A Computational Model for Integrating Genomic Data with Public Datasets For Molecular Tumor Board Recommendations

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Abstract

Recent genomic profiling studies in pancreatic adenocarcinoma (PDA) have revealed actionable mutations affecting multiple signaling pathways, but in spite of these mutations, targeted inhibitors of these pathways have low success rates. A possible reason for these failures is that single-gene biomarkers (e.g. a *KRAS* mutation as an indicator of MEK inhibitor sensitivity) fail to account for crosstalk within and between dysregulated pathways. We have previously curated a knowledgebase of published studies as evidence to support molecular tumor board recommendations to cancer patients after multi-omic profiling. Here we present a computational framework for integrating this knowledgebase with drug response data from cancer cell lines to propose "actionable" biomarkers based on a panel of pathways instead of targeting a single gene mutation.

We constructed drug-specific computational models based on an interaction network encompassing a broad range of cancer-related pathways, including RAS/RAF/MEK/ERK, PI3K/AKT, cell cycle regulation, and DNA repair. The interaction network used for a particular drug was informed by the curated information from the knowledgebase: all proteins with published evidence of drug effects were selected as seeds, followed by an expansion to include neighboring proteins. This drug-specific network was then converted to a computational model representing protein activities in the presence and absence of the drug. Simulations of mutations and drugs were conducted by modifying the activity of the target proteins and then propagating the signal through the network. We integrated two sources of publicly available data: 1) published studies correlating phosphoprotein measurements and resistance pathways to targeted inhibitors in clinical development; and 2) mutation data correlated with drug-specific response metrics (e.g. IC50 values), such as CCLE and NCI-60.

We systematically screened frequently observed overlapping disrupted signaling pathways (i.e., combinations of mutations) using sequencing data from TCGA. We present two applications of this computational approach: a comparison of CDK4/6 inhibition in *CDKN2A*-mutated PDA vs. hormone receptor-positive breast cancer and a comparison of PARP inhibition in *BRCA1/2*-mutated PDA and ovarian cancer. The predictions generated by our simulations were consistent with clinical trends in that fewer combinations of mutations in PDA were sensitive to CDK4/6 inhibitors than in breast cancer, suggesting ways to refine biomarkers for sensitivity to these drugs in PDA.

The computational approach presented here integrates published evidence from a knowledgebase to provide a means of prioritizing treatments that match a patient's molecular profile while also providing the rationale for the recommendation. This represents a step toward incorporation of systems biology in precision oncology.

Background

- Precision cancer approaches allow for administration of therapies targeted specifically to the molecular characteristics of a tumor; Perthera provides multi-omic profiling of tumors, along with a virtual tumor board that lists treatment options that match the tumor profile.
- Mutations are often poor predictors of response to targeted inhibitors despite strong biological rationale; systems-level effects, such as crosstalk between signaling pathways, may render single gene biomarkers ineffective in many cases.
- Here we propose a computational framework that incorporates published experimental data from the literature to prioritize mutations as modifiers of treatment response.

Methodology

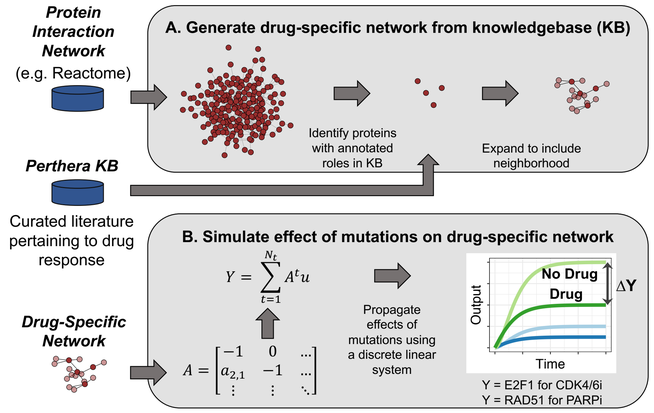

Figure 1: Overview of workflow. (A) Genes with mutations that alter drug sensitivity (based on the KB) are identified within a larger network, and interactions are retained only if they fall within a certain distance. **(B)** The drug-specific network is converted into a model that can be used to simulate drug-induced changes in the network under multiple genetic conditions (matrix **A** contains interactions; **u** represents mutation state of each gene).

Network Analysis of CDK4/6 Inhibitor Sensitivity

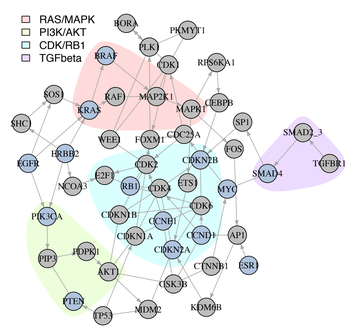

Figure 2: Protein interaction network from CDK4/6 inhibitor knowledgebase. The network comprises proteins with potential roles in regulating CDK4/6 inhibitor sensitivity, as well as all proteins that link these proteins to the simulation output, E2F1 (which is inhibited by pRB). Conversion of this network to a model, as shown in Figure 1B, allowed for simulations in both the presence and absence of a CDK4/6 inhibitor, using molecular profiles from the TCGA dataset.

Table 1: Examples of published literature pertaining to CDK4/6 inhibition in knowledgebase.

