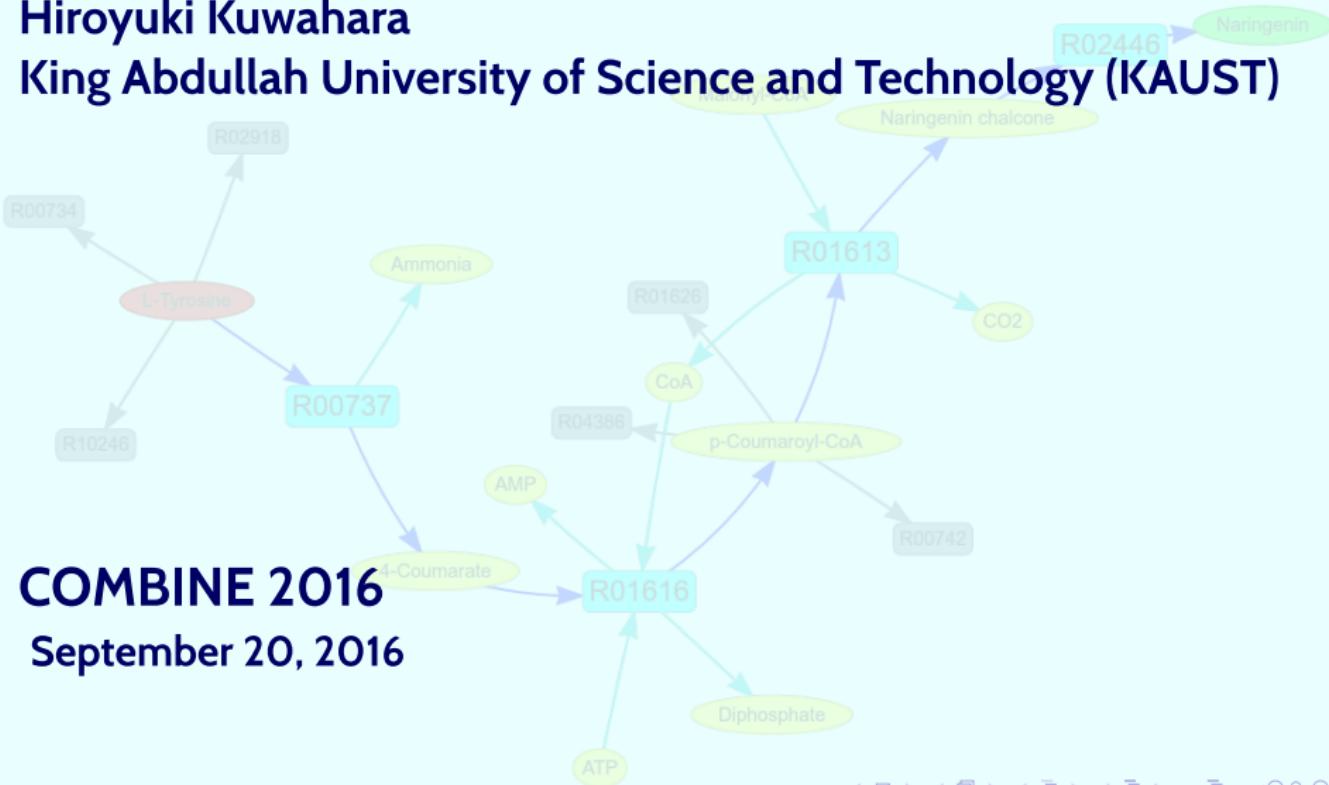


A new thermodynamics-based approach to aid the design of natural-product biosynthetic pathways

