

Chapter 3

Using Biological Networks to Guide Biomedical Prediction

Xiaoyu Zhao, JungHo Kong, Karen Pu, Christopher Churas, Jillian A. Parker and Trey Ideker

Abstract

Predictive modeling is a transformative tool for understanding complex biological systems and advancing biomedical discovery. A central challenge is ensuring that predictive models are not only accurate but also biologically interpretable. One way to address this challenge is through network-guided approaches, which integrate prior biological knowledge into bioinformatic algorithms and model architectures. By aligning predictive models with biological networks at various scales, these approaches can improve biological interpretability while maintaining strong predictive performance. In this chapter, we introduce the fundamentals of biological networks and describe strategies for incorporating networks into modeling frameworks for predicting biomedically relevant phenotypes. These concepts are explored via a case study of network-guided drug response prediction, in which hierarchical knowledge of cell biology is instrumental to achieving interpretable predictions and biological insights into chemoresistance.

Keywords Biological networks, Predictive modeling, Interpretability, Drug response

1 Introduction

Networks provide a natural scaffold for organizing biological data. They bridge the gap between large-scale biological datasets and interpretable insights, allowing predictions to be directly linked with underlying cellular and systems-level mechanisms. Several decades of network biology research have produced key analysis approaches that have proven generally useful across diverse applications. For example, network propagation diffuses information across connected nodes in biological networks to identify disease-relevant pathways or functionally related genes [1–4]. Biological networks have also been embedded into predictive models to improve generalization and reproducibility across heterogeneous datasets [5, 6]. In other applications, maps of subcellular networks have been aligned with

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deep learning architectures to enhance interpretability and uncover pathway-level biomarkers across diverse disease contexts [7–12].

In this chapter, we survey the main types of biological networks, including both flat and hierarchical representations, along with approaches for hierarchy construction from flat network data. We then turn to strategies for integrating network knowledge into predictive modeling, including network propagation, graph neural networks, and the hierarchical models known as visible neural networks or VNNs (Fig. 1). We end with a case study of hierarchy-guided drug response prediction.

While this chapter largely focuses on molecular networks, network-guided modeling can also be extended to higher levels of organization, including hierarchies of cell types, tissues, and even individuals.

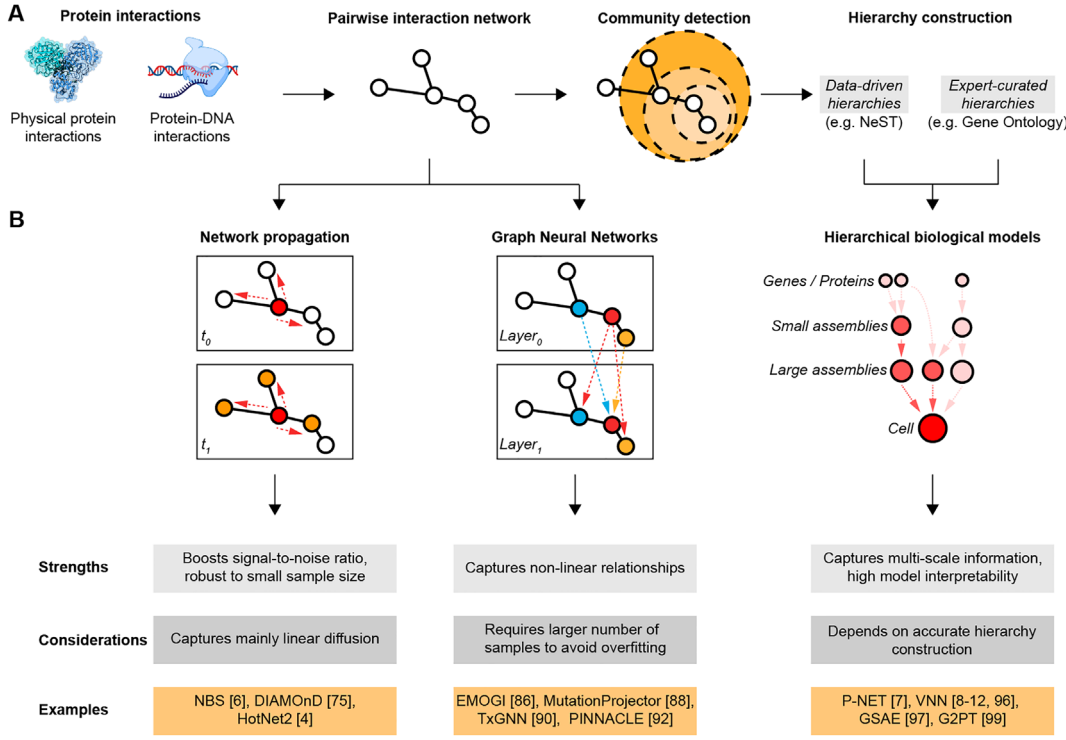

Fig. 1 Network-based biological modeling strategies. (**A**) Flat pairwise interaction networks and multiscale biological hierarchies derived from these networks or from expert-curated knowledge. (**B**) Flat interaction networks guide message passing in network propagation and graph neural networks, while expert-curated ontologies or data-driven hierarchies inform hierarchical biological models

2 Biological Networks

Networks are pervasive in the biological sciences, from flat interaction networks to multiscale hierarchies. Flat interaction networks capture relationships of within-scale entities (e.g., protein–protein interactions; cell–cell communications), whereas hierarchies model multiscale organization, interrelating nanometer-scale proteins, and complexes to micrometer-scale organelles, cells, and tissues (Fig. 1A).

2.1 Flat Interaction Networks

Extensive efforts have mapped networks among biological entities, including physical protein–macromolecule interactions, genetic interactions, signal transduction pathways, and cell–cell interactions. These networks are represented as graphs $G = (V, E)$, where V is the set of biological entities (nodes) and E is the set of pairwise interactions (edges). Edges are directed for causal or regulatory relations (e.g., phosphorylation) and undirected for symmetric associations (e.g., binding), and they can be weighted (strength or confidence) and/or signed (activation or inhibition). Experimentally, physical protein interactions can be mapped by yeast two-hybrid (Y2H) [13] and mass spectrometry-based approaches [14, 15], genetic interactions by combinatorial CRISPR screens [16–18], and post-translational modifications by phosphoproteomics [19], among many other methods [20–26]. Computational approaches infer functional associations from shared patterns in biological signals such as coexpression, coabundance, colocalization, and sequence similarity. More recently, modeling approaches such as AlphaFold-Multimer [27] and AlphaFold 3 [28] can predict protein interactions by leveraging three-dimensional structural knowledge.

A variety of public interaction network resources exist, derived from either single data types or integrated evidence sources. Representative examples include: BioPlex 3.0 [29], a large-scale human PPI network generated using affinity purification-mass spectrometry (AP-MS); STRING [30], which integrates experimental and predicted associations; Parsimonious Composite Network (PCNet) [31], which merges high-confidence interactions from curated and experimental datasets; HumanNet, which combines diverse genomic and proteomic evidence to infer functional gene networks; SIGNOR [32] and SignaLink [33], which focus on signaling pathways; TRRUST [34], a curated transcriptional regulatory network; PhosphoSitePlus [35], a resource for post-translational modifications; ISLE [36] and SynLethDB [37], which compile genetic and synthetic lethal interactions; and CellCHAT [38], which infers intercellular communications from single cell RNA sequencing data.

2.2 Multiscale Biological Hierarchies

Multiscale hierarchies are networks that involve hierarchical relationships among biological entities at different scales. They are typically represented as directed acyclic graphs (DAGs) [39], where nodes

are biological entities and directed edges (A → B) indicate complete or partial containment of one entity (A) by another (B) (Fig. 1A).

