

# Incorporating biological structure into machine learning models in biomedicine

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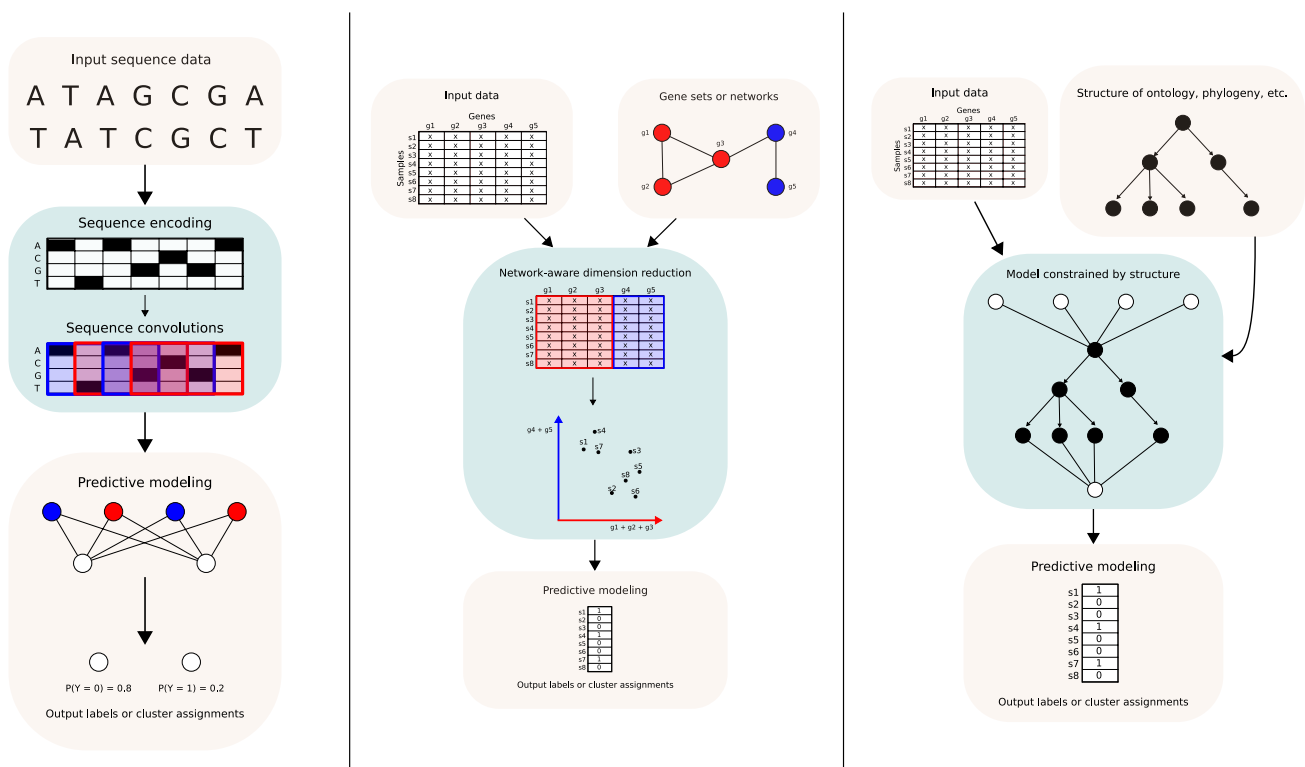
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## Abstract

In biomedical applications of machine learning, relevant information often has a rich structure that is not easily encoded as real-valued predictors. Examples of such data include DNA or RNA sequences, gene sets or pathways, gene interaction or coexpression networks, ontologies, and phylogenetic trees. We highlight recent examples of machine learning models that use structure to constrain model architecture or incorporate structured data into model training. For machine learning in biomedicine, where sample size is limited and model interpretability is critical, incorporating prior knowledge in the form of structured data can be particularly useful. The area of research would benefit from performant open source implementations and independent benchmarking efforts.

## Graphical abstract



Schematic showing the main categories of models incorporating structured biological data covered in this review. The first panel shows an example of a model operating on sequence data, the second panel shows a model in which dimension reduction is influenced by the connections in a gene network, and the third panel shows a neural network with structure constrained by a phylogeny or ontology. The “x” values in the data tables represent gene expression measurements.

## Introduction

It can be challenging to distinguish signal from noise in biomedical datasets, and machine learning methods are particularly hampered when the amount of available training data is small. Incorporating biomedical knowledge into machine learning models can reveal patterns in noisy data [1] and aid model interpretation [2]. Biological knowledge can take many forms, including genomic sequences, pathway databases, gene interaction networks, and knowledge hierarchies such as the Gene Ontology [3]. However, there is often no canonical way to encode these structures as real-valued predictors. Modelers must creatively decide how to encode biological knowledge that they expect will be relevant to the task.

Biomedical datasets often contain more input predictors than data samples [4,5]. A genetic study may genotype millions of single nucleotide polymorphisms (SNPs) in thousands of individuals, or a

gene expression study may profile the expression of thousands of genes in tens of samples. Thus, it can be useful to include prior information describing relationships between predictors to inform the representation learned by the model. This contrasts with non-biological applications of machine learning, where one might fit a model on millions of images [6] or tens of thousands of documents [7], making inclusion of prior information unnecessary.

We review approaches that incorporate external information about the structure of desirable solutions to learn from biomedical data. One class of commonly used approaches learns a representation that considers the context of each base pair from raw sequence data. For models that operate on gene expression data or genetic variants, it can be useful to incorporate networks or pathways describing relationships between genes. We also consider other examples, such as neural network architectures that are constrained based on biological knowledge.

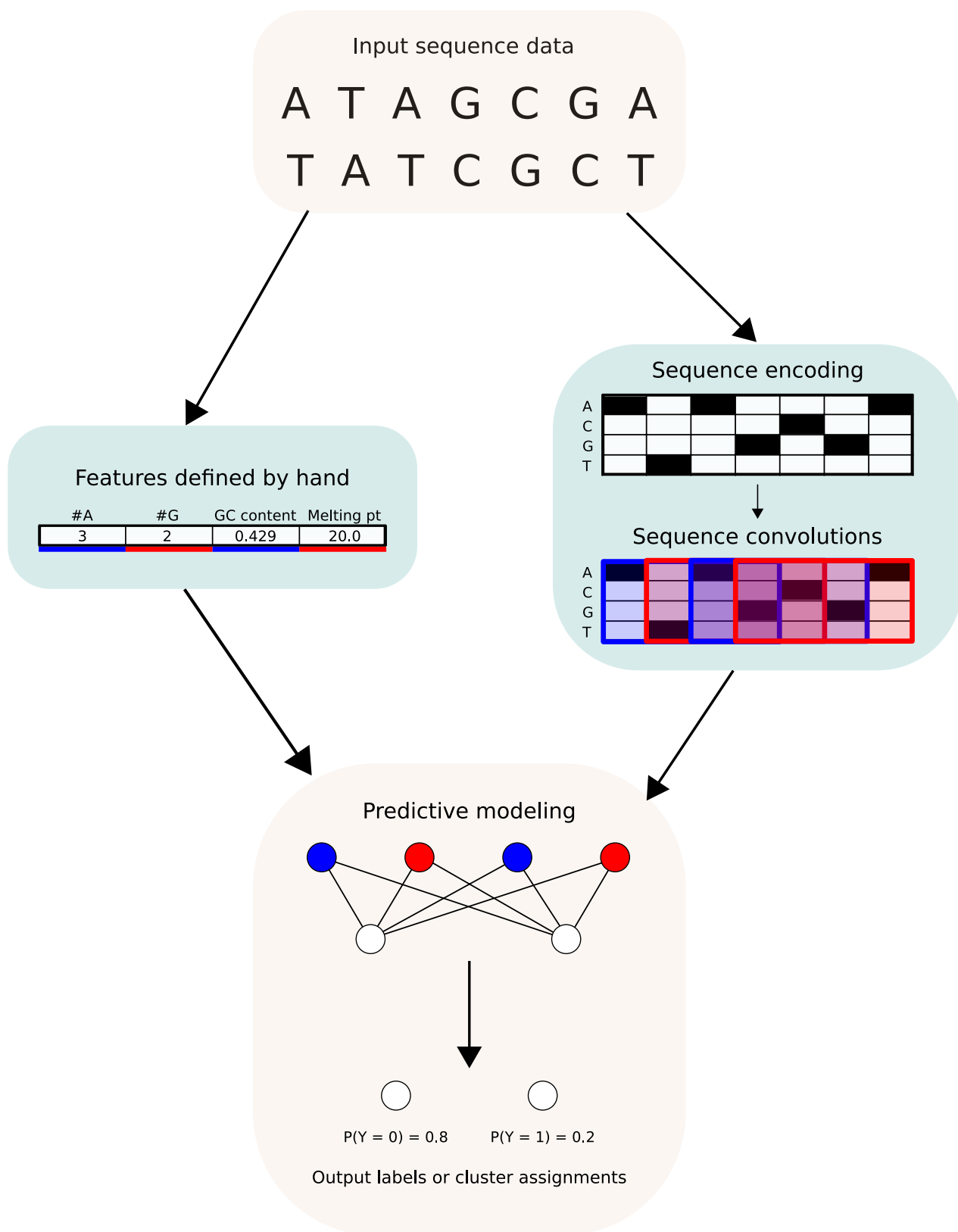
There are many complementary ways to incorporate heterogeneous sources of biomedical data into the learning process, which have been covered elsewhere [8,9]. These include feature extraction or representation learning prior to modeling and/or other data integration methods that do not necessarily involve customizing the model itself.

