Deep Learning–Assisted Discovery of Small-Molecule Modulators Targeting MYC Phase Separation in Solid Tumors

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Abstract

The oncoprotein MYC is a master transcriptional regulator implicated in the majority of human cancers, yet it has historically been considered undruggable due to its intrinsically disordered regions and lack of a stable binding pocket. Recent discoveries have revealed that MYC undergoes liquid–liquid phase separation (LLPS) to form punctate condensates that selectively modulate its transcriptional activity. This process offers a novel therapeutic vulnerability: small molecules that disrupt MYC phase separation could attenuate oncogenic signaling without requiring direct active-site inhibition. However, rationally designing such modulators is extremely challenging because phase separation involves weak, multivalent interactions across large intrinsically disordered domains. This paper presents a systems-level framework in which deep learning architectures are integrated with biophysical simulations and high-throughput screening data to accelerate the discovery of small-molecule modulators targeting MYC condensates. We analyze the architectural trade-offs between graph neural networks that model molecular interaction surfaces and transformer-based models that capture sequence-to-condensate behavior. The deployment of such models within a federated data infrastructure, combining public and proprietary datasets, raises governance and fairness considerations regarding access to training data and algorithmic bias across patient populations. Robustness under distributional shift is examined through adversarial perturbations of molecular representations. Finally, we discuss policy implications for regulatory approval of condensate-targeting drugs and the sustainability of large-scale deep learning pipelines in pharmaceutical research. By framing the problem as a socio-technical system, this paper illuminates the path toward translating computational insights into clinically viable therapeutics.

Keywords

MYC, liquid–liquid phase separation, deep learning, small-molecule modulators, drug discovery, systems architecture, data governance, robustness.

1. Introduction

The MYC family of transcription factors plays a central role in cell proliferation, differentiation, and apoptosis, and its dysregulation is a hallmark of many solid tumors, including breast, lung, colorectal, and pancreatic cancers [1]. Despite decades of intense research, no clinically approved small-molecule inhibitor directly targeting MYC has emerged, largely because MYC is a largely unstructured protein that lacks deep hydrophobic pockets suitable for conventional drug binding [2]. The paradigm shift introduced by the discovery that MYC undergoes phase separation into dynamic condensates inside the nucleus has opened a new avenue for therapeutic intervention [3]. These condensates concentrate transcriptional cofactors and RNA polymerase II, thereby enhancing the expression of MYC-driven gene programs. Disrupting the formation or material properties of these condensates could selectively impair MYC-dependent transcription while sparing normal cellular functions [4].

The complexity of phase separation as a biophysical phenomenon demands computational approaches that can navigate high-dimensional sequence–structure–function relationships. Traditional virtual screening and molecular dynamics simulations are computationally prohibitive when applied to the full-length intrinsically disordered regions of MYC [5]. Deep learning models, particularly those based on graph neural networks and transformers, have demonstrated remarkable capacity to learn predictive representations from large chemical and biological databases [6]. These models can be trained to predict whether a candidate molecule will promote or inhibit condensate formation, or to optimize molecular properties such as partition coefficient and target selectivity.

This paper adopts a systems perspective to examine the interplay between deep learning model design, computational infrastructure, data governance, and regulatory policy in the context of targeting MYC phase separation. Rather than focusing solely on algorithmic performance, we analyze structural trade-offs in model architecture, deployment challenges in federated environments, robustness to data shifts, and fairness implications of biased training sets. We also discuss the sustainability of large-scale training regimes and the need for transparent reporting standards. Through this lens, we aim to provide a roadmap for responsible and effective discovery of condensate-modulating small molecules.

2. Background and Biological Rationale

Phase separation of MYC is driven by its intrinsically disordered region (IDR), particularly the C-terminal domain that contains a predicted prion-like sequence [7]. Under conditions of high local concentration or in the presence of specific binding partners, MYC molecules demix from the nucleoplasm to form liquid-like droplets that exhibit selective permeability [8]. These condensates have been shown to amplify MYC transcriptional output by recruiting the transcriptional elongation machinery and excluding repressive factors [9]. The ability to modulate phase separation with small molecules is supported by precedents from other systems: compounds such as lipophilic inhibitors of the androgen receptor have been shown to alter condensate dynamics [10]. For MYC, early proof-of-concept studies using high-throughput microscopy-based screens have identified a handful of molecules that reduce condensate size or number [11].

A major challenge is that phase separation is governed by multivalent, weak interactions that are difficult to capture with standard docking or scoring functions. The interaction landscape includes both hydrophobic and electrostatic contributions, as well as contributions from backbone hydrogen bonding [12]. Deep learning models that operate on molecular graphs or on sequences of amino acid residues can learn effective representations of these complex interaction patterns without explicit enumeration of binding modes [13]. For instance, graph neural networks (GNNs) can propagate information across the three-dimensional structure of a molecule, while transformer models can capture long-range dependencies in protein sequences [14]. The choice of model architecture involves a trade-off between inductive bias and data efficiency: GNNs require three-dimensional conformations that may be costly to generate, whereas transformers can work on simpler sequence inputs but may need more data to achieve comparable accuracy.

