Synteettisen biologin kontrollimenetelmiä uusiutuvan polttoaineen tuotannossa sekä yksilöllisesti kohdennetuissa syöpähoidoissa

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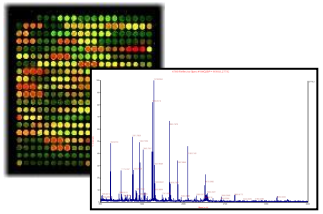
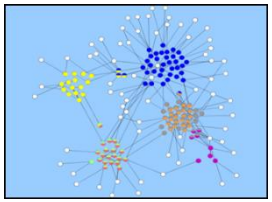
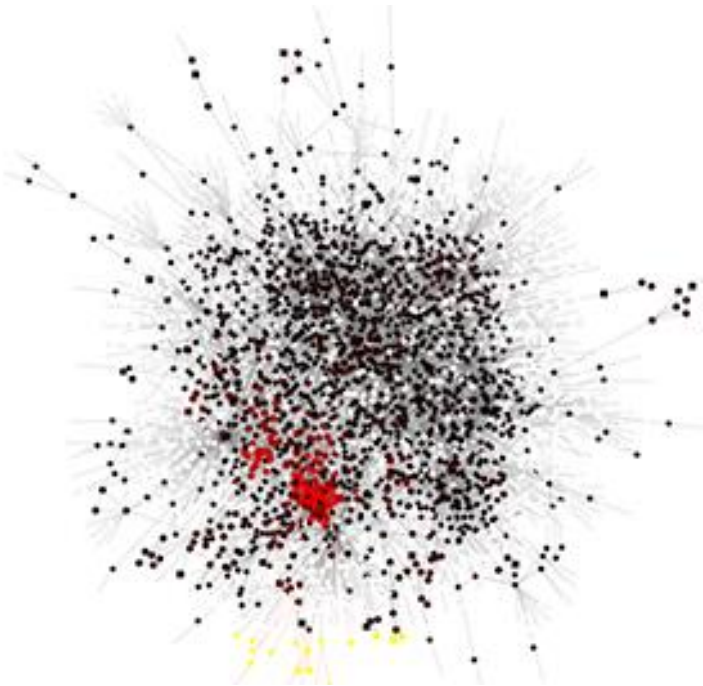
From **systems biology** to **synthetic biology**