## Sequence models

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Early neural network models primarily used hand-engineered sequence features as input to a fully connected neural network [10,11] (Figure 1). As convolutional neural network (CNN) approaches matured for image processing and computer vision, researchers leveraged biological sequence proximity similarly. CNNs are a neural network variant that groups input data by spatial context to extract features for prediction.

The definition of “spatial context” is specific to the input: one might group image pixels that are nearby in 2D space, or genomic base pairs that are nearby in the linear genome. In this way, CNNs consider context without making strong assumptions about exactly how much context is needed or how it should be encoded; the data informs the encoding. A detailed description of how CNNs are applied to sequences can be found in Angermueller et al. [12].



**Figure 1:** Contrasting approaches to extracting features from DNA or RNA sequence data. Early models defined features of interest by hand based on prior knowledge about the prediction or clustering problem of interest, such as GC content or sequence melting point, as depicted in the left branch in the figure. Convolutional models, depicted in the right branch, use sequence convolutions to derive features directly from sequence proximity, without requiring quantities of interest to be identified before the model is trained. Red or blue emphasis denotes inputs to the predictive model (either the hand-defined numeric features on the left or the outputs of convolutional filters on the right).

## Applications in regulatory biology

Many early applications of deep learning to biological sequences were in regulatory biology. Early CNNs for sequence data predicted binding protein sequence specificity from DNA or RNA sequence [13], variant effects from noncoding DNA sequence [14], and chromatin accessibility from DNA sequence [15].

Recent sequence models take advantage of hardware advances and methodological innovation to incorporate more sequence context and rely on fewer modeling assumptions. BPNet, a CNN that predicts transcription factor binding profiles from DNA sequences, accurately mapped known locations of binding motifs in mouse embryonic stem cells [16]. BPNet considers 1000 base pairs of context around each position when predicting binding probabilities with a technique called dilated convolutions [17], which is particularly important because motif spacing and periodicity can influence binding. cDeepbind [18] combines RNA sequences with information about secondary structure to predict RNA binding protein affinities. Its convolutional model acts on a feature vector combining sequence and structural information, using context for both to inform predictions. APARENT [19] is a CNN that predicts alternative polyadenylation (APA) from a training set of over 3 million synthetic APA reporter sequences. These diverse applications underscore the power of modern deep learning models to synthesize large sequence datasets.

Models that consider sequence context have also been applied to epigenetic data. DeepSignal [20] is a CNN that uses contextual electrical signals from Oxford Nanopore single-molecule sequencing data to predict 5mC or 6mA DNA methylation status. MRCNN [21] uses sequences of length 400, centered at CpG sites, to predict 5mC methylation status. Deep learning models have also been used to predict gene expression from histone modifications [22,23]. Here, a neural network model consisting of long short-term memory (LSTM) units was used to encode the long-distance interactions of histone marks in both the 3' and 5' genomic directions. In each of these cases, proximity in the linear genome helped model the complex interactions between DNA sequence and epigenome.

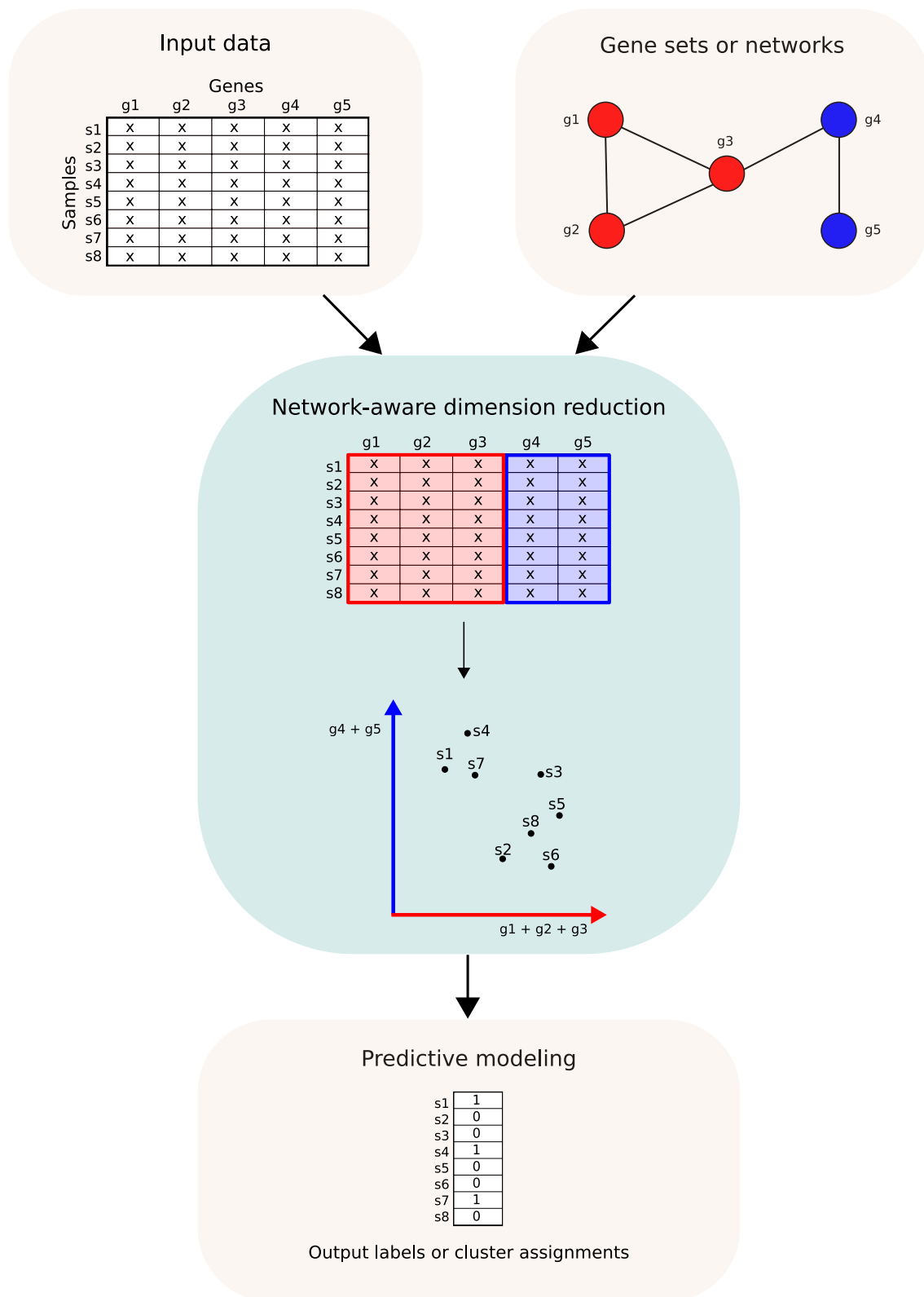
## Applications in variant calling and mutation detection

Identification of genetic variants also benefits from models that include sequence context. DeepVariant [24] applies a CNN to images of sequence read pileups, using read data around each candidate variant to accurately distinguish true variants from sequencing errors. CNNs have also been applied to single molecule (PacBio and Oxford Nanopore) sequencing data [25], using a different sequence encoding that results in better performance than DeepVariant on single molecule data. However, many variant calling models still use hand-engineered sequence features as input to a classifier, including current state-of-the-art approaches to insertion/deletion calling [26,27]. Detection of somatic mutations is a distinct but related challenge to detection of germline variants, and has also recently benefitted from use of CNNs [28].