Multiscale hierarchies include ontologies curated from expert knowledge along with multiscale maps formulated directly from biological or biomedical data. An ontology is a controlled, formal vocabulary of domain entities and their relationships. For example, the Gene Ontology (GO), a widely used biological expert knowledgebase, consists of three distinct ontologies: Biological Process (BP) refers to the biological objectives or processes to which a gene or gene product contributes (e.g., cell cycle), Cellular Component (CC) specifies the locations within the cell where a gene product is active (e.g., nucleus), and Molecular Function (MF) describes the elemental activities performed by a gene product at the molecular level (e.g., ATP binding) [40]. Reactome is a hierarchical map of human biological systems, progressing from broad processes to specific molecular pathways and individual reactions [41]. The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a multispecies hierarchy of conceptual pathway maps that integrate genomic, chemical, and functional information [42]. Beyond molecular ontologies, the Cell Ontology (CL) [43, 44] provides a standardized vocabulary for cell types across species, while the Human Phenotype Ontology (HPO) organizes phenotypic abnormalities in a hierarchical structure [45].

Data-driven multiscale hierarchies complement expert-curated ontologies by revealing novel, context-specific structures that curated resources may miss [46]. These hierarchies have enabled de novo modeling of biological processes in yeast [47, 48], mammalian cells [49–51], and disease [52–55]. Examples include NeST (Nested Systems in Tumors) [54], a pan-cancer cell map of hallmark systems that interprets rare tumor mutations by their convergence on protein assemblies, and a multiscale map of cell–cell organization in kidney and brain tissues built from spatial transcriptomics data [55].

3 Biological Hierarchy Construction

Biological hierarchy construction involves two stages: (i) hierarchy inference and (ii) hierarchy evaluation and annotation. Here, we use the construction of a multiscale cell map as a working example. With appropriate adaptations, the same approach can be applied to other data types, such as spatial cell organization in tissues.

3.1 Hierarchy Inference

Hierarchy inference uses multiresolution community detection to identify nested clusters in a flat network [56–63]. Common algorithms include Louvain [64], modularity-based clustering [65], clique percolation [66], Infomap [67, 68], OSLOM (Order Statistics Local

Optimization Method) [69], CliXO (Clique Extracted Ontology) [62], and HiDef (Hierarchical community Decoding Framework) [70]. For multiscale cell maps, we can construct the hierarchy via either a scripted pipeline (Cell Mapping Toolkit [71]) or an interactive route (Cytoscape Desktop [72, 73]). In the scripted path, *CellMapsGenerateHierarchy* runs on protein embeddings, sweeping the resolution (community granularity) to identify assemblies that persist across nearby scales (Fig. 2A) with a result that can be visualized in tree or cell view in Cytoscape Web [72, 73]. In the interactive path, a network is imported into Cytoscape, community detection is executed, via the CommunityDetection app, with real-time parameter tuning (e.g., Louvain γ, Infomap trials) [74], and assemblies are visually refined prior to export (Fig. 2B). Both routes output a directed acyclic graph with assemblies as nodes and containment as edges.

3.2 Hierarchy Evaluation and Annotation

After generating a hierarchical cell map, we evaluate whether assemblies are coherent (well separated; not hub-driven or diffuse), biologically plausible (members within an assembly share localization or function), and hierarchically consistent (children largely contained within parents; no cycles). We then perform enrichment analysis using *CellMapsHierarchyEvaluation* (Fig. 3A) or Cytoscape apps (e.g., Run Functional Enrichment/g:Profiler) (Fig. 3B) against HPA, CORUM, and GO-CC. Significantly enriched assemblies are named using specific terms, with brief curator notes added as needed; unenriched groups remain unnamed as candidate novel assemblies.

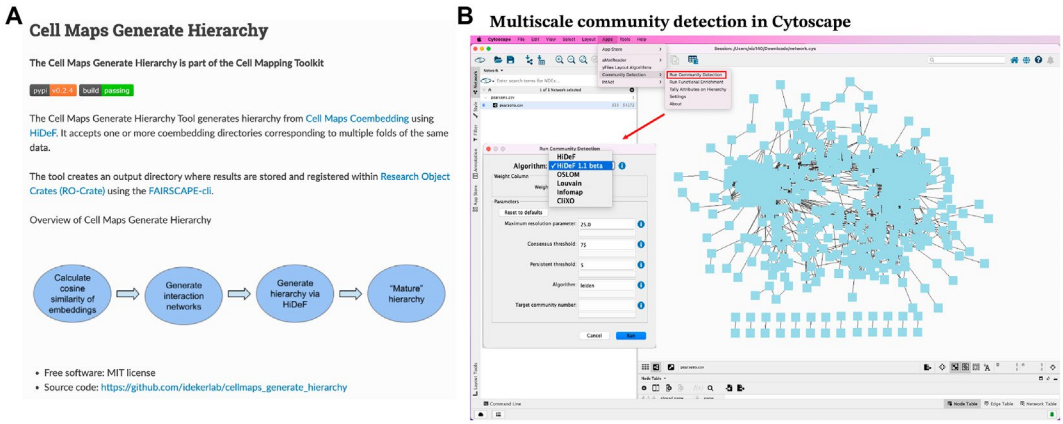

Fig. 2 Tools for building multiscale cell maps. (**A**) Scripted pipeline using *CellMapsGenerateHierarchy* in the Cell Mapping Toolkit. (**B**) An interactive Cytoscape workflow

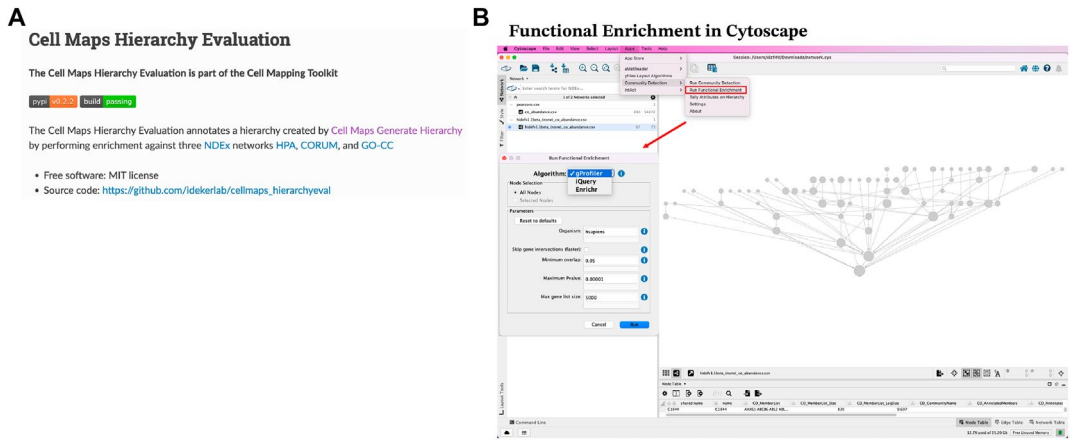

Fig. 3 Tools for assembly annotation. (**A**) Scripted pipeline using *CellMapsHierarchyEvalution* in the Cell Mapping Toolkit. (**B**) Functional enrichment analysis in Cytoscape

4 Flat Network-Guided Modeling

This section presents strategies for flat network-guided modeling. We introduce two representative approaches: (1) network propagation and (2) graph neural networks (Fig. 1B). Each of these approaches is supported by a collection of exemplary tools (Table 1).

