CONTROL - Synthetic controllability of biological networks through understanding and engineering their control elements

Tero Aittokallio, EMBL Group Leader, Institute for Molecular Medicine Finland (FIMM), University of Helsinki (consortium PI)

Consortium partners

ÅBO AKADEMI

TUCS

Ion Petre, Department of Information Technologies, Åbo Akademi University
Turku Centre for Computer Science
Computational Biomodelling

FIMM
UNIVERSITY OF HELSINKI

Tero Aittokallio, Institute for Molecular Medicine Finland (FIMM),
University of Helsinki
Computational Systems Medicine

Turun yliopisto
University of Turku

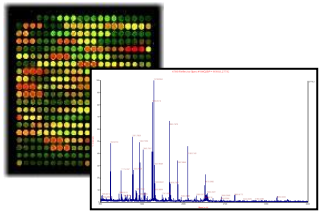
Imperial College
London

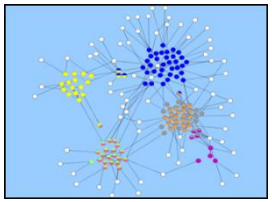
Patrik Jones, Turku Centre for Biotechnology, University of Turku;
Department of Life Sciences, ICL
Integrative Systems Biology - Biofuel

FIMM
UNIVERSITY OF HELSINKI

Krister Wennerberg, Institute for Molecular Medicine Finland (FIMM),
University of Helsinki
Chemical Systems Biology - Cancer

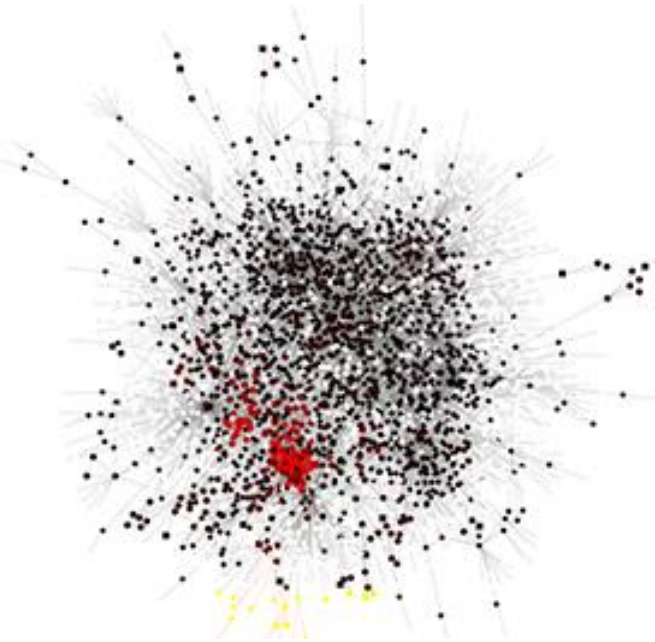
From systems biology to synthetic biology