## Network- and pathway-based models

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Rather than operating on sequences, many machine learning models in biomedicine operate on inputs that lack intrinsic order. Models may make use of gene expression data matrices from RNA sequencing or microarray experiments in which rows represent samples and columns represent genes. To account for relationships between genes, one might incorporate known interactions or correlations when making predictions or generating a low-dimensional representation of the data (Figure 2). This is comparable to the manner in which sequence context pushes models to consider nearby base pairs similarly.



**Figure 2:** The relationships between genes provide structure that can be incorporated into machine learning models. One common approach is to use a network or collection of gene sets to embed the data in a lower-dimensional space, in which genes that are in the same gene sets or that are well-connected in the network have a similar representation in the lower-dimensional space. The embedded data can then be used for classification or clustering tasks. The “x” values in the data table represent gene expression measurements.

## Applications in transcriptomics

Models built from gene expression data can benefit from incorporating gene-level relationships. One form that this knowledge commonly takes is a database of gene sets, which may represent biological pathways or gene signatures for a biological state of interest. PLIER [29] uses gene set information from MSigDB [30] and cell type markers to extract a representation of gene expression data that corresponds to biological processes and reduces technical noise. The resulting gene set-aligned representation accurately decomposed cell type mixtures. MultiPLIER [31] applied PLIER to the recount2 gene expression compendium [32] to develop a model that shares information across multiple tissues and diseases, including rare diseases with limited sample sizes. PASNet [33] uses MSigDB to inform the structure of a neural network for predicting patient outcomes in glioblastoma multiforme (GBM) from gene expression data. This approach aids interpretation, as pathway nodes in the network with high weights can be inferred to correspond to certain pathways in GBM outcome prediction.

Gene-level relationships can also be represented with networks. Network nodes typically represent genes and real-valued edges may represent interactions or correlations between genes, often in a tissue or cell type context of interest. Network-based stratification [34] is an early example of a method for utilizing gene interaction network data in this manner, applied to improve subtyping across several cancer types. More recently, netNMF-sc [35] incorporates coexpression networks [36] as a smoothing term for dimension reduction and dropout imputation in single-cell gene expression data. The coexpression network improves performance for identifying cell types and cell cycle marker genes, as compared to using raw gene expression or other single-cell dimension reduction methods. Combining gene expression data with a network-derived smoothing term also improved prediction of patient drug response in acute myeloid leukemia [37] and detection of mutated cancer genes [38]. PIMKL [39] combines network and pathway data to predict disease-free survival from breast cancer cohorts. This method takes as input both RNA-seq gene expression data and copy number alteration data, but can also be applied to gene expression data alone.

Gene regulatory networks can also augment models for gene expression data. These networks describe how the expression of genes is modulated by biological regulators such as transcription factors, microRNAs, or small molecules. creNET [40] integrates a gene regulatory network, derived from STRING [41], with a sparse logistic regression model to predict phenotypic response in clinical trials for ulcerative colitis and acute kidney rejection. The gene regulatory information allows the model to identify the biological regulators associated with the response, potentially giving mechanistic insight into differential clinical trial response. GRRANN [42], which was applied to the same data as creNET, uses a gene regulatory network to inform the structure of a neural network. Several other methods [43,44] have also used gene regulatory network structure to constrain the structure of a neural network, reducing the number of parameters to be fit and facilitating interpretation.

## Applications in genetics

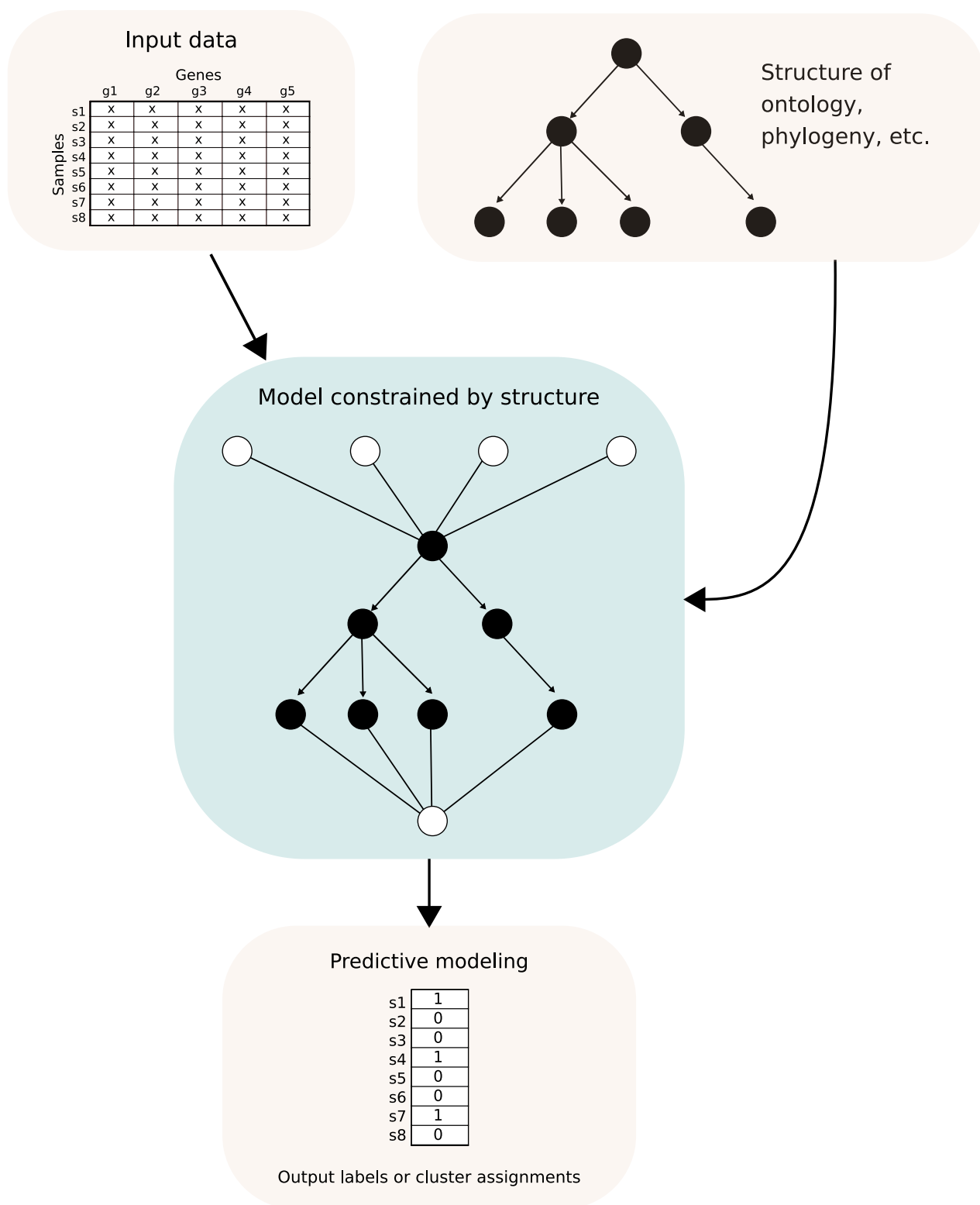
Approaches that incorporate gene set or network structure into genetic studies have a long history [45,46]. Recent applications include expression quantitative trait loci (eQTL) mapping studies, which aim to identify associations between genetic variants and gene expression. netReg [47] implements a graph-regularized dual LASSO algorithm for eQTL mapping [48] in a publicly available R package. This model smooths regression coefficients simultaneously based on networks describing associations between genes (target variables in the eQTL regression model) and between variants (predictors in the eQTL regression model). eQTL information is also used in conjunction with genetic variant information to predict phenotypes, in an approach known as Mendelian randomization (MR). In [49], a smoothing term derived from a gene regulatory network is used in an MR model. The model with the network smoothing term, applied to a human liver dataset, more robustly identifies genes that influence enzyme activity than a network-agnostic model. As genetic datasets grow, we expect that researchers will continue to develop models that leverage gene set and network databases.