4.1 Network Propagation

Network propagation is a group of methods that annotate nodes with numerical information (e.g., gene mutation counts or expression levels) and propagate, or diffuse, this information across the network (Fig. 1). Propagation is usually done using a linear update operation, canonically defined as [2]:

$$f^{(t+1)} = \alpha W f^{t} + (1-\alpha) f^{(0)} \tag{1}$$

The variable $f^{(0)}$ is the initial network state represented by a vector of input values on all nodes, while f^{t} is the updated state of all nodes at the tth iteration. The parameter α controls the rate of diffusion across the network structure, represented by adjacency matrix W. The propagation equation is run iteratively until the overall state reaches an equilibrium. The benefit of using network propagation is that the process is fast and can detect local network clusters, which may be used for downstream applications. Indeed, network propagation is widely used in various applications including disease gene and functional prediction [75], cancer driver gene prediction [4, 6], identification of disease treatment mechanisms [76], in silico drug screening [77], and prediction of anti-cancer drug treatments in cancer cell lines [78] or patients [79].

Table 1
Exemplary tools for network-guided modeling

Method	Tool	Description	Software
Network propagation	NetworkX [116]	Random walk propagation can be performed via the Pagerank algorithm	Python
	HotNet2 [4]	Identifies mutated subnetworks in genomic datasets via a heat diffusion model	Python
	Igraph [117]	Supports high performance network analysis in R	R
	Cytoscape [72]	Network propagation via Diffusion app; Desktop and web application for general network analysis/visualization	Multiple (R, Python, Javascript)
Graph neural network (GNN)	Pytorch Geometric [118]	Deep learning library built on PyTorch providing ready-to-use GNN layers (e.g., GCNConv, GATConv, GraphSAGEConv, GINConv)	Python
	Deep Graph Library [119]	Similar to Pytorch Geometric. Supports major deep learning frameworks (PyTorch and TensorFlow)	Python
	Graph Convolutional Network for R (GCN4R) [120]	Integrates PyTorch GNNs into the R ecosystem	R
Hierarchy-guided neural network	Visible neural network (VNN) [100]	Hierarchical deep neural network analyzing genomic alteration profiles	Python
	Pathway-aware multilayered hierarchical NETwork (P-NET) [7]	Updated VNN, trained on prostate cancer data	Python

4.2 Graph Neural Networks

Graph neural networks (GNNs) are used to capture complex, non-linear interactions between input features. GNN operations follow a message passing framework to aggregate information about a node from its neighbors, canonically defined as [80]:

$$h_v^{(l+1)} = \sigma(W^{(l)} \cdot AGGREGATE(\{h_v^{(l)}, h_u^{(l)} \mid u \in N(v)\})) \quad (2)$$

where $h_v^{(l)}$ and $h_u^{(l)}$ are feature vectors of node v and u at layer l, respectively. $N(v)$ is the set of network neighbors of v. $W^{(l)}$ is a

learnable weight vector optimized during training. The AGGREGATE function merges information from network neighbors of v, using a method such as sum, average, max, or attention-based weighted sum. Finally, σ is a nonlinear squashing function such as REctified Linear Unit (RELU), sigmoid, or hyperbolic tangent (Tanh).

Popular conventional GNN architectures include the Graph Convolutional Network (GCN) [81], Graph Isomorphism Network (GIN) [82], and Graph Attention Network (GAT) [83, 84]. The attention mechanism in GAT can learn different weights between neighboring nodes, thereby allowing the model to focus on important edges. One limitation of these GNN architectures is that message passing is strictly between neighboring nodes without the ability to detect novel edges. More advanced GNN architectures, such as graph transformers [85], borrow ideas from the transformer approach to allow new edges to be learned. Key recent applications of GNNs in biology are shared with those of network propagation, such as detection of cancer driver genes (EMOGI [86], EMGNN [87]). GNNs have also been used in foundation modeling of cancer genomes (MutationProjector [88]), prediction of polypharmacology side effects (Decagon) [89], drug repurposing (TxGNN) [90], modeling transcriptomic gene perturbation effects (GEARS) [91], and generating protein representations (PINNACLE) [92].

5 Hierarchy-Guided Neural Networks

Hierarchy-guided neural networks, also known as visible neural networks (VNNs), explicitly embed curated or data-driven biological hierarchies into the model architecture [93–95]. VNNs aggregate information along predefined edges in a hierarchy (e.g., genes → pathways; child assembly → parent assembly), allowing them to reflect the structured organization of biological systems across scales. VNNs have been implemented using architectures such as feedforward neural networks (FFNNs) (e.g., DCell [96], P-NET [7], DrugCell [8]), variational autoencoders (VAEs) (e.g., GSAE [97], ExpiMap [98]), GNNs (e.g., GraphGONet [11]), and transformers (e.g., G2PT [99]). VNNs provide intrinsic interpretability, enabling a wide range of biomedical applications, including therapeutic outcome prediction [100–102], biomarker discovery [7], and single-cell data analysis [103]. Representative hierarchy-guided models are listed in Table 1.

5.1 VNN Architecture

Here, we adopt the multidrug-VNN model in Zhao et al [100] as a running example and detail a full workflow for VNN modeling including model architecture, training, testing, and interpretation. The multidrug VNN ingests tumor genomic profiles, maps them onto a hierarchical cancer cell map, and predicts responses

to chemotherapeutic agents [100]. Strategies for selecting genes included in the hierarchical map are provided in **Note 1**.

The model comprises: (i) a genomic feature input layer, (ii) a gene layer, (iii) hierarchy constrained assembly layers, and (iv) output layers (Fig. 4A). In the input layer, each gene i is represented by a feature vector x_i (e.g., mutations, copy-number amplifications or deletions). The multidrug-VNN model uses binary representation for genomic alterations but can also accommodate continuous mutation impact scores, as detailed in **Note 2**. The input vector is

