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A NETWORK VISUALIZATION AND FLUX ANALYSIS TOOL

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Metabolic Network Model-based Design

“All models are wrong, some are useful”

-- George Box

- “wrong” is a tautology
- Why do we need to maximize usefulness?
 - New organisms, new networks
 - Increasing accuracy and robustness
 - Expanding coverage more subsystems

Metabolic Network Models

Design networks for bioproduct production and optimization

- Understand biochemical networks
- Gene knockouts
- Gene additions
- Media optimization
- Construction and validation

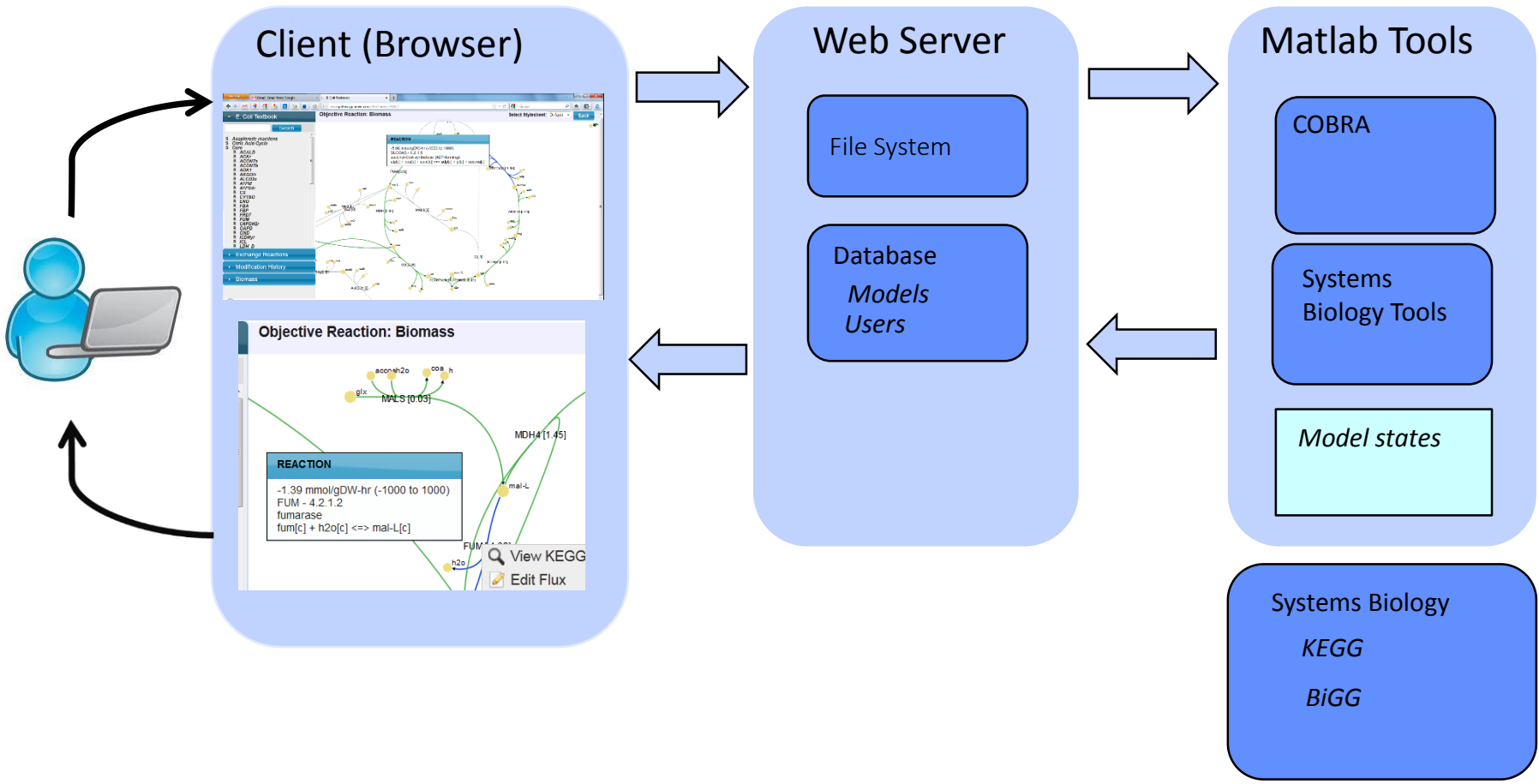
Optimizing Design Process

- Increase efficiency and effectiveness
 - Maximally exploit existing knowledge
 - Organism network models
 - Metabolite/Reaction databases
 - Optimized design environment
 - Enhance human capability
 - Human--software interface
 - Manage cognitive load
- Present prototype web-based tool
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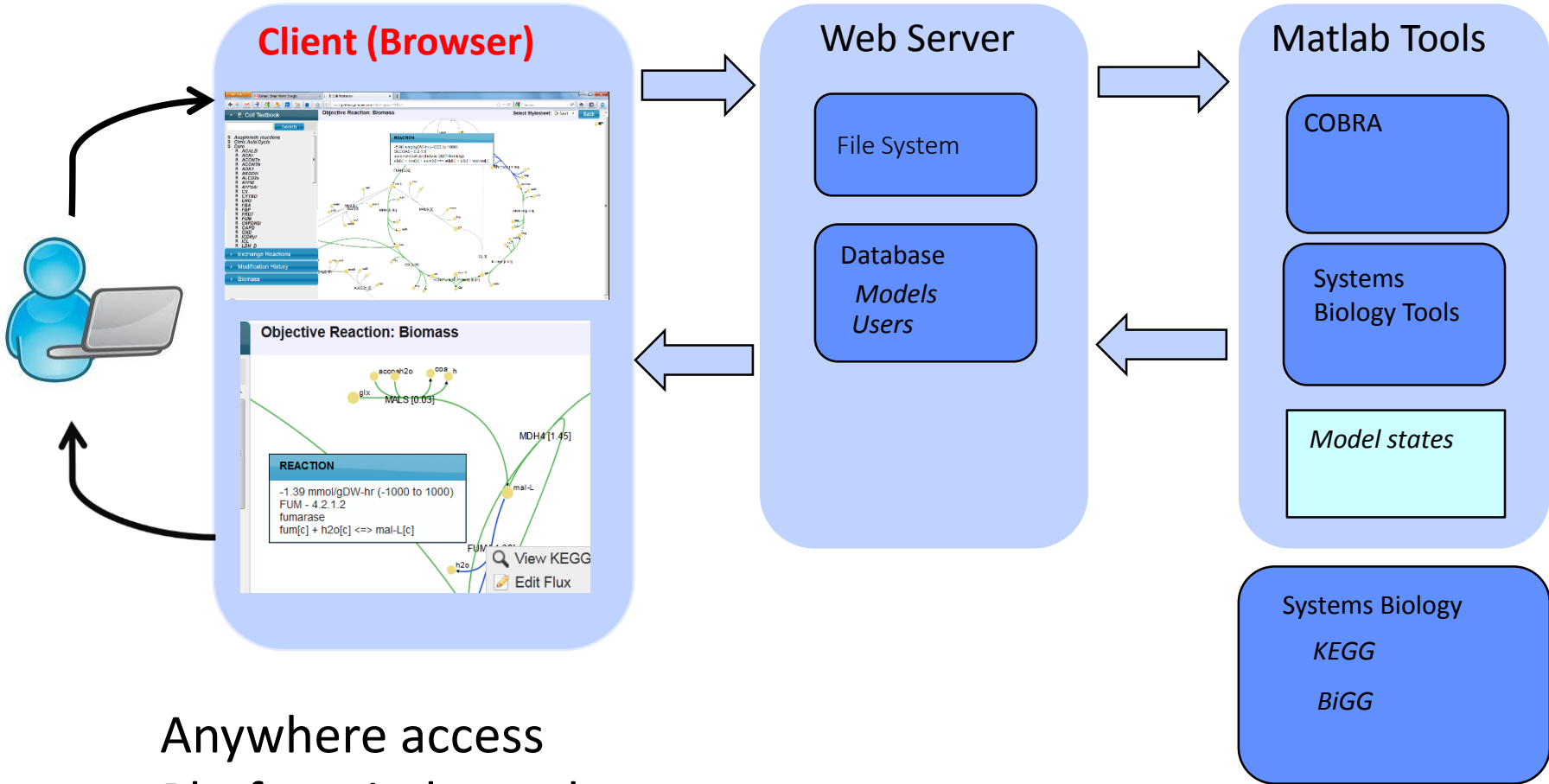
Barriers to Rapid Design