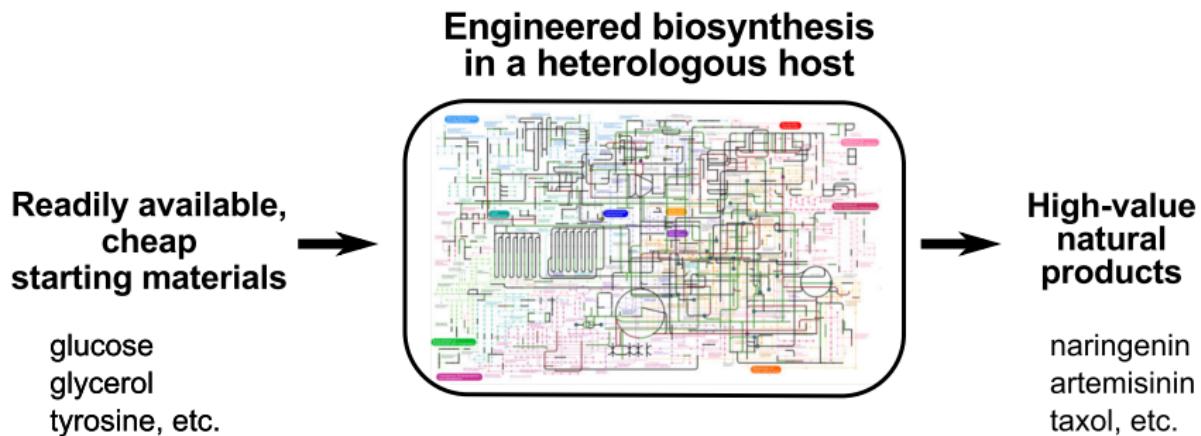
Hiroyuki Kuwahara

King Abdullah University of Science and Technology (KAUST)



COMBINE 2016
September 20, 2016

Engineering of organisms for the biosynthesis of high-value natural products



- ▶ Design of biosynthesis systems involves a large search space.
- ▶ Essential to have a computational tool to predict productive pathways to aid the design.

Previous work

- ▶ Flux balance analysis-based:
 - ▶ Tight flux bounds are needed to obtain meaningful flux distributions.
 - ▶ Host often limited to *E. coli*.
- ▶ Reaction count-based:
 - ▶ Each reaction is assumed to have the same weight.
 - ▶ Ranking doesn't depend on the host's metabolic system.
- ▶ Thermodynamic favorability-based
 - ▶ Effects of competing reactions cannot be captured.
 - ▶ Ranking doesn't depend on the host's metabolic system.

Problem statement

- ▶ Synthetic-biology-wise:
 - ▶ Given a starting material, a target product, and a host organism, find promising biosynthetic routes by allowing the introduction of foreign metabolic enzymes into the host.
- ▶ Computer-science-wise:
 - ▶ Given a source node and destination node in a weighted directed graph that represents all allowed chemical transformations, find K shortest routes.
 - ▶ Problem is how to assign a weight to each edge to capture the effects of the insertion of foreign enzymes into the host's metabolic infrastructure.

Our host-dependent weighting scheme

The weight of an edge that transforms compound C based on reaction r is $\ln[f(r)]$ where

$$f(r) = \frac{e^{-\Delta_r G'^{\circ}/RT}}{1 + e^{-\Delta_r G'^{\circ}/RT} + \sum_{r' \in R_N \setminus \{r\}} e^{-\Delta_{r'} G'^{\circ}/RT}}$$

Boltzmann factor
of reaction r

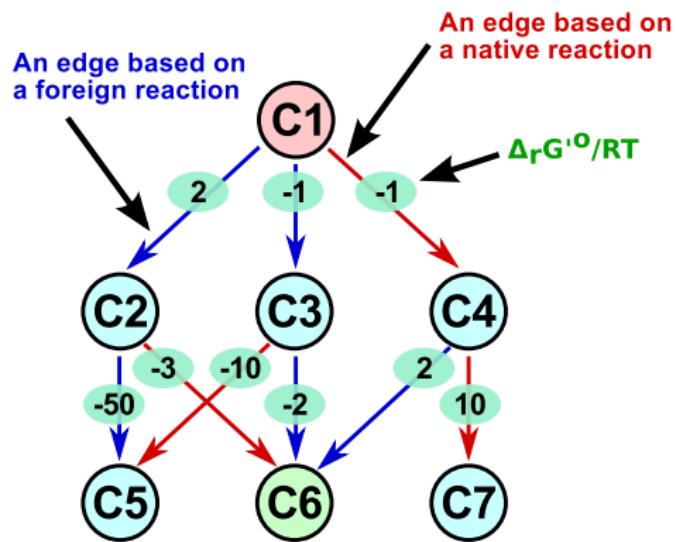
Partition function based on all reactions in the host that can transform C, assuming reaction r is present

$\Delta_r G'^{\circ}$: standard reaction Gibbs energy of r .

