# Graph Neural Networks for Deciphering Condensate-Mediated Gene Regulatory Networks in YAP-MAML2–Associated Tumorigenesis

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**Abstract**

The emergence of biomolecular condensates as a fundamental organizing principle in cellular regulation has reshaped the understanding of transcriptional control, particularly in oncogenic contexts where aberrant phase separation drives aberrant gene expression. This paper presents a systems-level framework that integrates graph neural networks (GNNs) with high-throughput sequencing and imaging data to decode condensate-mediated gene regulatory networks (GRNs) in YAP-MAML2–associated tumorigenesis. We argue that conventional network inference approaches, which treat regulatory interactions as static and pairwise, are insufficient to capture the dynamic, multivalent, and cooperative nature of condensate-driven transcription. GNNs, by virtue of their relational inductive biases and ability to propagate information over graph structures, offer a principled mechanism to model the interplay between phase-separated complexes and downstream transcriptional programs. The paper systematically examines the architectural trade-offs between expressivity and trainability when applying GNNs to spatially resolved genomic data, and discusses the computational infrastructure required for scalable deployment across heterogeneous clinical cohorts. Furthermore, we analyze the governance and fairness implications of deploying such models in precision oncology, emphasizing the need for interpretable predictions and robustness to distributional shifts arising from diverse patient populations. By situating the technical methodology within broader socio-technical considerations, this work provides a roadmap for building sustainable, equitable, and scientifically rigorous artificial intelligence systems that can elucidate the regulatory logic of liquid–liquid phase separation in cancer.

**Keywords**

graph neural networks, gene regulatory networks, biomolecular condensates, YAP-MAML2, tumorigenesis, phase separation, precision oncology, socio-technical systems.

## 1. Introduction

The discovery that many cellular processes are compartmentalized through liquid–liquid phase separation has fundamentally altered the conceptual landscape of molecular biology [1,2]. These biomolecular condensates, which include stress granules, nucleoli, and transcriptional hubs, concentrate specific proteins and nucleic acids without the need for a lipid membrane, enabling the spatiotemporal control of biochemical reactions [3]. Among the most striking implications of phase separation is its role in transcriptional regulation: transcription factors and co-activators that form condensates can dramatically enhance gene expression by locally increasing the effective concentration of the transcriptional machinery at enhancer and promoter regions [4]. This paradigm is particularly relevant in cancer, where

mutations or fusions that alter phase behavior can drive oncogenic transcriptional programs [5].

The transcriptional co-activator YAP and its fusion partner MAML2 exemplify such a mechanism. The YAP-MAML2 fusion protein, initially identified in head and neck carcinomas, exhibits enhanced phase separation properties compared to wild-type YAP, leading to the formation of aberrant nuclear condensates that alter chromatin accessibility and gene expression [6]. Recent work has demonstrated that these condensates differentially modulate the transcriptome, activating a set of pro-tumorigenic genes while repressing tumor-suppressive loci [7]. However, the full architecture of the resulting gene regulatory network remains incompletely mapped due to the complexity of the interactions: condensates recruit multiple transcription factors, co-activators, and chromatin remodelers simultaneously, creating a highly connected and dynamic regulatory landscape.

Traditional computational methods for inferring gene regulatory networks, such as Bayesian networks, mutual information-based approaches, and regression models, typically assume pairwise, static, and often linear relationships between regulators and their targets [8,9]. While these methods have been successful in simpler contexts, they are ill-suited to capture the higher-order, cooperative, and context-dependent nature of condensate-mediated regulation. Graph neural networks, which operate directly on the structure of graphs and learn representations that incorporate both node features and topological information, offer a more expressive framework for modeling such complex systems [10]. By representing genes as nodes and regulatory interactions as edges, a GNN can propagate information through the network while simultaneously learning the influence of condensate-localized factors on each node's state.

In this paper, we develop a conceptual and architectural framework for applying GNNs to decipher condensate-mediated GRNs, using YAP-MAML2–associated tumorigenesis as a case study. We focus on the system-level design choices that must be made when integrating GNNs with heterogeneous biological data sources, including single-cell RNA sequencing, chromatin immunoprecipitation sequencing, and live-cell imaging of condensates. The discussion extends beyond technical performance to examine the computational infrastructure, reproducibility, fairness, and policy implications of deploying such models in clinical settings. By addressing both the scientific and socio-technical dimensions, this work aims to provide a holistic perspective on the role of artificial intelligence in understanding phase separation–based transcriptional regulation.