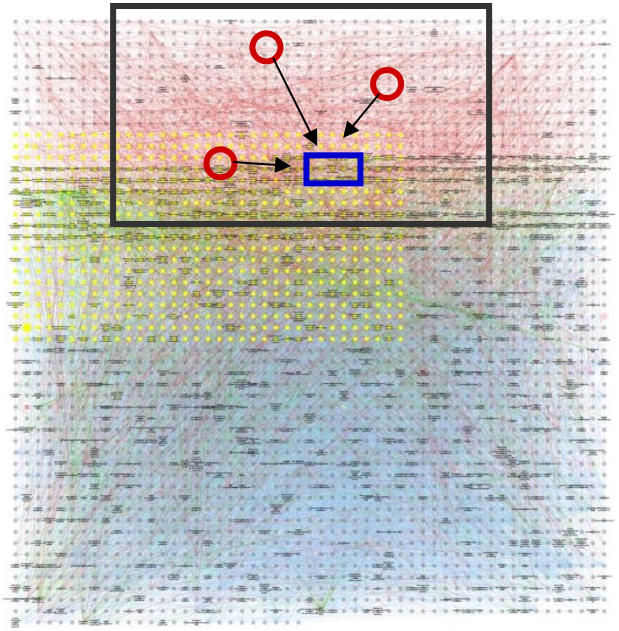




$$\frac{d[RNA]}{dt} = \frac{\alpha k^h}{k^h + [Protein(t-\tau)]}$$

$$\frac{d[Protein]}{dt} = \beta[RNA(t)]$$

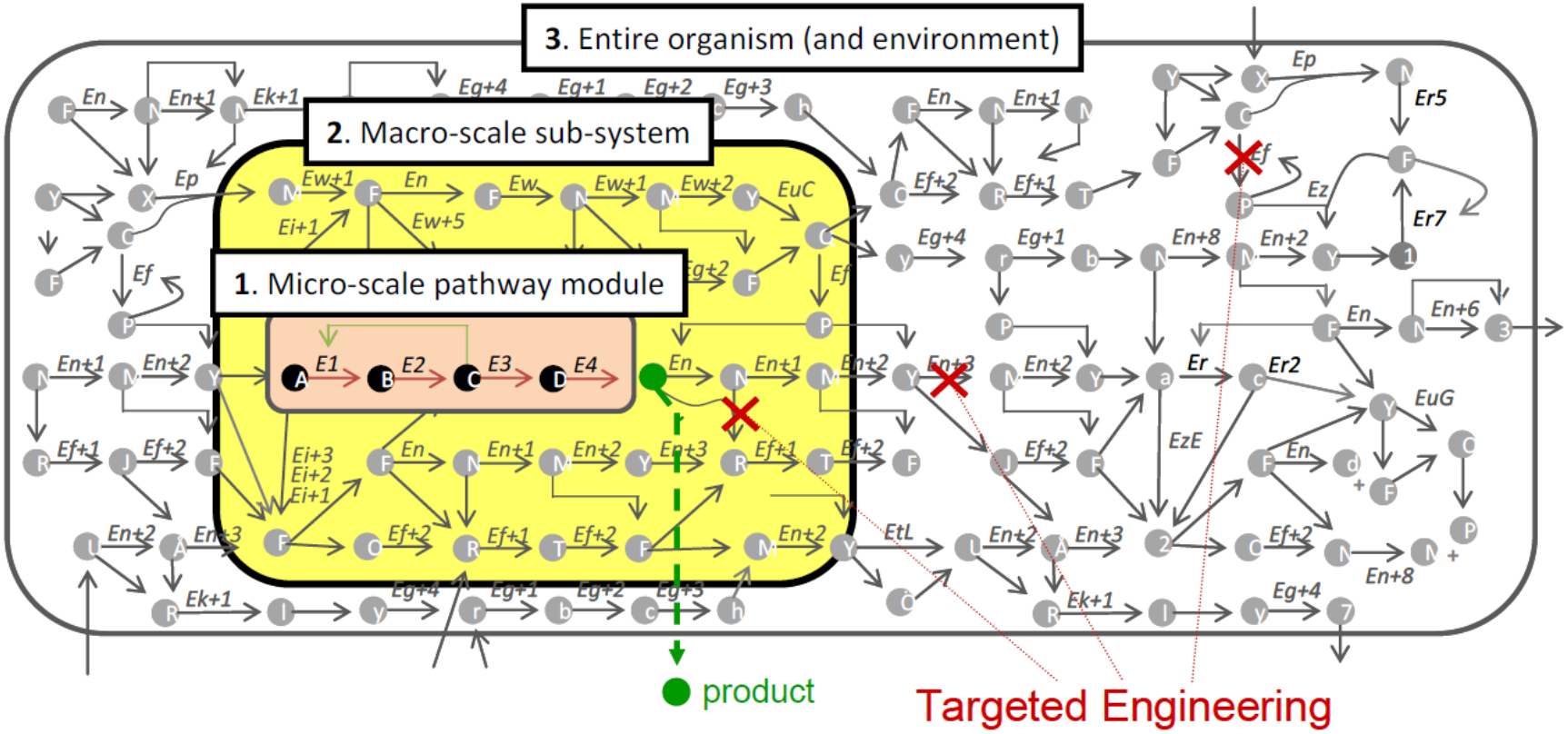




Identify system modules (sub-networks), which can be subsequently modelled (understood) using mathematical models

Identify control properties (driver nodes), which can be used to engineer the system to yield significant and predictable impact