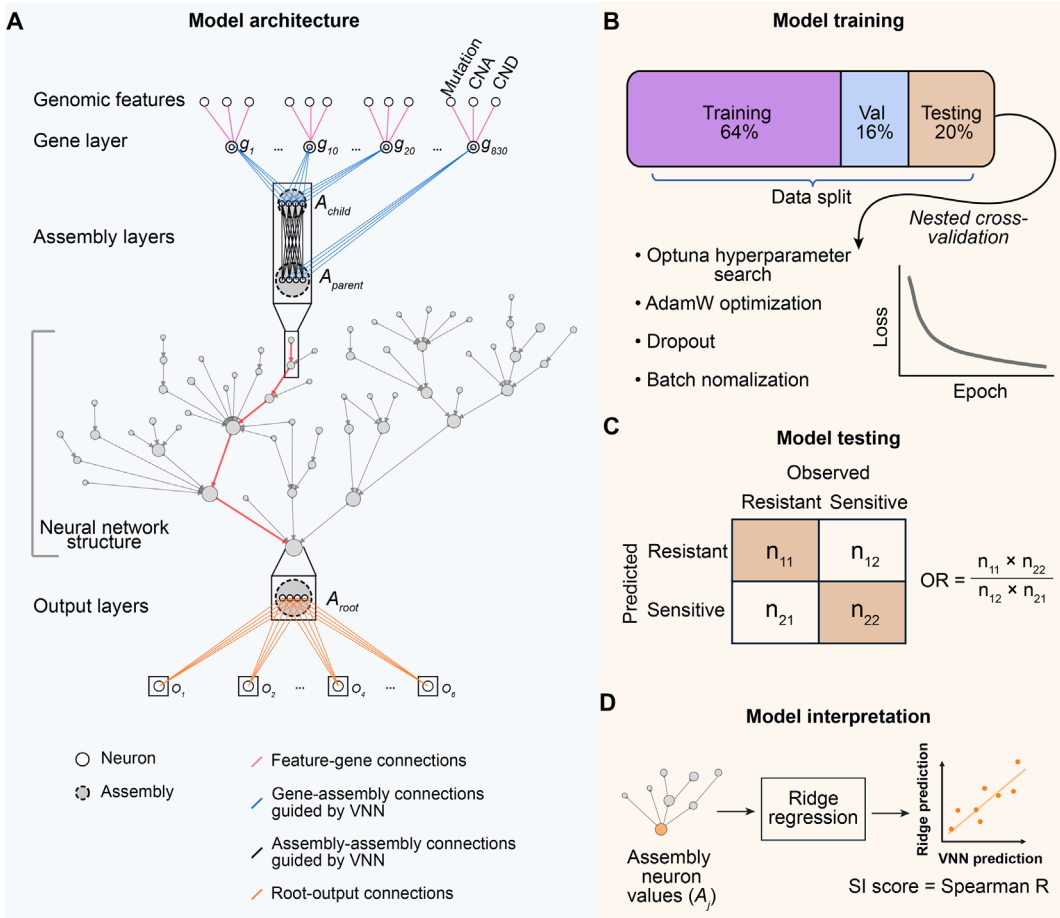

Fig. 4 VNN model architecture, training, testing, and interpretability. (**A**) Model architecture. Genomic features [mutation, copy number alteration (CNA), and copy number deletion (CND)] are integrated at the gene layer, which connects hierarchically to protein assemblies, converging at the root (representing the whole cell or overall biological system), which predicts multidrug responses. An example path of information flow is shown in red. (**B**) Model training under a nested cross-validation framework. Hyperparameters tuned with Optuna, weights optimized with AdamW, and generalization improved with dropout and batch normalization; performance monitored by loss curves. (**C**) Model testing and evaluation based on odds ratios (OR) computed from contingency tables comparing predicted and observed drug responses. (**D**) Assembly importance assessed by System Importance (SI) scores

transformed to a gene embedding via a learned linear projection, followed by nonlinear activation (e.g., *Tanh* in the multidrug-VNN) and normalization:

$$g_i = BatchNorm(Tanh(Linear(x_i))) \tag{3}$$

In the hierarchy constrained layers, each assembly A_j is modeled with n neurons (a tunable hyperparameter) and receives inputs from connected genes and child assemblies. For an assembly A_j connected to k child assemblies and m genes, the input vector $I_j \in R^{n\cdot(n\cdot k+m)}$ is constructed by concatenating the m gene vectors (each of dimension $n\times 1$) and k flattened child assembly matrices (each of dimension $n\times n$). The output $A_j \in R^n$ is computed as:

$$A_j = BatchNorm(Tanh(Linear(Dropout(I_j)))) \tag{4}$$

In the output layers, the root assembly representation A_{root} is linearly transformed and passed through a nonlinear activation (e.g., *Tanh* in the multidrug-VNN) to yield a scalar prediction in the range [0,1]:

$$O = Tanh(Linear(A_{root})) \tag{5}$$

The objective function aggregates three components: (i) the mean squared error (MSE) between the predicted and observed drug responses for each drug d, (ii) an auxiliary MSE loss, weighted by a tunable hyperparameter α, which ensures intermediate assembly representations A_j remain predictive by linearly projecting them to scalars and comparing against y^d, and (iii) a L2 penalty term on model weights, scaled by another hyperparameter β, to discourage overfitting. The full loss is:

$$\begin{aligned} Loss = \sum_d \Big(& MSE(O^d, y^d) + \\ & \alpha \sum_{j\neq root} MSE(Linear(A_j), y^d) + \beta ||W||_2 \Big) \end{aligned} \tag{6}$$

5.2 Model Training

We train the model by iteratively minimizing the composite loss objective (as defined in Sect. 5.1), using a fivefold nested cross-validation procedure. In each fold, 64% of cell lines are used for training, 16% for validation (for hyperparameter tuning), and 20% for testing. We tune hyperparameters using Optuna [104] and use AdamW [105] for model weight optimization. We implement the model in PyTorch and run it on a high-performance computing setup with multiple GPU servers, each equipped with four NVIDIA Tesla V100 GPUs (5120 CUDA cores and 32 GB GDDR6 RAM) (Fig. 4B).

5.3 Model Testing

Model performance is evaluated using the Odds Ratio (OR). In each test set, cell lines within the top 25% and bottom 25% of observed area under the dose-response curve (AUC) values are classified as resistant and sensitive, respectively. Predicted scores from the multidrug-VNN are then used to stratify cell lines, with those in the top 50% labeled as resistant and those in the bottom 50% labeled as sensitive. These predicted and observed classifications are compared in a 2×2 contingency table, from which OR is computed to assess predictive performance (Fig. 4C).

5.4 Model Interpretation

Protein assemblies in the multidrug-VNN are evaluated using the System Importance (SI) score, which quantifies each assembly's contribution to predicted drug response. For each assembly, ridge regression is applied to its neuron values, and the Spearman correlation coefficient between Ridge-predicted and VNN-predicted drug responses (Fig. 4D). Assemblies are deemed significant if they achieved an SI score above 0.5 for at least one chemotherapy drug and contained fewer than 100 proteins to reduce size-related bias. Additional interpretation methods are listed in **Note 3**.

6 Case Study: Therapy Response Prediction with Proteome Maps

We now present a case study in which we generate and use a hierarchical network as the basis for a visible neural network model. Together, these two steps integrate protein abundance [106] and pharmacogenomics profiles from human cancer lines [107–111] to predict chemotherapy response.

6.1 COMET: A CO-Abundance Map of thE Tumor Proteome

We analyzed the abundance profiles of 8498 proteins measured from 949 human cancer cell lines [106], yielding a high-confidence network comprising 830 proteins linked by 54,172 pairwise protein–protein coabundance relations (only proteins involved in Pearson correlation >0.8 were retained; Fig. 5A). Interacting protein pairs were enriched for physical and functional interactions in STRING, supporting their biological relevance (Fig. 5B). Analyzing this network with the Cell Mapping Toolkit yielded a hierarchical cell map which we termed COMET (CO-abundance Map of thE Tumor proteome), which organizes proteins into 61 assemblies (51 annotated and 10 unannotated) (Fig. 5C).

6.2 COMET-VNN Predicts Multidrug Response

This information was used to develop COMET-VNN, a visible neural network whose architecture mirrors the COMET hierarchy. COMET-VNN was trained to predict cellular responses to chemotherapeutic agents, including camptothecin, CD437, etoposide, gemcitabine, cisplatin, and olaparib, from cell-line genomic profiles. We implemented the VNN model architecture (Sect. 5.1), with the standard

