PATRIC Bioinformatics Resource Center

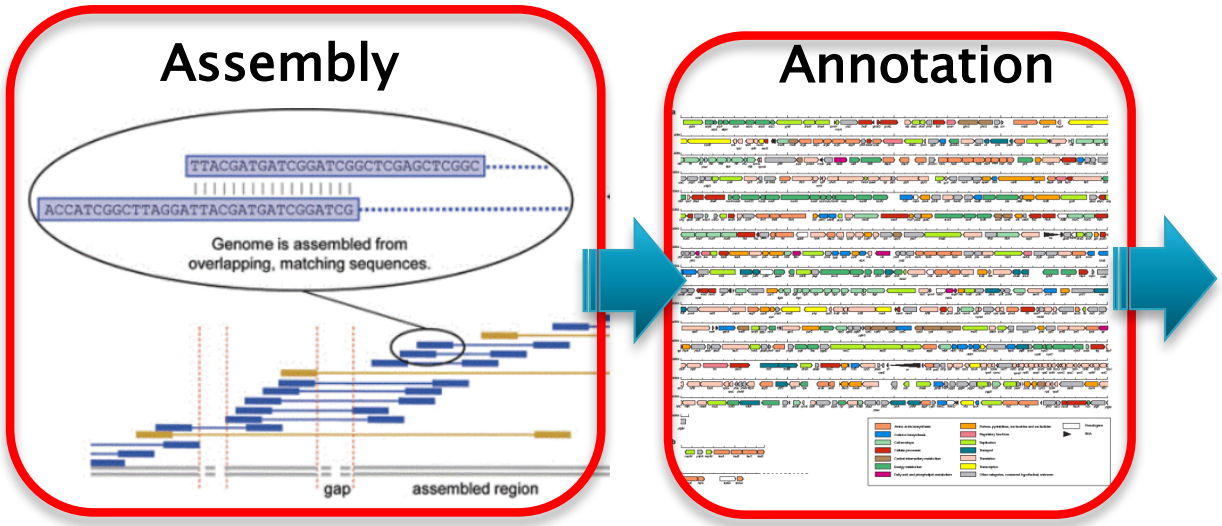
Automated Metabolic Modeling in PATRIC

Jim Davis and Fangfang Xia

jimdavis@uchicago.edu

Fangfang.xia@gmail.com

Metabolic Modeling



- Media Requirements and growth conditions?
- Can you optimize growth?
- How much biomass is produced?
- How much of a given metabolite is produced?
- What pathways are essential?
- What enzymes did you miss?

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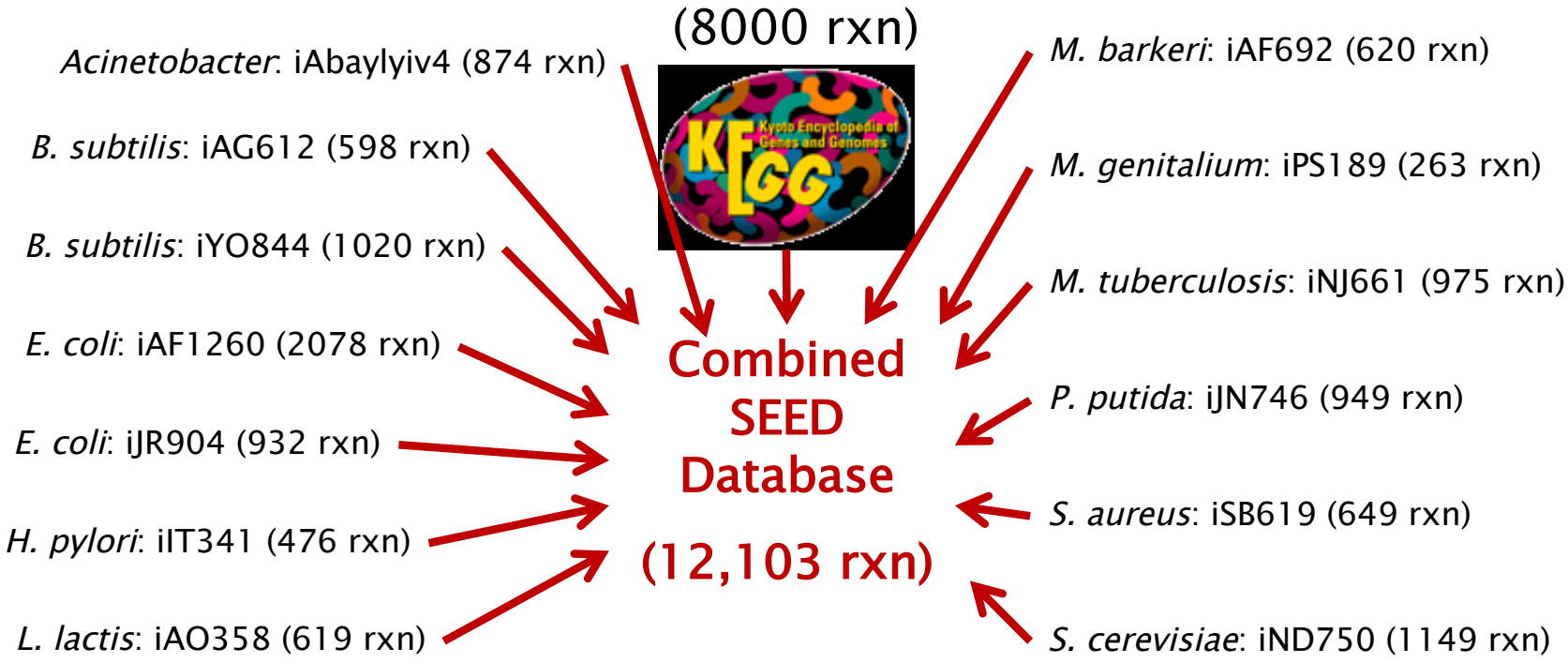
What is a metabolic model?