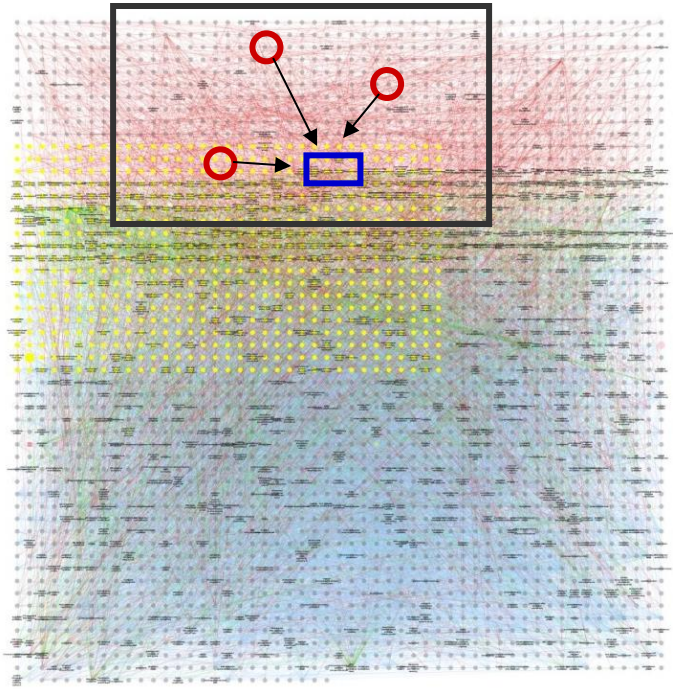


$$\frac{d[RNA]}{dt} = \frac{\alpha k^h}{k^h + [Protein(t-\tau)]}$$

$$\frac{d[Protein]}{dt} = [k(RNA(\tau)]$$

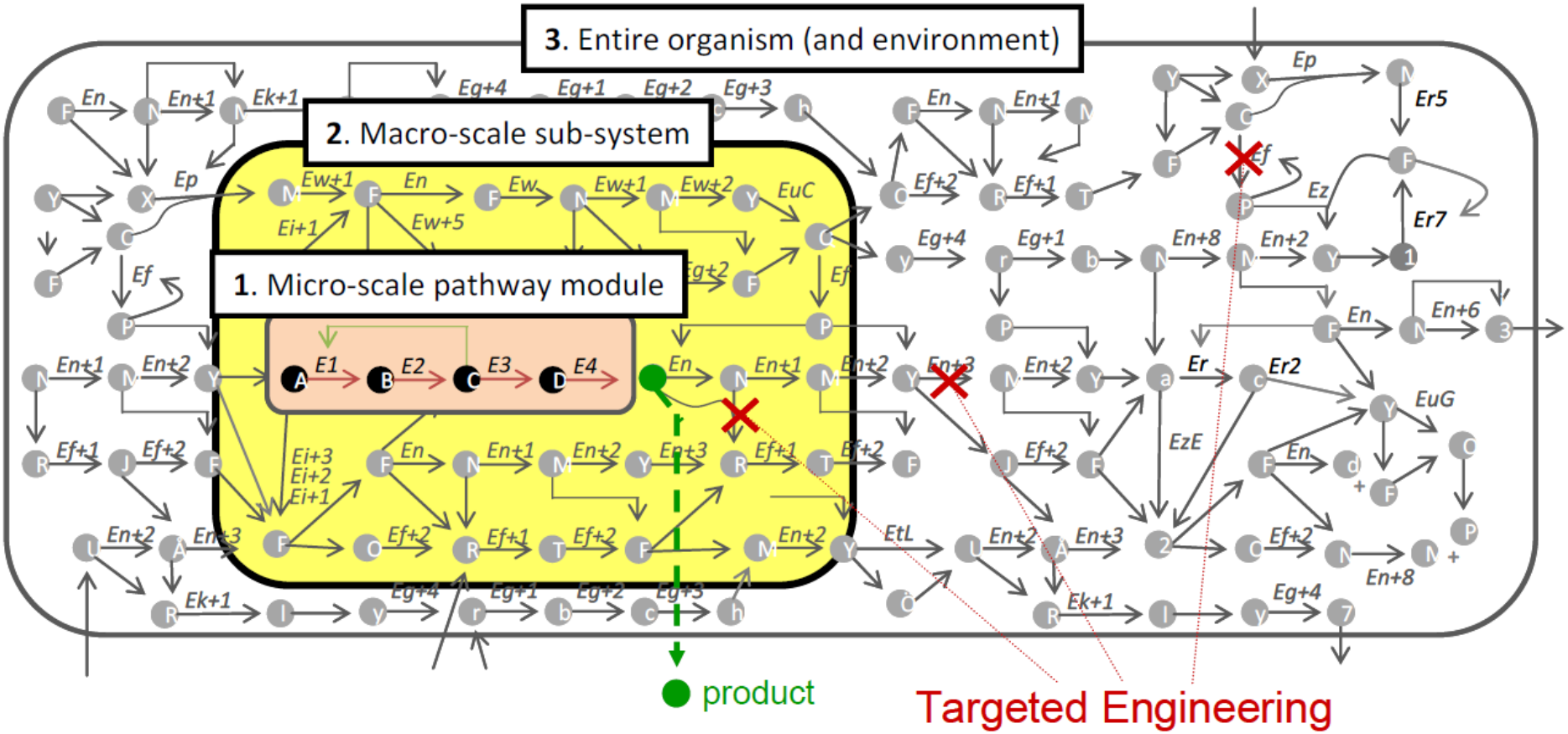


Identify system modules (sub-networks), which can be subsequently modelled (understood) using mathematical models



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

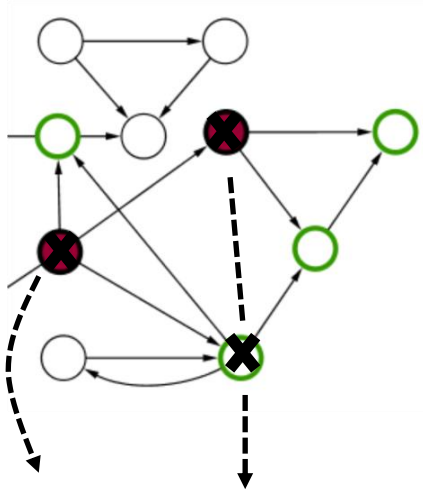
Biological engineering at different levels



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

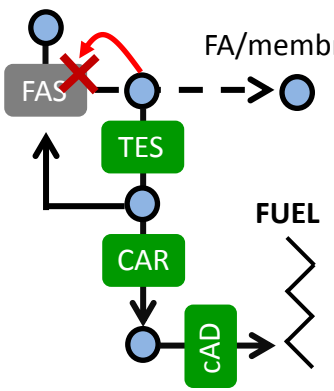
Network modeling framework

Targeted network analysis



Network control principle:

