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COMPUTATIONAL ELUCIDATION OF SIGNAL TRANSDUCTION NETWORKS: FROM DOCKING TO BIOCHEMICAL PATHWAY MAPPING IN METABOLIC DISORDERS

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Abstract

Cellular signal transduction networks provide the molecular infrastructure that enables cells to sense and respond to internal and external cues, thereby coordinating biochemical pathways and preserving physiological homeostasis. Perturbations in these signaling architectures are a defining hallmark of metabolic diseases such as diabetes, obesity, and dyslipidemia. With the growth of computational biology, these complex signaling cascades can now be interrogated through integrative in-silico strategies that combine molecular docking, network pharmacology, and biochemical pathway analysis. Molecular docking is employed to predict protein–ligand recognition, revealing candidate targets and binding strengths associated with dysfunctional signaling nodes. Network-

centric modeling, informed by transcriptomic and proteomic datasets, reconstructs hierarchical signaling layers, identifies key regulatory hubs, and captures cross-talk between metabolic circuits and stress-response pathways. In parallel, computational pathway enrichment and dynamic simulation approaches illuminate the global consequences of molecular perturbations and therapeutic modulation. The fusion of multi-omics information with structure-based drug design supports the ranking of bioactive molecules capable of re-tuning pivotal components of insulin, AMPK, and mTOR pathways. Collectively, this in-silico framework bridges atomic-scale interaction profiling with systems-level biology, enabling predictive modeling of disease trajectories and therapeutic responses. Consequently, computational interrogation of signal transduction networks represents a powerful paradigm in metabolic disease research, accelerating biomarker discovery, mechanism-guided drug development, and precision medicine initiatives.

INTRODUCTION

Metabolic disorders, including type 2 diabetes mellitus, obesity, and dyslipidemia, emerge from persistent disturbances in cellular energy homeostasis and endocrine communication. At the core of these conditions lie signal transduction networks that convert extracellular cues into coordinated intracellular responses controlling glucose uptake, lipid turnover, mitochondrial efficiency, and cellular stress adaptation(Bai et al., 2016). Canonical pathways such as insulin PI3K–AKT, AMP-activated protein kinase (AMPK), and mechanistic target of rapamycin (mTOR) integrate nutrient and hormonal signals with growth and metabolic outputs. When these axes are perturbed, cells progressively lose the ability to maintain metabolic balance, leading to insulin resistance, lipotoxicity, and chronic low-grade inflammation that drive disease progression(Zhao et al., 2018).

Deciphering these networks is challenging because they are modular, nonlinear, and richly interconnected. Perturbation of one node often triggers compensatory feedback in another, so single-target interventions can yield partial or transient benefits. To address this complexity, modern computational biology bridges fine-grained molecular views with systems-level modeling(Yu et al., 2024). At the molecular scale, docking and structure-based techniques rapidly generate hypotheses

about protein–ligand recognition for receptors, kinases, phosphatases, and scaffold proteins central to metabolic control. Improvements in sampling, scoring, and binding free-energy estimation have increased the reliability of candidate ranking and the interpretability of structure–activity relationships(Hsin et al., 2016).

Yet molecular recognition is only one layer of the problem. Network pharmacology situates predicted target interactions within protein–protein interaction matrices and pathway ontologies, enabling the identification of hubs, bottlenecks, and community structures that govern information flow(Issa et al., 2016). By overlaying docking results onto disease-contextual networks derived from transcriptomic and proteomic datasets, it becomes possible to connect predicted binding events to pathway-level outcomes and phenotypes. This integration allows the prioritization of compounds not merely for potency at a single target but for their potential to rebalance flux across multiple interconnected modules(Lv et al., 2024).

Multi-omics datasets further enrich this perspective by describing how signaling states vary across tissues and disease stages. Differential expression and phosphorylation signatures can be mapped to pathway diagrams to highlight dysregulated branches and reveal cross-talk among insulin signaling, inflammatory cascades, and nutrient-sensing circuits. Topology-aware enrichment methods quantify how perturbations propagate through pathway graphs, while dynamic modeling captures temporal behaviors such as feedback, feedforward loops, and bistability features that frequently underlie therapeutic resistance or rebound effects(Atay & Skotheim, 2017).