1. A list of all reactions involved in the metabolic pathways
2. A list of rules associating reaction activity to gene activity
   - Comes from the annotations
3. A biomass reaction listing essential building blocks needed for growth and division

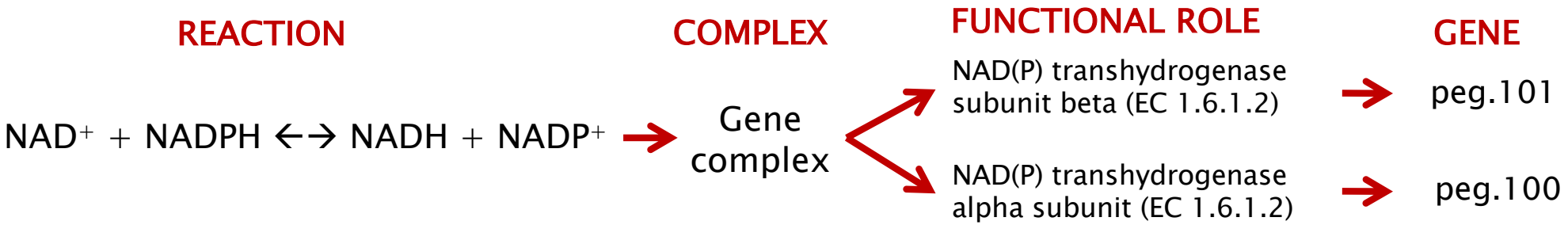
Where does the biochemistry data come from?

- KEGG
- Published hand-curated models



How is the biochemical data encoded?

Reactions are mapped to functional roles in the SEED



- Chemical equations are text encoded
- Reactions are mapped to the annotations

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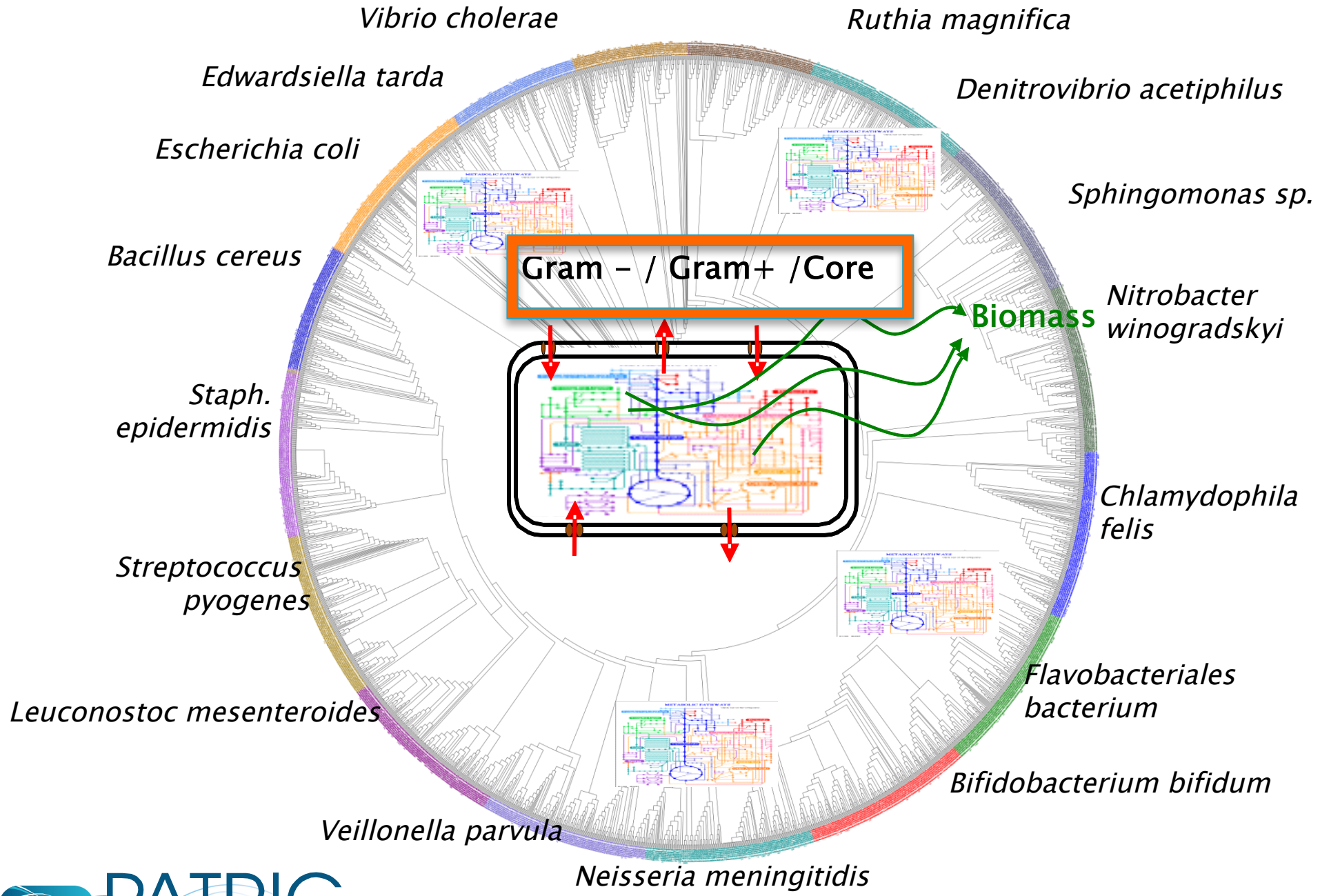
Automated models are created based on a template