R_N : a set of native reactions that can transform C.

Ranking of pathways based on this can be widely different from the thermodynamic favorability approach.

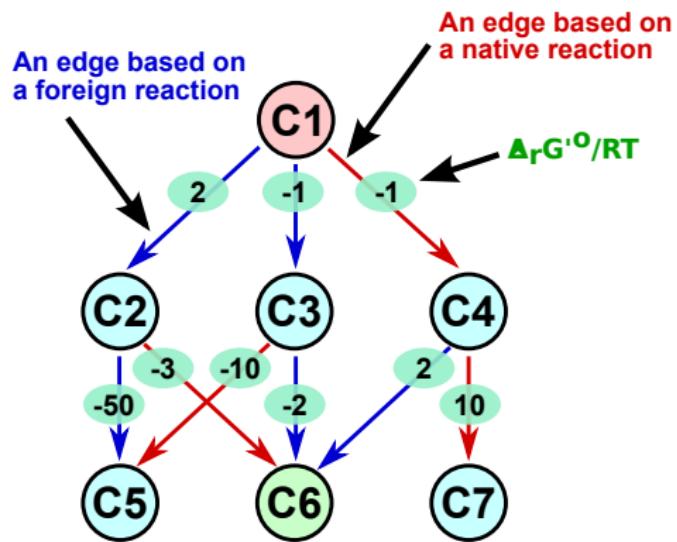
Differences between the thermodynamic favorability approach and our new approach



Thermodynamic favorability-based method

#	Reaction	score
#1	C1 → C3 → C6	-3
#2	C1 → C2 → C6	-1
#3	C1 → C4 → C6	1

Differences between the thermodynamic favorability approach and our new approach



Thermodynamic favorability-based method

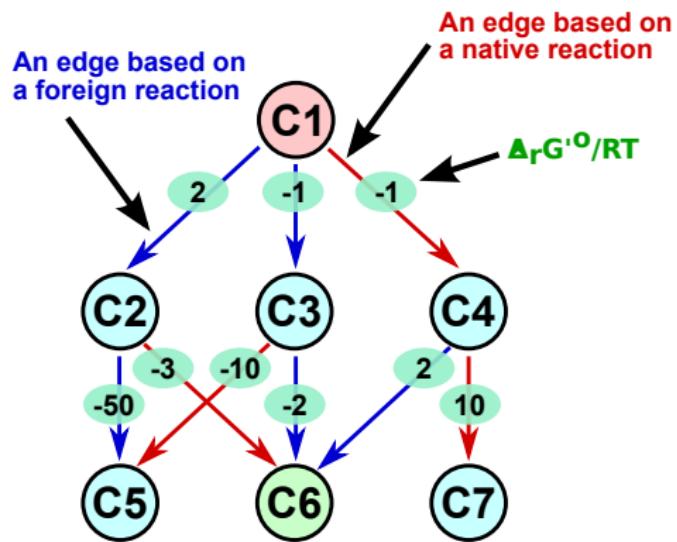
#	Path	score
#1	C1 → C3 → C6	-3
#2	C1 → C2 → C6	-1
#3	C1 → C4 → C6	1

Our new approach

#	Path	score
#1	C1 → C4 → C6	-2.44
#2	C1 → C2 → C6	-3.40
#3	C1 → C3 → C6	-8.86

The weight of $C1 \rightarrow C2$: $\ln[e^{-2} / (1 + e^{-2} + e^{-1})] = -3.35$.