## Other models incorporating biological structure

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Knowledge about biological entities is often organized in an ontology, which is a directed graph that encodes relationships between entities (see Figure 3 for a visual example). The Gene Ontology (GO) [3] describes the relationships between cellular subsystems and other attributes describing proteins or genes. DCell [50] uses GO to inform the connectivity of a neural network predicting the effects of gene deletions on yeast growth. DCell performs comparably to an unconstrained neural network for this task. Additionally, it is easier to interpret: a cellular subsystem with high neuron outputs under a particular gene deletion can be inferred to be strongly affected by the gene deletion, providing a putative genotype-phenotype association. DeepGO [51] uses a similar approach to predict protein function from amino acid sequence with a neural network constrained by the dependencies of GO. However, a follow-up paper by the same authors [52] showed that this hierarchy-aware approach can be outperformed by a hierarchy-naïve CNN, which uses only amino acid sequence and similarity to labeled training set proteins. This suggests a tradeoff between interpretability and predictive accuracy for protein function prediction.





**Figure 3:** Directed graph-structured data, such as an ontology or phylogenetic tree, can be incorporated into machine learning models. Here, the connections in the neural network used to predict a set of labels parallel those in the tree graph. This type of constraint can also be useful in model interpretation: for example, if the nodes in the right tree branch have high neuron outputs for a given sample, then the subsystem encoded in the right branch of the tree graph is most likely important in making predictions for that sample. The “x” values in the data table represent gene expression measurements.

Phylogenetic trees, or hierarchies describing the evolutionary relationships between species, can be useful for a similar purpose. `glmmTree` [53] uses a phylogenetic tree describing the relationship between microorganisms to improve predictions of age based on gut microbiome data. The same

authors combine a similar phylogeny smoothing strategy with sparse regression to model caffeine intake and smoking status based on microbiome data [54]. Phylogenetic trees can also describe the relationships between subclones of a tumor, which are fundamental to understanding cancer evolution and development. Using a tumor phylogeny inferred from copy number aberration (CNA) sequencing data as a smoothing term for deconvolving tumor subclones provided more robust predictions than a phylogeny-free model [55]. The tree structure of the phylogeny and the subclone mixture model are fit jointly to the CNA data.

Depending on the application, other forms of structure or prior knowledge can inform predictions and interpretation of the model's output. CYCLOPS [56] uses a circular node autoencoder [57] to order periodic gene expression data and estimate circadian rhythms. The authors validated the method by correctly ordering samples without temporal labels and identifying genes with known circadian expression. They then applied it to compare gene expression in normal and cancerous liver biopsies, identifying drug targets with circadian expression as candidates for chronotherapy. NetBiTE [58] uses drug-gene interaction information from GDSC [59], in addition to protein interaction data, to build a tree ensemble model with splits that are biased toward high-confidence drug-gene interactions. The model predicts sensitivity to drugs that inhibit critical signaling pathways in cancer, showing improved predictive performance compared to random forests, another commonly used tree ensemble model.

## Conclusions and future directions

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As the quantity and richness of biomedical data has increased, sequence repositories and interaction databases have expanded and become more robust. This raises opportunities to integrate these resources into the structure of machine learning models. There have been several past attempts to benchmark and compare approaches to integrating structured data into predictive models in biomedicine, including the evaluation in [60] and more recent studies in [61] and [62]. Extending and broadening benchmarking efforts such as these will be vital, improving our understanding of the suitability of problem domains and datasets for the classes of methods described in this review.

Many methods described in this review have open-source implementations available; however, increased availability of performant and extensible implementations of these models and algorithms would facilitate further use and development. In the future, we foresee that incorporating structured biomedical data will become commonplace for improving model interpretability and boosting performance when sample size is limited.

## Acknowledgements

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The authors would like to thank Daniel Himmelstein for a critical reading of the manuscript and helpful discussion.

## Reference Annotations

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[\*\*] Annotation for BPNet [16]:

This paper describes BPNet, a neural network for predicting transcription factor (TF) binding profiles from raw DNA sequence. The model is able to accurately infer the spacing and periodicity of pluripotency-related TFs in mouse embryonic stem cells, leading to an improved understanding of the motif syntax of combinatorial TF binding in cell development.

[\*] Annotation for cDeepbind [18]:

cDeepbind is a neural network model for predicting RNA binding protein (RBP) specificity from RNA sequence and secondary structure information. The authors show that this combined approach provides an improvement over previous models that use only sequence information.

[\*] Annotation for DeepDiff [[23](#)]:

DeepDiff uses a long short-term memory neural network to predict differential gene expression from the spatial structure of histone modification measurements. The network has a multi-task objective, enabling gene expression predictions to be made simultaneously in multiple cell types.

[\*\*] Annotation for DeepVariant [[24](#)]:

This paper describes DeepVariant, a neural network model for distinguishing true genetic variants from errors in next-generation DNA sequencing data. The model adapts techniques from the image processing community to fit a model on images of read pileups around candidate variants, using information about the sequence around the candidate variant site to make predictions about the true genotype at the site.

[\*\*] Annotation for PLIER [[29](#)]:

This paper describes a “pathway-level information extractor” (PLIER), a method for reducing the dimension of gene expression data in a manner that aligns with known biological pathways or informative gene sets. The method can also reduce the effects of technical noise. The authors show that PLIER can be used to improve cell type inference and as a component in eQTL studies.

[\*\*] Annotation for netNMF-sc [[35](#)]:

netNMF-sc is a dimension reduction method that uses network information to “smooth” a matrix factorization of single-cell gene expression data, such that genes that are connected in the network have a similar low-dimensional representation. Inclusion of network information is particularly useful when analyzing single-cell expression data, due to its ability to mitigate “dropouts” and other sources of variability that are present at the single cell level.

[\*] Annotation for Attribution Priors [[37](#)]:

This paper describes “model attribution priors”, or a method for constraining a machine learning model’s behavior during training with prior beliefs or expectations about the data or problem structure. As an example of this concept, the authors show that incorporation of network data improves the performance of a model for drug response prediction in acute myeloid leukemia.

[\*] Annotation for PIMKL [[39](#)]:

In this paper, the authors present an algorithm for combining gene expression and copy number data with prior information, such as gene networks and pathways or gene set annotations, to predict survival in breast cancer. The weights learned by the model are also interpretable, providing a putative set of explanatory features for the prediction task.

[\*\*] Annotation for creNET [[40](#)]:

This work describes creNET, a regression model for gene expression data that uses information about gene regulation to differentially weight or penalize gene sets that are co-regulated. The authors show that the model can be used to predict phenotype from gene expression data in clinical trials. The model also provides interpretable weights for each gene regulator.

[\*\*] Annotation for DCell [[50](#)]:

This paper presents DCell, a neural network model for prediction of yeast growth phenotype from gene deletions. The structure of the neural network is constrained by the relationships encoded in the Gene Ontology (GO), enabling predictions for a given input to be interpreted based on the subsystems of GO that they activate. Thus, the neural network can be seen as connecting genotype to phenotype.