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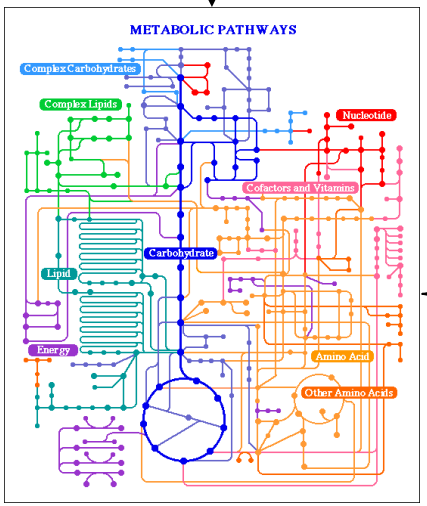
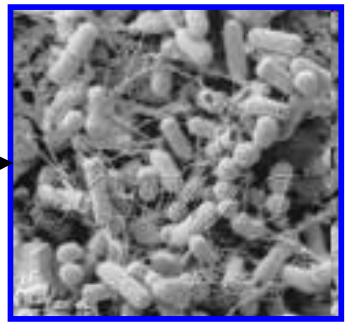
Biomass Composition

- To test growth of the model, we build a biomass objective function template

Nutrients



ATP+H2O→ADP+Pi	Universal	Energy
dATP, dGTP, dCTP, dTTP	Universal	DNA
ATP, GTP, CTP, UTP	Universal	RNA
Amino acids	Universal	Protein
Cofactors and ions	Depends on genome	Misc
Various acylglycerols	Depends on genome	Lipids
Peptioglycan	Any genome with cell wall	Cell wall
Teichoic acid	Gram positive	Cell wall
Core lipid A	Gram negative	Cell wall



Biomass

- Each biomass component may be rejected from the biomass reaction of a model based on the following criteria:
  - Subsystem representation
  - Functional role presence
  - Taxonomy
  - Cell wall types

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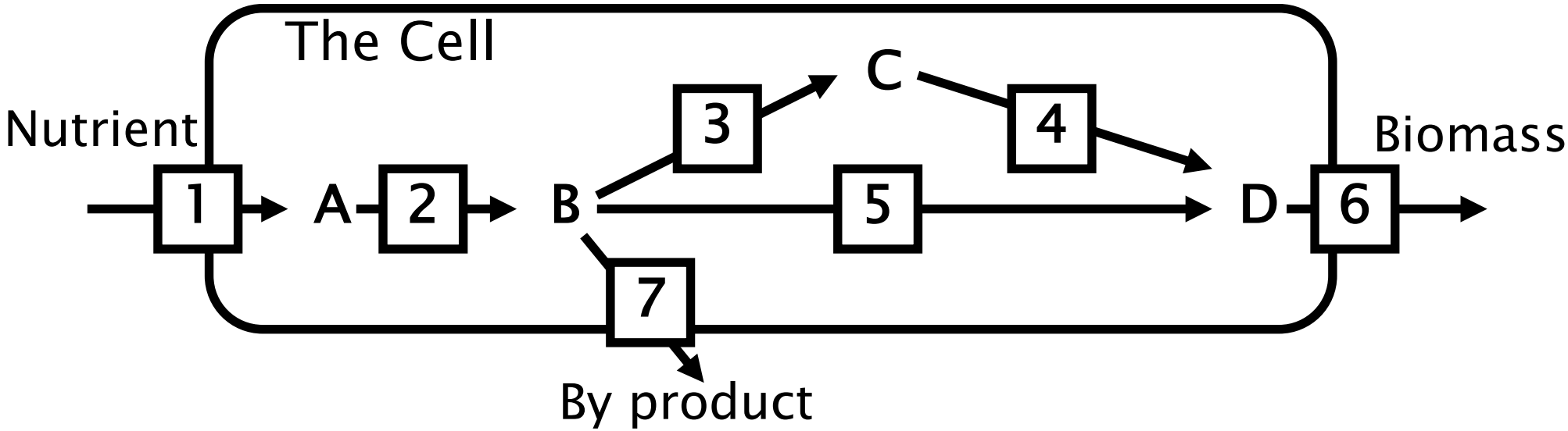
Simulating Metabolism with Flux Balance Analysis



Assuming Steady State:

No internal metabolite is allowed to accumulate

Thus, reaction rates are constrained by mass balances

For example:

At Steady State:

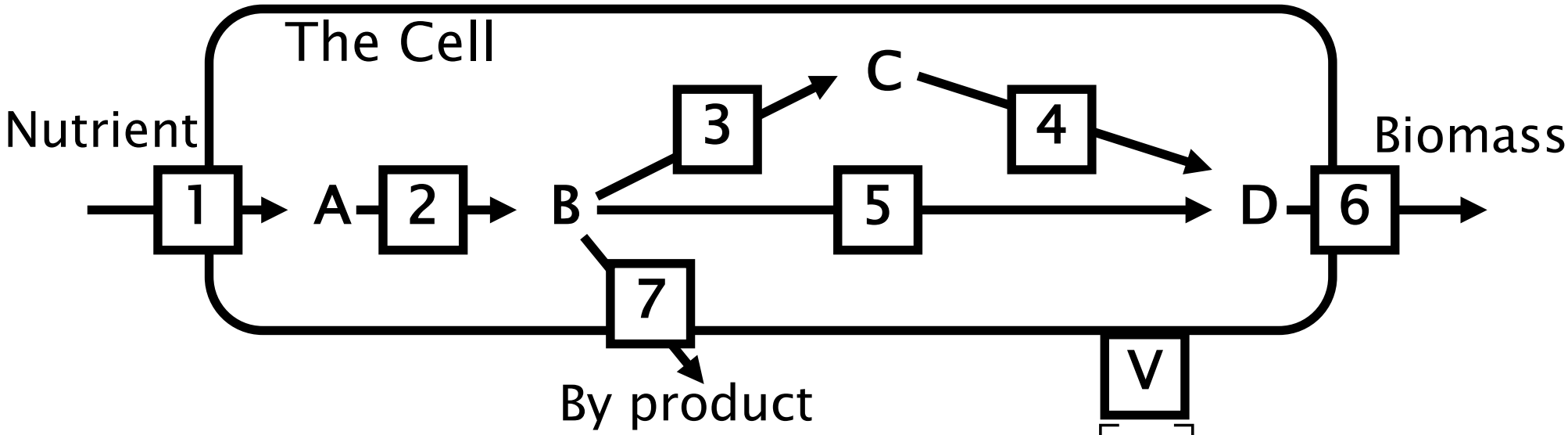
$v_1 = v_2$

$v_2 = v_3 + v_5 + v_7$

$v_3 = v_4$

$v_4 + v_5 = v_6$

Simulating Metabolism with Flux Balance Analysis



$$
\begin{array}{c} \\ A \\ B \\ C \\ D \end{array}
\begin{array}{c}
\begin{array}{ccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 \end{array} \\
\begin{bmatrix}
1 & -1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & -1 & 0 & -1 \\
0 & 0 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 1 & -1 & 0
\end{bmatrix}
\end{array}
\bullet
\begin{array}{c} V \\ \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ v_7 \end{bmatrix} \end{array}
=
\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}
$$