Differences between the thermodynamic favorability approach and our new approach



Thermodynamic favorability-based method

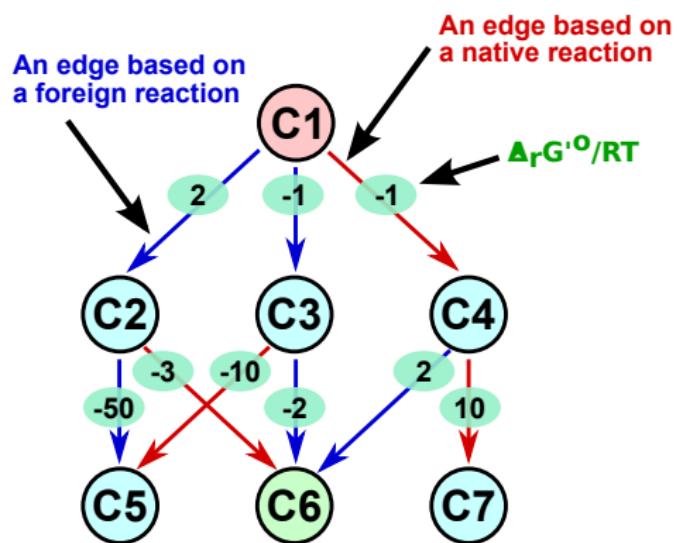
		score
#1	C1 → C3 → C6	-3
#2	C1 → C2 → C6	-1
#3	C1 → C4 → C6	1

Our new approach

		score
#1	C1 → C4 → C6	-2.44
#2	C1 → C2 → C6	-3.40
#3	C1 → C3 → C6	-8.86

The weight of C1 → C3: $\ln[e^{-1} / (1 + e^{-1} + e^{-1})] = -0.86$.

Differences between the thermodynamic favorability approach and our new approach



Thermodynamic favorability-based method

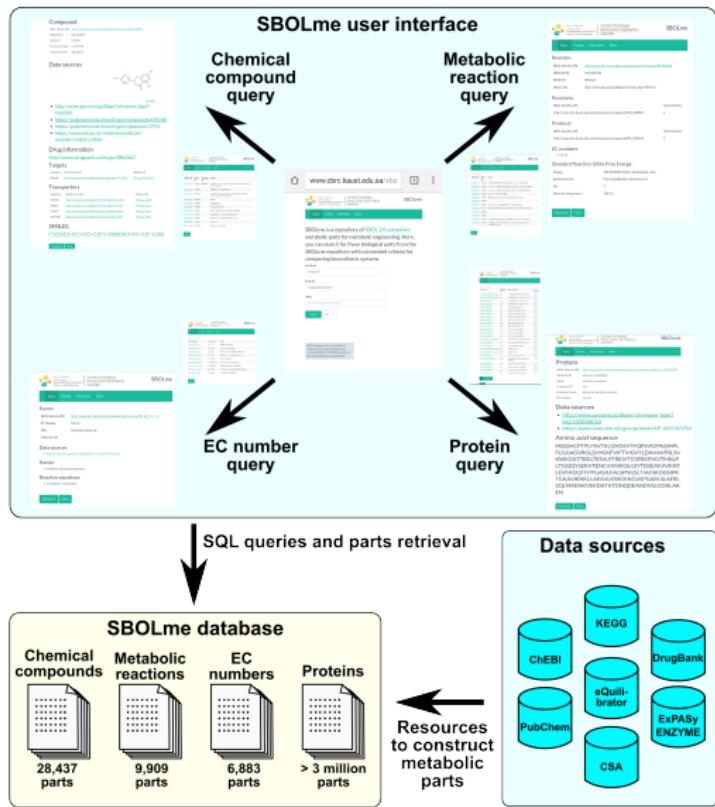
		score
#1	C1 → C3 → C6	-3
#2	C1 → C2 → C6	-1
#3	C1 → C4 → C6	1

Our new approach

		score
#1	C1 → C4 → C6	-2.44
#2	C1 → C2 → C6	-3.40
#3	C1 → C3 → C6	-8.86

The weight of C1 → C4: $\ln[e^{-1} / (1 + e^{-1})] = -0.31$.

SBOLme (<http://www.cbrc.kaust.edu.sa/sbolme>)



Acknowledgments



Xuefeng Cui, Assistant Professor at Tsinghua University



Meshari Alazmi, Ph.D. student at KAUST



Xin Gao, Associate Professor at KAUST