- Knowledge is dispersed
- Analysis tools are difficult to use
- State of design hard to manage
- Too slow with complex models
- Collaboration is hard

Modeling Framework

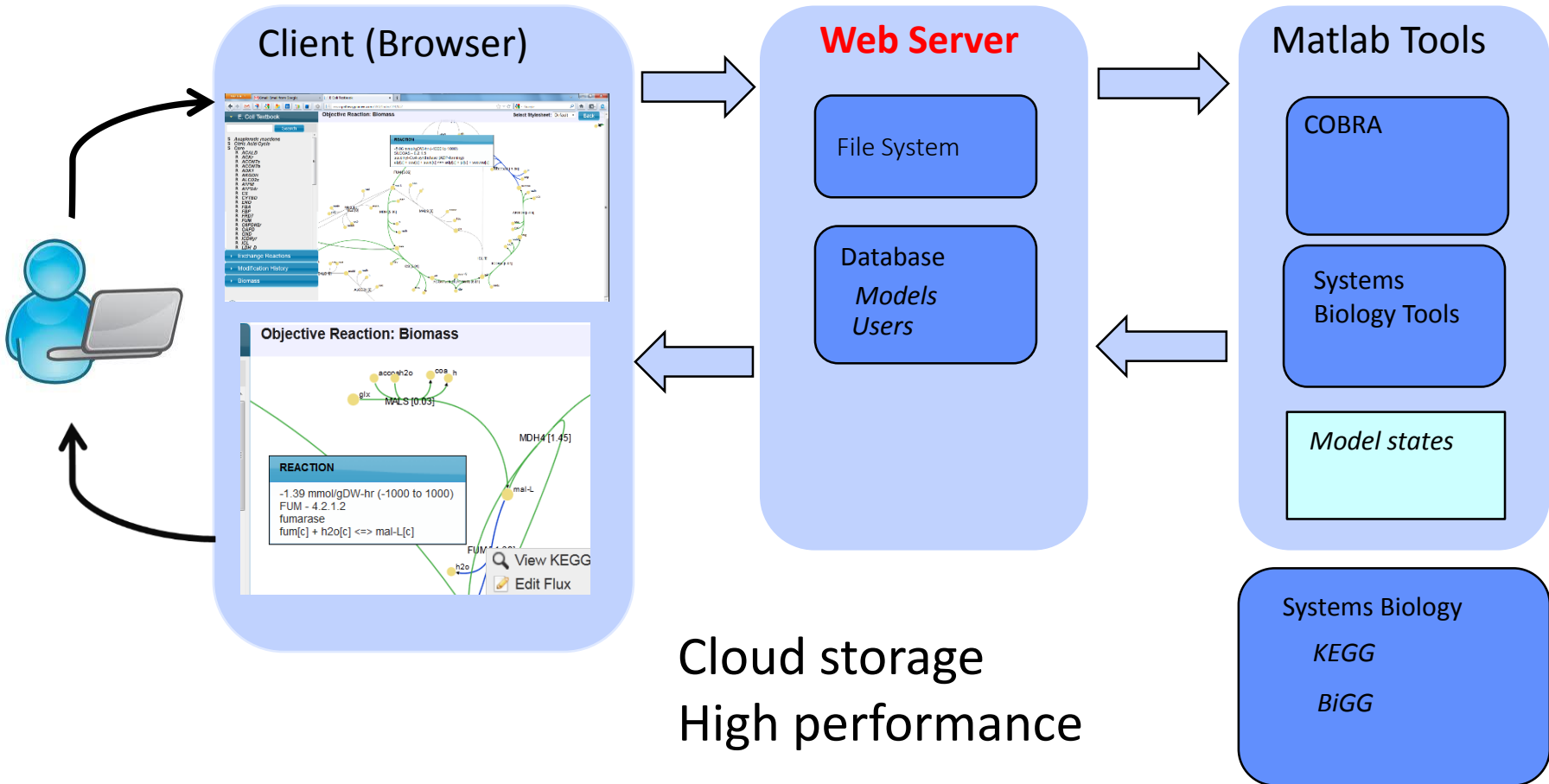


Modeling Framework

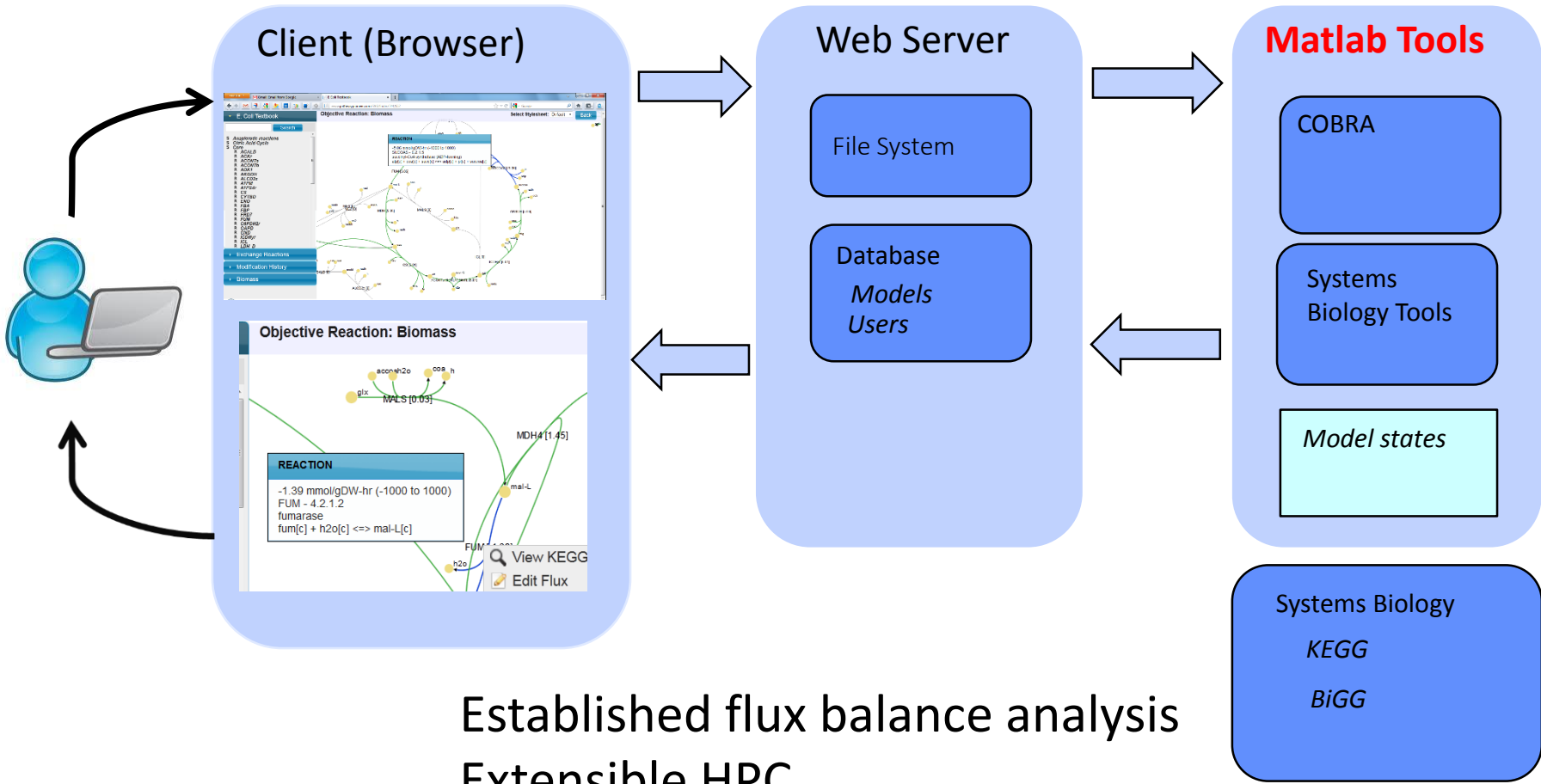


Anywhere access
Platform independent

Modeling Framework



Modeling Framework



Demonstration

- Search
- Visualization
- Navigation
- Modification

Dynamic Solution Framework

- **Tools and knowledge together in web-based system**
- Tools run on design objects (reaction)
- Results visualized on the design (flux)
- Design state is visually organized
- Alternative model designs shared among members