PMID	Association
25557169	CCNE1 amplification leads to resistance to CDK4/6 inhibitors
26833126	HER2 can directly activate E2F1, independent of pRB
26369631	MEK inhibition can synergize with CDK4/6 inhibition

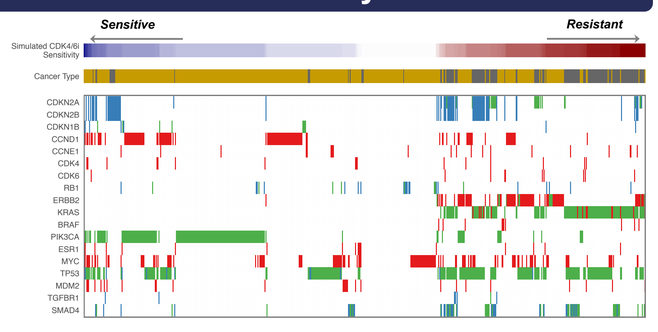

Figure 4: CDK4/6 inhibitor sensitivity in the pancreatic cancer and ER/PR+ breast cancer TCGA datasets. Each column corresponds to a patient, with patients sorted by network-based CDK4/6 inhibitor sensitivity scores (ΔY in Figure 1B), given in the top row. Pancreatic cancers are gray, breast cancers are orange.

- Tumors with *CDKN2A/B* loss had high predicted sensitivity to CDK4/6 inhibitors only in the absence of *KRAS* mutations and *ERBB2* amplifications.
- *PIK3CA* mutations were correlated with higher sensitivity to CDK4/6i, potentially through Akt-mediated inhibition of p21/p27 (*CDKN1A/B*).

Network Analysis of PARP Inhibitor Sensitivity

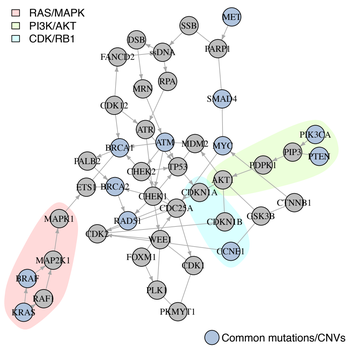

Figure 3: Protein interaction network from PARP inhibitor knowledgebase. The network comprises proteins with potential roles in regulating PARP inhibitor sensitivity, as well as all proteins that link these proteins to the simulation output, RAD51 (reduced RAD51 foci formation is correlated with PARP inhibitor sensitivity). Conversion of this network to a model, as shown in Figure 1B, allowed for simulations in both the presence and absence of a PARP inhibitor, using molecular profiles from the TCGA dataset.

Table 2: Examples of published literature pertaining to PARP inhibition in knowledgebase.

PMID	Association
26779812	MET phosphorylates PARP1, rendering it insensitive to inhibition
22915752	PI3K inhibition sensitizes cells to PARP inhibition
25117293	WEE1 inhibition sensitizes cells to PARP inhibition

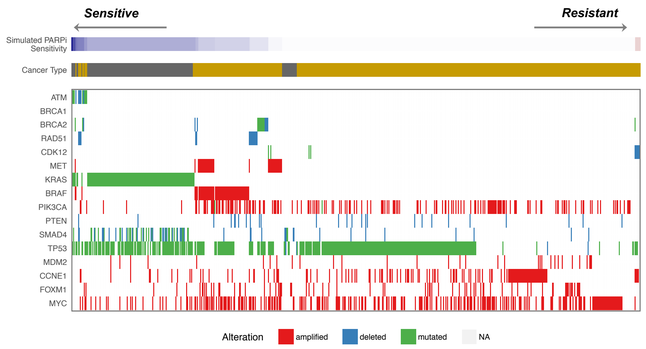

Figure 5: PARP inhibitor sensitivity in the pancreatic cancer and ovarian cancer TCGA datasets. Each column corresponds to a patient, with patients sorted by network-based PARP inhibitor sensitivity scores (ΔY in Figure 1B), given in the top row. Pancreatic cancers are gray, ovarian cancers are orange.

- *ATM*, *BRCA2*, and *RAD51* mutations led to higher sensitivity; samples with mutations in two of these genes had the highest predicted sensitivity of all.
- *KRAS* mutations and *BRAF* amplifications led to higher predicted sensitivity due to ETS1-mediated *BRCA1/2* suppression.
- Future applications of this method will need to account for concurrent chemotherapies and targeted therapies.

Conclusions and Future Directions

- The method presented here can be useful in summarizing the available evidence linking mutations with drug response, and in prioritizing multiple, sometimes conflicting, biomarkers:
  - Hypothesis generation for *in vitro* validation
  - Interpretation of the impact of molecular profiles on observed differences in drug response across patient populations
- Computational challenges related to scale-up of this approach:
  - Parameter estimation against cell line and other experimental data[2,3]
  - Simulation of networks with cycles (feedback loops)[4]
- As outcomes data are collected for Perthera patients, molecular profiles of patients will be simulated to suggest potential mechanism for observed response/lack of response to targeted therapies

Citations

(1) Hofree et al. 2013 *Nature Methods* 10: 1108-1115
(2) Garnett et al. 2012 *Nature* 483: 570-575
(3) Barretina et al. 2012 *Nature* 483: 603-607
(4) Molinelli et al. 2013 *PLoS Comp Biol* 9(12): e1003290