Computational Biology Lab

Constraint-Based Modeling - BE21B037

Section A

1. Referring to scientific literature summarize the principle and scope of Genome-Scale Metabolic Modelling (Less than 300 words)

Principles and scope of Genome-Scale Metabolic Modelling

- Genome-scale metabolic modelling is used to quantitatively define the relationship between genotype and phenotype by using different types of genomics, metabolomics and transcriptomics data
- It can be divided into 4 major phases, each of which builds from the previous one. For each phase specific data types are necessary that range from high-throughput data types to detailed studies that characterize individual components
- **Step 1: Automated Genome-based reconstruction**
  Reconstruction starts with annotated genomes for a particular target organism or strain. These genome annotations can be found in organism specific databases such as SGD - for Saccharomyces Genome Database or EcoCyc - for E.coli. The annotation is useful as it provides identifiers for reconstruction and also the metabolic enzymes that are needed. It also indicates how the gene products interact to form active enzymes that catalyze metabolic reactions
- **Step 2: Curating the draft reconstruction**
  With the initial set of biochemical reactions encoded on a genome, we need to establish substrate or cofactor specificity and subcellular localization. So the draft network reconstruction is manually curated.
- **Step 3: Converting a genome-scale reconstruction to a computational model**
  The reconstruction is now converted to a mathematical representation. This conversion translates GENRE into a mathematical format that becomes a basis for genome scale model. This computation serves as a way to check data consistency and to compute which functions a reconstruction can and cannot carry out
- **Step 4: Reconstruction uses and integration of high-throughput data**
  The high-throughput data sets that evaluate a large number of interactions across different genetic conditions can be used to refine and expand the metabolic content of a network. This type of comparison and analyses can evaluate genome-scale omics datasets.

Section B

2.

R1: $\rightarrow$ Glucose

V1: Glucose + 2 ADP + 2 NAD $\rightarrow$ 2 Pyruvate + 2 ATP + 2 NADH + 2 H_2O

V2: Pyruvate + NADH $\leftrightarrow$ Lactate + NAD

V3: Pyruvate + CoA + NAD $\rightarrow$ Acetyl CoA + CO_2 + NADH

V4: Pyruvate + CoA $\rightarrow$ Formate + Acetyl CoA

V5: Acetyl CoA + ADP $\rightarrow$ Acetate + CoA + ATP

V6: Acetyl CoA + 2 NADH → Ethanol + CoA + 2 NAD
V7: ATP → ADP
R2: Lactate →
R3: Ethanol →
R4: Acetate →
Constructing a Stoichiometric Matrix and write down the Bounds for each reaction

	R1	V1	V2	V3	V4	V5	V6	V7	R2	R3	R4
Glucose	1	-1	0	0	0	0	0	0	0	0	0
ADP	0	-2	0	0	0	-1	0	1	0	0	0
NAD	0	-2	1	-1	0	0	2	0	0	0	0
Pyruvate	0	2	-1	-1	-1	0	0	0	0	0	0
ATP	0	2	0	0	0	1	0	-1	0	0	0
NADH	0	2	-1	1	0	0	-2	0	0	0	0
H2O	0	2	0	0	0	0	0	0	0	0	0
Lactate	0	0	1	0	0	0	0	0	-1	0	0
CoA	0	0	0	-1	-1	1	1	0	0	0	0
Formate	0	0	0	0	1	0	0	0	0	0	0
Acetyl CoA	0	0	0	1	1	-1	-1	0	0	0	0
Acetate	0	0	0	0	0	1	0	0	0	0	-1
Ethanol	0	0	0	0	0	0	1	0	0	-1	0
CO2	0	0	0	1	0	0	0	0	0	0	0

Glucose : R1 - V1
ADP : – 2V1 - V5 + V7
NAD : –2V1 + V2 – V3 + 2V6
Pyruvate : 2V1 –V2–V3–V4
ATP : 2V1 + V5 – V7
NADH : 2V1 – V2 + V3 – 2V6
H2O : 2V1
Lactate : V2 – R2
CoA : –V3–V4+V5+V6
Formate : V4
Acetyl CoA : V3 + V4 – V5 –V6
Acetate : V5–R4
Ethanol : V6 – R3
CO2 : V3

V1: Irreversible : $-\infty \leq V1 \leq 0$
V2: Reversible : $-\infty \leq V2 \leq 0$
V3: Irreversible : $-\infty \leq V3 \leq 0$
V4: Irreversible : $-\infty \leq V4 \leq 0$
V5: Irreversible : $-\infty \leq V5 \leq 0$
V6: Irreversible : $-\infty \leq V6 \leq 0$
V7: Irreversible : $-\infty \leq V7 \leq 0$
R1: Irreversible : $-\infty \leq R1 \leq 0$ (uptake)
R2: Irreversible : $0 \leq R2 \leq \infty$ (secretory)
R3: Irreversible : $0 \leq R3 \leq \infty$ (secretory)
R4: Irreversible : $0 \leq R4 \leq \infty$ (secretory)

Section C

3.a

In the paper there is a sharp decline in growth rate after 3.35 oxygen uptake rate but we didn't find it in the simulation because we didn't constrain the uptake rate of sucrose.

The simulation results can be found here

3.b

The sucrose hydrolyzed to only glucose in our simulation while in the paper it was consumed and hydrolyzed to glucose and fructose. This is due to constraints applied in the paper, which we did not have in our simulation

The simulation results can be found here

3.c

The simulation results can be found here

3.d

The simulation results can be found here.