BITS :: Call for Abstracts 2024 - Oral communication

Type	Oral communication
Session	Systems Biology
Title	SignalingProfiler bridges multi-omics data with phenotypic hallmarks and empowers drug repurposing
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Affiliation

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Motivation

Unraveling how signaling remodels in response to perturbations is crucial for understanding disease mechanisms and finding new drug targets. Computational methods like footprint-based techniques and mechanistic modeling have been essential to this purpose. Despite being powerful in reducing data complexity and noise, these methods are currently disjointed. Integrating protein activity estimation with network reconstruction and phenotypic interpretation continues to pose a challenge.
To this scope, we recently developed SignalingProfiler, a unified pipeline capable of drawing coherent insights from multi-omics data on signaling events affecting hallmark phenotypes.

Methods

SignalingProfiler (SP) is an R-developed pipeline that combines novel (e.g., PhosphoScore, and PhenoScore functions) and already published algorithms (e.g., VIPER) with publicly available information derived from resources such as SIGNOR, PhosphoSitePlus, and the Serine/Threonine Kinome atlas (Johnson et al., 2023).
The SP pipeline is articulated in three key steps:
1) Protein activity inference: a user can potentially infer nearly the entire kinome, 62 phosphatases, 1174 transcription factors, and 1559 other signaling proteins;

2) Connect signaling proteins in a causal network: the signal propagation is reconstructed in a two-step process: (i) generation of a naïve network that connects a user-defined set of receptors to the previously inferred proteins through causal interactions annotated in public resources; (ii) optimization of causal edges over the experimentally derived activities of proteins through the CARNIVAL algorithm;

3) Hallmark phenotypes inference for functional interpretation: up to 200 distinct phenotypes (e.g., Proliferation, Apoptosis, etc.) can be incorporated into the model.

As a proof of principle, we applied SP to multi-omics data of metformin-treated breast cancer cell lines obtained from Sacco et al, 2016. To benchmark the performance of the tool, we manually curated a gold standard of 74 proteins and 10 phenotypes, and their expected activity upon metformin treatment. Next, we tested SP under every technical hyperparameters' combination (3524 runs). Each combination was evaluated by combining accuracy metrics to the gold standard with the topological properties of the generated networks and their coverage in experimentally observed phosphorylation events.

Results

To showcase the potential of SP, we took advantage of a multi-omics dataset of breast cancer cells treated with metformin since its molecular targets and phenotypic impact are well characterized. As expected, the best combination of hyperparameters generated a network that accurately recapitulates the expected mTOR pathway inactivation and AMPK pathway activation upon metformin treatment, and the consequent activation of death-associated pathways and autophagy. These optimal hyperparameters were validated on two independent datasets (Olsen et al., 2006, Massacci et al., 2023).
Also, we successfully employed SP to prioritize FDA-approved drug compounds to treat Chronic Myeloid Leukemia cells resistant to Imatinib treatment.

In summary, SP is a flexible and customizable R workflow to unbiasedly integrate literature-derived causal networks with multi-omics data to deliver context-specific graphs connecting molecular entities and ending up on functional traits (phenotypes).