E. Coli Textbook

Search

- S Anaplerotic reactions
- S Citric Acid Cycle
- S Core
 - R ACALD
 - R ACKr
 - R ACONTa
 - R ACONTb
 - R ADK1
 - R AKGDH
 - R ALCD2x
 - R ATPM
 - R ATPS4r
 - R CS
 - R CYTBD
 - R ENO
 - R FBA
 - R FBP
 - R FRD7
 - R FUM
 - R G6PDH2r
 - R GAPD
 - R GND
 - R ICDHyf
 - R ICL
 - R LDH D

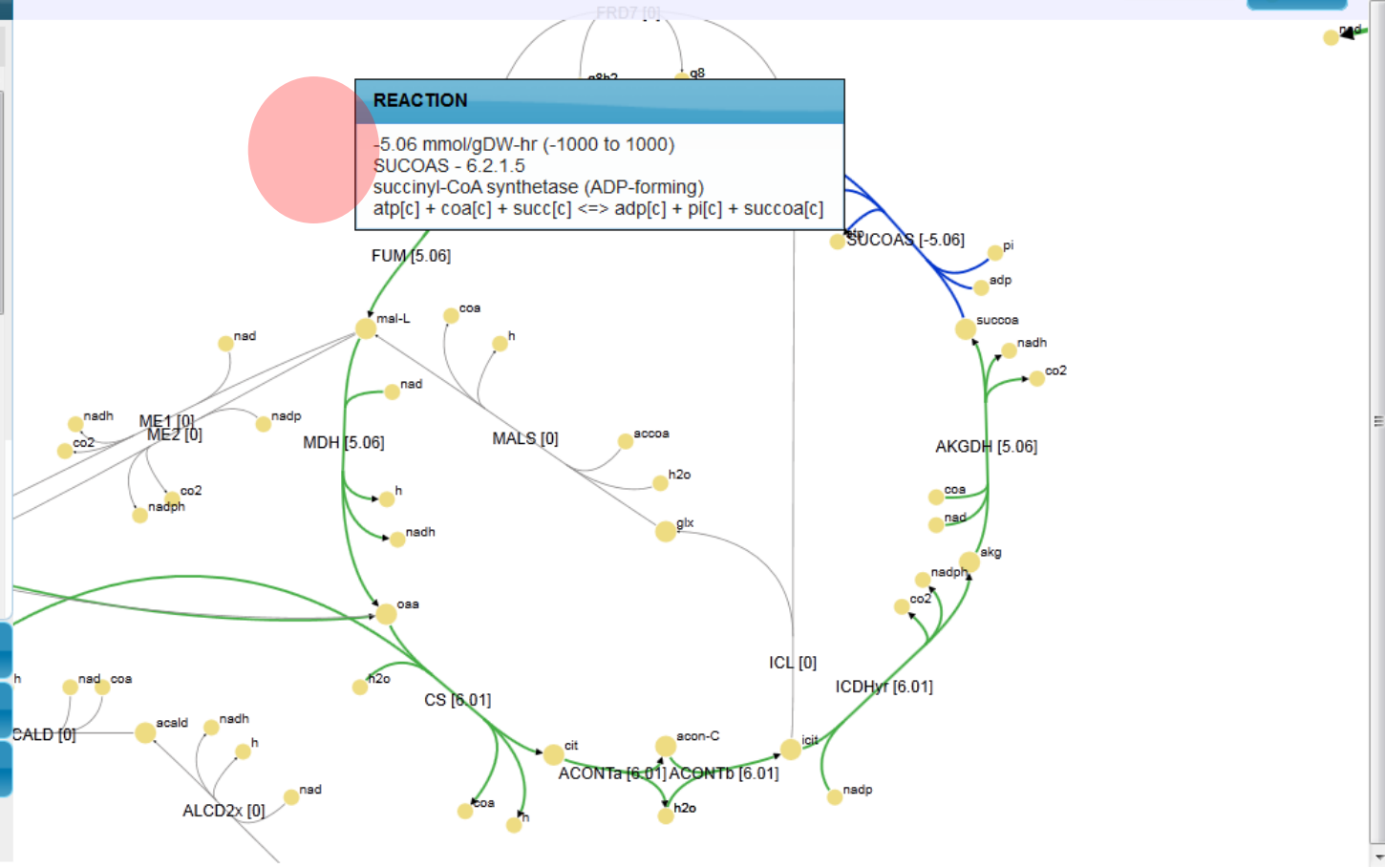
Exchange Reactions

Modification History

Biomass

Objective Reaction: Biomass

Select Stylesheet: Default Back



Solution Framework

- Tools and knowledge together in web-based system
- **Tools run on design objects (reaction)**
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Firefox | Gmail: Email from Google | H Pylori iIT341 | DBGET Search Result: KEGG polyhydr... | www.pathwaypioneer.com/SVG/Index/543/637