Biological engineering at different levels



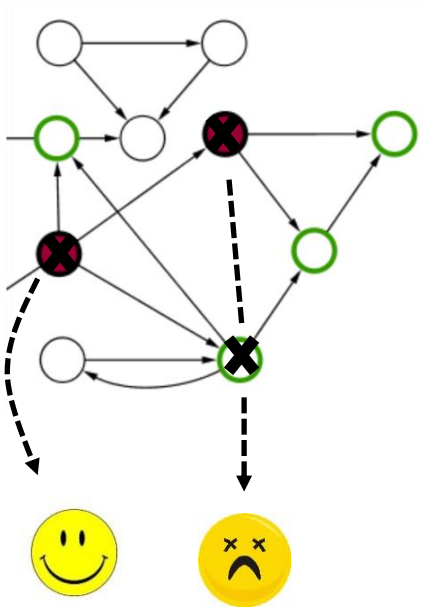
Synthetic pathway is introduced as a **micro-scale** (pink) module. The functionality of the pathway is influenced by the **macro-scale** (yellow) sub-system, we define as ‘sphere’ of the **partial controllability**. Driver elements (X) responsible for this macro-scale partial controllability will be identified and engineered to maximize product.

Our approach

- For complex networks with multiple regulatory mechanisms, understanding the regulation and robustness of networks is the key to control their behavior.
- Our approach will be based on quantitative network modeling and **identification of the control (or driver) nodes**, targeted engineering of which can influence the dynamic network behavior in a highly predictable and significant manner.
- We will address a so-far unexplored approach, namely ***partial controllability of biological networks***, in which controlling only a specific sub-network might be experimentally possible, yet sufficient for many practical applications.
- The aim is to create synthetic biological design tools that can guide the targeted network re-programming to maximize the outcome product (e.g. **optimize metabolic pathway flux** or **inhibit cancer signaling pathways**).

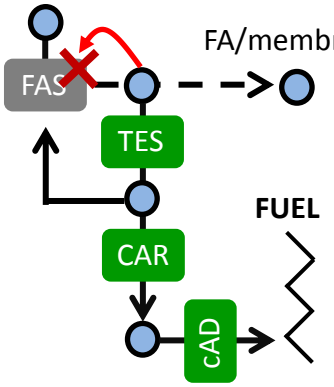
Network control modeling
- Non-linear, quantitative and dynamic network model
- Model optimization with response to synthetic control

WP1 – Petre
Quantitative modeling framework



Network control analysis
- System-level network construction applications
- Prediction of key targets and network driver elements

WP2 – Aittokallio
Targeted network analysis



WP3 – Jones
Sustainable biofuel production

WP4 -Wennerberg
Targeted anticancer therapies

Synthetic network control biotechnology
- Predicted engineering of metabolic flux to optimize catalytic system
- Experimental validation of network control principles

Reverse engineering of cancer networks
- Controlled perturbations through targeted siRNA and drug delivery
- Personalized multi-target treatment strategies for killing cancer cells

WP1+2: model network and identify sets of **experimentally actionable nodes** to control a specified part of the network behavior.

