Leveraging AI model and Directional Phosphorylation Network for Drug Response Prediction in BRAF-Mutant Colorectal Cancer

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ABSTRACT

Purpose: Kinase-substrate interactions are inherently directional, meaning that kinases phosphorylate substrates, not vice versa, yet most network-based prediction methods ignore this asymmetry.[1] We investigated whether respecting biological directionality improves classification of drug response in BRAF-mutant metastatic colorectal cancer (mCRC). Using PhosphoAtlas, a curated kinase-substrate database that expanded 4-fold from 2016 (PA1: 1,996 edges) to 2023 (PA2: 8,306 edges), we evaluated: (1) whether directed networks outperform undirected networks, and (2) whether network expansion further improves topology-based feature selection. [2]

Methods: We analyzed kinase activity profiles from 44 patient-derived mCRC tumor samples (24 untreated, 20 treated with Encorafenib + Panitumumab). Raw PhosphoAtlas data contains multiple phosphorylation sites per kinase-substrate pair; these site-level interactions (PA1: 3,682; PA2: 15,887) were collapsed to unique gene-level edges (PA1: 1,996; PA2: 8,306). We constructed directed (kinase→substrate) and bidirected (symmetric) networks from PA1 and PA2, applying heat kernel diffusion (β=1.0) for signal propagation through network topology. We compared three feature selection strategies: all 192 measured kinases, top 142 network hubs plus 1-hop neighbors, and top 105 hubs plus 1-hop neighbors. Classification used Random Forest (100 trees) with leave-one-out cross-validation, evaluating accuracy and AUC.

Results: Directed networks outperformed undirected versions, achieving 95.5% accuracy (AUC=0.990) compared to 93.2% (AUC=0.982) when using all 192 kinases. This 2.3% improvement demonstrates that biological directionality en codes predictive information lost in symmetric network representations. The expanded PA2 network further improved performance in topology-based feature selection, with PA2 directed achieving 93.2% accuracy (AUC=0.985) versus PA1 directed at 88.6% (AUC=0.939).

Conclusion: Our directionality-aware network model achieves 95.5% accuracy in drug response classification, demonstrating the benefits of respecting kinase-substrate asymmetry for predictive modeling. The results validate the effectiveness of graph signal propagation and network expansion in enhancing topology-based predictions, paving the way for broader adoption in kinase-based oncology applications.

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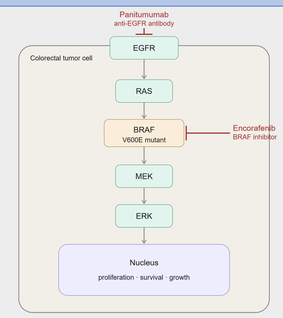
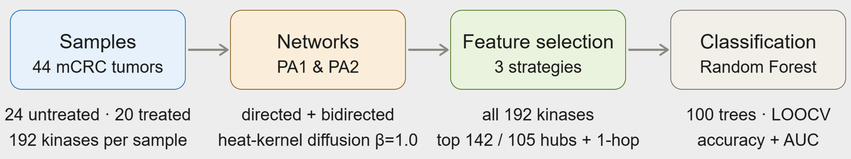
INTRODUCTION

BRAF-mutant mCRC accounts for 8–12% of metastatic colorectal cancers and carries a poor prognosis with standard chemotherapy.[3] The combination of encorafenib (a BRAF V600E inhibitor) and panitumumab (an anti-EGFR monoclonal antibody) targets this subtype, but predicting response remains difficult.[4,5]
Kinases drive cancer signaling by phosphorylating substrates in directional cascades (BRAF→MEK→ERK)[6]. Kinase–substrate networks encode these relationships, yet most models collapse them into symmetric graphs, discarding the biological asymmetry that defines signal flow.[1]
PhosphoAtlas expanded 4-fold between 2016 (PA1) and 2023 (PA2), letting us ask whether richer, directional network knowledge improves drug-response prediction. We evaluated two questions: (1) Does preserving directionality (kinase→substrate) improve classification? (2) Does network expansion (PA1→PA2) enhance topology-based feature selection? Because BRAF/MAPK signaling also modulates radiation sensitivity, a phosphoproteomic predictor of drug response is a step toward predicting radiotherapy response.[7,8]



METHODS AND MATERIALS



Samples: Kinase activity profiles from 44 patient-derived mCRC tumors (24 untreated, 20 Encorafenib + Panitumumab–treated); 192 kinases measured per sample.
Networks: PhosphoAtlas site-level interactions (PA1: 3,682; PA2: 15,887) collapsed to unique gene-level edges (PA1: 1,996; PA2: 8,306). Built directed (kinase→substrate) and bidirected (symmetric) networks; transition matrices enabled heat-kernel diffusion (β = 1.0) to propagate signal through topology.

Feature selection: Three strategies- all 192 kinases; top 142 hubs + 1-hop neighbors; top 105 hubs + 1-hop neighbors. Hubs ranked by out-degree centrality.
Classification: Random Forest (100 trees), leave-one-out cross-validation; accuracy and AUC reported.

