Construction of Genome Scale Models
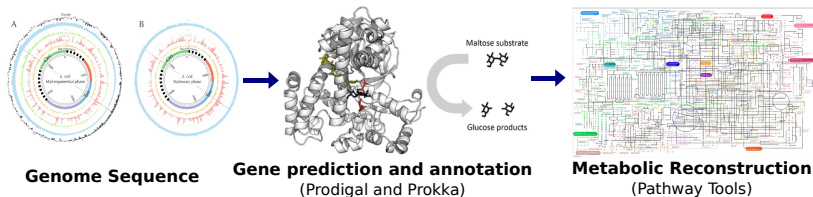
Mark Poolman/Dipali Singh

May 4, 2022

Genome-Scale Metabolic Model

Large size models: usually with 100s to 1000s reactions and metabolites
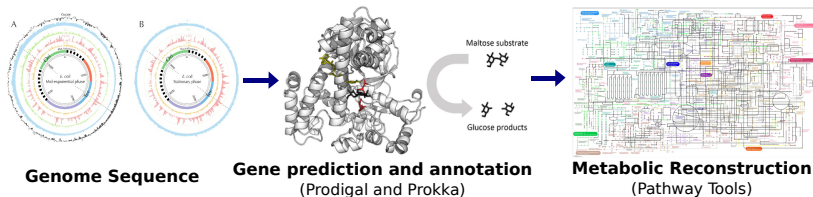
GSM describes the metabolic interactions in a given organism based on reaction network predicted from enzymes encoded by the genome

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Gene prediction and annotation
(Prodigal and Prokka)

Metabolic Reconstruction
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- Save the reactions in a suitable format
- Job done ($\approx$ 1 minute with a local db)

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- incorrect reaction stoichiometries and reversibility
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- "Some-tRNA"
- "Long-Chain-Fatty-Acids"
- "An alcohol"

Inconsistent metabolites identifiers e.g. :

- multiple identifiers for same metabolite
- example of Ribose: D-Ribofuranose, D-Ribopyranose, CPD0-1108, CPD0-1110 etc
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    " ADP – D – GLUCOSE" –>"ADP" + "Starch"

- single glucose moiety is added to starch

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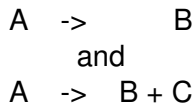
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Clearly:

$$A \rightarrow B$$
$$\text{and}$$
$$A \rightarrow B + C$$

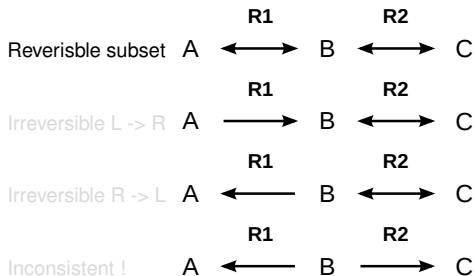Cannot both be true.
(Violation of mass conservation)

Stoichiometric inconsistencies

Even without empirical formulae such sets of reactions can be identified by a combination of:

- Analysis of left null-space
- Linear programming
- Provides an automatic method for identification of the polymer problem.
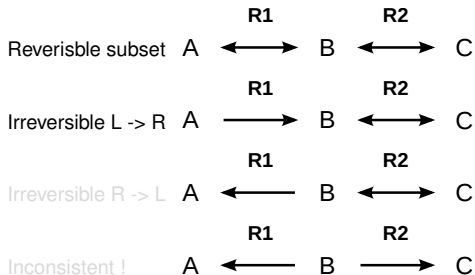- See: Gevorgyan *et al* 2008, Bioinformatics

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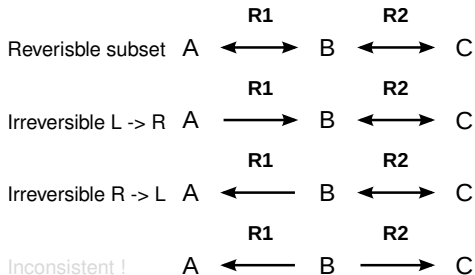
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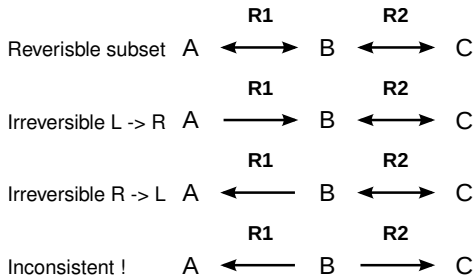
Violations of conservation of energy:

- Identify from LP:

  1. Constrain all transporters to zero flux.

  2. Set a demand for ATP and/or NAD(P)H.

  3. If the LP has a viable solution an inconsistency exists.

  4. All reactions in the solution must now be examined.

Mis-annotation:

