

Construction of Genome Scale Models

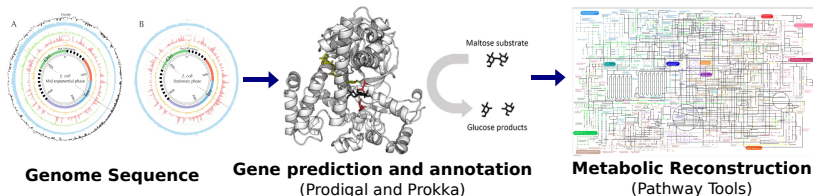
Dipali Singh

June 2, 2023

Genome-Scale Metabolic Model

Large size models: usually with 100s to 1000s reactions and metabolites

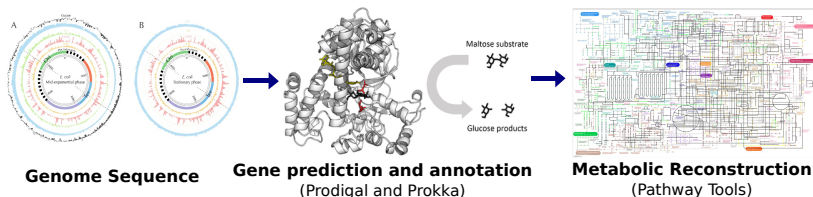
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- Save the reactions in a suitable format
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Non-specific metabolites e.g. :

- “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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The problem with polymers

Polymeric species, consisting of an undefined number of monomeric units, can give rise to mass inconsistencies e.g

- BioCyc database reports a starch synthesis reaction as:

"ADP-D-GLUCOSE" → "ADP" + "Starch"

- single glucose moiety is added to starch

- Amylase reaction as:

"Starch" → "MALTOPENTAOSE"

- with an overall conversion of 1 glucose moiety into five glucose moieties

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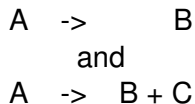
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Stoichiometric inconsistencies

Clearly:



Cannot both be true.
(Violation of mass conservation)

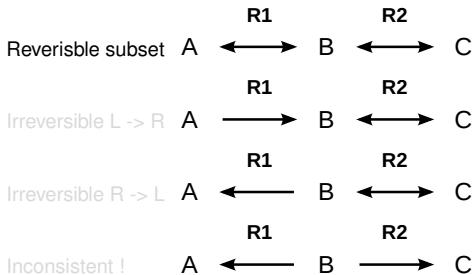
Stoichiometric inconsistencies

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

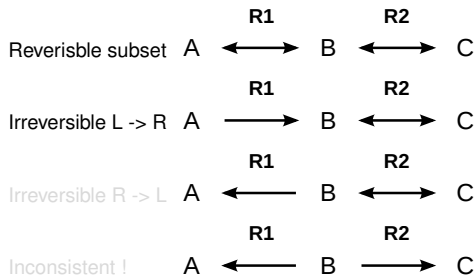
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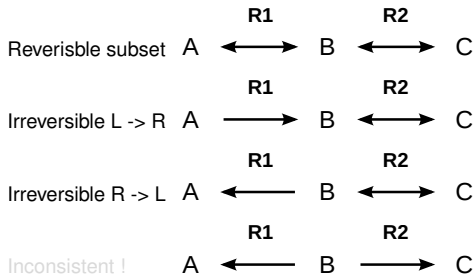
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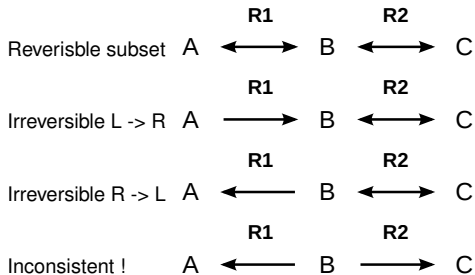
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Violations of conservation of energy:

- 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.

Problems in construction

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
- This was due to over-predicted reaction from Bioinformatic tools

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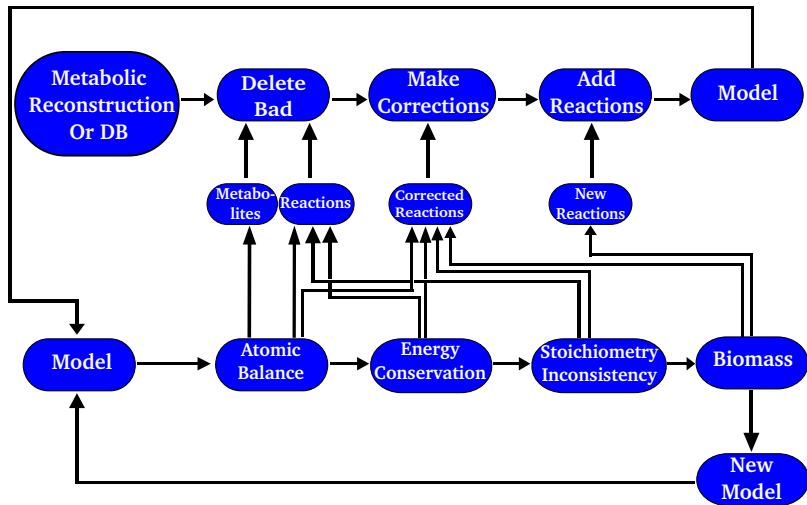
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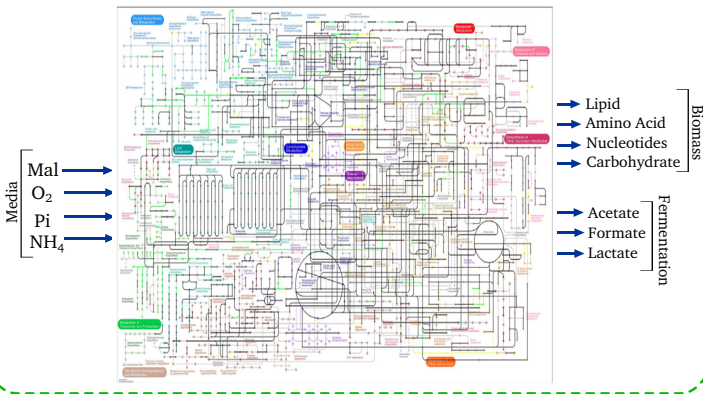
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Genome-Scale Metabolic Model Construction Pipeline



Genome-Scale Metabolic Model

System Boundaries



Genome-Scale Metabolic Model

Naming Convention: Transporters

For our convenience:

- 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'
 - Example: $\text{glucose} + \text{H}_2\text{O} \rightarrow \text{glucose}_x + \text{H}_2\text{O}_x$
 - Media transporters: $\text{glucose}_x \rightarrow \text{glucose}$
- All transport reactions are defined with external species on the left side such that positive flux represents transport of metabolite into the system and negative flux represents transport of metabolites out of the system.

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Naming Convention: Compartments

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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- Lastly, not all the published models are correct. Do your quality checks before using them!

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