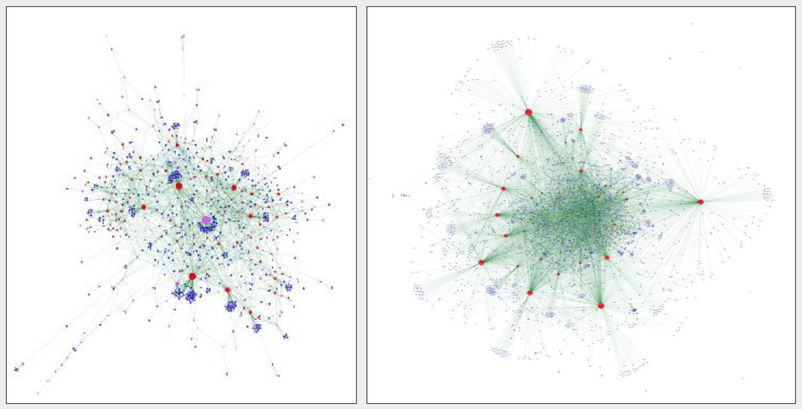


Figure 1. PhosphoAtlas network expansion from 2016 to 2023. (A) PA1 network containing 1,030 nodes and 1,996 gene-level edges. (B) PA2 network containing 3,121 nodes and 8,306 gene-level edges, representing a 4-fold expansion. Node colors indicate kinases (blue), substrates (green), and proteins acting as both kinase and substrate (orange). Node size reflects degree centrality.

DISCUSSION

- Our best model hit 95.5% accuracy (AUC 0.990), and the gains came from *how* we represented the kinase–substrate network, not just how much of it we knew. Directed networks beat undirected ones by a steady +2.3% across all configurations shown, which fits the idea that phosphorylation cascades carry directional information that symmetric graphs throw away. Heat-kernel diffusion spread each kinase's activity to its downstream substrates, turning raw measurements into network-aware features.
- The PA2 database helped when we used the network to pick features. Using all 192 kinases, PA1 and PA2 tied. But once we trimmed to the top hubs, the sparse PA1 network dropped to 88.6% while the denser PA2 held near 93%, so the extra curated edges mattered exactly when the model leaned on network structure.
- With only 44 tumors, we read these as consistent trends that need testing in larger cohorts. Still, directionality helped across both databases, and expansion paid off when it was used most, two signs that respecting biological structure improves prediction. And because BRAF/MAPK signaling also shapes radiosensitivity, these features may eventually extend toward predicting radiotherapy response.

RESULTS

Table 1. Effect of network directionality on drug response classification. Directed networks (kinase → substrate) were compared to undirected (bidirectional) networks using heat kernel diffusion (β=1.0) for signal propagation. Accuracy and AUC (in parentheses) are shown. All experiments used leave-one-out cross-validation with Random Forest classification (n=44 samples). Right: slope graph of the same comparison.

Strategy	Network	Directed	Undirected	Δ Accuracy
All 192	PA1	95.5% (0.990)	93.2% (0.971)	+2.3%
All 192	PA2	95.5% (0.990)	93.2% (0.982)	+2.3%
Top 142+hop	PA2	93.2% (0.973)	90.9% (0.966)	+2.3%

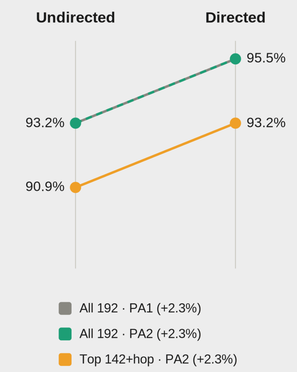


Table 2. Effect of PhosphoAtlas network expansion on drug response classification. PA1 (2016: 1,996 edges) was compared to PA2 (2023: 8,306 edges) using directed networks with topology-based feature selection. Hub kinases were identified by out-degree centrality, and 1-hop neighbors were included as features. Accuracy and AUC (in parentheses) are shown. Right: slope graph of the same comparison

Strategy	Direction	PA1 (2016)	PA2 (2023)	Δ Accuracy
All 192	Directed	95.5% (0.990)	95.5% (0.990)	Tie
Top 142+hop	Directed	90.9% (0.966)	93.2% (0.973)	+2.3%
Top 105+hop	Directed	88.6% (0.939)	93.2% (0.985)	+4.6%
Top 105+hop	Undirected	90.9% (0.966)	93.2% (0.973)	+2.3%

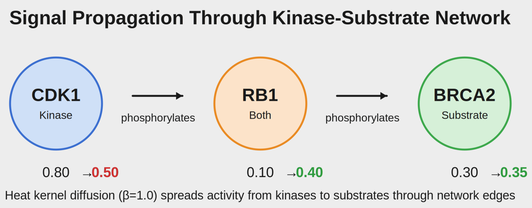


Figure 2. Signal propagation through kinase-substrate network using heat kernel diffusion (β=1.0). Activity values spread from upstream kinases to downstream substrates, transforming raw measurements into network-aware features. Original values shown in gray; propagated values in color.

CONCLUSIONS

Our directionality-aware model classified Encorafenib + Panitumumab response in BRAF-mutant mCRC with 95.5% accuracy (AUC 0.990). Keeping kinase→substrate direction added a steady +2.3% over symmetric networks, and the bigger PA2 database improved hub-based prediction by up to +4.6%. Better kinase–substrate curation means better predictions, and a possible path toward predicting radiotherapy response in mCRC.

AKNOWLEDGEMENTS

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