- Reactions absent that should be present
- Example, Campylobacter model was not able to produce asparagine
- Due to missing reaction in the model
- Reactions present that should be absent
- Alternatively, the model was able to synthesis niacinamide, though Campylobacter is auxotrophic to niacinamide
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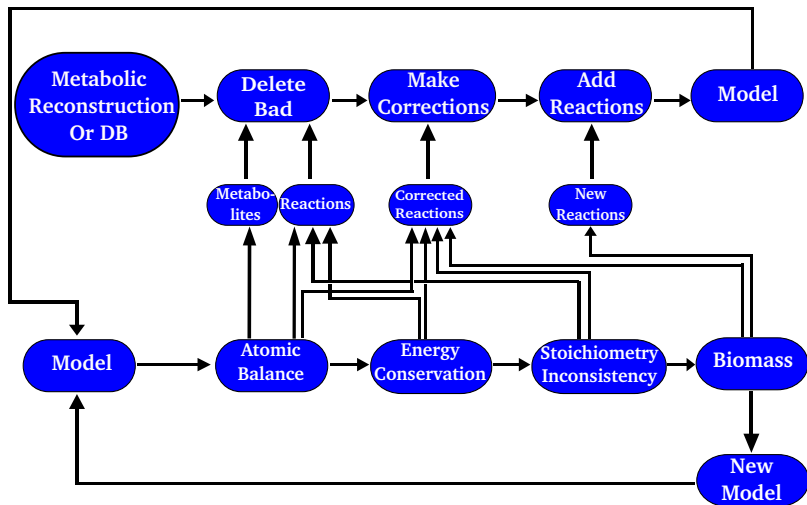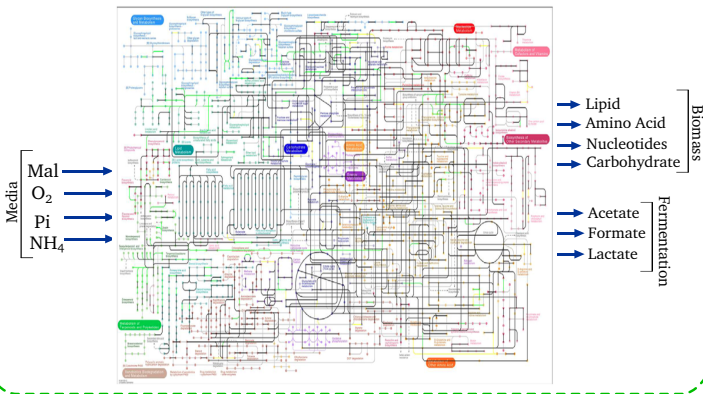Bioinformatic tools along with experimental data can be used for the curation

Genome-Scale Metabolic Model

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For our convevience:

- Environmental/external metabolites are distinguished from internal metabolites by using prefix 'x_'

- Transport reactions exchange metabolites between the model and the environment.

  - Transport reactions are differentiated from other reactions by using suffix '_tx'

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Naming Convention: Transporters

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Reactions between compartments can be differentiated using suffix. e.g. eukaryotic models

- Reactions in cytosol: '_Cyto'

- Reactions in mitochondria: '_Mito'

- Reactions in mitochondria: '_Plas'

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Constructing models - Summary

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BioCyc (http://BioCyc.org) a suite of organism specific
data-bases ('EcoCyc', 'AraCyc' etc.)
Three levels (tiers) of curation:

1. Exhaustively checked by experts in the field

2. Some manual checking

3. Purely automatically generated

Most are tier 3

Organism specific data bases describe:

- Metabolites

- Reactions

- Enzymes

- Proteins

- Genes

This proides a convenient framework for constructing GSMs and establishing reaction/enzyme/gene relationships.

Transporters and compartmental information is relatively poor.

A database consists of a set of *Records*.

Each record is identified by its uniqe identifier (UID)

Each record is comprised of a set of *fields* specific to the type of record.

ScrumPy provides the 'PyoCyc' package to access local BioCyc data-bases (downloaded from the BioCyc web-site):

from Bioinf import PyoCyc db = PyoCyc.Organism('EColi')

If no organism name is specified the *MetaCyc* database will be loaded.

In ScrumPy, the database acts as a dictionary, the BioCyc UIDs are the keys:

g = db['GLC']

g is the record for glucose (UID GLC)
This is also a dictionary, the keys refer to the fields of that record.

print g
UNIQUE-ID - GLC . . COMMON-NAME - beta -D-glucose
MOLECULAR-WEIGHT - 180.157 . . CHEMICAL-FORMULA -
(C 6) CHEMICAL-FORMULA - (H 12) CHEMICAL-FORMULA -
(O 6) . .

Likewise for reactions

fk = db['FRUCTOKINASE-RXN'] fk FRUCTOKINASE-RXN

These can also be accessed by EC number:

db['EC-2.7.1.4'] [FRUCTOKINASE-RXN]

Accessing BioCyc From ScrumPy

Reaction records of a number of properties, including the ability to represent themselves in ScrumPy format:

print r.AsScrumPy() "FRUCTOKINASE-RXN":
"BETA-D-FRUCTOSE" + "ATP"<>"PROTON" +
"FRUCTOSE-6P" + "ADP"   #LEFT-TO-RIGHT