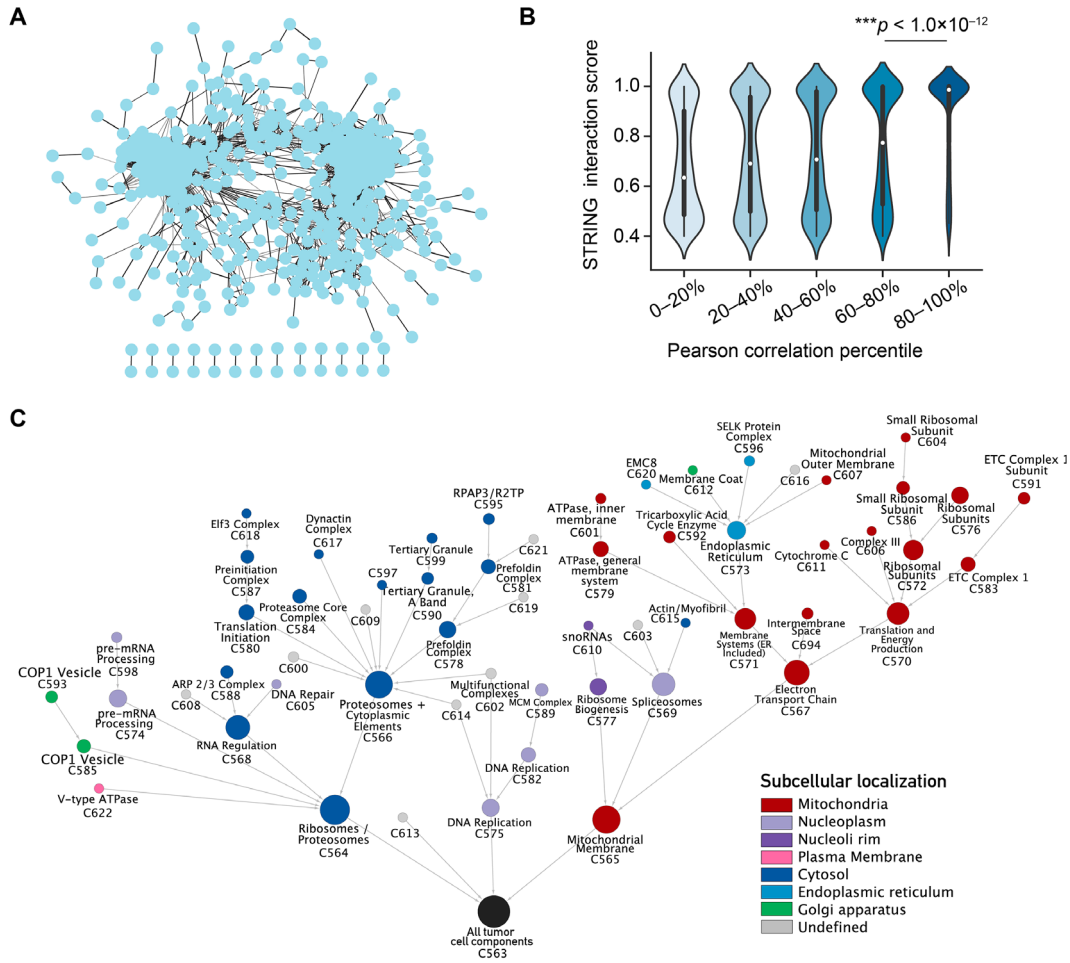

Fig. 5 Construction and annotation of COMET. (**A**) High-confidence protein coabundance network constructed from protein pairs with Pearson correlation $r > 0.8$ in cancer proteomics data. (**B**) Violin plot showing STRING interaction scores for protein pairs binned by Pearson correlation percentiles. $***p < 1.0 \times 10^{-12}$, Mann–Whitney U test. (**C**) COMET cell map visualization in Cytoscape showing annotated protein assemblies (nodes) across subcellular locations (colors). Arrows A→B indicate containment of an assembly A within a larger assembly B

training and evaluation procedure (Sect. 5.2). Implementation details and scripts are available in the GitHub repository https://github.com/idekerlab/multitask_vnn. COMET-VNN robustly separated resistant from sensitive cell lines (Fig. 6A), after which model interpretation identified nine response-associated assemblies spanning established biology and potential novel mechanisms (Fig. 6B). For example, C575 ("DNA Replication") includes the MCM complex, a key regulator of replication initiation and elongation linked to replication-stress tolerance, whereas C577 ("Ribosome Biogenesis") points to ribosome maturation as a previously underappreciated contributor to resistance.

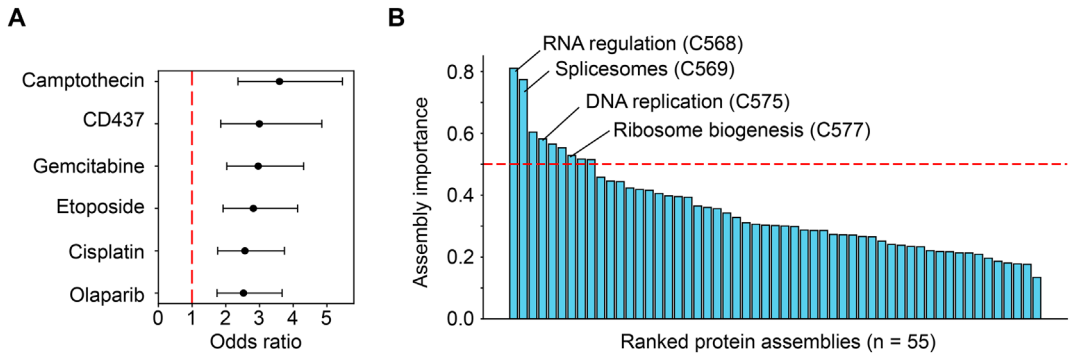

Fig. 6 Model performance and ranked importance of protein assemblies. (**A**) Odds ratios with 95% confidence intervals for model predictions across six drugs. (**B**) Ranked importance scores of protein assemblies ($n = 55$) derived from COMET-VNN. Assemblies with size <100 are shown

6.3 Conclusion

Together, this case study integrated genomic alterations, proteomic organization, and pharmacologic responses from cancer cell line screens into a single interpretable hierarchy-model, revealing a novel way to address a central question in cancer biology.

7 Notes

1. Selecting a limited and informative set of gene features is important for building an effective VNN model. Strategies include using predefined gene panels (e.g., 718 clinical genes in multidrug-VNN), selecting highly connected proteins within the network (as in COMET-VNN), or applying simpler models like random forests to prioritize features that guide hierarchy design.
2. Binary input representations are commonly used in VNN models to denote genomic alterations; however, incorporating quantitative mutation impact scores from variant effect prediction algorithms such as CADD and CHASMplus may enhance the model's ability to capture mutation functionality [112].
3. Alternative methods for interpreting network-guided neural networks include: LIME (Local Interpretable Model-agnostic Explanations) [113], which provides linear explanations; SHAP (SHapley Additive exPlanations), which captures nonlinear contributions of input features [114]; attention mechanisms [99], which highlight informative features or assemblies during transformer-based learning; and GNNExplainer for generating explanations for graph neural networks [115].

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Conflicts of Interest T.I. is a cofounder, member of the advisory board, and has an equity interest in Data4Cure and Serinus Biosciences. T.I. is a consultant for and has an equity interest in Ideaya Biosciences and Eikon Therapeutics. The terms of these arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict-of-interest policies.

References

1. Köhler S, Bauer S, Horn D et al (2008) Walking the interactome for prioritization of candidate disease genes. Am J Hum Genet 82:949–958. https://doi.org/10.1016/j.ajhg.2008.02.013
2. Cowen L, Ideker T, Raphael BJ et al (2017) Network propagation: a universal amplifier of genetic associations. Nat Rev Genet 18:551–562. https://doi.org/10.1038/nrg.2017.38
3. Scelsi MA, Napolioni V, Greicius MD et al (2021) Network propagation of rare variants in Alzheimer's disease reveals tissue-specific hub genes and communities. PLOS Comput Biol 17:e1008517. https://doi.org/10.1371/journal.pcbi.1008517
4. Leiserson MDM, Vandin F, Wu HT et al (2015) Pan-cancer network analysis identifies combinations of rare somatic mutations across pathways and protein complexes. Nat Genet 47:106. https://doi.org/10.1038/ng.3168
5. Chuang H-Y, Lee E, Liu Y-T et al (2007) Network-based classification of breast cancer metastasis. Mol Syst Biol 3:140. https://doi.org/10.1038/msb4100180
6. Hofree M, Shen JP, Carter H et al (2013) Network-based stratification of tumor mutations. Nat Methods 10:1108. https://doi.org/10.1038/nmeth.2651
7. Elmarakeby HA, Hwang J, Arafeh R et al (2021) Biologically informed deep neural network for prostate cancer discovery. Nature 598:348–352. https://doi.org/10.1038/s41586-021-03922-4
8. Kuenzi BM, Park J, Fong SH et al (2020) Predicting drug response and synergy using a deep learning model of human cancer cells. Cancer Cell 38:672–684.e6. https://doi.org/10.1016/j.ccell.2020.09.014
9. Fortelny N, Bock C (2020) Knowledge-primed neural networks enable biologically interpretable deep learning on single-cell sequencing data. Genome Biol 21:190. https://doi.org/10.1186/s13059-020-02100-5
10. Kaynar G, Cakmakci D, Bund C et al (2023) PiDeeL: metabolic pathway-informed deep learning model for survival analysis and pathological classification of gliomas. Bioinformatics 39:btad684. https://doi.org/10.1093/bioinformatics/btad684
11. Bourgeais V, Zehraoui F, Hanczar B (2022) GraphGONet: a self-explaining neural network encapsulating the Gene Ontology graph for phenotype prediction on gene expression. Bioinformatics 38:2504–2511. https://doi.org/10.1093/bioinformatics/btac147
12. Huang X, Huang K, Johnson T et al (2021) ParsVNN: parsimony visible neural networks for uncovering cancer-specific and drug-sensitive genes and pathways. NAR Genom Bioinform 3:lqab097. https://doi.org/10.1093/nargab/lqab097