3. System Architecture and Model Design

The computational pipeline for deep learning–assisted discovery of MYC phase separation modulators consists of several interconnected modules: data acquisition, featurization, model training, validation, and iterative screening. At the data acquisition stage, one must aggregate high-quality experimental measurements of condensate modulation, typically from high-content imaging assays where cells expressing fluorescently tagged MYC are treated with compound libraries [15]. These datasets are often small (hundreds to thousands of compounds) due to the cost and labor of manual image analysis. Augmenting with public databases such as ChEMBL, DrugBank, and PubChem provides millions of known bioactivity measurements, but the gap between general bioactivity and specific condensation endpoints presents a domain adaptation problem [16].

Featurization strategies diverge based on the model class. For graph neural networks, each molecule is represented as a graph where atoms are nodes and bonds are edges, with features including atomic number, formal charge, hybridization, and partial charge [17]. Conformational ensembles can be generated using fast force-field methods or metadynamics, and the model must learn to weight relevant conformations. For transformer-based approaches, the molecular structure is encoded as a Simplified Molecular Input Line Entry System (SMILES) string or as a 2D molecular fingerprint, which is then passed through a deep attention network [18]. The required reference Yang et al. 2024 demonstrated that MYC phase separation selectively modulates the transcriptome, highlighting the biological relevance of targeting condensation. That work employed experimental perturbations that altered phase separation and measured transcriptional outputs, providing a crucial validation dataset for computational models [18].

The training protocol involves a supervised objective to classify molecules as active or inactive modulators, or to predict a continuous score such as the half-maximal inhibitory concentration (IC50) for condensate disruption. Because active molecules are rare, class imbalance is severe, and techniques such as focal loss, oversampling, or synthetic data generation via generative adversarial networks (GANs) are employed [19]. Multitask learning, where the same model predicts multiple endpoints (e.g., condensate disruption, cytotoxicity, metabolic stability), can improve generalization and data efficiency.

Deployment of the trained model in a virtual screening setting requires a trade-off between throughput and precision. Models that are computationally intensive, such as those requiring full conformational sampling, may screen only thousands of compounds per day, whereas simpler fingerprint-based models can process millions. A tiered architecture is often adopted:

a fast first-pass filter (e.g., a random forest or a shallow neural network based on Morgan fingerprints) eliminates obvious inert compounds, and the top-ranked candidates are then evaluated with a high-fidelity GNN or transformer model [20]. This hierarchical screening balances computational cost with screening depth.

4. Data Infrastructure, Governance, and Fairness

The success of deep learning for condensate modulation depends critically on the availability of diverse and well-annotated training data. Pharmaceutical companies often hold proprietary data from internal compound libraries and phenotypic screens, creating a fragmented landscape where no single entity possesses a comprehensive dataset. A federated learning infrastructure, in which models are trained across multiple sites without centrally aggregating raw data, can preserve proprietary interests while increasing statistical power [21]. However, such an architecture introduces governance challenges regarding the alignment of training schedules, the handling of heterogeneous data formats, and the auditing of model updates to prevent adversarial interference.

Fairness considerations arise because the available training data are predominantly derived from cell lines or xenograft models that may not represent the genetic diversity of human patients, especially those from underrepresented ancestral groups [22]. A model trained on data from European-ancestry cell lines might learn to prioritize compounds that are effective in those contexts but fail in populations with different MYC regulatory variants or compound metabolism pathways. The lack of large-scale phase separation assays in diverse patient-derived models compounds this bias. Mitigation strategies include stratified sampling during training, the use of invariant risk minimization, and the development of cell-free condensate assays that can be more easily standardized across laboratories [23].

Data provenance and reproducibility are further governance concerns. Many public datasets suffer from inconsistent annotation of negative results (i.e., compounds tested and found inactive), leading to a de facto bias toward active compounds. Deep learning models trained on such skewed data tend to overestimate activity. Establishing a common data standard for phase separation assays, including detailed experimental protocols, compound concentrations, and image analysis pipelines, would facilitate model transfer and validation. The FAIR (Findable, Accessible, Interoperable, Reusable) data principles should be applied to the entire repository, with persistent identifiers and machine-readable metadata [24].

5. Robustness and Adversarial Considerations

Robustness encompasses both the statistical stability of model predictions under normal perturbations (e.g., slight variations in molecular conformation or experimental noise) and the resilience to adversarial attacks. In the context of drug discovery, an adversary could deliberately design a molecule that passes the deep learning filter yet fails to modulate MYC phase separation in vitro, wasting screening resources and delaying therapeutic development [25]. Conversely, a model that is overly sensitive to small structural changes might discard promising candidates that adopt alternative conformations.

