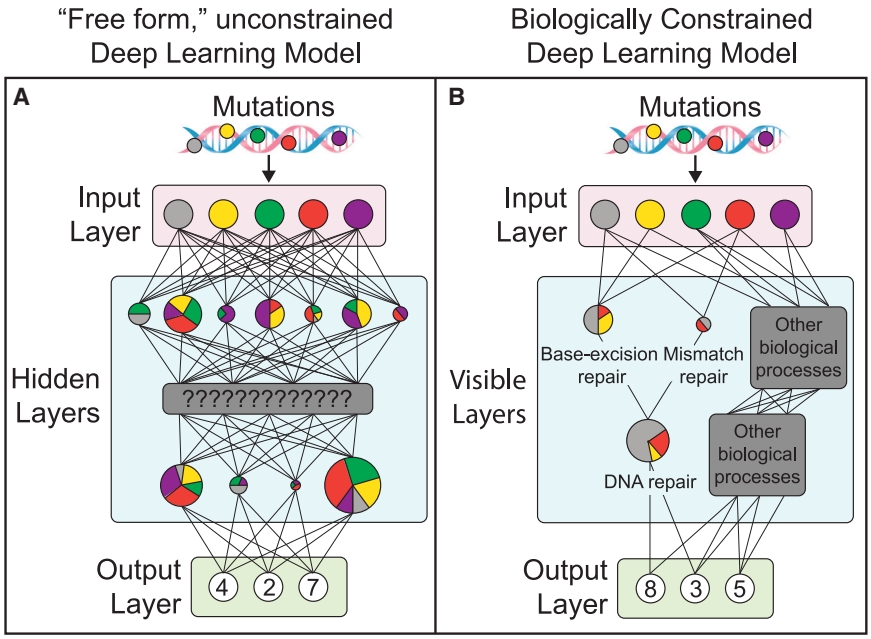

Figure 1. Deep Learning Network Structures

(A) Deep neural networks have the general structure of an input layer, hidden layers, and an output layer. Biological data must be transformed into an array of input values. These values are then fed forward into the hidden layers. A challenge with deep neural networks is defining the depth (number of hidden layers) and width (number of nodes at each layer). Each node in a layer takes input information from all nodes in the previous layer, which is then mathematically transformed before feedforward again. The output layer then represents the final transformation of the input data. The number of non-linear transformations involved makes the highest-level layers particularly difficult to interpret.

(B) In contrast, in this issue Kuenzi et al. (2020) use the network structure of the hierarchical Gene Ontology to define how the input and output layers are connected. Since the values of the output layer can be traced back through the network, the hidden layers are replaced with what the authors refer to as visible layers.

from Kuenzi et al. (2020) suggest that Gene Ontology-defined and unconstrained neural networks have similar performance for drug sensitivity prediction. The heavily specified network is better for some drug-genotype combinations, while an unconstrained one is better for others, though differences are generally small. Even though there is not a large performance difference, neural networks grounded in prior findings will be easier to interpret, which is a key benefit of DrugCell.

Deep neural networks operate in an abstract, mathematically transformed space called the embedding space. This space is the result of one or more non-linear transformations of the input data. The input data get changed at each layer of the network, forming new, abstract features that are aggregations and transformations from the previous layer (Figure 1A). The hope is that the predominant patterns in this embedding space will identify the elements that are highly predictive for the given task. The authors demonstrate that their embedding space has these properties: genotypes sensitive to certain compounds cluster in a different part of the embedding space than the resistant genotypes. Since these clusters map to biological processes, the embeddings offer insights into the processes that are predictive of drug response. The authors use targeted CRISPR-Cas9 screens to validate selected predictions. DrugCell identifies certain cellular subsystems as being important for response to certain small molecules. In one example, the authors use the DrugCell model to select subsystems that are predictive of response to olaparib, a *PARP* inhibitor. The authors knock out *PARP1* and find that knocking out genes in subsystems highly ranked for olaparib sensitivity produces more of an effect than knocking out genes in random subsystems. This provides evidence that the model can prioritize subsystems related to the response to small molecules. Additional post hoc analysis of datasets with genotypes, treatments, and outcomes shows that DrugCell may stratify patients by their response to treatment.

The observation that these highly constrained networks perform similarly to unstructured ones with approximately 500,000 drug-cell line pairs suggests that attempting to train deep neural networks in data-limited settings may particularly benefit from network architectures that incorporate external biological resources. In the setting of rare cancers, it is likely to be difficult to acquire so many compound-genotype-sensitivity measurements. Neural network architectures that incorporate prior knowledge, potentially combined with efforts to include other measurements in the training process through transfer learning, are likely to be necessary to achieve performances with the potential for clinical application.

DrugCell takes a necessary step to advance deep neural networks for drug sensitivity and combination prediction. However, there are some caveats that should be considered. DrugCell is trained on data from tumor-derived cancer cell lines to represent a tumor, but tumors are comprised of highly heterogenous cell types, along with varying degrees of penetrance of the genotypes used to train the model. Other factors, such as the tumor microenvironment, will also need to be considered. Finally, it is not always clear how drug synergies found in cell culture translate to patients (Palmer and Sorger, 2017). The current model primarily considers one measure of drug response, the area under the dose response curve, but considering drug efficacy and potency separately could be informative clinically, both for single drugs and particularly for combinations (Meyer et al., 2019).

As we imagine how neural networks and other machine-learning methods are likely to impact practice, these methods may one day support decision-making by molecular tumor boards. Such methods can be remarkably good at identifying combinations of features that relate to an outcome. However, machine-learning models can also be brittle in strange ways (Goodfellow et al., 2015).

Integrating prior knowledge and complementary data sources can help to place the results into a context that should help treating physicians begin to interpret the model and attribute outcomes to certain processes. For artificial intelligence to have maximum impact, models will need to not only be accurate but also explainable. Unexplainable methods pose a significant risk that their predictions are driven by factors correlated with, but unrelated to, the desired endpoint (Zech et al., 2018). Thus, it is particularly encouraging that neural networks that use prior biological knowledge to define their structure are equally predictive while providing a more straightforward interpretation. We anticipate that future work will build on this modeling approach to account for increasingly more complex and clinically realistic scenarios.

ACKNOWLEDGMENTS

This work was supported in part by grants from the National Institutes of Health (R01 CA237170, R01 CA200854, and U01 CA231978).

DECLARATION OF INTERESTS

J.C.C. is a founder of PrecisionProfile, Inc., and has ownership in the company.

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PD-L1 Blockade Therapy: Location, Location, Location

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https://doi.org/10.1016/j.ccell.2020.10.017

The mechanisms by which PD-1/PD-L1 inhibition elicits anti-tumor immunity are not fully understood. In this issue of *Cancer Cell*, Dammeijer et al. address the role of PD-L1 inhibition specifically within the tumor-draining lymph node, identifying a potential role for PD-L1 expressing dendritic cells within the lymph node in regulation of anti-tumor immune responses.

PD-1/PD-L1 inhibition forms a cornerstone of immunotherapy for many cancers. However, the mechanisms underlying therapeutic efficacy are not fully understood. Until recently, anti-PD-L1 was thought to invoke anti-tumor immunity by disrupting inhibitory interactions between PD-L1$^+$ tumor cells and PD-1$^+$ T cells, reinvigorating exhausted T cells. However, recent studies have demonstrated the emergence of novel T cell clones following anti-PD-1 treatment (Callahan and Wolchok, 2019; Yost et al., 2019). T cell priming to antigen occurs in lymph nodes, suggesting that PD-1 blockade may disrupt inhibitory interactions between antigen-presenting cells (APCs) and T cells within