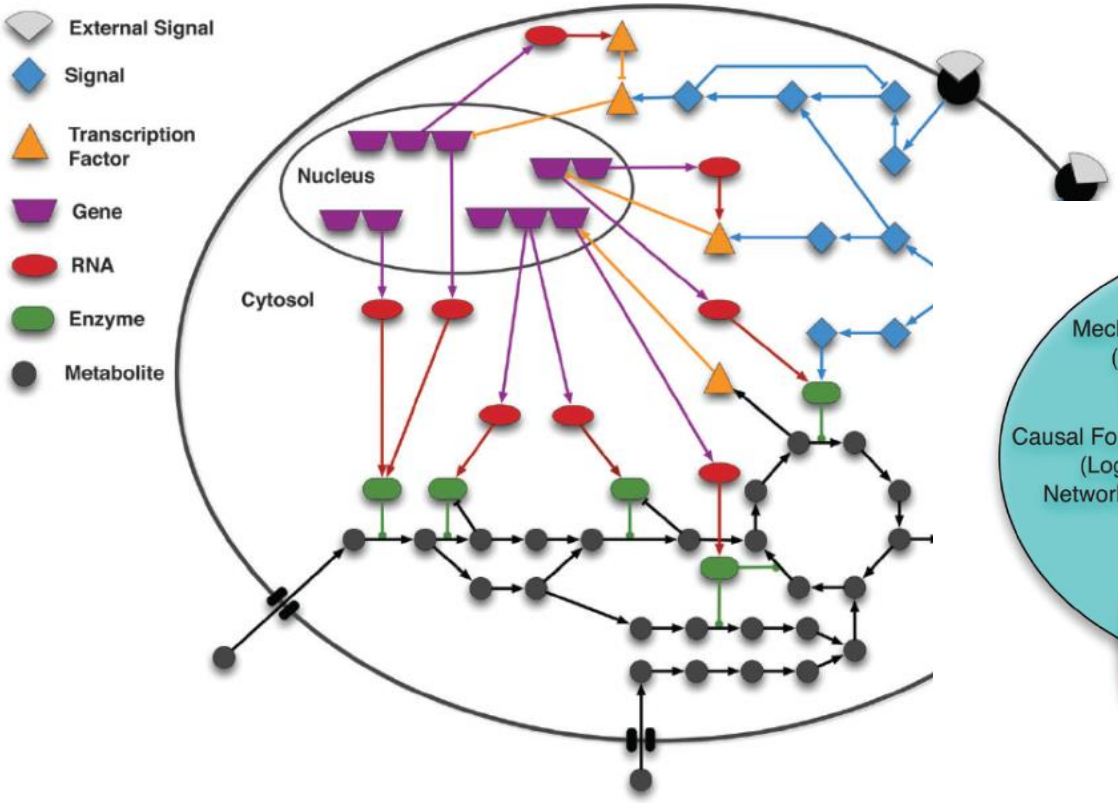
WP3: targeted engineering of the control nodes (X) to enable optimization of metabolic pathways and networks in order to **maximize biofuel production.**

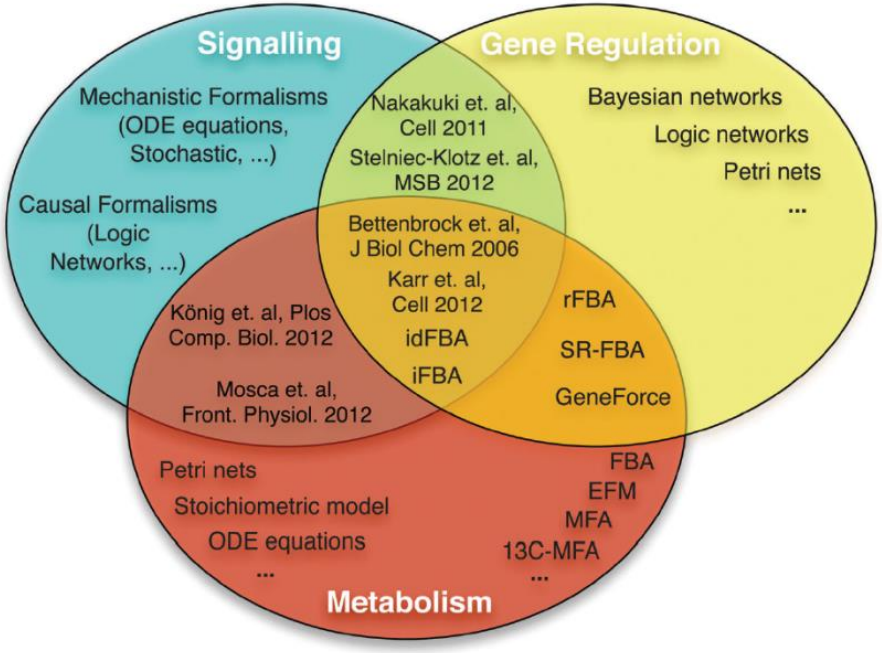
WP4: detected control nodes (e.g. cancer drivers) or their interactions (synthetic lethal interactions) are used to detect druggable vulnerabilities of cancer networks to selectively **inhibit cancer cells**.