13. Brückner A, Polge C, Lentze N et al (2009) Yeast two-hybrid, a powerful tool for systems biology. Int J Mol Sci 10:2763–2788. https://doi.org/10.3390/ijms10062763
14. Richards AL, Eckhardt M, Krogan NJ (2021) Mass spectrometry-based protein-protein interaction networks for the study of human diseases. Mol Syst Biol 17:e8792. https://doi.org/10.15252/msb.20188792
15. Liu X, Abad L, Chatterjee L et al (2024) Mapping protein-protein interactions by mass spectrometry. Mass Spectrom Rev 45:69. https://doi.org/10.1002/mas.21887
16. Shen JP, Zhao D, Sasik R et al (2017) Combinatorial CRISPR-Cas9 screens for de novo mapping of genetic interactions. Nat Methods 14:573–576. https://doi.org/10.1038/nmeth.4225
17. Zhao X, Li J, Liu Z et al (2021) Combinatorial CRISPR/Cas9 screening reveals epistatic networks of interacting tumor suppressor genes and therapeutic targets in human breast cancer. Cancer Res 81:6090–6105. https://doi.org/10.1158/0008-5472.CAN-21-2555
18. Zhou P, Chan BKC, Wan YK et al (2020) A three-way combinatorial CRISPR screen for analyzing interactions among druggable targets. Cell Rep 32:108020. https://doi.org/10.1016/j.celrep.2020.108020
19. Gerritsen JS, White FM (2021) Phosphoproteomics: a valuable tool for uncovering molecular signaling in cancer cells. Expert Rev Proteom 18:661–674. https://doi.org/10.1080/14789450.2021.1976152
20. Sahu I, Zhu H, Buhrlage SJ et al (2023) Proteomic approaches to study ubiquitinomics. Biochim Biophys Acta Gene Regul Mech 1866:194940. https://doi.org/10.1016/j.bbagrm.2023.194940
21. Boone C, Bussey H, Andrews BJ (2007) Exploring genetic interactions and networks with yeast. Nat Rev Genet 8:437–449. https://doi.org/10.1038/nrg2085
22. Sundell GN, Ivarsson Y (2014) Interaction analysis through proteomic phage display. BioMed Res Int 2014:176172. https://doi.org/10.1155/2014/176172
23. MacBeath G, Schreiber SL (2000) Printing proteins as microarrays for high-throughput function determination. Science 289:1760–1763. https://doi.org/10.1126/science.289.5485.1760
24. Zhu H, Bilgin M, Bangham R et al (2001) Global analysis of protein activities using proteome chips. Science 293:2101–2105. https://doi.org/10.1126/science.1062191
25. Tong AH, Evangelista M, Parsons AB et al (2001) Systematic genetic analysis with ordered arrays of yeast deletion mutants. Science 294:2364–2368. https://doi.org/10.1126/science.1065810
26. Yan Y, Marriott G (2004) Analysis of protein interactions using fluorescence technologies. Drug Discov Today 9(Supp 2):S27–S31
27. Evans R, O'Neill M, Pritzel A et al (2021) Protein complex prediction with AlphaFold-Multimer. bioRxiv 2021.10.04.463034. https://doi.org/10.1101/2021.10.04.463034
28. Abramson J, Adler J, Dunger J et al (2024) Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature 630:493–500. https://doi.org/10.1038/s41586-024-07487-w
29. Huttlin EL, Bruckner RJ, Navarrete-Perea J et al. (2021) Bi dual proteome-scale networks reveal cell-specific remodeling of the human interactome. Cell 184:3022–3040.e28. https://doi.org/10.1016/j.cell.2021.04.011
30. Szklarczyk D, Kirsch R, Koutrouli M et al (2023) The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res 51:D638–D646. https://doi.org/10.1093/nar/gkac1000
31. Huang JK, Carlin DE, Yu MK et al (2018) Systematic evaluation of molecular networks for discovery of disease genes. Cell Syst 6:484–495.e5. https://doi.org/10.1016/j.cels.2018.03.001
32. Lo Surdo P, Iannuccelli M, Contino S et al (2023) SIGNOR 3.0, the SIGnaling network open resource 3.0: 2022 update. Nucleic Acids Res 51:D631–D637. https://doi.org/10.1093/nar/gkac883
33. Csabai L, Fazekas D, Kadlecsik T et al (2022) SignaLink3: a multi-layered resource to uncover tissue-specific signaling networks. Nucleic Acids Res 50:D701–D709. https://doi.org/10.1093/nar/gkab909
34. Han H, Cho J-W, Lee S et al (2018) TRRUST v2: an expanded reference database of human and mouse transcriptional regulatory interactions. Nucleic Acids Res 46:D380–D386. https://doi.org/10.1093/nar/gkx1013
35. Hornbeck PV, Zhang B, Murray B et al (2015) PhosphoSitePlus, 2014: mutations, PTMs and recalibrations. Nucleic Acids Res 43:D512–D520. https://doi.org/10.1093/nar/gku1267
36. Lee JS, Das A, Jerby-Arnon L et al (2018) Harnessing synthetic lethality to predict the response to cancer treatment. Nat Commun 9: 2546. https://doi.org/10.1038/s41467-018-04647-1
37. Wang J, Wu M, Huang X et al (2022) SynLethDB 2.0: a web-based knowledge graph database on synthetic lethality for novel