## 2. Background: Condensate Biology and Gene Regulation

Biomolecular condensates form through liquid–liquid phase separation driven by multivalent interactions between intrinsically disordered regions and RNA-binding domains [1,2]. In the context of transcription, condensates assemble at super-enhancers and gene clusters, where they serve as hubs that concentrate RNA polymerase II, Mediator complex components, and transcription factors [4]. The resulting high local concentrations facilitate robust transcriptional activation and can also promote the repression of competing loci through mechanisms such as sequestration of common cofactors [3].

The YAP-MAML2 fusion protein arises from a chromosomal translocation that links the transcriptional co-activator YAP to the Notch co-activator MAML2. Both YAP and MAML2 contain intrinsically disordered regions that promote phase separation, and the fusion protein exhibits enhanced condensation propensity [6]. In cells carrying this fusion, discrete nuclear

puncta are observed, and these puncta colocalize with active chromatin marks and RNA polymerase II. Transcriptomic analysis has revealed that the fusion drives a distinct expression program that overlaps with but is not identical to that of wild-type YAP activation [7]. Notably, the condensates appear to differentially regulate target genes: some genes are hyperactivated, while others are repressed, likely due to competition for transcriptional resources or spatial segregation of repressive factors.

From a network perspective, the regulatory influence of a condensate on a target gene depends not only on the direct binding of YAP-MAML2 to its promoter but also on the indirect effects mediated by other transcription factors that are recruited to or excluded from the condensate. Moreover, the condensate's physical properties—size, dynamics, and composition—vary across cell states and genetic backgrounds, adding an additional layer of regulatory complexity [5]. Therefore, any computational model that aspires to capture the full GRN must incorporate both the local connectivity of molecular interactions and the global influence of condensate organization.

## 3. Graph Neural Networks for Gene Regulatory Networks

Graph neural networks have emerged as a powerful class of deep learning models for relational data [10]. In a typical GNN architecture, each node is associated with a feature vector, and the network learns to update these features by aggregating information from neighboring nodes according to a message-passing scheme. This inductive bias is naturally suited for gene regulatory networks, where each gene's expression level is influenced by its upstream regulators and downstream targets. GNNs can be trained to predict gene expression from regulator activity or to infer missing regulatory edges from expression data, tasks that are central to the reconstruction of GRNs [11,12].

For condensate-mediated GRNs, several architectural modifications are necessary. First, the graph must incorporate a representation of the condensate itself, either as a special node or as a hyperedge that connects all genes and regulators concentrated within the same condensate. This hypergraph or heterogeneous graph formulation allows the model to capture the many-to-many interactions that characterize phase-separated compartments [13]. Second, the node features should include not only gene expression levels but also epigenetic states, chromatin accessibility, and proximity to condensates as measured by imaging data. Third, the message-passing function should be capable of modeling cooperative effects: for example, the simultaneous binding of multiple transcription factors within a condensate may have a synergistic effect on transcription that is not a simple sum of individual contributions [14].

Recent advances in geometric deep learning have provided tools to incorporate spatial information into GNNs, which is particularly relevant when using imaging data that localize condensates and genes in three-dimensional nuclear space [15]. Additionally, temporal GNNs that model changes in condensate composition over time can capture the dynamic nature of phase separation [16]. The choice of architecture must balance expressivity with computational tractability, as the number of potential regulatory edges can be very large, and the training data from high-throughput experiments are often limited and noisy.

## 4. Application to YAP-MAML2–Driven Tumorigenesis

To apply GNNs to the specific case of YAP-MAML2–driven tumorigenesis, one must assemble a multi-modal dataset that captures both molecular and spatial information. Single-cell RNA sequencing profiles the transcriptomes of thousands of individual cells, allowing the identification of distinct cell states within a tumor [17]. Chromatin immunoprecipitation

sequencing for YAP-MAML2 and associated factors identifies genomic binding sites, while Hi-C data provides chromatin conformation information. Live-cell imaging using tagged fusion proteins reveals the size, number, and dynamics of condensates [6].

A natural graph construction would treat each gene as a node, with its expression level as the primary feature. Edges could be defined based on co-regulation, physical proximity, or known interactions from databases such as STRING [18]. A super-node representing the condensate could connect to all genes that are within a certain spatial radius or that are bound by YAP-MAML2. The GNN would then be trained to predict gene expression levels under different perturbations, such as knockdown of the fusion or treatment with drugs that modulate phase separation [19].

In initial feasibility studies, a graph attention network variant demonstrated that the inclusion of condensate proximity improved the prediction accuracy of target gene expression compared to models that only used sequence-based features [20]. Moreover, the learned attention weights highlighted genes that are critical hubs in the condensate network, many of which correspond to known oncogenic drivers. This suggests that the GNN is not only predictive but also interpretable, potentially revealing new therapeutic targets.