Bridging the layers: towards integration of signal transduction, regulation and metabolism into mathematical models

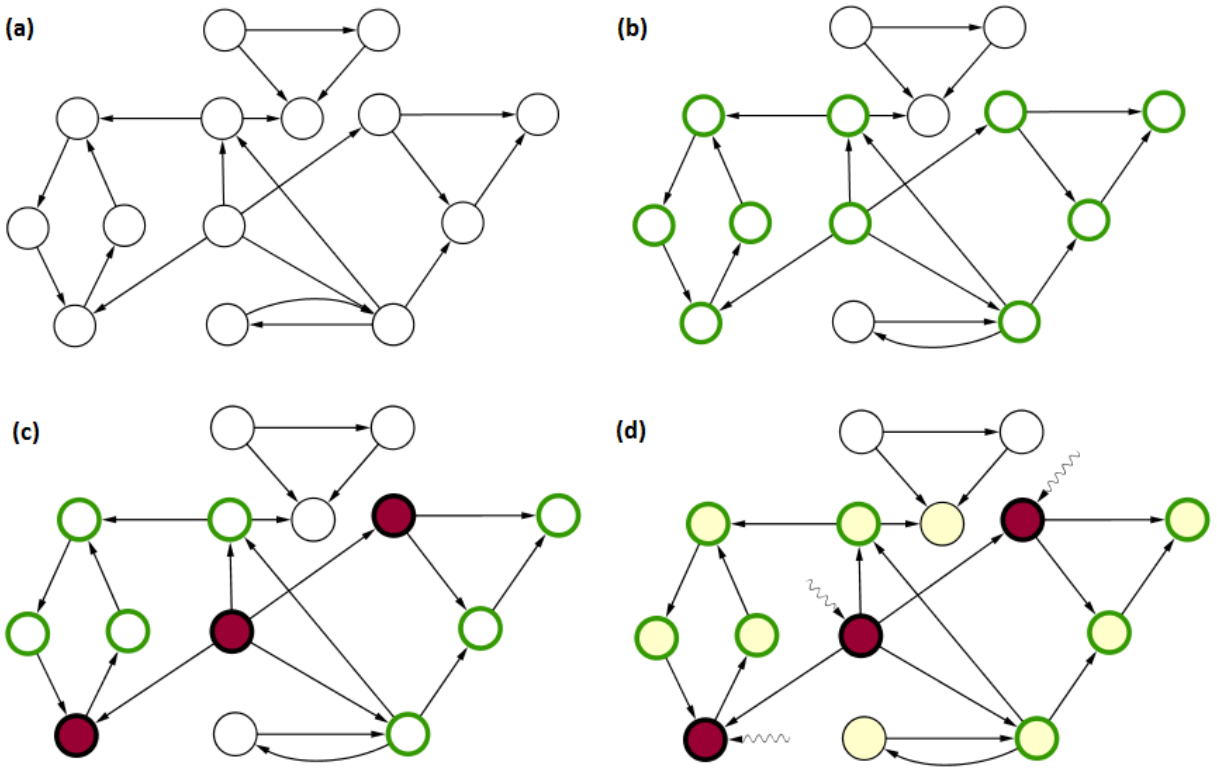
Emanuel Gonçalves,[a] Joachim Bucher,[b] Anke Ryll,[c] Jens Niklas,[b] Klaus Mauch,[b] Steffen Klamt,[c] Miguel Rocha[d] and Julio Saez-Rodriguez*[a]

EMBL-EBI





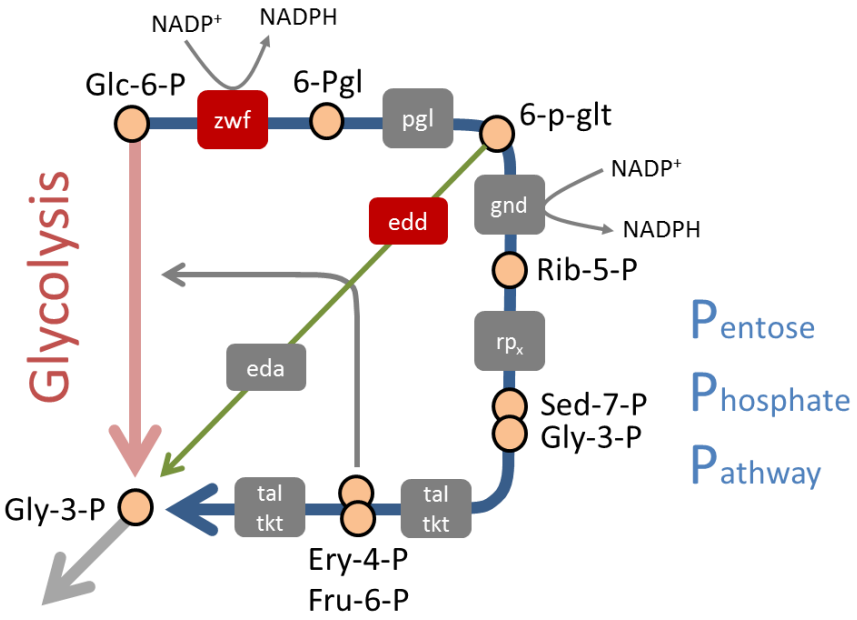
Network control identification and exploitation