Objective Reaction: Biomass | Select Stylesheet: Default | Back

H. Pylori iIT341

Search

- Alanine Metabolism
- Amino Acid Degradation
- Aminosugar Metabolism
- Asparagine Metabolism
- Aspartate Metabolism
- ATP de novo Synthesis
- Biotin Biosynthesis
- Chorismate Biosynthesis
- Chorismate Metabolism
- Core
- dATP Biosynthesis
- dCTP Biosynthesis
- dGTP Biosynthesis
- dTTP Biosynthesis
- dUTP Biosynthesis
- Entner-Doudouroff Pathway
- Exchange
- Fatty Acid Synthesis
- Folate Biosynthesis
- Fucose Biosynthesis
- Gln Biosynthesis
- Glutamate Biosynthesis
- Glutamate Metabolism
- Glycerolipid Synthesis
- Glycolysis

Exchange Reactions
Modification History
Biomass

REACTION
-1.39 mmol/gDW-hr (-1000 to 1000)
FUM - 4.2.1.2
fumarase
fum[c] + h2o[c] <=> mal-L[c]

View KEGG
Edit Flux
Knockout
Set as Objective
Set Biomass Objective
Cancel

Solution Framework

- Tools and knowledge together in web-based system
- Tools run on design objects (reaction)
- **Results visualized on the design (flux)**
- Design state is visually organized
- Alternative model designs shared among members

Firefox | Gmail: Email from Google | E Coli Textbook | DBGET Search Result: KEGG polyhydr... | www.pathwaypioneer.com/SVG/Index/544/638

E. Coli Textbook | **Objective Reaction: Biomass** | Select Stylesheet: Default | Back

Search

- S Anaplerotic reactions
- S Citric Acid Cycle
- S Core
- S Exchange
- S Glutamate Metabolism
- S Glycolysis/Gluconeogenesis
- S Inorganic Ion Transport and Metabolism
- S Oxidative Phosphorylation
- S Pentose Phosphate Pathway
- S Pyruvate Metabolism
- S Transport, Extracellular

Exchange Reactions

Modification History

Biomass

REACTION

45.51 mmol/gDW-hr (-1000 to 1000)
 ATPS4r - 3.6.3.14
 ATP synthase (four protons for one ATP)
 $adp[c] + 4 h[e] + pi[c] \rightleftharpoons atp[c] + h2o[c] + 3 h[c]$

Solution Framework

- Tools and knowledge together in web-based system
- Tools run on design objects (reaction)
- Results visualized on the design (flux)
- **Design state is visually stored**
 - **No hidden state**
- Alternative model designs shared among members

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Objective Reaction: Biomass | Select Stylesheet: Default | Back