[\*] Annotation for DeepGO [[51](#)]:

Here, the authors describe a method for predicting protein function from amino acid sequence, incorporating the dependency structure of the Gene Ontology (GO) into their neural network used for prediction. Using the GO information provides a performance improvement over similar models that do not incorporate this information.

[\*\*] Annotation for NetBITE [[58](#)]:

This paper describes a method for using prior knowledge about drug targets to inform the structure of a tree ensemble model, used for predicting IC50 drug sensitivity from gene expression data. The model also uses a protein interaction network to “smooth” the gene weights, such that genes that are related in the network will have a similar influence on predictions.

## References

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### 1. Network propagation: a universal amplifier of genetic associations

Lenore Cowen, Trey Ideker, Benjamin J. Raphael, Roded Sharan  
*Nature Reviews Genetics* (2017-06-12) <https://doi.org/gbhkwn>  
DOI: [10.1038/nrg.2017.38](https://doi.org/10.1038/nrg.2017.38) · PMID: [28607512](https://pubmed.ncbi.nlm.nih.gov/28607512/)

### 2. Visible Machine Learning for Biomedicine

Michael K. Yu, Jianzhu Ma, Jasmin Fisher, Jason F. Kreisberg, Benjamin J. Raphael, Trey Ideker  
*Cell* (2018-06) <https://doi.org/gdqcd8>  
DOI: [10.1016/j.cell.2018.05.056](https://doi.org/10.1016/j.cell.2018.05.056) · PMID: [29906441](https://pubmed.ncbi.nlm.nih.gov/29906441/) · PMCID: [PMC6483071](https://pubmed.ncbi.nlm.nih.gov/PMC6483071/)

### 3. The Gene Ontology Resource: 20 years and still GOing strong *Nucleic Acids Research* (2018-11-05)

<https://doi.org/gf63mb>  
DOI: [10.1093/nar/gky1055](https://doi.org/10.1093/nar/gky1055) · PMID: [30395331](https://pubmed.ncbi.nlm.nih.gov/30395331/) · PMCID: [PMC6323945](https://pubmed.ncbi.nlm.nih.gov/PMC6323945/)

### 4. Machine Learning in Genomic Medicine: A Review of Computational Problems and Data Sets

Michael K. K. Leung, Andrew Delong, Babak Alipanahi, Brendan J. Frey  
*Proceedings of the IEEE* (2016-01) <https://doi.org/f75grb>  
DOI: [10.1109/jproc.2015.2494198](https://doi.org/10.1109/jproc.2015.2494198)

### 5. Diet Networks: Thin Parameters for Fat Genomics

Adriana Romero, Pierre Luc Carrier, Akram Erraqabi, Tristan Sylvain, Alex Auvolat, Etienne Dejoie, Marc-André Legault, Marie-Pierre Dubé, Julie G. Hussin, Yoshua Bengio  
*arXiv* (2016-11-28) <https://arxiv.org/abs/1611.09340v3>

### 6. ImageNet: A large-scale hierarchical image database

Jia Deng, Wei Dong, Richard Socher, Li-Jia Li, Kai Li, Li Fei-Fei  
*2009 IEEE Conference on Computer Vision and Pattern Recognition* (2009-06) <https://doi.org/cvc7xp>  
DOI: [10.1109/cvpr.2009.5206848](https://doi.org/10.1109/cvpr.2009.5206848)

### 7. Learning Word Vectors for Sentiment Analysis

Andrew L. Maas, Raymond E. Daly, Peter T. Pham, Dan Huang, Andrew Y. Ng, Christopher Potts  
*Proceedings of the 49th Annual Meeting of the Association for Computational Linguistics: Human Language Technologies* (2011-06) <https://www.aclweb.org/anthology/P11-1015>

### 8. To Embed or Not: Network Embedding as a Paradigm in Computational Biology

Walter Nelson, Marinka Zitnik, Bo Wang, Jure Leskovec, Anna Goldenberg, Roded Sharan  
*Frontiers in Genetics* (2019-05-01) <https://doi.org/gf8rdf>  
DOI: [10.3389/fgene.2019.00381](https://doi.org/10.3389/fgene.2019.00381) · PMID: [31118945](https://pubmed.ncbi.nlm.nih.gov/31118945/) · PMCID: [PMC6504708](https://pubmed.ncbi.nlm.nih.gov/PMC6504708/)

### 9. Machine learning for integrating data in biology and medicine: Principles, practice, and opportunities

Marinka Zitnik, Francis Nguyen, Bo Wang, Jure Leskovec, Anna Goldenberg, Michael M. Hoffman  
*Information Fusion* (2019-10) <https://doi.org/gf7rj8>  
DOI: [10.1016/j.inffus.2018.09.012](https://doi.org/10.1016/j.inffus.2018.09.012) · PMID: [30467459](https://pubmed.ncbi.nlm.nih.gov/30467459/) · PMCID: [PMC6242341](https://pubmed.ncbi.nlm.nih.gov/PMC6242341/)

### 10. DEEP: a general computational framework for predicting enhancers

Dimitrios Kleftogiannis, Panos Kalnis, Vladimir B. Bajic  
*Nucleic Acids Research* (2014-11-05) <https://doi.org/gcgk83>  
DOI: [10.1093/nar/gku1058](https://doi.org/10.1093/nar/gku1058) · PMID: [25378307](https://pubmed.ncbi.nlm.nih.gov/25378307/) · PMCID: [PMC4288148](https://pubmed.ncbi.nlm.nih.gov/PMC4288148/)

**11. The human splicing code reveals new insights into the genetic determinants of disease**

H. Y. Xiong, B. Alipanahi, L. J. Lee, H. Bretschneider, D. Merico, R. K. C. Yuen, Y. Hua, S. Gueroussov, H. S. Najafabadi, T. R. Hughes, ... B. J. Frey

*Science* (2014-12-18) <https://doi.org/f6wzj2>

DOI: [10.1126/science.1254806](https://doi.org/10.1126/science.1254806) · PMID: [25525159](https://pubmed.ncbi.nlm.nih.gov/25525159/) · PMCID: [PMC4362528](https://pubmed.ncbi.nlm.nih.gov/PMC4362528/)

**12. Deep learning for computational biology**

Christof Angermueller, Tanel Pärnamaa, Leopold Parts, Oliver Stegle

*Molecular Systems Biology* (2016-07) <https://doi.org/f8xtvh>

DOI: [10.15252/msb.20156651](https://doi.org/10.15252/msb.20156651) · PMID: [27474269](https://pubmed.ncbi.nlm.nih.gov/27474269/) · PMCID: [PMC4965871](https://pubmed.ncbi.nlm.nih.gov/PMC4965871/)

**13. Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning**

Babak Alipanahi, Andrew DeLong, Matthew T Weirauch, Brendan J Frey

*Nature Biotechnology* (2015-07-27) <https://doi.org/f7mkrd>

DOI: [10.1038/nbt.3300](https://doi.org/10.1038/nbt.3300) · PMID: [26213851](https://pubmed.ncbi.nlm.nih.gov/26213851/)

**14. Predicting effects of noncoding variants with deep learning-based sequence model**

Jian Zhou, Olga G Troyanskaya

*Nature Methods* (2015-08-24) <https://doi.org/gcgc8g>

DOI: [10.1038/nmeth.3547](https://doi.org/10.1038/nmeth.3547) · PMID: [26301843](https://pubmed.ncbi.nlm.nih.gov/26301843/) · PMCID: [PMC4768299](https://pubmed.ncbi.nlm.nih.gov/PMC4768299/)

**15. Basset: learning the regulatory code of the accessible genome with deep convolutional neural networks**

David R. Kelley, Jasper Snoek, John L. Rinn

*Genome Research* (2016-05-03) <https://doi.org/f8sw35>

DOI: [10.1101/gr.200535.115](https://doi.org/10.1101/gr.200535.115) · PMID: [27197224](https://pubmed.ncbi.nlm.nih.gov/27197224/) · PMCID: [PMC4937568](https://pubmed.ncbi.nlm.nih.gov/PMC4937568/)