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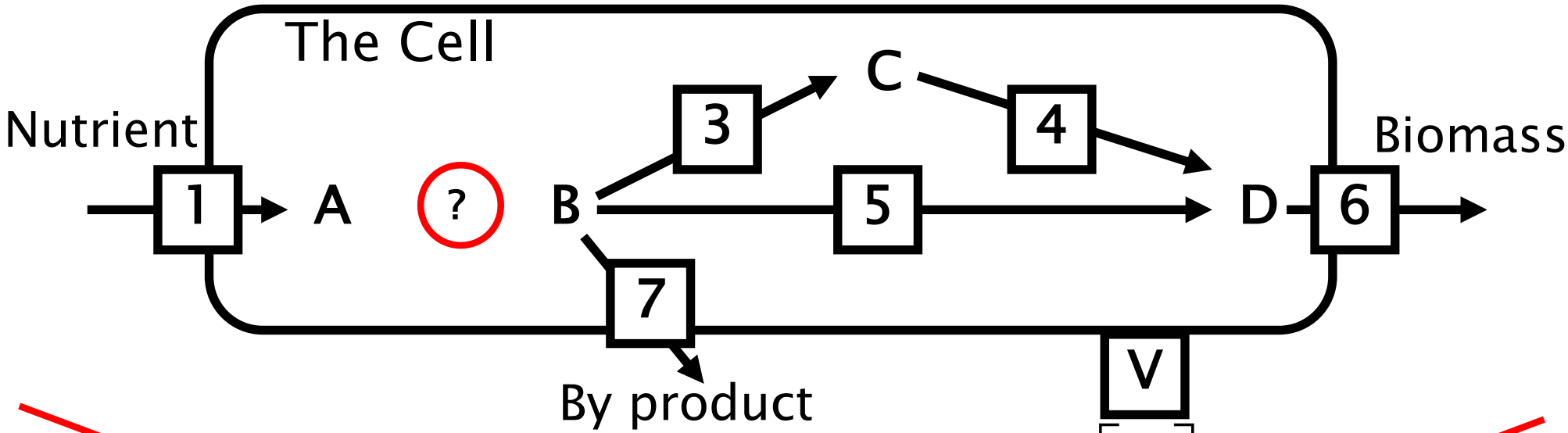
Gapfilling Annotations to Identify Missing Functions



V

	1	2	3	4	5	6	7
A	1	-1	0	0	0	0	0
B	0	1	-1	0	-1	0	-1
C	0	0	1	-1	0	0	0
D	0	0	0	1	1	-1	0

$$\begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ v_7 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

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Modeling Workflow in PATRIC

1. Reconstruct the metabolic model from genome annotations
2. Gapfill metabolic model in specified media condition
3. Run flux balance analysis in specified media condition to simulate all single gene knockouts and predict essential genes
4. Create download files for model in SBML and table formats
5. View model in ModelSEED website for additional browsing and analysis

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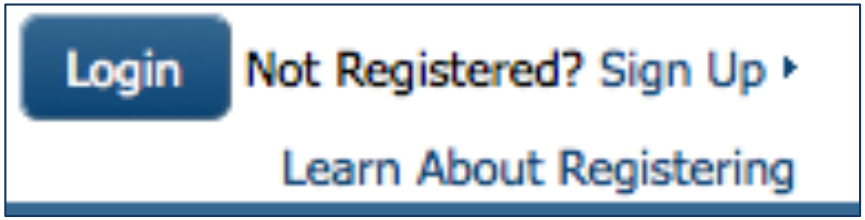
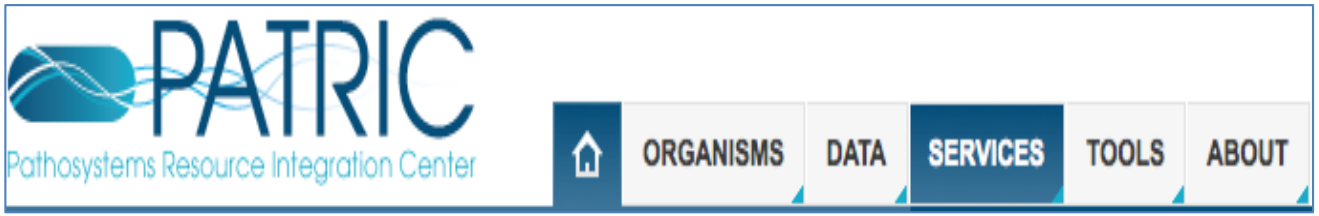
- Login to the PATRIC website at www.patricbrc.org so that you can use your workspace in the downstream analysis.



- On the PATRIC homepage (www.patricbrc.org), open the Services tab at the top of the page.