E. Coli Textbook
 Exchange Reactions
 Modification History

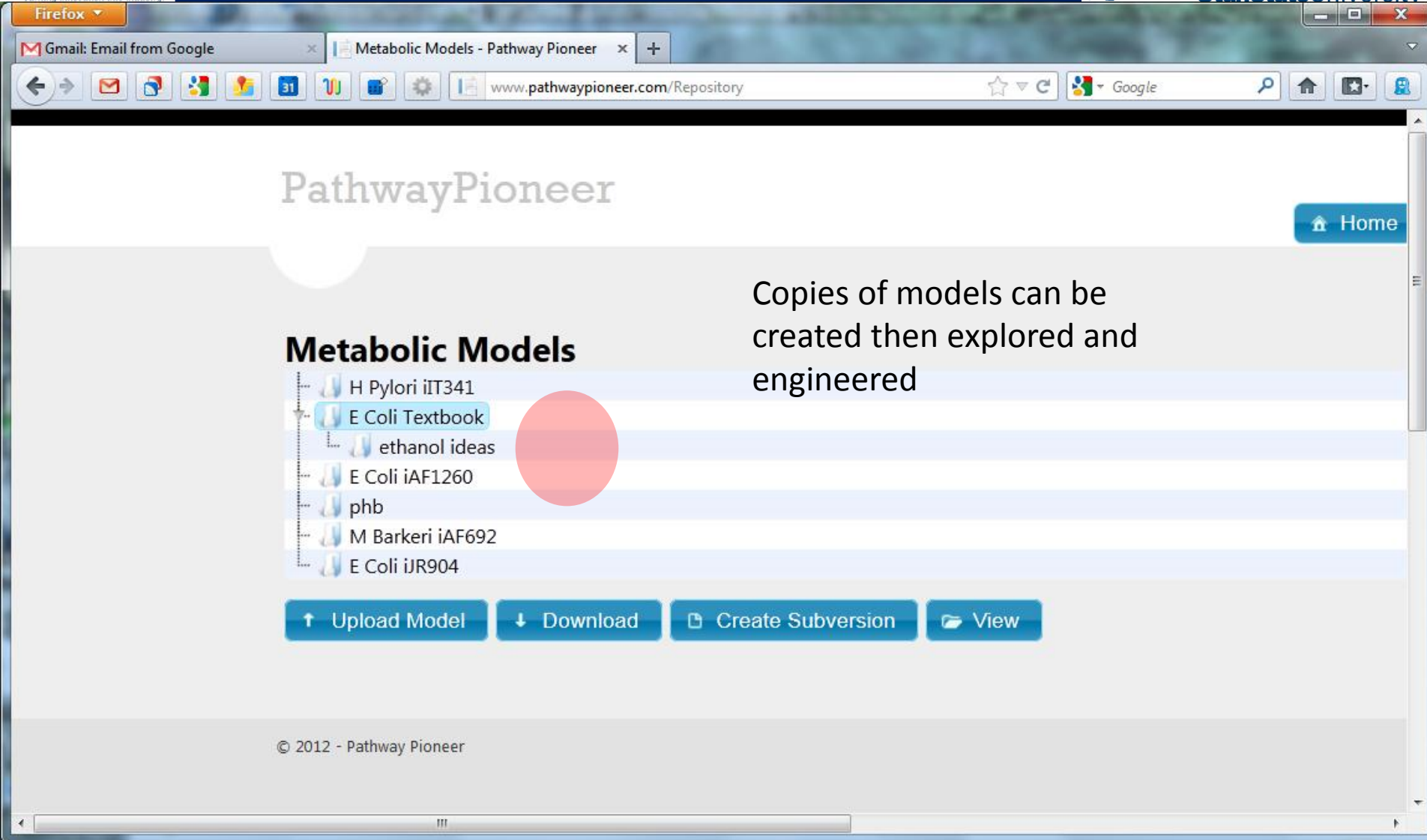
Reaction	Lower	Upper
CYTBD	0	0

r5p [0.15]
 THDZ [3.83]
 nadh
 nad
 nadp
 NADTRHD [0]
 nadph
 amp
 atp
 h2o
 h
 ADK1 [0]
 ATPM [8.39]
 pi
 ATPS4r [-0.46]
 o2
 h2o
 h
 CYTBD [0]
 q3
 q3h2
 nadh
 h
 nad
 NADH16 [0]
 h
 nad
 FRD7 [0]
 q3h2
 q6

Which reaction was knocked out?
What is the objective?

Solution Framework

- Tools and knowledge together in web-based system
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Firefox

Gmail: Email from Google

Metabolic Models - Pathway Pioneer

www.pathwaypioneer.com/Repository

PathwayPioneer

Home

Copies of models can be created then explored and engineered

Metabolic Models

- H Pylori iIT341
- E Coli Textbook
- ethanol ideas
- E Coli iAF1260
- phb
- M Barkeri iAF692
- E Coli iJR904

Upload Model Download Create Subversion View

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- Applicable over multiple models
- Visually centered
- Intuitive to use
- Rapid design exploration
- Save and share designs/results
- Multiple applications within bioengineering

Future work

- Short term:
 - Expand user base
 - Apply to SBI systems
- Longer term:
 - Scale to larger more complex systems
 - Server cloud computing
 - Eukaryotic cells: SF9
 - Regulatory and Signaling
 - Model reconstruction support

Thank you
Questions?