- Identify **experimentally actionable nodes** to control a specified part of the network behavior.
- **Partial controllability** is often more practical, rather than aiming for controlling the full system



Sustainable biofuel production

Targeted anticancer therapies

Synthetic biotechnology

- Targeted engineering of metabolic pathway fluxes to **maximize biofuel production**

Cancer network re-wiring

- Personalized multi-target treatment strategies for selective killing cancer cells

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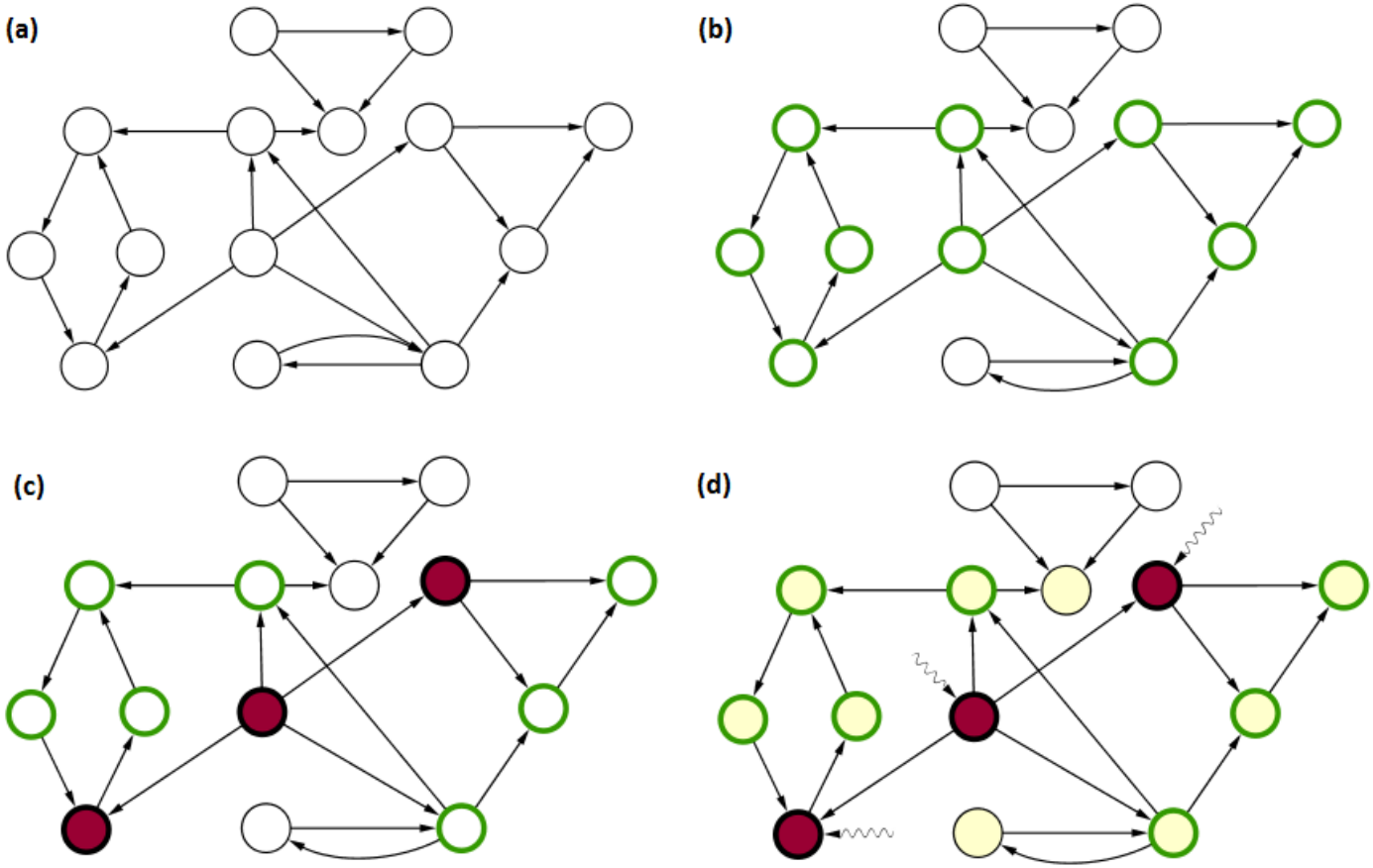
Mikä tässä on synteettistä biologiaa? Mahdolliset hyödyt yhteiskunnalle?

