PHONEMeS 2.0: Systematic integration of phosphoproteomic data with comprehensive molecular interaction prior knowledge to model signalling networks

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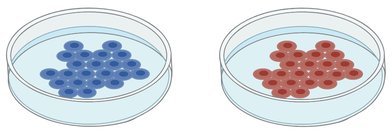
Inferring signalling cascades from phosphoproteomic data

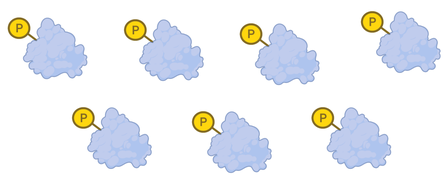
How to model changes in intracellular signalling networks

Phosphoproteomic data

Control Perturbation



Phosphoproteomic measurements

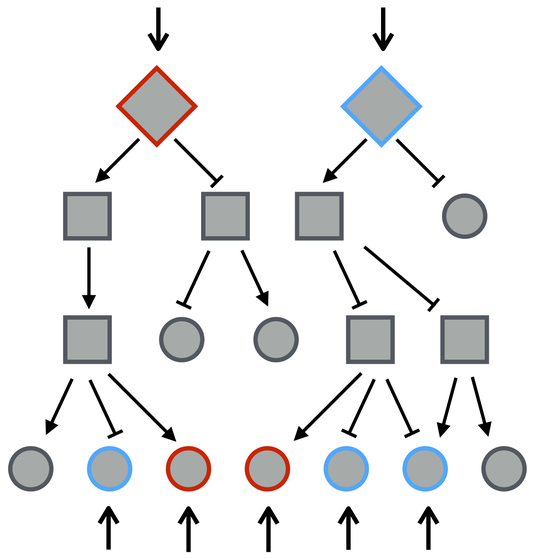


Abundance changes in phosphorylation sites

Selecting phosphorylation sites to map on prior knowledge

Prior knowledge network

Target kinases of perturbation
a priori known or putative

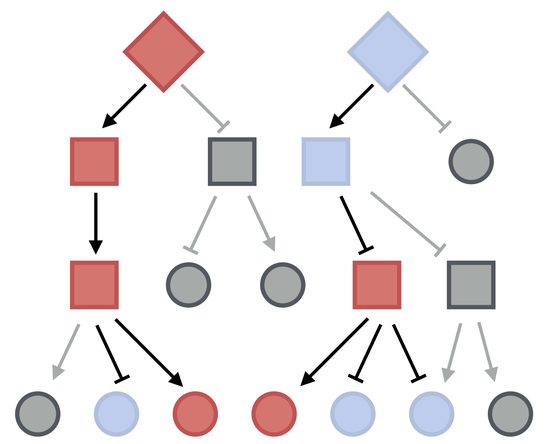


Deregulated phosphorylation sites

Consisting of kinase-substrate and protein-protein interactions

Network contextualisation

Combining phosphoproteomics data and prior knowledge

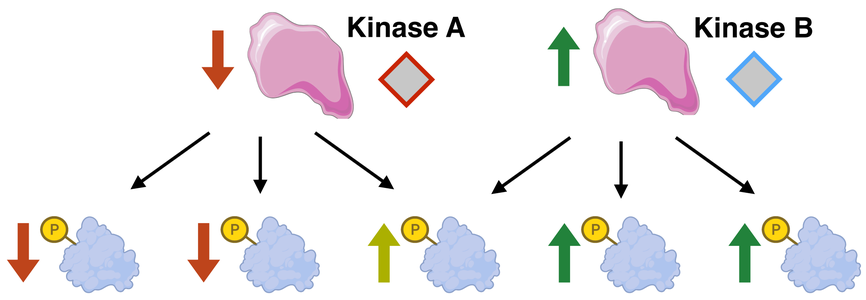


Identifying **smallest coherent path** connecting perturbed kinases to deregulated phosphorylation sites