(**a**) Construct a sub-network model for the biological system. (**b**) Identify the part of the sub-network that should be controlled (green nodes). (**c**) Compute the set of actionable control nodes (red). (**d**) Engineer the control nodes to drive the network into a more favorable dynamics and internal state (yellow nodes).

Sustainable biofuel application case

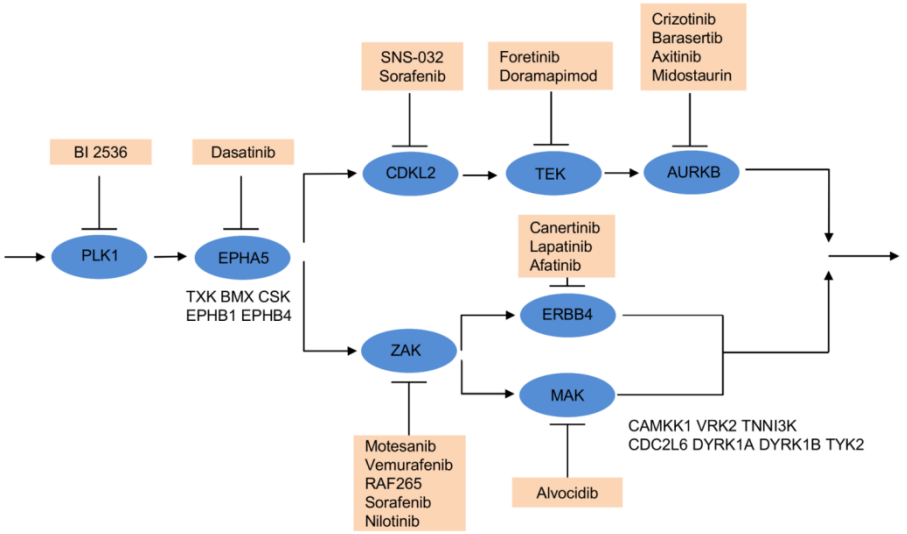
1) To experimentally evaluate the network control concept in a relatively simple and well-understood metabolic system (*distribution of flux between glycolysis and the pentose phosphate pathway in E. coli*)
2) To utilize the developed network control identification process to optimize host metabolism for the renewable production of biofuel (through *fatty acid biosynthesis*)



Outcome: Identification of key-regulatory elements will speed-up and enable us to optimize metabolically engineered systems and consequently enhance our chances to reach economically sustainable biofuel production