anticancer drug discovery. Database (Oxford) 2022:baac030. https://doi.org/10.1093/database/baac030
38. Jin S, Guerrero-Juarez CF, Zhang L et al (2021) Inference and analysis of cell-cell communication using CellChat. Nat Commun 12: 1088. https://doi.org/10.1038/s41467-021-21246-9
39. Thulasiraman K, Swamy MNS (2011) Graphs: theory and algorithms. Wiley-Interscience, New York
40. Ashburner M, Ball CA, Blake JA et al (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 25:25–29. https://doi.org/10.1038/75556
41. Milacic M, Beavers D, Conley P et al (2024) The reactome pathway knowledgebase 2024. Nucleic Acids Res 52:D672–D678. https://doi.org/10.1093/nar/gkad1025
42. Kanehisa M, Goto S (2000) KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res 28:27–30. https://doi.org/10.1093/nar/28.1.27
43 Bard J, Rhee SY, Ashburner M (2005) An ontology for cell types. Genome Biol 6: R21. https://doi.org/10.1186/gb-2005-6-2-r21
44. Diehl AD, Meehan TF, Bradford YM et al (2016) The cell ontology 2016: enhanced content, modularization, and ontology interoperability. J Biomed Semant 7:44. https://doi.org/10.1186/s13326-016-0088-7
45. Robinson PN, Köhler S, Bauer S et al (2008) The human phenotype ontology: a tool for annotating and analyzing human hereditary disease. Am J Hum Genet 83:610–615. https://doi.org/10.1016/j.ajhg.2008.09.017
46. Dolinski K, Botstein D (2013) Automating the construction of gene ontologies. Nat Biotechnol 31:34–35. https://doi.org/10.1038/nbt.2476
47. Kramer MH, Farré J-C, Mitra K et al (2017) Active interaction mapping reveals the hierarchical organization of autophagy. Mol Cell 65:761–774.e5. https://doi.org/10.1016/j.molcel.2016.12.024
48. Dutkowski J, Kramer M, Surma MA et al (2013) A gene ontology inferred from molecular networks. Nat Biotechnol 31:38–45. https://doi.org/10.1038/nbt.2463
49. Guo G, Luc S, Marco E et al (2013) Mapping cellular hierarchy by single-cell analysis of the cell surface repertoire. Cell Stem Cell 13:492–505. https://doi.org/10.1016/j.stem.2013.07.017
50. Osumi-Sutherland D, Xu C, Keays M et al (2021) Cell type ontologies of the Human Cell Atlas. Nat Cell Biol 23:1129–1135. https://doi.org/10.1038/s41556-021-00787-7
51. Kratz A, Kim M, Kelly MR et al (2023) A multi-scale map of protein assemblies in the DNA damage response. Cell Syst 14:447–463.e8. https://doi.org/10.1016/j.cels.2023.04.007
52. Qin Y, Huttlin EL, Winsnes CF et al (2021) A multi-scale map of cell structure fusing protein images and interactions. Nature 600:536–542. https://doi.org/10.1038/s41586-021-04115-9
53. Schaffer LV, Hu M, Qian G et al (2025) Multimodal cell maps as a foundation for structural and functional genomics. Nature 642:222–231. https://doi.org/10.1038/s41586-025-08878-3
54. Zheng F, Kelly MR, Ramms DJ et al (2021) Interpretation of cancer mutations using a multiscale map of protein systems. Science 374:eabf3067. https://doi.org/10.1126/science.abf3067
55. Benjamin K, Bhandari A, Kepple JD et al (2024) Multiscale topology classifies cells in subcellular spatial transcriptomics. Nature 630:943–949. https://doi.org/10.1038/s41586-024-07563-1
56. Jaimovich A, Rinott R, Schuldiner M et al (2010) Modularity and directionality in genetic interaction maps. Bioinformatics 26:i228–i236. https://doi.org/10.1093/bioinformatics/btq197
57. Kelley R, Ideker T (2005) Systematic interpretation of genetic interactions using protein networks. Nat Biotechnol 23:561–566. https://doi.org/10.1038/nbt1096
58. Park Y, Bader JS (2011) Resolving the structure of interactomes with hierarchical agglomerative clustering. BMC Bioinform 12(Suppl 1):S44. https://doi.org/10.1186/1471-2105-12-S1-S44
59. Tanay A, Sharan R, Kupiec M et al (2004) Revealing modularity and organization in the yeast molecular network by integrated analysis of highly heterogeneous genomewide data. Proc Natl Acad Sci U S A 101:2981–2986. https://doi.org/10.1073/pnas.0308661100
60. Schaffer LV, Ideker T (2021) Mapping the multiscale structure of biological systems. Cell Syst 12:622–635. https://doi.org/10.1016/j.cels.2021.05.012
61. Chang Y, Wang K-D, Hsieh P-C et al (2025) DDOT: a derivative-directed dual-decoder ordinary differential equation transformer for dynamic system modeling. arXiv:2506.18522. https://doi.org/10.48550/arXiv.2506.18522
62. Kramer M, Dutkowski J, Yu M et al (2014) Inferring gene ontologies from pairwise similarity data. Bioinformatics 30:i34–i42. https://doi.org/10.1093/bioinformatics/btu282

63. Ravasz E, Somera AL, Mongru DA et al (2002) Hierarchical organization of modularity in metabolic networks. Science 297(5586):1551–1555. https://doi.org/10.1126/science.1073374
64. Blondel V, Guillaume J-L, Lambiotte R (2024) Fast unfolding of communities in large networks: 15 years later. J Stat Mech 2024:10R001. https://doi.org/10.1088/1742-5468/ad6139
65. Newman MEJ (2004) Fast algorithm for detecting community structure in networks. Phys Rev E Stat Nonlin Soft Matter Phys 69:066133. https://doi.org/10.1103/PhysRevE.69.066133
66. Palla G, Derényi I, Farkas I et al (2005) Uncovering the overlapping community structure of complex networks in nature and society. Nature 435:814–818. https://doi.org/10.1038/nature03607
67. Rosvall M, Bergstrom CT (2008) Maps of random walks on complex networks reveal community structure. Proc Natl Acad Sci U S A 105:1118–1123. https://doi.org/10.1073/pnas.0706851105
68. Rosvall M, Bergstrom CT (2011) Multilevel compression of random walks on networks reveals hierarchical organization in large integrated systems. PLoS One 6:e18209. https://doi.org/10.1371/journal.pone.0018209
69. Lancichinetti A, Radicchi F, Ramasco JJ et al (2011) Finding statistically significant communities in networks. PLoS One 6:e18961. https://doi.org/10.1371/journal.pone.0018961
70. Zheng F, Zhang S, Churas C et al (2021) HiDeF: identifying persistent structures in multiscale'omics data. Genome Biol 22:21. https://doi.org/10.1186/s13059-020-02228-4
71. Lenkiewicz J, Churas C, Hu M et al (2025) Cell mapping toolkit: an end-to-end pipeline for mapping subcellular organization. Bioinformatics 41:btaf205. https://doi.org/10.1093/bioinformatics/btaf205
72. Shannon P, Markiel A, Ozier O et al (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13:2498–2504. https://doi.org/10.1101/gr.1239303
73. Ono K, Fong D, Gao C et al (2025) Cytoscape Web: bringing network biology to the browser. Nucleic Acids Res 53:W203–W212. https://doi.org/10.1093/nar/gkaf365
74. Singhal A, Cao S, Churas C et al (2020) Multiscale community detection in Cytoscape. PLOS Comput Biol 16:e1008239. https://doi.org/10.1371/journal.pcbi.1008239
75. Ghiassian SD, Menche J, Barabási A-L (2015) A DIseAse MOdule Detection (DIAMOnD) algorithm derived from a systematic analysis of connectivity patterns of disease proteins in the human interactome. PLOS Comput Biol 11:e1004120. https://doi.org/10.1371/journal.pcbi.1004120
76. Ruiz C, Zitnik M, Leskovec J (2021) Identification of disease treatment mechanisms through the multiscale interactome. Nat Commun 12:1796. https://doi.org/10.1038/s41467-021-21770-8
77. Guney E, Menche J, Vidal M et al (2016) Network-based in silico drug efficacy screening. Nat Commun 7:10331. https://doi.org/10.1038/ncomms10331
78. Fernández-Torras A, Duran-Frigola M, Aloy P (2019) Encircling the regions of the pharmacogenomic landscape that determine drug response. Genome Med 11:17. https://doi.org/10.1186/s13073-019-0626-x
79. Kong JKS, Ha D, Lee J et al (2022) Network-based machine learning approach to predict immunotherapy response in cancer patients. Nat Commun 13:3703. https://doi.org/10.1038/s41467-022-31535-6
80. Zhou J, Cui G, Hu S et al (2018) Graph neural networks: a review of methods and applications. AI Open 1:57. https://doi.org/10.1016/j.aiopen.2021.01.001
81. Kipf TN, Welling M (2016) Semi-supervised classification with graph convolutional networks. arXiv:1609.02907. https://doi.org/10.48550/arXiv.1609.02907
82. Xu K, Hu W, Leskovec J et al (2018) How powerful are graph neural networks? arXiv:1810.00826. https://doi.org/10.48550/arXiv.1810.00826
83. Veličković P, Cucurull G, Casanova A et al (2017) Graph attention networks. arXiv:1710.10903. https://doi.org/10.48550/arXiv.1710.10903
84. Brody S, Alon U, Yahav E (2021) How attentive are graph attention networks? arXiv:2105.14491. https://doi.org/10.48550/arXiv.2105.14491
85. Ying C, Cai T, Luo S et al (2021) Do transformers really perform bad for graph representation? arXiv:2106.05234. https://doi.org/10.48550/arXiv.2106.05234
86. Schulte-Sasse R, Budach S, Hnisz D et al (2021) Integration of multiomics data with graph convolutional networks to identify new cancer genes and their associated molecular mechanisms. Nat Mach Intell 3:513. https://doi.org/10.1038/s42256-021-00325-y
87. Chatzianastasis M, Vazirgiannis M, Zhang Z (2023) Explainable multilayer graph neural network for cancer gene prediction.