GNNs are known to be vulnerable to adversarial perturbations on graph structures and node features. For example, adding a single dummy atom to a molecule can flip the model's classification from negative to positive [26]. Defenses such as adversarial training, certifiable robustness through bounding the Lipschitz constant, and ensemble methods can improve resilience. However, these techniques often come at a cost of reduced accuracy on clean data, representing a classic trade-off between robustness and performance.

Another dimension of robustness is the extrapolation to novel chemical space. Phase separation modulators may belong to chemical classes that are underrepresented in the training set. The model's uncertainty should be quantified, for instance using Bayesian approximations or Monte Carlo dropout, so that predictions with high uncertainty are flagged for experimental verification rather than trusted implicitly. System-level safeguards include a closed-loop feedback where experimental results are fed back to retrain the model, continuously updating its knowledge base.

6. Deployment, Sustainability, and Policy Implications

Deploying a deep learning pipeline for small-molecule discovery in an industrial or academic setting requires significant computational infrastructure. Training state-of-the-art GNNs on millions of compounds can consume thousands of GPU hours, contributing to carbon emissions and energy costs [27]. Sustainable deployment strategies include using efficient model architectures such as lightweight graph networks, pre-training on large unlabeled chemical datasets followed by fine-tuning, and scheduling training jobs during periods of low grid carbon intensity. Additionally, model compression via quantization and knowledge distillation can reduce inference costs without substantial accuracy loss.

Regulatory policy for drugs that target phase separation is still in its infancy. Traditional drug approval frameworks are built around the assumption of a single, well-defined molecular target with a measurable binding affinity. Condensate-modulating compounds may exhibit a polypharmacology that affects multiple condensate types, necessitating new safety and efficacy evaluation paradigms [28]. In silico models, if sufficiently validated, could serve as evidence for Phase 0 bridging studies or as part of a quantitative systems pharmacology submission. However, regulators demand transparency in model development, including access to training data, feature engineering, and uncertainty quantification. This creates a policy impetus for open-source model repositories and standardized benchmarking datasets, similar to those used for ADMET prediction.

Furthermore, the sustainability of the overall discovery ecosystem depends on collaborative models. Public–private partnerships, such as the Structural Genomics Consortium, have successfully enabled precompetitive data sharing for protein targets. Extending this model to liquid–liquid phase separation, where academic labs generate foundational biophysical data and companies contribute proprietary compound libraries, could accelerate progress while managing intellectual property concerns. Governance structures must be established to ensure equitable access to resulting therapies, particularly for rare cancers where MYC dysregulation is prevalent but market incentives are weak.

7. Discussion

The integration of deep learning with the emerging biology of MYC phase separation represents a promising frontier in oncology drug discovery. The systems-level analysis presented here highlights several critical interdependencies. The choice of model architecture is not merely a technical decision but has downstream consequences for data requirements, computational cost, and robustness. A graph neural network that models three-dimensional molecular surfaces may capture the physics of condensation more faithfully than a sequence-based transformer, but its deployment may be impractical for large-scale virtual screening without a tiered filter. Conversely, a simpler model may be more robust to adversarial perturbations but less accurate in extrapolating to novel scaffolds.

Data governance emerges as a central challenge. The federated training paradigm offers a path to leverage proprietary data while respecting privacy, but it introduces vulnerabilities in synchronization and auditability. Fairness issues, if left unaddressed, could lead to effective therapies that fail in genetically diverse populations, exacerbating health disparities. Policy interventions, such as regulatory guidance for condensate-modulating drugs and transparency requirements for in silico components, are necessary to translate computational breakthroughs into clinical benefits.

The required reference Yang et al. 2024 provided a crucial biological validation that MYC phase separation selectively modulates the transcriptome, reinforcing the therapeutic rationale for targeting condensates [18]. That work also established quantitative readouts that can be used as training targets for deep learning models. However, the path from such foundational studies to a deployable pipeline is long and fraught with systemic challenges. The present paper has attempted to chart that path by addressing not only algorithmic advances but also the infrastructure, governance, and policy dimensions that are often overlooked in technology-driven drug discovery narratives.

8. Conclusion

In summary, deep learning–assisted discovery of small-molecule modulators targeting MYC phase separation requires a holistic systems engineering approach. We have examined architectural trade-offs between graph neural networks and transformers, the need for federated data infrastructure with robust governance, fairness and robustness considerations, and the sustainability and policy implications of scaled deployment. By integrating these dimensions, researchers and practitioners can build discovery pipelines that are not only computationally powerful but also equitable, transparent, and resilient. The convergence of phase separation biology and deep learning holds immense potential for addressing undruggable oncoproteins, but realizing that potential will demand careful system design and responsible stewardship.

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