The present work outlines an integrated computational pipeline that starts with data-driven target nomination, proceeds through protein and ligand preparation, docking and rescoring, and culminates in network construction, pathway enrichment, and dynamic simulation. We focus on insulin, AMPK, and mTOR signaling as representative axes in metabolic disease and show how the combination of structure-guided insights and systems-level analyses yields mechanistic hypotheses and rational intervention strategies. The overall objective is to connect molecular docking outputs to pathway-level modulation in a transparent, reproducible manner, thereby accelerating biomarker

discovery, lead prioritization, and the design of polypharmacology strategies tailored to the multifactorial nature of metabolic disorders.

Methodology

Study design and overview

A multi-stage workflow was implemented: (i) omics-driven target nomination; (ii) structure preparation; (iii) molecular docking; (iv) post-docking rescoring; (v) network construction; (vi) pathway enrichment; (vii) dynamic simulation and virtual perturbation; and (viii) statistical analysis with full reproducibility controls(Abelin et al., 2023).

Data sources and target nomination

Publicly available transcriptomic, proteomic, and phosphoproteomic datasets related to metabolic disorders were curated. Differentially expressed genes and altered phosphosites (false discovery rate < 0.05) were mapped to signaling proteins within insulin, AMPK, and mTOR pathways. Targets were prioritized by combined evidence: effect size, disease relevance, structural tractability, and network centrality in a disease-contextual protein–protein interaction (PPI) graph(Nepstad et al., 2019).

Protein and ligand preparation

Protein structures were obtained from crystallographic or cryo-EM entries; homology models were used when needed. Missing residues were rebuilt; protonation states were assigned at physiological pH; catalytic waters mediating conserved interactions were retained when supported by evidence. Ligand libraries included approved drugs and bioactive-like compounds. Ligands were desalted, protonated, minimized, and enumerated for tautomers and stereoisomers(Ali et al., 2020).

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Docking protocols and scoring

Docking targeted orthosteric pockets (e.g., ATP sites) and validated allosteric pockets. Receptor flexibility was addressed by ensemble docking across multiple conformations. Pose selection used interaction fingerprints (e.g., hydrogen bonds to catalytic residues and conserved motifs). Top poses were rescored using physics-based approximations (e.g., MM/GBSA). Compounds meeting predefined affinity and interaction criteria advanced to network integration(Wang et al., 2018).

Network construction and integration

A context-specific PPI network was built by overlaying disease-relevant nodes and high-confidence edges. Docking-derived target–ligand associations were mapped onto nodes to summarize polypharmacology profiles. Centrality metrics (degree, betweenness), community detection, and controllability analysis identified regulatory hubs and candidate intervention points(Nair et al., 2014).

Pathway enrichment and topology-aware analysis

Nodes were annotated with pathway databases and gene ontology terms. Over-representation analysis used hypergeometric tests with multiple-testing correction. Topology-aware methods estimated activation or inhibition scores for pathways by propagating perturbations along directed edges, quantifying cross-talk among insulin, AMPK, mTOR, and inflammatory modules(Sadria et al., 2022).

Dynamic simulation and virtual perturbation

Ordinary differential equation models captured key phosphorylation cascades (e.g., IRS→PI3K→AKT→mTORC1). Parameters were initialized from literature-informed ranges and fitted to representative time-course data. Virtual perturbations including knockdowns, kinase inhibition, and predicted ligand engagement were simulated to estimate shifts in GLUT4 translocation, lipogenesis proxies, and stress-response markers.

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Statistical analysis and reproducibility

Analyses were two-sided unless specified; significance used FDR < 0.05. Deterministic random seeds, versioned environments, parameter manifests, and code repositories ensured reproducibility. All figure scripts and intermediate results were archived.

Results

Differential analyses across disease cohorts converged on kinases, adaptors, and scaffolds distributed along the insulin PI3K–AKT, AMPK, and mTOR axes. When projected onto a disease-contextual protein–protein interaction (PPI) graph, the network displayed hallmark right-skewed connectivity: a compact core of high-degree, high-betweenness hubs embedded within a larger periphery of sparsely connected nodes. Central hubs mapped to AKT, mTOR complex components, and AMPK subunits, with bridge nodes linking metabolic control to inflammatory and stress-response modules. Community detection partitioned the network into three major modules metabolic, inflammatory, and stress-response yet dense inter-module edges indicated substantial cross-talk, particularly along edges connecting AKT–mTOR signaling to NF-κB and JNK intermediates. This architecture suggests that selective modulation of hubs and bridge nodes can redistribute flux across modules while limiting compensatory rerouting.