Työkaluilla on mahdoolista ymmärtää miten monimutkaisia biologisia säätelyverkkoja voidaan kontrolloida, sekä miten näillä kontrolliperiaatteita voidaan hyödyntää kun halutaan optimaalisesti vaikuttaa verkon dynaamiseen lopputilaan.

Tavoitteiden toteutuessa, kehitetyillä synteettisen biologian työkaluilla on mahdollista viedä eteenpäin monia uraauurtavia sovelluksia sekä uusituvan bioteknologiassa että yksilöllisesti kohdennetuissa syöpähoidoissa (personalized medicine).

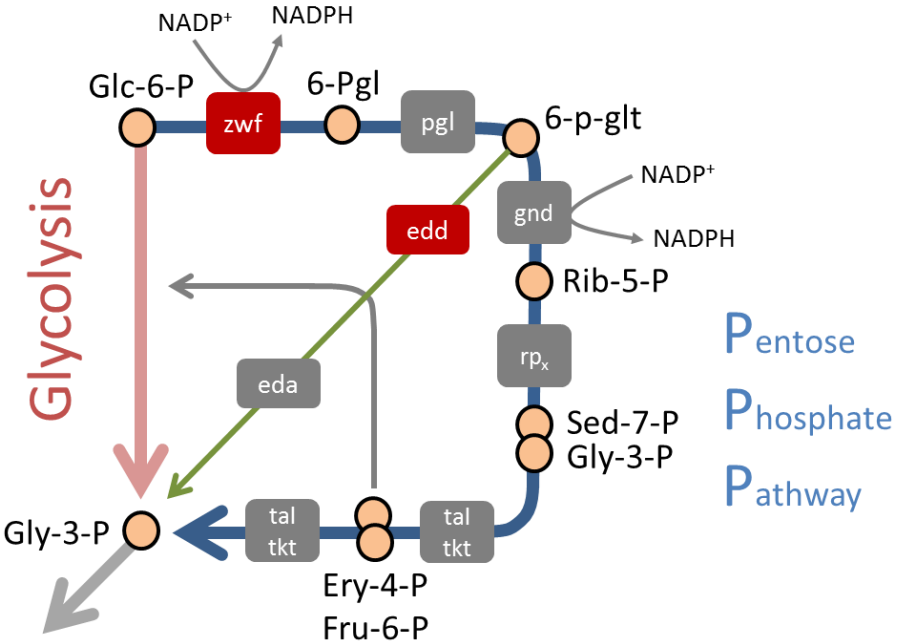
Partial network control principle



(**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*)

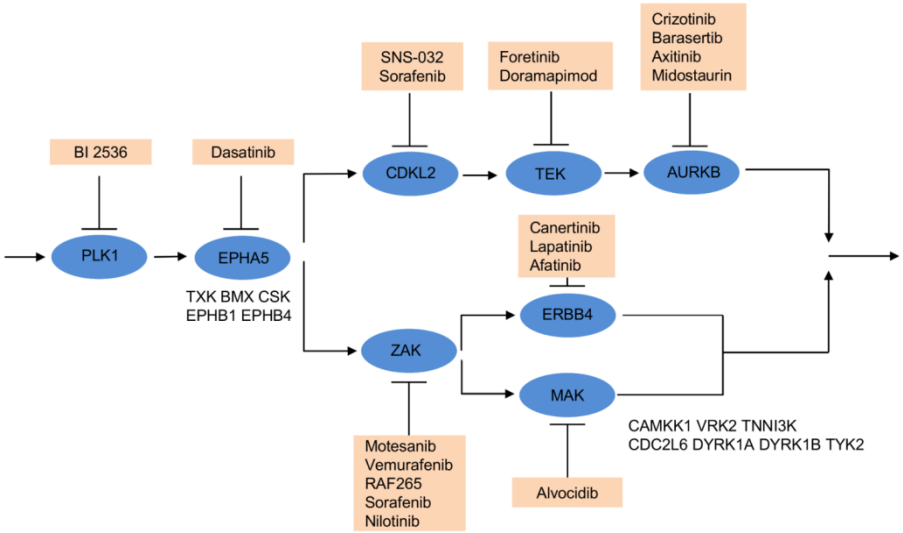


Outcome: Identification of key-regulatory elements may speed-up and enable us to optimize metabolically engineered systems and enhance our chances to reach sustainable biofuel production

Nature Communications 2014

Targeted cancer treatment application

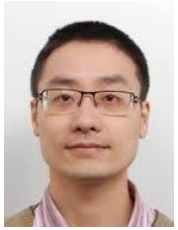
1) To identify novel combinatorial drug targets for given cancer cells and evaluate their therapeutic effects initially using chemical perturbations and targeted RNAi knockdowns in breast cancer cells *in vitro*
2) To apply the optimized principles in primary AML patient cells *ex-vivo* to identify individualized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