Info

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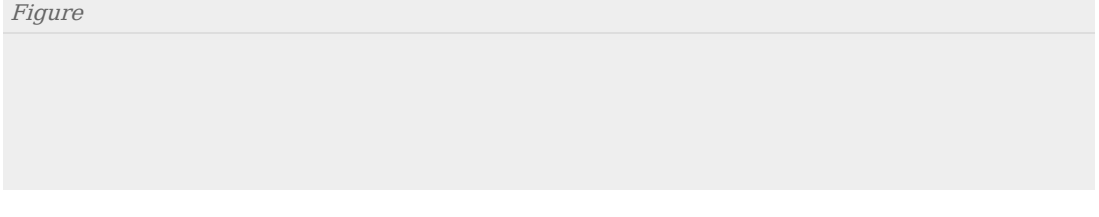
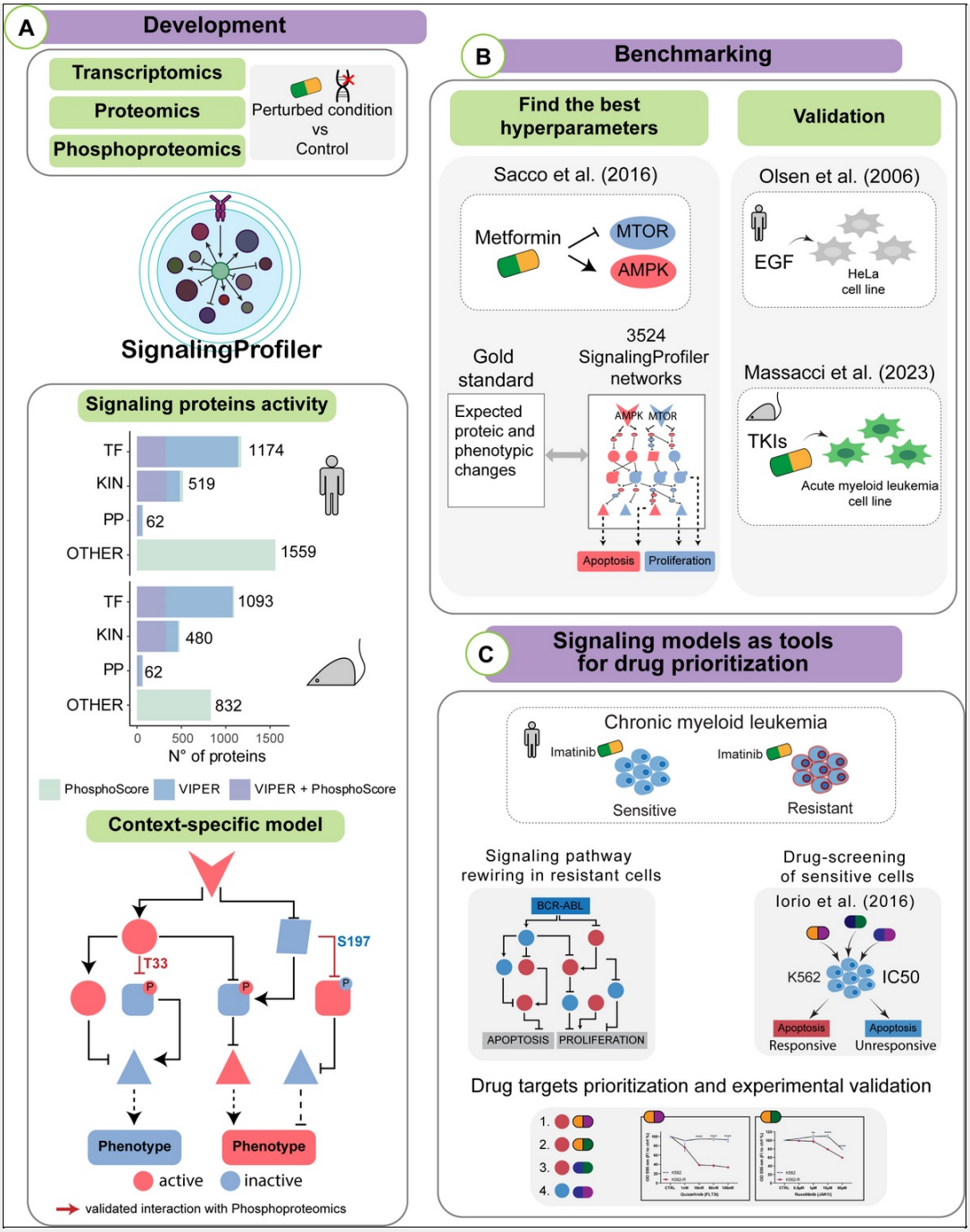
Figure





Availability	https://www.biorxiv.org/content/10.1101/2024.01.25.577229v1.full

Dissemination Material

Social

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Summary

SignalingProfiler 2.0 a pipeline for decoding complex cellular signaling in disease and finding new drug targets

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Submitted on	29.04.2024