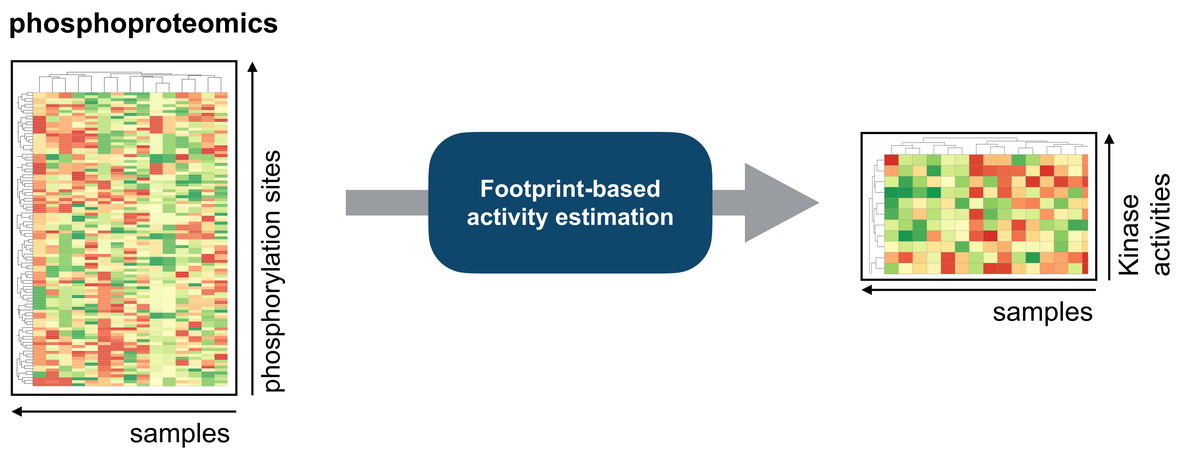
Identifying putative perturbed kinases

Footprint-based activity estimation

A **footprint of a kinase is the collection of downstream phosphorylation sites** regulated by it. These reflect the regulatory state of a kinase and **can be used to robustly infer its activity**. Prior knowledge is required to link phosphorylation sites to the respective kinase.

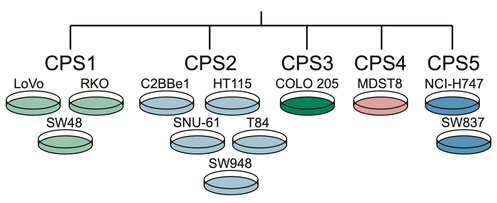


For the estimation of kinase activities, existing computational approaches summarise changes in abundance of phosphorylation sites into an activity score for each kinase. This allows the **identification of deregulated kinases upon perturbation**.



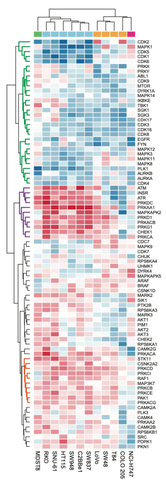
Case study: Elucidation of Metformin-Signalling in Heterogenous Colorectal Cancer Cells

Experimental setup

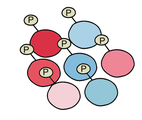


12 colon cancer cell lines were treated with Metformin and phosphoproteomic data was generated

Kinase activity estimation



Input selection

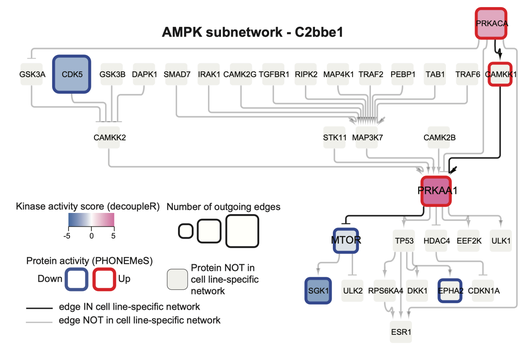


Deregulated phosphorylation sites

Metformin-perturbed kinases

Prior knowledge network

AMPK-focused network contextualisation



Differences between cell lines in response to metformin induced AMPK activation and downstream signal propagation

How to run PHONEMeS 2.0 with your data

All our tools are freely available on GitHub https://github.com/saezlab or bioconductor. We also provide a tutorial on how to run PHONEMeS: https://github.com/saezlab/PHONEMeS/blob/master/vignettes/tutorial.md. Feel free to contact us for support: sophia.mueller-dott@uni-heidelberg.de

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References

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