Bioinformatics 39:btad643. https://doi.org/10.1093/bioinformatics/btad643
88. Kong J, Lee I, Boecher D et al (2025) Translating clinical gene sequencing into a foundational representation of tumor subtype. bioRxiv 2025.09.08.674723. https://doi.org/10.1101/2025.09.08.674723
89. Zitnik M, Agrawal M, Leskovec J (2018) Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics 34:i457–i466. https://doi.org/10.1093/bioinformatics/bty294
90. Huang K, Chandak P, Wang Q et al (2024) A foundation model for clinician-centered drug repurposing. Nat Med 30:3601–3613. https://doi.org/10.1038/s41591-024-03233-x
91. Roohani Y, Huang K, Leskovec J (2024) Predicting transcriptional outcomes of novel multigene perturbations with GEARS. Nat Biotechnol 42:927–935. https://doi.org/10.1038/s41587-023-01905-6
92. Li MM, Huang Y, Sumathipala M et al (2024) Contextual AI models for single-cell protein biology. Nat Methods 21:1546–1557. https://doi.org/10.1038/s41592-024-02341-3
93. Selby DA, Jakhmola R, Sprang M et al (2025) Visible neural networks for multi-omics integration: a critical review. Front Artif Intell 8:1595291. https://doi.org/10.3389/frai.2025.1595291
94. Wysocka M, Wysocki O, Zufferey M et al (2023) A systematic review of biologically-informed deep learning models for cancer: fundamental trends for encoding and interpreting oncology data. BMC Bioinform 24:198. https://doi.org/10.1186/s12859-023-05262-8
95. Selby DA, Sprang M, Ewald J et al (2025) Beyond the black box with biologically informed neural networks. Nat Rev Genet 26:371–372. https://doi.org/10.1038/s41576-025-00826-1
96. Ma J, Yu MK, Fong S et al (2018) Using deep learning to model the hierarchical structure and function of a cell. Nat Methods 15:290–298. https://doi.org/10.1038/nmeth.4627
97. Chen H-IH, Chiu Y-C, Zhang T et al (2018) GSAE: an autoencoder with embedded gene-set nodes for genomics functional characterization. BMC Syst Biol 12:142. https://doi.org/10.1186/s12918-018-0642-2
98. Lotfollahi M, Rybakov S, Hrovatin K et al (2023) Biologically informed deep learning to query gene programs in single-cell atlases. Nat Cell Biol 25:337–350. https://doi.org/10.1038/s41556-022-01072-x
99. Lee I, Wallace ZS, Wang Y et al (2025) A genotype-phenotype transformer to assess and explain polygenic risk. bioRxiv 2024.10.23.619940. https://doi.org/10.1101/2024.10.23.619940
100. Zhao X, Singhal A, Park S et al (2024) Cancer mutations converge on a collection of protein assemblies to predict resistance to replication stress. Cancer Discov 14:508–523. https://doi.org/10.1158/2159-8290.CD-23-0641
101. Park S, Silva E, Singhal A et al (2024) A deep learning model of tumor cell architecture elucidates response and resistance to CDK4/6 inhibitors. Nat Cancer 5:996–1009. https://doi.org/10.1038/s43018-024-00740-1
102. Hao J, Kim Y, Mallavarapu T et al (2019) Interpretable deep neural network for cancer survival analysis by integrating genomic and clinical data. BMC Med Genomics 12: 189. https://doi.org/10.1186/s12920-019-0624-2
103. Seninge L, Anastopoulos I, Ding H et al (2021) VEGA is an interpretable generative model for inferring biological network activity in single-cell transcriptomics. Nat Commun 12: 5684. https://doi.org/10.1038/s41467-021-26017-0
104. Akiba T, Sano S, Yanase T et al (2019) Optuna: a next-generation hyperparameter optimization framework. arXiv:1907.10902. https://doi.org/10.48550/arXiv.1907.10902
105. Loshchilov I, Hutter F (2017) Decoupled weight decay regularization. arXiv:1907.10902. https://doi.org/10.48550/arXiv.1907.10902
106. Gonçalves E, Poulos RC, Cai Z et al (2022) Pan-cancer proteomic map of 949 human cell lines. Cancer Cell 40:835–849.e8. https://doi.org/10.1016/j.ccell.2022.06.010
107. Basu A, Bodycombe NE, Cheah JH et al (2013) An interactive resource to identify cancer genetic and lineage dependencies targeted by small molecules. Cell 154:1151–1161. https://doi.org/10.1016/j.cell.2013.08.003
108. Seashore-Ludlow B, Rees MG, Cheah JH et al (2015) Harnessing connectivity in a large-scale small-molecule sensitivity dataset. Cancer Discov 5:1210–1223. https://doi.org/10.1158/2159-8290.CD-15-0235
109. Garnett MJ, Edelman EJ, Heidorn SJ et al (2012) Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 483:570–575. https://doi.org/10.1038/nature11005
110. Iorio F, Knijnenburg TA, Vis DJ et al (2016) A landscape of pharmacogenomic interactions in cancer. Cell 166:740–754. https://doi.org/10.1016/j.cell.2016.06.017
111. Barretina J, Caponigro G, Stransky N et al (2012) The cancer cell line encyclopedia

enables predictive modelling of anticancer drug sensitivity. Nature 483:603–607. https://doi.org/10.1038/nature11003
112. Wall P, Ideker T (2024) Representing mutations for predicting cancer drug response. Bioinformatics 40:i160–i168. https://doi.org/10.1093/bioinformatics/btae209
113. Ribeiro MT, Singh S, Guestrin C (2016) "Why should I trust you?": explaining the predictions of any classifier. arXiv:1602.04938. https://doi.org/10.48550/arXiv.1602.04938
114. A unified approach to interpreting model predictions. https://proceedings.neurips.cc/paper/2017/hash/8a20a8621978632d76c43dfd28b67767-Abstract.html. Accessed 17 Aug 2023
115. Ying R, Bourgeois D, You J et al (2019) GNNExplainer: generating explanations for graph neural networks. arXiv:1903.03894. https://doi.org/10.48550/arXiv.1903.03894
116. Hagberg AA, Schult DA, Swart PJ (2008) Exploring network structure, dynamics, and function using NetworkX. In: 7th Python in Science Conference (SciPy 2008)
117. Antonov M, Csárdi G, Horvát S et al (2023) Igraph enables fast and robust network analysis across programming languages. arXiv:2311.10260. https://doi.org/10.48550/arXiv.2311.10260
118. Fey M, Lenssen JE (2019) Fast graph representation learning with PyTorch Geometric. arXiv:1903.02428. https://doi.org/10.48550/arXiv.1903.02428
119. Wang M, Zheng D, Ye Z et al (2019) Deep graph library: a graph-centric, highly-performant package for graph neural networks. arXiv:1909.01315. https://doi.org/10.48550/arXiv.1909.01315
120. Levy J, Bobak C, Christensen B et al (2020) Estimating latent positions in social and biological networks using Graph Neural Networks in R with GCN4R. bioRxiv 2020.11.02.364935. https://doi.org/10.1101/2020.11.02.364935