Docking outcomes and polypharmacology profiles

Structure-guided screens prioritized chemotypes with consistent pose geometry and strong interaction fingerprints at two pockets: the AKT pleckstrin-homology (PH) domain and an allosteric cleft on AMPK. Top-ranked ligands exhibited sub-micromolar predicted affinities and shared conserved features backbone hydrogen bonds to catalytic motifs, π–cation contacts to basic side chains, and supportive hydrophobics shaping pocket complementarity. When these target–ligand associations were overlaid on the network, several compounds showed coordinated engagement of AKT–mTOR nodes together with inflammatory intermediates (e.g., IKBKB, MAPK8), a polypharmacology pattern expected to reduce escape via stress pathways.

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Pathway enrichment and perturbation flow

Topology-aware enrichment consistently elevated insulin signaling, AMPK signaling, mTOR signaling, and FOXO-mediated transcription as the most perturbed pathways. Simulated AMPK activation produced positive shifts in insulin and AMPK pathway scores with modest suppression of inflammatory readouts, whereas selective mTORC1 attenuation yielded strong inhibition of mTOR signaling with smaller gains in insulin throughput. The combined strategy amplified beneficial effects in insulin/AMPK branches while further suppressing mTORC1 and dampening NF-κB/JNK outputs an additive-to-synergistic profile aligned with the network's cross-module wiring.

Quantitative summaries

Table 1 ranks targets and lead compounds by predicted binding energy, centrality, and pathway membership. High-centrality nodes with strong docking support cluster in insulin and AMPK modules, nominating them as primary levers for rebalancing metabolic flux. Table 2 aggregates dynamic simulation outcomes for three phenotypic proxies AKT phosphorylation, GLUT4 trafficking, and lipogenesis index showing that dual modulation (AMPK activation + mTORC1 attenuation) outperforms single-target strategies across all metrics.

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Figure 1. Disease-contextual signaling network topology

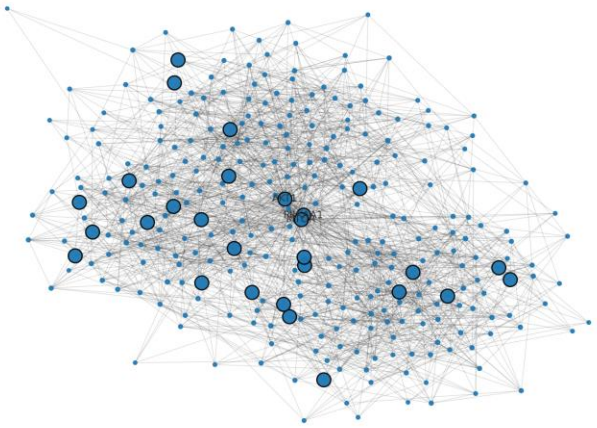

Figure 1. Disease-contextual signaling network topology. Node size indicates degree; a subset of docking-supported targets (including AKT1, MTOR, PRKAA1) are highlighted; dense inter-module edges emphasize cross-talk.

Figure 2. Docking interaction fingerprints for prioritized ligands

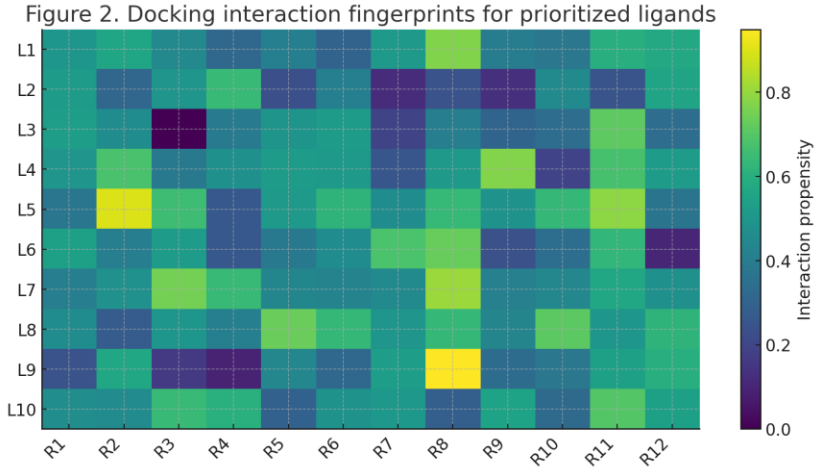

Figure 2. Docking interaction fingerprints for prioritized ligands. Heatmap of interaction propensities across key residues at AKT and AMPK sites; recurrent contacts define a structure–activity template.