However, the deployment of such models in a clinical research setting poses several challenges. The training data are often derived from cell lines or patient-derived xenografts, which may not fully represent the heterogeneity of primary tumors [21]. The computational cost of training large GNNs on whole-genome networks can be prohibitive, necessitating sampling strategies or graph coarsening techniques that preserve the essential regulatory topology [22]. Additionally, the inclusion of imaging data requires sophisticated preprocessing pipelines that are not yet standardized across laboratories.

## 5. System-Level Considerations in Model Architecture and Deployment

The design of a GNN for condensate-mediated GRNs must consider trade-offs between model capacity and data efficiency. Deeper GNNs with many message-passing layers can in principle capture long-range regulatory effects, but they are prone to oversmoothing, where node representations become indistinguishable after many layers [23]. For biological networks where the regulatory influence may decay rapidly with distance, shallow architectures with skip connections may be more appropriate. Another trade-off concerns the use of attention mechanisms: while attention allows the model to learn the importance of different edges, it increases the number of parameters and requires more training data to avoid overfitting.

From an infrastructure perspective, the computational pipeline must handle the integration of multiple data modalities, each with its own format, resolution, and noise characteristics. A cloud-based platform that provides standardized preprocessing modules and scalable graph construction tools can accelerate research and enable reproducibility [24]. Containerization and workflow management systems, such as Nextflow or Snakemake, are essential for ensuring that the analysis can be replicated across different computing environments.

Data governance is another critical dimension. Patient-derived samples raise privacy concerns, and models trained on such data must be protected against reidentification attacks [25]. Federated learning, where model updates are aggregated across institutions without sharing raw data, offers a promising approach for collaborative model development [26]. However, federated GNN training introduces additional communication overhead and requires careful tuning of aggregation strategies to maintain model accuracy.

Fairness and equity considerations are paramount when deploying AI models in oncology. If training data are dominated by samples from patients of European ancestry, the resulting GNN may generalize poorly to under-represented populations, leading to disparities in diagnostic or prognostic accuracy [27]. Strategies to mitigate this include stratified sampling during data collection, domain adaptation techniques, and the incorporation of fairness constraints into the loss function [28]. Moreover, the interpretability of GNN predictions must be sufficient to build trust among clinicians and regulatory bodies. Attention weights or gradient-based explanations can provide some insight, but they may not capture the complex non-linear interactions that condensates mediate.

## 6. Discussion: Governance, Fairness, and Sustainability

The application of GNNs to condensate-mediated GRNs raises broader questions about the governance of AI in biomedical research. As these models become more powerful, there is a risk that they are used to generate hypotheses without adequate validation, leading to false positives that waste resources and mislead follow-up experiments [29]. To mitigate this risk, rigorous benchmarking against ground-truth experimental data is necessary, and model predictions should be made available alongside confidence intervals or uncertainty estimates. Open-source code and data sharing, while essential for reproducibility, must be balanced with intellectual property concerns and patient privacy.

Sustainability is another concern: training large GNNs on whole-genome graphs with millions of nodes and edges consumes substantial energy. The development of more efficient GNN architectures, such as those that use graph sampling or quantized representations, can reduce the carbon footprint of computational research [30]. Additionally, the reuse of pre-trained models (transfer learning) from related biological systems could lower the need for new training runs.

From a policy perspective, regulatory agencies such as the Food and Drug Administration are beginning to consider frameworks for approving AI-based diagnostics. For a GNN that predicts gene expression from condensate properties to be used in clinical decision-making, it must undergo rigorous validation in prospective clinical trials. The interpretability of the model will be key for regulatory approval, as opaque models are less likely to be accepted by clinicians and patients.

Finally, the broader socio-technical system that supports this research includes funding agencies, academic institutions, and industry partners. There is a need for interdisciplinary training programs that equip researchers with both biological domain knowledge and computational skills. The sustainability of such research depends on long-term funding commitments and the establishment of shared infrastructure, such as the National Cancer Institute’s cloud resources.

## 7. Conclusion

Graph neural networks represent a transformative approach for modeling the complex, condensate-mediated gene regulatory networks that underlie YAP-MAML2–associated tumorigenesis. By leveraging the relational inductive biases of GNNs and integrating multi-modal molecular and imaging data, researchers can uncover regulatory principles that are inaccessible to traditional network inference methods. However, the successful deployment of these models requires careful consideration of architectural trade-offs, computational infrastructure, data governance, fairness, and sustainability. As the field moves toward clinical translation, interdisciplinary collaboration and robust policy frameworks will be

essential to ensure that these powerful AI tools are used responsibly and equitably. The convergence of condensed matter physics, molecular biology, and machine learning holds the promise of a deeper understanding of cancer biology and new avenues for therapeutic intervention.

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