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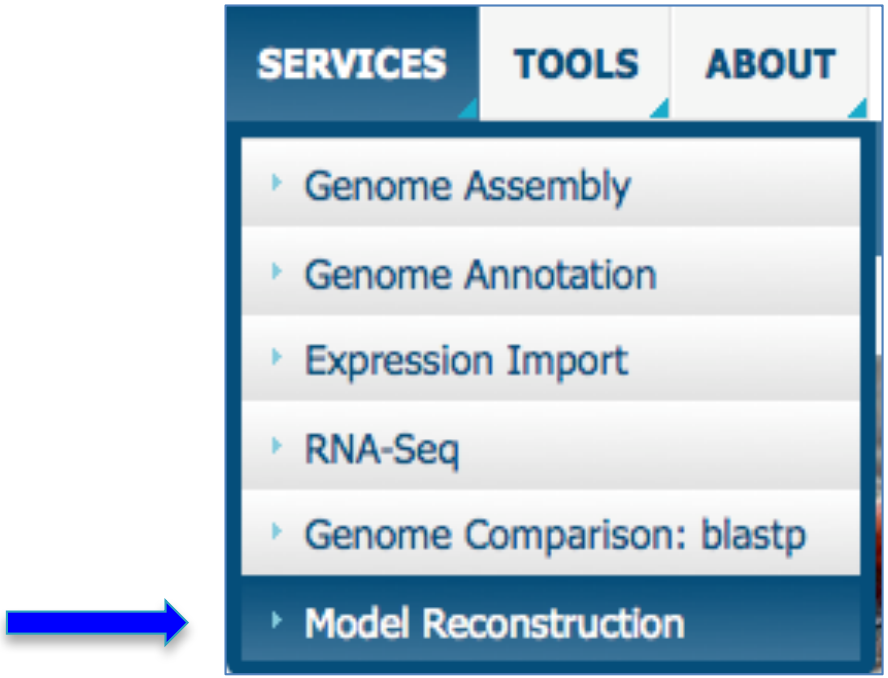
- Using the dropdown menu that appears click on Model Reconstruction. (Highlighted in dark blue below).



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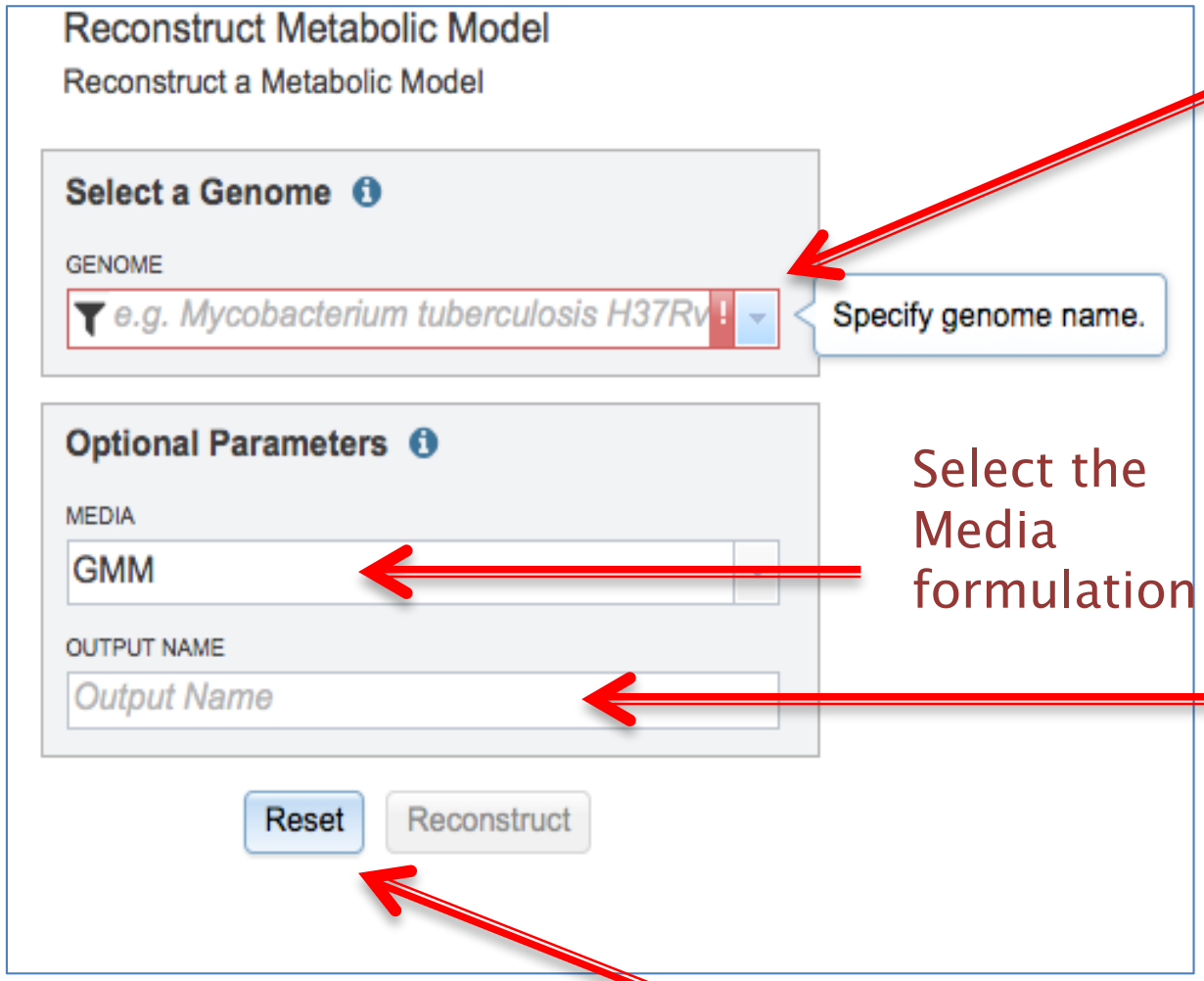
- In PATRIC model reconstruction app user will select