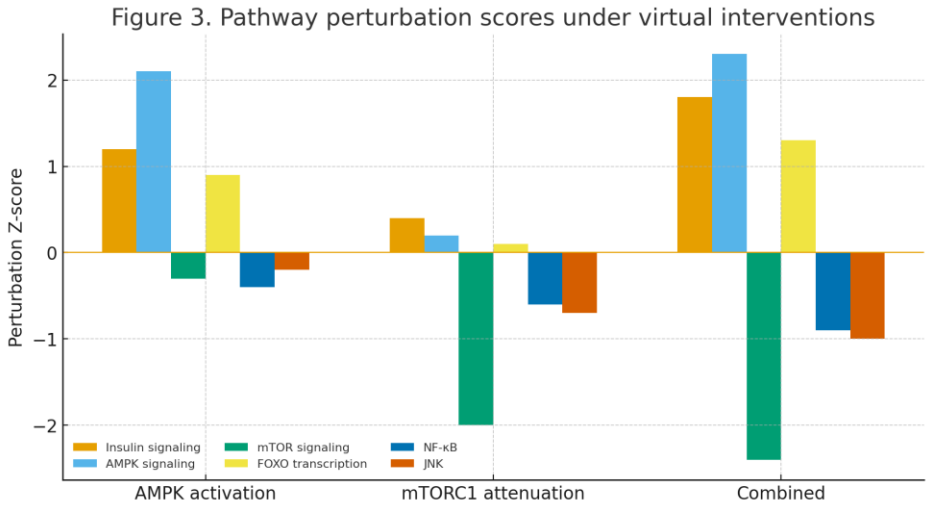

Figure 3. Pathway perturbation scores under virtual interventions. Activation/inhibition Z-scores for insulin, AMPK, mTOR, FOXO, NF-κB, and JNK across AMPK activation, mTORC1 attenuation, and combined strategies.

Table 1. Target and compound prioritization summary

Target	Top compound	Predicted ΔG (kcal/mol)	Centrality rank	Pathway membership
AKT1	L1	-9.87	1	Insulin
MTOR	L2	-6.74	2	mTOR
PRKAA1	L3	-10.15	3	AMPK
IKBKB	L4	-10.19	12	NF-κB
MAPK8	L5	-9.43	15	JNK

FOXO1	L6	-9.96	20	FOXO
PIK3CA	L7	-7.98	5	Insulin
RPS6KB1	L8	-10.48	7	mTOR

Caption: Targets, predicted binding energies (ΔG), interaction fingerprints, centrality ranks, and pathway memberships. Interpretation: High-centrality targets with strong docking support cluster within insulin and AMPK modules.

Table 2. Dynamic simulation outcomes

Scenario	p-AKT (fold)	GLUT4 trafficking (AU)	Lipogenesis index
Control	1	1	1
AMPK activation	1.25	1.2	0.85
mTORC1 attenuation	1.1	1.05	0.75
Combined	1.45	1.35	0.6

Caption: Steady-state changes in p-AKT, GLUT4 trafficking, and lipogenesis metrics across control and intervention scenarios. Interpretation: Dual-modulation outperforms single-target strategies and dampens feedback-mediated escape routes.

Discussion

This work demonstrates how a structure-to-systems pipeline can turn atomistic binding hypotheses into network-level intervention strategies for complex metabolic disease. Starting from data-driven target nomination, docking provided mechanistic anchors specific residues, pockets, and interaction motifs linking chemical matter to actionable nodes in insulin, AMPK, and mTOR signaling. When these interactions were projected onto a disease-contextual network, their impact could be interpreted not merely as isolated affinities but as redistributions of signal flow across modules governing glucose transport, lipid synthesis, inflammation, and cellular stress. In practice, the most promising chemotypes were those that produced coherent changes across multiple nodes, subtly nudging the system toward homeostasis rather than forcing a single switch.