**16. Deep learning at base-resolution reveals motif syntax of the cis-regulatory code**

Žiga Avsec, Melanie Weilert, Avanti Shrikumar, Amr Alexandari, Sabrina Krueger, Khyati Dalal, Robin Froepf, Charles McAnany, Julien Gagneur, Anshul Kundaje, Julia Zeitlinger

*Cold Spring Harbor Laboratory* (2019-08-21) <https://doi.org/gf64fc>

DOI: [10.1101/737981](https://doi.org/10.1101/737981)

**17. Multi-Scale Context Aggregation by Dilated Convolutions**

Fisher Yu, Vladlen Koltun

*arXiv* (2015-11-23) <https://arxiv.org/abs/1511.07122v3>

**18. cDeepbind: A context sensitive deep learning model of RNA-protein binding**

Shreshth Gandhi, Leo J. Lee, Andrew DeLong, David Duvenaud, Brendan J. Frey

*Cold Spring Harbor Laboratory* (2018-06-12) <https://doi.org/gf68nk>

DOI: [10.1101/345140](https://doi.org/10.1101/345140)

**19. A Deep Neural Network for Predicting and Engineering Alternative Polyadenylation**

Nicholas Bogard, Johannes Linder, Alexander B. Rosenberg, Georg Seelig

*Cell* (2019-06) <https://doi.org/gf66nc>

DOI: [10.1016/j.cell.2019.04.046](https://doi.org/10.1016/j.cell.2019.04.046) · PMID: [31178116](https://pubmed.ncbi.nlm.nih.gov/31178116/) · PMCID: [PMC6599575](https://pubmed.ncbi.nlm.nih.gov/PMC6599575/)

**20. DeepSignal: detecting DNA methylation state from Nanopore sequencing reads using deep learning**

Peng Ni, Neng Huang, Zhi Zhang, De-Peng Wang, Fan Liang, Yu Miao, Chuan-Le Xiao, Feng Luo, Jianxin Wang

*Bioinformatics* (2019-04-17) <https://doi.org/gf66qw>

DOI: [10.1093/bioinformatics/btz276](https://doi.org/10.1093/bioinformatics/btz276) · PMID: [30994904](https://pubmed.ncbi.nlm.nih.gov/30994904/)

**21. MRCNN: a deep learning model for regression of genome-wide DNA methylation**

Qi Tian, Jianxiao Zou, Jianxiong Tang, Yuan Fang, Zhongli Yu, Shicai Fan

*BMC Genomics* (2019-04) <https://doi.org/gf48g6>

DOI: [10.1186/s12864-019-5488-5](https://doi.org/10.1186/s12864-019-5488-5) · PMID: [30967120](https://pubmed.ncbi.nlm.nih.gov/30967120/) · PMCID: [PMC6457069](https://pubmed.ncbi.nlm.nih.gov/PMC6457069/)

**22. Attend and Predict: Understanding Gene Regulation by Selective Attention on Chromatin**

Ritambhara Singh, Jack Lanchantin, Arshdeep Sekhon, Yanjun Qi

*Cold Spring Harbor Laboratory* (2018-05-25) <https://doi.org/gf66qz>

DOI: [10.1101/329334](https://doi.org/10.1101/329334)

**23. DeepDiff: DEEP-learning for predicting DIFFerential gene expression from histone modifications**

Arshdeep Sekhon, Ritambhara Singh, Yanjun Qi

*Bioinformatics* (2018-09-01) <https://doi.org/gd9mk4>

DOI: [10.1093/bioinformatics/bty612](https://doi.org/10.1093/bioinformatics/bty612) · PMID: [30423076](https://pubmed.ncbi.nlm.nih.gov/30423076/)

**24. A universal SNP and small-indel variant caller using deep neural networks**

Ryan Poplin, Pi-Chuan Chang, David Alexander, Scott Schwartz, Thomas Colthurst, Alexander Ku, Dan Newburger, Jojo Dijamco, Nam Nguyen, Pegah T Afshar, ... Mark A DePristo

*Nature Biotechnology* (2018-09-24) <https://doi.org/gd8gkf>

DOI: [10.1038/nbt.4235](https://doi.org/10.1038/nbt.4235) · PMID: [30247488](https://pubmed.ncbi.nlm.nih.gov/30247488/)

**25. A multi-task convolutional deep neural network for variant calling in single molecule sequencing**

Ruibang Luo, Fritz J. Sedlazeck, Tak-Wah Lam, Michael C. Schatz

*Nature Communications* (2019-03-01) <https://doi.org/gf4c37>

DOI: [10.1038/s41467-019-09025-z](https://doi.org/10.1038/s41467-019-09025-z) · PMID: [30824707](https://pubmed.ncbi.nlm.nih.gov/30824707/) · PMCID: [PMC6397153](https://pubmed.ncbi.nlm.nih.gov/PMC6397153/)

**26. SICaRiO: Short Indel Call filteriNg with bOosting**

Md Shariful Islam Bhuyan, Itsik Pe'er, M. Sohel Rahman

*Cold Spring Harbor Laboratory* (2019-04-07) <https://doi.org/gf68d6>

DOI: [10.1101/601450](https://doi.org/10.1101/601450)

**27. Machine learning-based detection of insertions and deletions in the human genome**

Charles Curnin, Rachel L. Goldfeder, Shruti Marwaha, Devon Bonner, Daryl Waggott, Matthew T. Wheeler, Euan A. Ashley,

*Cold Spring Harbor Laboratory* (2019-05-05) <https://doi.org/gf68d7>

DOI: [10.1101/628222](https://doi.org/10.1101/628222)

**28. Deep convolutional neural networks for accurate somatic mutation detection**

Sayed Mohammad Ebrahim Sahraeian, Ruolin Liu, Bayo Lau, Karl Podesta, Marghoob Mohiyuddin, Hugo Y. K. Lam

*Nature Communications* (2019-03-04) <https://doi.org/gf68f8>

DOI: [10.1038/s41467-019-09027-x](https://doi.org/10.1038/s41467-019-09027-x) · PMID: [30833567](https://pubmed.ncbi.nlm.nih.gov/30833567/) · PMCID: [PMC6399298](https://pubmed.ncbi.nlm.nih.gov/PMC6399298/)

**29. Pathway-level information extractor (PLIER) for gene expression data**

Weiguang Mao, Elena Zaslavsky, Boris M. Hartmann, Stuart C. Sealfon, Maria Chikina

*Nature Methods* (2019-06-27) <https://doi.org/gf75g6>

DOI: [10.1038/s41592-019-0456-1](https://doi.org/10.1038/s41592-019-0456-1) · PMID: [31249421](https://pubmed.ncbi.nlm.nih.gov/31249421/)

**30. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles**

A. Subramanian, P. Tamayo, V. K. Mootha, S. Mukherjee, B. L. Ebert, M. A. Gillette, A. Paulovich, S. L.



Pomeroy, T. R. Golub, E. S. Lander, J. P. Mesirov

*Proceedings of the National Academy of Sciences* (2005-09-30) <https://doi.org/d4qbh8>

DOI: [10.1073/pnas.0506580102](https://doi.org/10.1073/pnas.0506580102) · PMID: [16199517](https://pubmed.ncbi.nlm.nih.gov/16199517/) · PMCID: [PMC1239896](https://pubmed.ncbi.nlm.nih.gov/PMC1239896/)

### 31. **MultiPLIER: A Transfer Learning Framework for Transcriptomics Reveals Systemic Features of Rare Disease**

Jaclyn N. Taroni, Peter C. Grayson, Qiwen Hu, Sean Eddy, Matthias Kretzler, Peter A. Merkel, Casey S. Greene

*Cell Systems* (2019-05) <https://doi.org/gf75g5>

DOI: [10.1016/j.cels.2019.04.003](https://doi.org/10.1016/j.cels.2019.04.003) · PMID: [31121115](https://pubmed.ncbi.nlm.nih.gov/31121115/) · PMCID: [PMC6538307](https://pubmed.ncbi.nlm.nih.gov/PMC6538307/)