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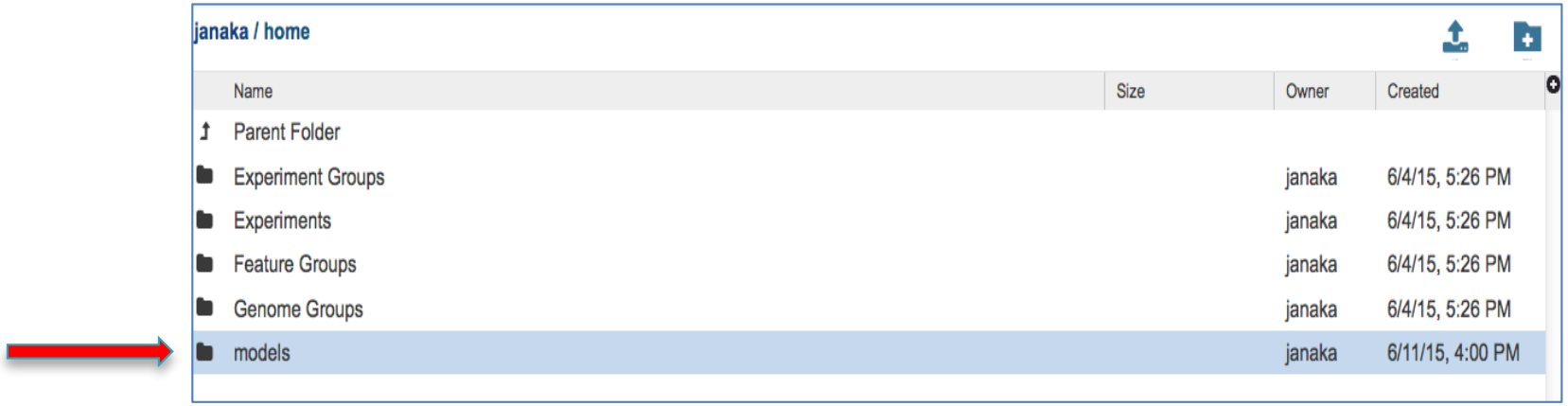
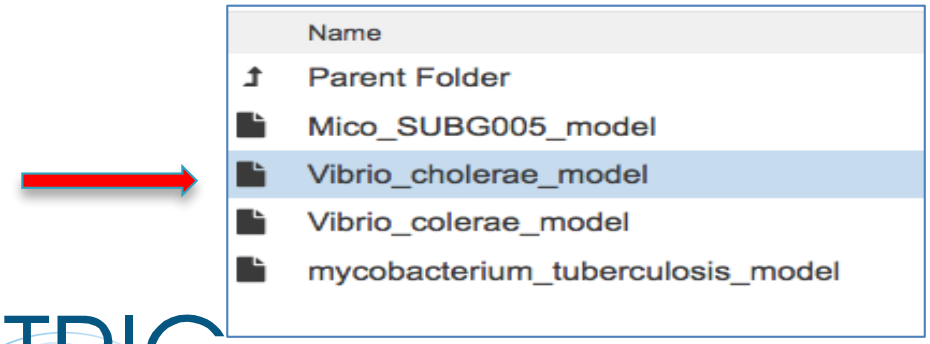
- Output will appear in the 'models' folder where your models are stored



Select the models folder, you can find all of your metabolic model files listed by the user assigned names



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- Select the desired model by clicking on the model file. A table will be displayed consisting of model information (such as organism name, number of genes, reactions, compounds and biomass equations in the model).

Metabolic Model - Vibrio_cholerae_model

Organism	Vibrio cholerae O1 biovar El Tor
File Name	Vibrio_cholerae_model
Reactions	1127
Compounds	1114
Genes	876
Biomasses	1
Source	PATRIC

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❑ In addition you can find downloadable links to

- Flux Balance Analysis table
- Gapfill reaction analysis table
- Set of essential genes
- SBML version of the model
- Model reactions table
- Model compounds table.

A_baumanni_AYE.model.cpdtbl

File Path : ~/Downloads/A_baumanni_AYE.model.cpdtbl

	ID	Name	Formula	Charge	Compartment
1	cpd00113_c0	Isopentenyldiphosphate_c0	C5H10O7P2	-2	Cytosol_0
2	cpd02590_c0	all-trans-Heptaprenyl diphosphate_c0	C35H58O7P2	-2	Cytosol_0
3	cpd02557_c0	Farnesylfarnesylgeraniol_c0	C40H66O7P2	-2	Cytosol_0
4	cpd00012_c0	PPi_c0	H2O7P2	-2	Cytosol_0
5	cpd00067_c0	H+_c0	H	1	Cytosol_0
6	cpd00002_c0	ATP_c0	C10H13N5O13P3	-3	Cytosol_0
7	cpd00196_c0	Acetylphosphate_c0	C2H4O5P	-1	Cytosol_0
8	cpd00029_c0	Acetate_c0	C2H3O2	-1	Cytosol_0
9	cpd00008_c0	ADP_c0	C10H13N5O10P2	-2	Cytosol_0
10	cpd00067_e0	H+_e0	H	1	Extracellular_0
11	cpd00609_c0	D-Glucarate_c0	C6H8O8	-2	Cytosol_0
12	cpd00609_e0	D-Glucarate_e0	C6H8O8	-2	Extracellular_0

fba.0.fluxtbl

File Path : ~/Downloads/fba.0.fluxtbl

	ID	Name	Equation	Flux	Upper bound	Lower bound	Max	Min
1	bio1	GramPositiveBiomass	auto biomass	(0.00793965859468043)10-Formyltetrahydrofolate[c0]+(0.00793965859468043)2-Demethy				
2	rxn12008_c0	rxn12008_c0 (1) Farnesylfarnesylgeraniol[c0] + (1) PPi[c0] <= (1) Isopentenyldiphosphate[c0] + (1) all-trans-Hept						
3	rxn00225_c0	ATP:acetate phosphotransferase_c0	(1) ATP[c0] + (1) Acetate[c0] + (1) H+[c0] <=> (1) ADP[c0] + (1) Acetylphosph					
4	rxn05572_c0	glucarate transport in via proton symport_c0	(1) D-Glucarate[e0] + (1) H+[e0] <=> (1) D-Glucarate[c0] + (1) H+					
5	rxn10215_c0	anteisoheptadecanoyl-1-acylglycerol-3-phosphate O-acyltransferase_c0	(1) 1-anteisoheptadecanoyl-sn-glycerol 3-					
6	rxn02483_c0	4-Carboxymuconolactone carboxy-lyase_c0 (1) 4-Carboxymuconolactone[c0] + (1) H+[c0] => (1) 3-oxoadipate-enol-lact						
7	rxn00802_c0	N-(L-Argininosuccinate) arginie-lyase_c0	(1) L-Argininosuccinate[c0] <=> (1) Fumarate[c0] + (1) L-Arginine[c0]					
8	rxn03638_c0	Acetyl-CoA:D-glucosamine-1-phosphate N-acetyltransferase_c0 (1) Acetyl-CoA[c0] + (1) D-Glucosamine1-phosphate[c0]						
9	rxn08851_c0	Lysophospholipase L2 (2-acylglycerophosphoglycerol, n-C18:1) c0 (1) 2-Acyl-sn-glycero-3-phosphoglycerol octadec-1						