Targeted cancer treatment application

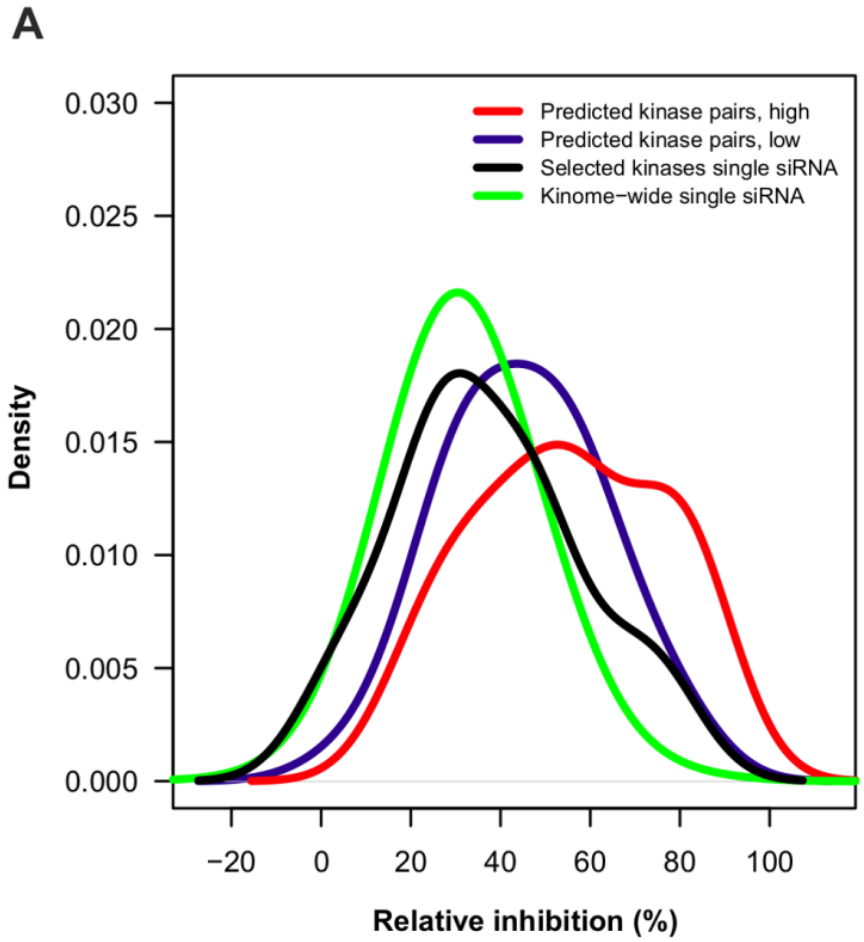
1) To identify novel combinatorial drug targets for given cancer cells and evaluate their therapeutic effects initially using chemical perturbations and targeted RNAi knockdowns in breast cancer cells *in vitro*
2) To apply the optimized principles in primary AML patient cells *ex-vivo* to identify individualized and druggable vulnerabilities that can kill target cancer cells without severe side-effects to healthy control cells

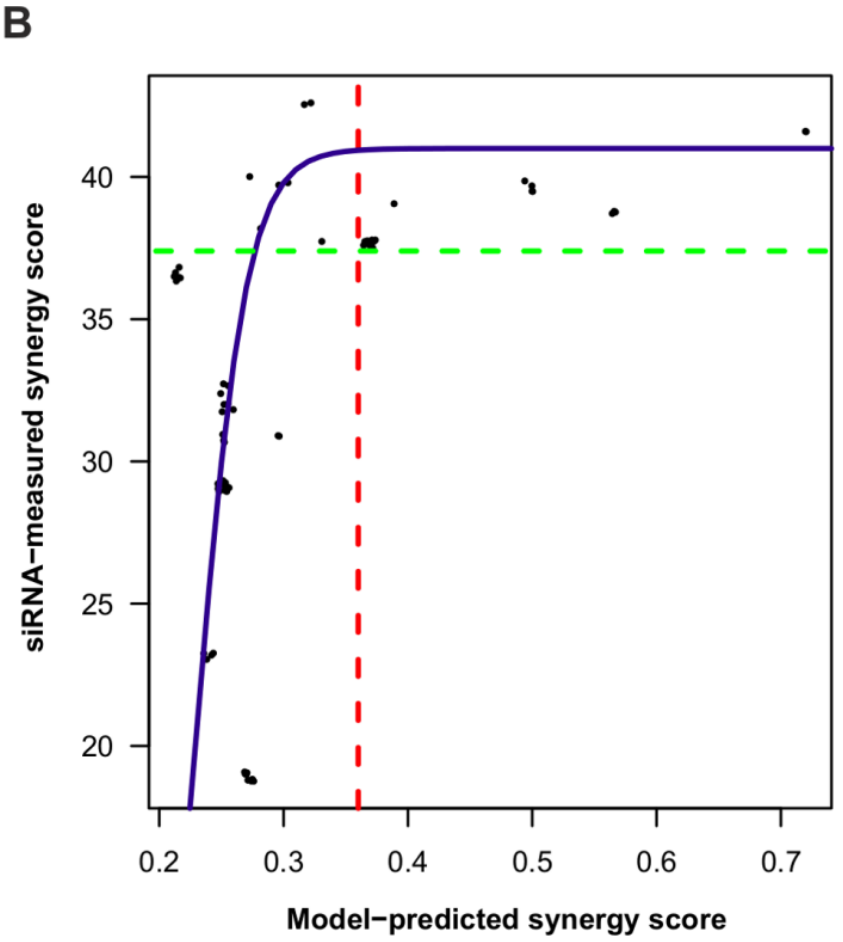


Example of MDA-MB-231 breast cancer

Outcome: Identification of targets that maximize selective cancer killing will facilitate the prioritization of targeted therapeutic strategies into clinical applications (perhaps using CRISPR-based genetic therapies in the future)