### 32. **Reproducible RNA-seq analysis using recount2**

Leonardo Collado-Torres, Abhinav Nellore, Kai Kammers, Shannon E Ellis, Margaret A Taub, Kasper D Hansen, Andrew E Jaffe, Ben Langmead, Jeffrey T Leek

*Nature Biotechnology* (2017-04) <https://doi.org/gf75hp>

DOI: [10.1038/nbt.3838](https://doi.org/10.1038/nbt.3838) · PMID: [28398307](https://pubmed.ncbi.nlm.nih.gov/28398307/) · PMCID: [PMC6742427](https://pubmed.ncbi.nlm.nih.gov/PMC6742427/)

### 33. **PASNet: pathway-associated sparse deep neural network for prognosis prediction from high-throughput data**

Jie Hao, Youngsoon Kim, Tae-Kyung Kim, Mingon Kang

*BMC Bioinformatics* (2018-12) <https://doi.org/gf75g9>

DOI: [10.1186/s12859-018-2500-z](https://doi.org/10.1186/s12859-018-2500-z) · PMID: [30558539](https://pubmed.ncbi.nlm.nih.gov/30558539/) · PMCID: [PMC6296065](https://pubmed.ncbi.nlm.nih.gov/PMC6296065/)

### 34. **Network-based stratification of tumor mutations**

Matan Hofree, John P Shen, Hannah Carter, Andrew Gross, Trey Ideker

*Nature Methods* (2013-09-15) <https://doi.org/gbd257>

DOI: [10.1038/nmeth.2651](https://doi.org/10.1038/nmeth.2651) · PMID: [24037242](https://pubmed.ncbi.nlm.nih.gov/24037242/) · PMCID: [PMC3866081](https://pubmed.ncbi.nlm.nih.gov/PMC3866081/)

### 35. **netNMF-sc: Leveraging gene-gene interactions for imputation and dimensionality reduction in single-cell expression analysis**

Rebecca Elyanow, Bianca Dumitrascu, Barbara E. Engelhardt, Benjamin J. Raphael

*Cold Spring Harbor Laboratory* (2019-02-08) <https://doi.org/gf386x>

DOI: [10.1101/544346](https://doi.org/10.1101/544346)

### 36. **COEXPEDIA: exploring biomedical hypotheses via co-expressions associated with medical subject headings (MeSH)**

Sunmo Yang, Chan Yeong Kim, Sohyun Hwang, Eiru Kim, Hyojin Kim, Hongseok Shim, Insuk Lee

*Nucleic Acids Research* (2016-09-26) <https://doi.org/f9v38k>

DOI: [10.1093/nar/gkw868](https://doi.org/10.1093/nar/gkw868) · PMID: [27679477](https://pubmed.ncbi.nlm.nih.gov/27679477/) · PMCID: [PMC5210615](https://pubmed.ncbi.nlm.nih.gov/PMC5210615/)

### 37. **Learning Explainable Models Using Attribution Priors**

Gabriel Erion, Joseph D. Janizek, Pascal Sturmfels, Scott Lundberg, Su-In Lee

*arXiv* (2019-06-25) <https://arxiv.org/abs/1906.10670v1>

### 38. **A novel network regularized matrix decomposition method to detect mutated cancer genes in tumour samples with inter-patient heterogeneity**

Jianing Xi, Ao Li, Minghui Wang

*Scientific Reports* (2017-06-06) <https://doi.org/gcq9j7>

DOI: [10.1038/s41598-017-03141-w](https://doi.org/10.1038/s41598-017-03141-w) · PMID: [28588243](https://pubmed.ncbi.nlm.nih.gov/28588243/) · PMCID: [PMC5460199](https://pubmed.ncbi.nlm.nih.gov/PMC5460199/)

### 39. **PIMKL: Pathway-Induced Multiple Kernel Learning**

Matteo Manica, Joris Cadow, Roland Mathis, María Rodríguez Martínez



*npj Systems Biology and Applications* (2019-03-05) <https://doi.org/gf8ck6>  
DOI: [10.1038/s41540-019-0086-3](https://doi.org/10.1038/s41540-019-0086-3) · PMID: [30854223](https://pubmed.ncbi.nlm.nih.gov/30854223/) · PMCID: [PMC6401099](https://pubmed.ncbi.nlm.nih.gov/PMC6401099/)

**40. Robust phenotype prediction from gene expression data using differential shrinkage of co-regulated genes**

Kourosh Zarringhalam, David Degras, Christoph Brockel, Daniel Ziemek  
*Scientific Reports* (2018-01-19) <https://doi.org/gcwzdn>  
DOI: [10.1038/s41598-018-19635-0](https://doi.org/10.1038/s41598-018-19635-0) · PMID: [29352257](https://pubmed.ncbi.nlm.nih.gov/29352257/) · PMCID: [PMC5775343](https://pubmed.ncbi.nlm.nih.gov/PMC5775343/)

**41. STRING v10: protein–protein interaction networks, integrated over the tree of life**

Damian Szklarczyk, Andrea Franceschini, Stefan Wyder, Kristoffer Forslund, Davide Heller, Jaime Huerta-Cepas, Milan Simonovic, Alexander Roth, Alberto Santos, Kalliopi P. Tsafou, ... Christian von Mering  
*Nucleic Acids Research* (2014-10-28) <https://doi.org/f64rfn>  
DOI: [10.1093/nar/gku1003](https://doi.org/10.1093/nar/gku1003) · PMID: [25352553](https://pubmed.ncbi.nlm.nih.gov/25352553/) · PMCID: [PMC4383874](https://pubmed.ncbi.nlm.nih.gov/PMC4383874/)

**42. A biological network-based regularized artificial neural network model for robust phenotype prediction from gene expression data**

Tianyu Kang, Wei Ding, Luoyan Zhang, Daniel Ziemek, Kourosh Zarringhalam  
*BMC Bioinformatics* (2017-12) <https://doi.org/gf8cm6>  
DOI: [10.1186/s12859-017-1984-2](https://doi.org/10.1186/s12859-017-1984-2) · PMID: [29258445](https://pubmed.ncbi.nlm.nih.gov/29258445/) · PMCID: [PMC5735940](https://pubmed.ncbi.nlm.nih.gov/PMC5735940/)

**43. Using neural networks for reducing the dimensions of single-cell RNA-Seq data**

Chieh Lin, Siddhartha Jain, Hannah Kim, Ziv Bar-Joseph  
*Nucleic Acids Research* (2017-07-31) <https://doi.org/gcnzb7>  
DOI: [10.1093/nar/gkx681](https://doi.org/10.1093/nar/gkx681) · PMID: [28973464](https://pubmed.ncbi.nlm.nih.gov/28973464/) · PMCID: [PMC5737331](https://pubmed.ncbi.nlm.nih.gov/PMC5737331/)

**44. Genetic Neural Networks: an artificial neural network architecture for capturing gene expression relationships**

Ameen Eetemadi, Ilias Tagkopoulos  
*Bioinformatics* (2018-11-19) <https://doi.org/gfnks6>  
DOI: [10.1093/bioinformatics/bty945](https://doi.org/10.1093/bioinformatics/bty945) · PMID: [30452523](https://pubmed.ncbi.nlm.nih.gov/30452523/)

**45. Nonparametric pathway-based regression models for analysis of genomic data**

Z. Wei, H. Li  
*Biostatistics* (2006-06-13) <https://doi.org/fdmggm>  
DOI: [10.1093/biostatistics/kxl007](https://doi.org/10.1093/biostatistics/kxl007) · PMID: [16772399](https://pubmed.ncbi.nlm.nih.gov/16772399/)

**46. Network-constrained regularization and variable selection for analysis of genomic data**

C. Li, H. Li  
*Bioinformatics* (2008-03-01) <https://doi.org/fk8n4b>  
DOI: [10.1093/bioinformatics/btn081](https://doi.org/10.1093/bioinformatics/btn081) · PMID: [18310618](https://pubmed.ncbi.nlm.nih.gov/18310618/)