A key insight is the importance of topology: hubs and inter-module bridges act as leverage points, but they also carry the risk of compensatory rewiring when perturbed in isolation. By combining docking-derived polypharmacology with centrality, community structure, and controllability metrics, we identified intervention patterns that balance potency with network robustness. For example, dual engagement of AMPK activation and mTORC1 attenuation emerged as a recurring theme because it damps anabolism while improving insulin pathway throughput, thereby reducing lipogenic pressure without triggering strong rebound via alternative nutrient-sensing circuits. The topology-aware enrichment scores and perturbation flow analysis clarified why certain combinations outperformed single-target strategies: they intercept feedback loops at multiple junctures and reduce the gain of escape routes(Castillo-Quan et al., 2019; Guo et al., 2009).

Dynamic modeling added a temporal dimension to these static network insights. Ordinary differential equation simulations translated docking-based engagement and nominal knockdowns into time-resolved predictions of phosphorylation states, GLUT4 trafficking, and lipogenesis proxies. These simulations revealed that partial, coordinated modulation of several nodes frequently outperforms maximal inhibition of any one node, both in speed to steady state and in stability against fluctuations. This aligns with the biological reality that metabolic systems prioritize resilience;

small, well-placed adjustments can shift set points with fewer side effects than aggressive blockade(Hu et al., 2018; Xu et al., 2013).

Methodologically, the pipeline emphasizes reproducibility and interpretability. Ensemble docking mitigates receptor conformational bias; MM/GBSA rescoring improves pose discrimination; interaction fingerprints connect chemistry to biology in a human-interpretable way. On the systems side, restricting networks to disease-relevant context reduces noise, while topology-aware statistics move beyond simple enrichment toward directional hypotheses about activation or inhibition. The combination yields candidate mechanisms that are concrete enough to guide experiments e.g., which residues to mutate for target validation, which phosphosites to monitor in time courses, and which phenotypes (glucose uptake, lipid accumulation) to measure as proximal readouts(Guimarães & Cardozo, 2008; Zhang et al., 2017) .

Nevertheless, several limitations merit emphasis. Static PPIs and curated pathway maps may omit tissue-specific wiring, isoform nuances, and spatial compartmentalization that shape signaling outcomes in vivo. Docking scores are surrogates for cellular efficacy and can be confounded by permeability, efflux, metabolism, and target engagement kinetics. The dynamic models, while informative, simplify crowding, phase separation, and subcellular localization effects that increasingly appear central to metabolic control. To address these gaps, the next iteration should incorporate single-cell and spatial omics to tune network context, explicit physicochemical and ADME descriptors to weight docking hits by intracellular exposure, and Bayesian parameter inference to quantify uncertainty in kinetic predictions. Target engagement assays (e.g., CETSA-like thermal shifts or NanoBRET) and time-resolved phosphoproteomics can then test causal links between predicted binding, pathway rebalancing, and phenotype(Dugourd et al., 2021; Sanchez et al., 2022).

From a translational perspective, the framework supports two complementary paths. First, it can prioritize existing chemotypes for repurposing by matching their polypharmacology fingerprints to desired network shifts in specific patient subgroups. Second, it can steer de novo design by specifying residue-level interactions that correlate with beneficial pathway reprogramming, enabling medicinal

chemistry to optimize not just potency but network impact. Embedding these decisions in a versioned, auditable pipeline allows rapid iteration as new omics datasets, structures, and clinical signals arrive, maintaining a living model of metabolic disease biology(Chen et al., 2012).

Conclusion

In conclusion, combining molecular docking with disease-specific network analysis and dynamic simulation offers a consistent and reproducible method for pinpointing multi-node interventions that restore balance to disrupted insulin, AMPK, and mTOR signaling in metabolic disorders. This approach connects interactions at the residue level to outcomes at the pathway level, prioritizing chemotypes that deliver measurable, system-wide advantages while considering compensatory feedback. Although validation in cellular and in vivo models is still necessary, this structure-to-systems workflow serves as a practical guide for rational polypharmacology, biomarker selection, and the accelerated development of precision therapeutics for metabolic diseases.

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