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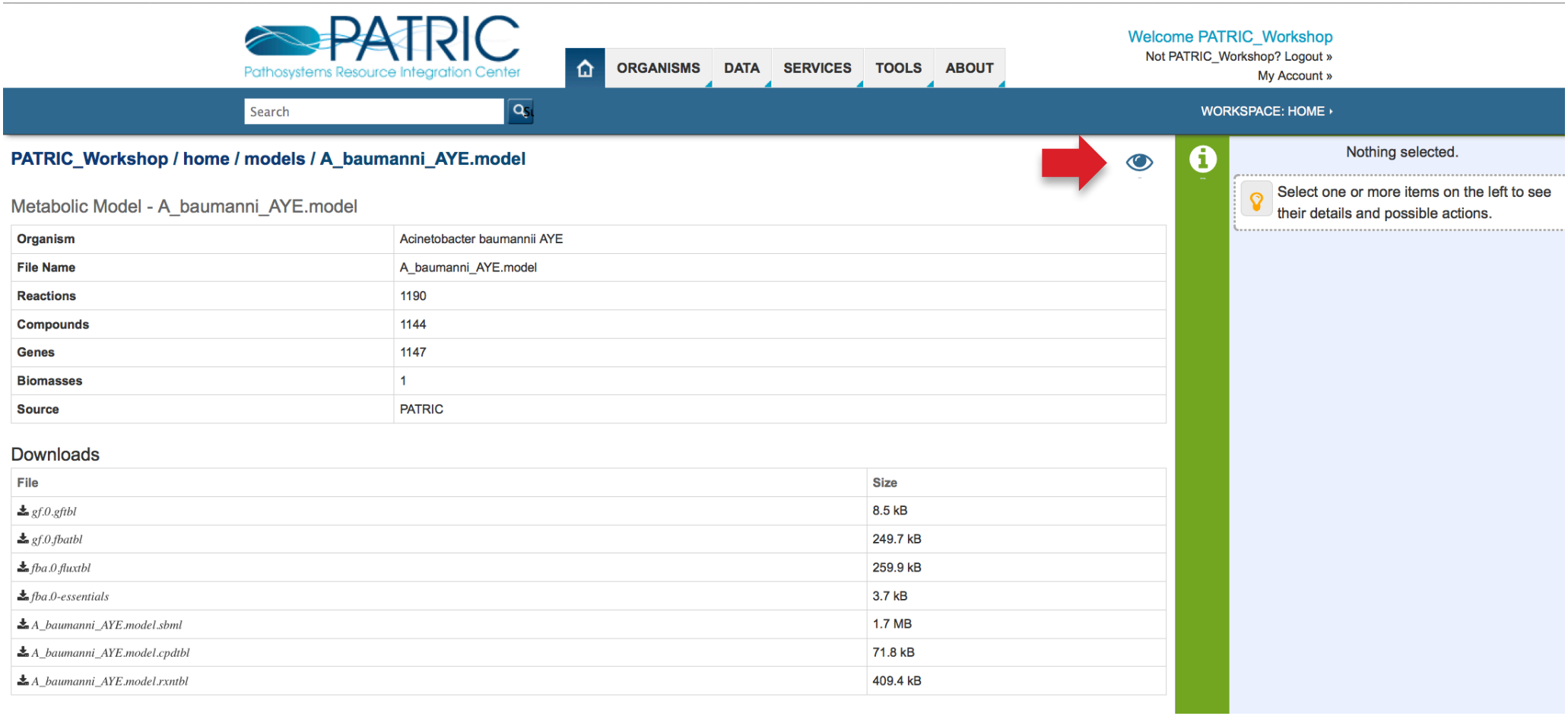