Pilot validation using siRNA double knock-downs

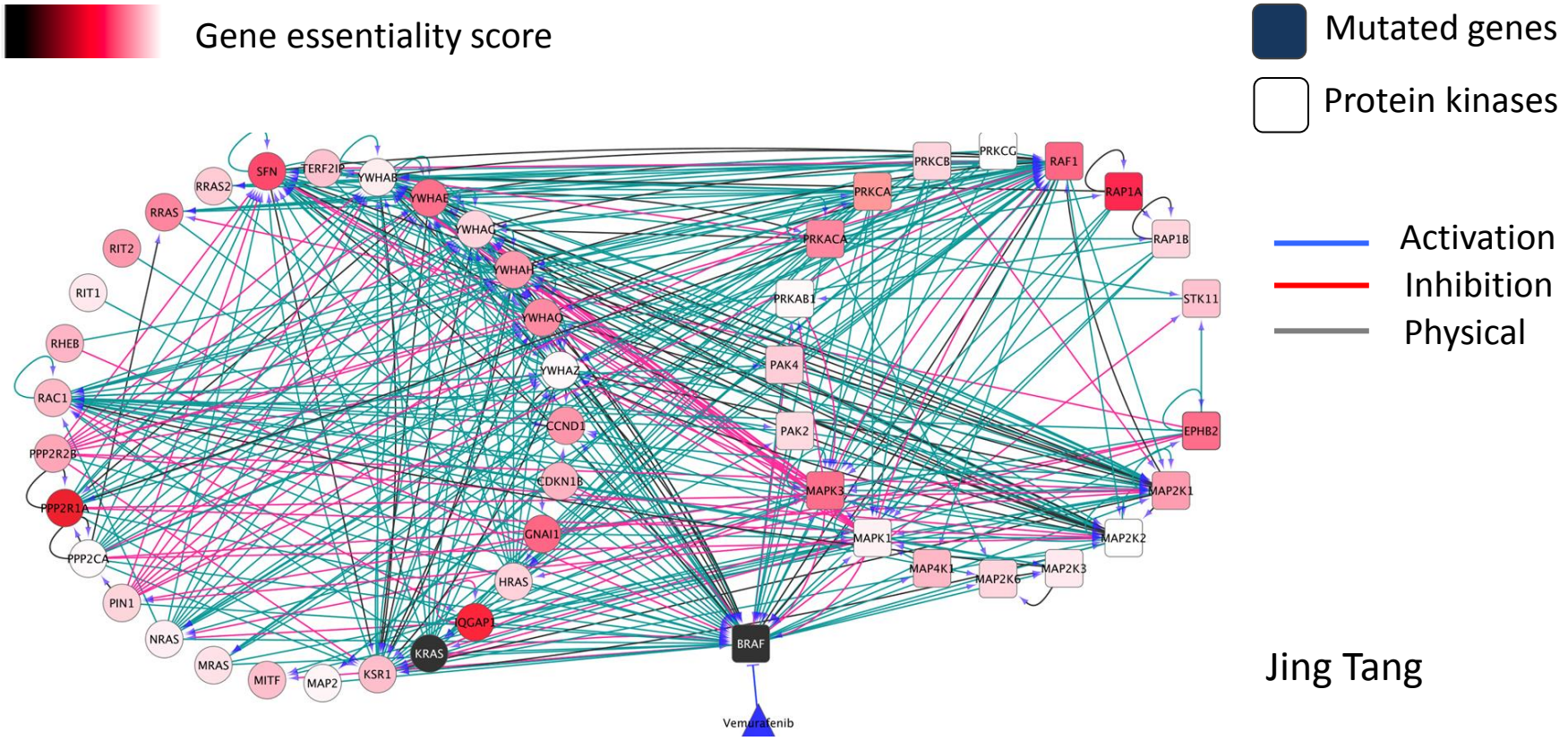




Significant differences between the model-selected kinase targets, when silenced individually or in combination

The synergy score predicted by the model correlated significantly with the synergy score calculated based on double siRNA screen

Future challenge: Controlling the complexity



Jing Tang

Downstream network-level effects of single drug/node perturbation in MDA-MB-231 cells