**47. netReg: network-regularized linear models for biological association studies**

Simon Dirmeier, Christiane Fuchs, Nikola S Mueller, Fabian J Theis  
*Bioinformatics* (2017-10-25) <https://doi.org/gcg9xq>  
DOI: [10.1093/bioinformatics/btx677](https://doi.org/10.1093/bioinformatics/btx677) · PMID: [29077797](https://pubmed.ncbi.nlm.nih.gov/29077797/) · PMCID: [PMC6030897](https://pubmed.ncbi.nlm.nih.gov/PMC6030897/)

**48. Graph-regularized dual Lasso for robust eQTL mapping**

Wei Cheng, Xiang Zhang, Zhishan Guo, Yu Shi, Wei Wang  
*Bioinformatics* (2014-06-11) <https://doi.org/f58j6m>  
DOI: [10.1093/bioinformatics/btu293](https://doi.org/10.1093/bioinformatics/btu293) · PMID: [24931977](https://pubmed.ncbi.nlm.nih.gov/24931977/) · PMCID: [PMC4058913](https://pubmed.ncbi.nlm.nih.gov/PMC4058913/)

**49. Integrative analysis of genetical genomics data incorporating network structures**

Bin Gao, Xu Liu, Hongzhe Li, Yuehua Cui

*Biometrics* (2019-04-29) <https://doi.org/gf8f9q>

DOI: [10.1111/biom.13072](https://doi.org/10.1111/biom.13072) · PMID: [31009063](https://pubmed.ncbi.nlm.nih.gov/31009063/)

**50. Using deep learning to model the hierarchical structure and function of a cell**

Jianzhu Ma, Michael Ku Yu, Samson Fong, Keiichiro Ono, Eric Sage, Barry Demchak, Roded Sharan, Trey Ideker

*Nature Methods* (2018-03-05) <https://doi.org/gc46jp>

DOI: [10.1038/nmeth.4627](https://doi.org/10.1038/nmeth.4627) · PMID: [29505029](https://pubmed.ncbi.nlm.nih.gov/29505029/) · PMCID: [PMC5882547](https://pubmed.ncbi.nlm.nih.gov/PMC5882547/)

**51. DeepGO: predicting protein functions from sequence and interactions using a deep ontology-aware classifier**

Maxat Kulmanov, Mohammed Asif Khan, Robert Hoehndorf

*Bioinformatics* (2017-10-03) <https://doi.org/gc3nb8>

DOI: [10.1093/bioinformatics/btx624](https://doi.org/10.1093/bioinformatics/btx624) · PMID: [29028931](https://pubmed.ncbi.nlm.nih.gov/29028931/) · PMCID: [PMC5860606](https://pubmed.ncbi.nlm.nih.gov/PMC5860606/)

**52. DeepGOPlus: improved protein function prediction from sequence**

Maxat Kulmanov, Robert Hoehndorf

*Bioinformatics* (2019-07-27) <https://doi.org/gf84d8>

DOI: [10.1093/bioinformatics/btz595](https://doi.org/10.1093/bioinformatics/btz595) · PMID: [31350877](https://pubmed.ncbi.nlm.nih.gov/31350877/)

**53. Predictive Modeling of Microbiome Data Using a Phylogeny-Regularized Generalized Linear Mixed Model**

Jian Xiao, Li Chen, Stephen Johnson, Yue Yu, Xianyang Zhang, Jun Chen

*Frontiers in Microbiology* (2018-06-27) <https://doi.org/gdtz4z>

DOI: [10.3389/fmicb.2018.01391](https://doi.org/10.3389/fmicb.2018.01391) · PMID: [29997602](https://pubmed.ncbi.nlm.nih.gov/29997602/) · PMCID: [PMC6030386](https://pubmed.ncbi.nlm.nih.gov/PMC6030386/)

**54. A Phylogeny-Regularized Sparse Regression Model for Predictive Modeling of Microbial Community Data**

Jian Xiao, Li Chen, Yue Yu, Xianyang Zhang, Jun Chen

*Frontiers in Microbiology* (2018-12-19) <https://doi.org/gf8qcc>

DOI: [10.3389/fmicb.2018.03112](https://doi.org/10.3389/fmicb.2018.03112) · PMID: [30619188](https://pubmed.ncbi.nlm.nih.gov/30619188/) · PMCID: [PMC6305753](https://pubmed.ncbi.nlm.nih.gov/PMC6305753/)

**55. Tumor Copy Number Deconvolution Integrating Bulk and Single-Cell Sequencing Data**

Haoyun Lei, Bochuan Lyu, E. Michael Gertz, Alejandro A. Schäffer, Xulian Shi, Kui Wu, Guibo Li, Liqin Xu, Yong Hou, Michael Dean, Russell Schwartz

*Lecture Notes in Computer Science* (2019) <https://doi.org/gf8qck>

DOI: [10.1007/978-3-030-17083-7\\_11](https://doi.org/10.1007/978-3-030-17083-7_11)

**56. CYCLOPS reveals human transcriptional rhythms in health and disease**

Ron C. Anafi, Lauren J. Francey, John B. Hogenesch, Junhyong Kim

*Proceedings of the National Academy of Sciences* (2017-04-24) <https://doi.org/f9796k>

DOI: [10.1073/pnas.1619320114](https://doi.org/10.1073/pnas.1619320114) · PMID: [28439010](https://pubmed.ncbi.nlm.nih.gov/28439010/) · PMCID: [PMC5441789](https://pubmed.ncbi.nlm.nih.gov/PMC5441789/)

**57. Circular Nodes in Neural Networks**

Michael J. Kirby, Rick Miranda

*Neural Computation* (1996-02-15) <https://doi.org/ffcww8>

DOI: [10.1162/neco.1996.8.2.390](https://doi.org/10.1162/neco.1996.8.2.390)

**58. Network-based Biased Tree Ensembles (NetBiTE) for Drug Sensitivity Prediction and Drug Sensitivity Biomarker Identification in Cancer**

Ali Oskooei, Matteo Manica, Roland Mathis, Maria Rodriguez Martinez  
*arXiv* (2018-08-18) <https://arxiv.org/abs/1808.06603v2>

**59. Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells**

Wanjuan Yang, Jorge Soares, Patricia Greninger, Elena J. Edelman, Howard Lightfoot, Simon Forbes, Nidhi Bindal, Dave Beare, James A. Smith, I. Richard Thompson, ... Mathew J. Garnett  
*Nucleic Acids Research* (2012-11-22) <https://doi.org/f4jrdn>  
DOI: [10.1093/nar/gks1111](https://doi.org/10.1093/nar/gks1111) · PMID: [23180760](https://pubmed.ncbi.nlm.nih.gov/23180760/) · PMCID: [PMC3531057](https://pubmed.ncbi.nlm.nih.gov/PMC3531057/)

**60. A Critical Evaluation of Network and Pathway-Based Classifiers for Outcome Prediction in Breast Cancer**

Christine Staiger, Sidney Cadot, Raul Kooter, Marcus Dittrich, Tobias Müller, Gunnar W. Klau, Lodewyk F. A. Wessels  
*PLoS ONE* (2012-04-27) <https://doi.org/gf8rgw>  
DOI: [10.1371/journal.pone.0034796](https://doi.org/10.1371/journal.pone.0034796) · PMID: [22558100](https://pubmed.ncbi.nlm.nih.gov/22558100/) · PMCID: [PMC3338754](https://pubmed.ncbi.nlm.nih.gov/PMC3338754/)

**61. Analysis of Gene Interaction Graphs for Biasing Machine Learning Models**

Paul Bertin, Mohammad Hashir, Martin Weiss, Geneviève Boucher, Vincent Frappier, Joseph Paul Cohen  
*arXiv* (2019-05-06) <https://arxiv.org/abs/1905.02295v1>

**62. Is graph-based feature selection of genes better than random?**

Mohammad Hashir, Paul Bertin, Martin Weiss, Vincent Frappier, Theodore J. Perkins, Geneviève Boucher, Joseph Paul Cohen  
*arXiv* (2019-10-21) <https://arxiv.org/abs/1910.09600v2>