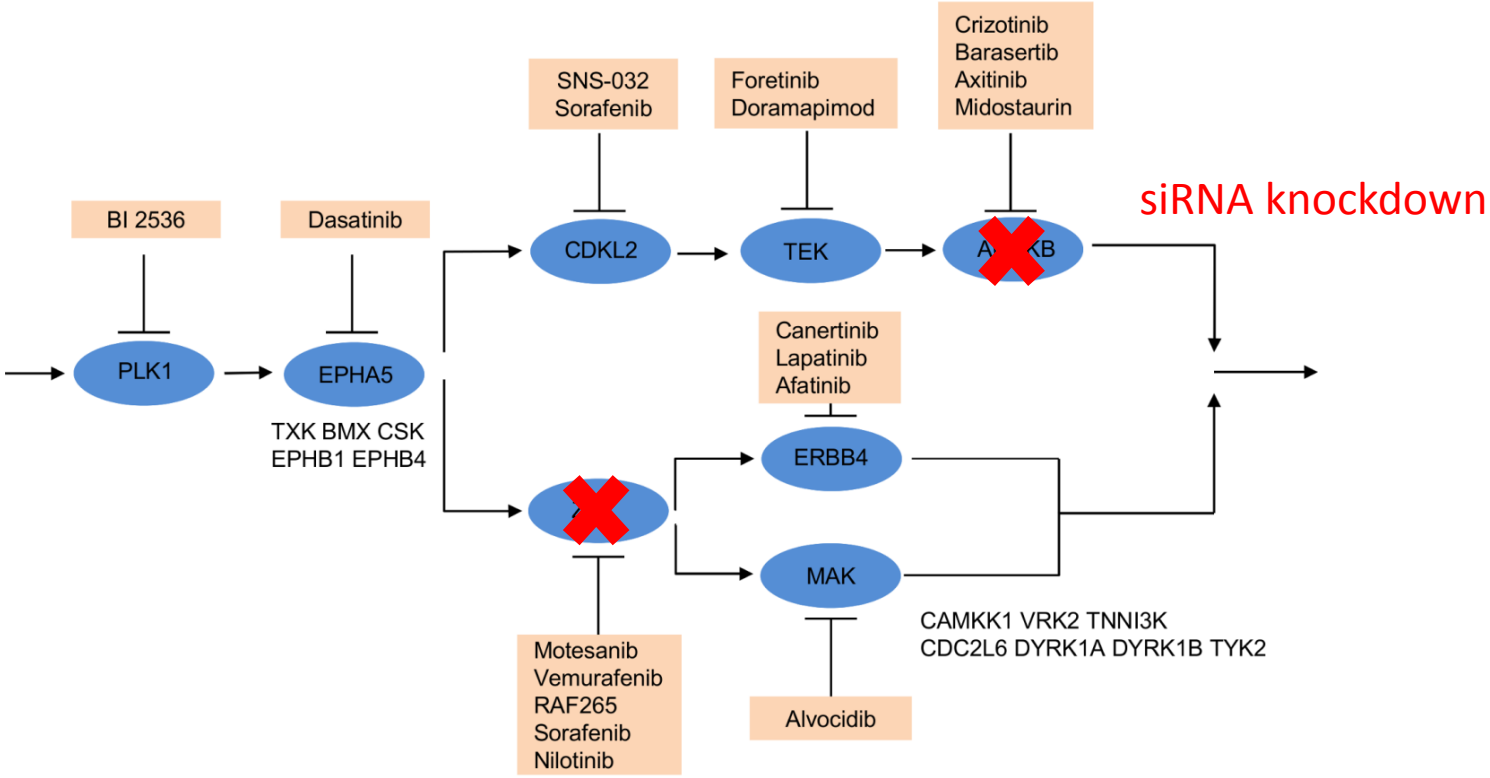
Example of MDA-MB-231 breast cancer

Outcome: Identification of therapeutic targets that can maximize selective cancer killing may facilitate development of effective and safe clinical strategies (e.g. CRISPR-based genetic therapies)

A triple-negative breast cancer application



- Highly aggressive cancer with no targeted treatments
- 41 kinase inhibitors with known target binding profiles
- Drug sensitivity measured in MDA-MB-231 cell line



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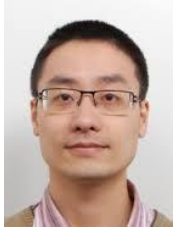

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