- Clicking the "eye ball" icon takes you to modelSEED for additional browsing

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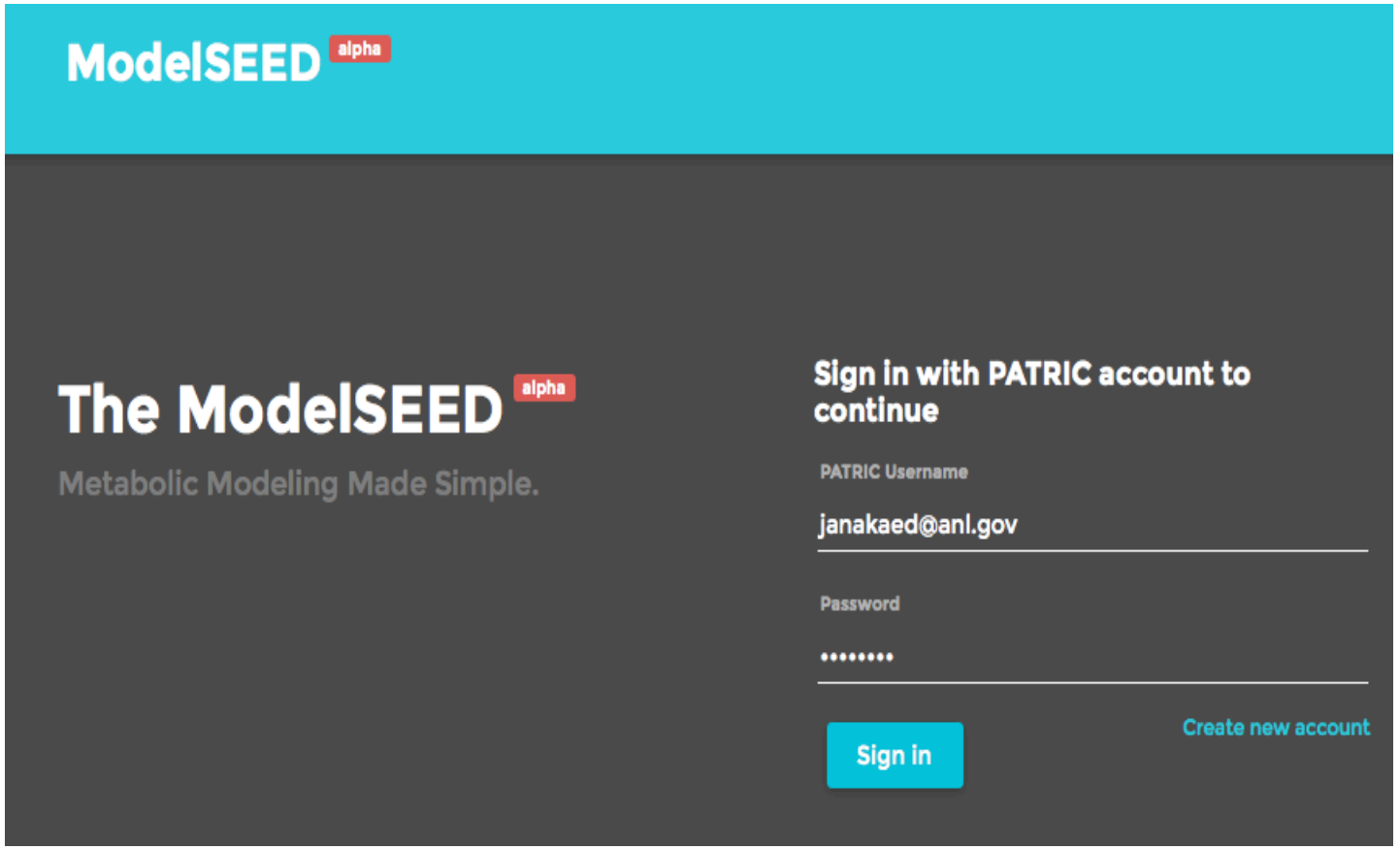
modelSEED browsing environment



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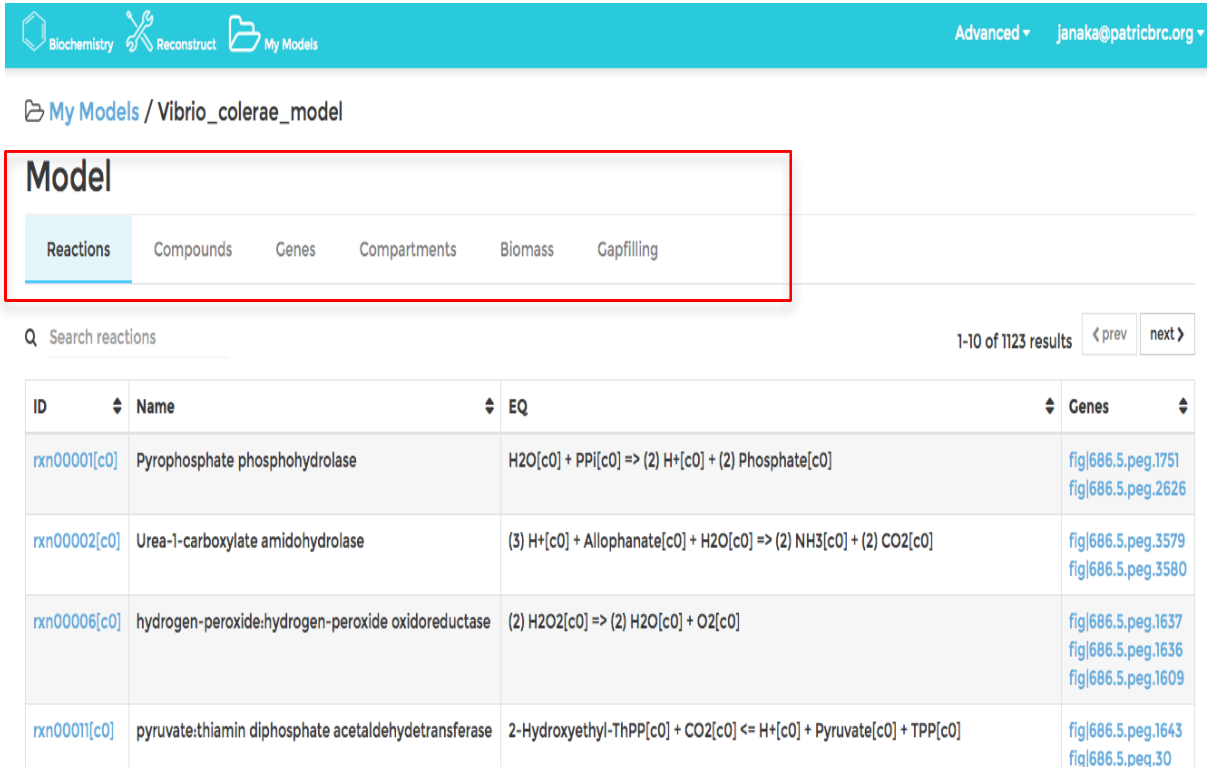
View model details in modelSEED



- Reactions
- Compounds
- Genes
- Gapfilled reactions
- Compartments of the model
- Weighted components of the Biomass

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Future Directions

- Short term
  - Enhanced visualization in PATRIC
  - Compare models
  - Increased curation of promiscuous enzymes, and peripheral reactions
- Longer term
  - RNAseq
  - TnSeq
  - Regulatory modeling

Acknowledgements

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