How to use modelBorgifier

Author: John T. Sauls, UCSD

INTRODUCTION

modelBorgifier is a package that allows users to compare and combine COBRA Toolbox ("Toolbox") style metabolic reconstructions ("models"). It is explicity designed with the notion that models from different sources use disparate naming and annotation schemes. It uses greedy string comparisons as well as network topology to identify reactions and metabolites shared and unique between models. The procedure is GUI based, and uses manual matches to train learning methods that facilitate auto-matching.

Please read the publication (1) and accompanying manual for more information. If you find this package helpful for your work please cite:

Sauls, J. T., & Buescher, J. M. (2014). Assimilating genome-scale metabolic reconstructions with modelBorgifier. *Bioinformatics* (Oxford, England), 30(7), 1036–8. http://doi.org/10.1093/bioinformatics/btt747

Correspondance: johntsauls@gmail.com

Developed at: BRAIN Aktiengesellschaft, Microbial Production Technologies Unit, Quantitative Biology and Sequencing Platform, Darmstaeter Str. 34-36, 64673 Zwingenberg, Germany. www.brain-biotech.de

PROCEDURE

In this tutorial we will compare the E. coli core metabolism model Ecoli_core to the Helicobacter pylori model iIT341 (2). An outline of the procedure is as follows:

1. Installation and set-up

Assuming you have succsessfully installed and tested the COBRA Toolbox for Matlab no additional configuration should be necessary.

2. Load and verify the comparision model (Cmodel)

The comparison model (Cmodel) is any model that can be read into the COBRA Toolbox. Cmodel is "compared to" the template model (see next step). Our Cmodel will be the Ecoli_core model.

3. Load and verify the template model (Tmodel)

The template model (Tmodel) can be simply any model, or it can be an amalgamation of models that have already been combined via modelBorgifier. Our Tmodel will be iIT341.

4. Compare models

Every reaction in Cmodel is compared against every reaction in Tmodel and given a similarity score based on 40 parameters. This computationally expensive step is done before user-guided matching.

5. Match models

Matching models is done with command reactionCompare. reactionCompare calls a GUI that allows the user to choose a match for a given reaction in Cmodel, and also to match the metabolites for that reaction. Comparison is facilitated by automation and proper weighting of the scoring parameters.

6. Merge models

Once all reactions and metabolites have been reviewed, Cmodel and Tmodel can be merged into a composite model. The composite model is the most direct way to return statistics on the similiarity between two models.

7. Extract a model

Models merged together or into an existing composite model can be later retrieved with readCbTmodel.m. This reproduces the initial model with additional annotation information.

8. Save work

As the composite model can be used as a template for future comparisions, save it.

2. Load and verify the comparision model (Cmodel)

Put longer description here

i. Load the E. coli core model

We are going to use the E. coli core model located in the test/models/ directory of the Toolbox.

```
% Load the model using the Toolbox function
Cmodel = readCbModel('ecoli_core_model.mat', ...
                     'modelDescription', 'Ecoli_core')
```

ii. Verify the model

modelBorgifier requires that both the comparison and template model have the proper data arrays before comparision. This function creates those arrays if they are absent and populates them when possible. You will also be prompted to keep or edit the model name ("description"). Simply press 'y' in for this tutorial.

Note that this verify function (verifyModelMB) is different from the Toolbox function verifyModel

```
% Verify model has the necessary fields required for later processing
Cmodel = verifyModelMB(Cmodel, 'keepName', 'Verbose');
```

3. Load and verify the template model (Tmodel)

Explain the point of loading the Tmodel

i. Load the model iIT384

We will be using the *Heliobacter pylori* model packaged with the Toobox as our template model. Load it the same way as any model. If you had previous combined two models using modelBorgifie, you could simply load that composite model as your Tmodel.

```
global CBTDIR
Tmodel = readCbModel([CBTDIR filesep 'test' filesep 'models' filesep 'iIT341.xml'], ...
                     'modelDescription', 'iIT341')
```

ii. Verify and convert Tmodel

Because we are just using an abritrary model as our template model, we need to verify it and convert it to a proper template model. You will be asked to confirm the name. Note that the final Tmodel, 'lb', 'ub', and 'Models are structures containing information specific to each model.

```
% If Tmodel is just another model, verify it as well and convert it to a
% proper format for comparison. Also make sure it carries flux.
Tmodel = verifyModelMB(Tmodel, 'keepName', 'Verbose');
Tmodel = buildTmodel(Tmodel);
```

4. Compare models

comparCbModels scores all reactions in Cmodel against all reactions in Tmodel. It returns Score, a 3D matrix with size (# of reactions in Cmodel, # of reactions in Tmodel, # of scoring parameters per reaction). There are 40 scoring parameters, such as name, E.C. number, metabolite similiarity, and network topology. The returned Cmodel and Tmodel have some appendend information, but are functionally the same as the inputs. The structure Stats contains information about the best matches per each reaction.

Additionally, the function outputs some graphs describing the reaction scores. In particular the bottom right graph shows a reaction by reaction matrix of the scores. Lighter colors indicate a higher matching score between any two reactions. Note the transport reactions along the bottom and right of the graph.

```
[Cmodel, Tmodel, score, Stats] = compareCbModels(Cmodel, Tmodel, 'Verbose');
```

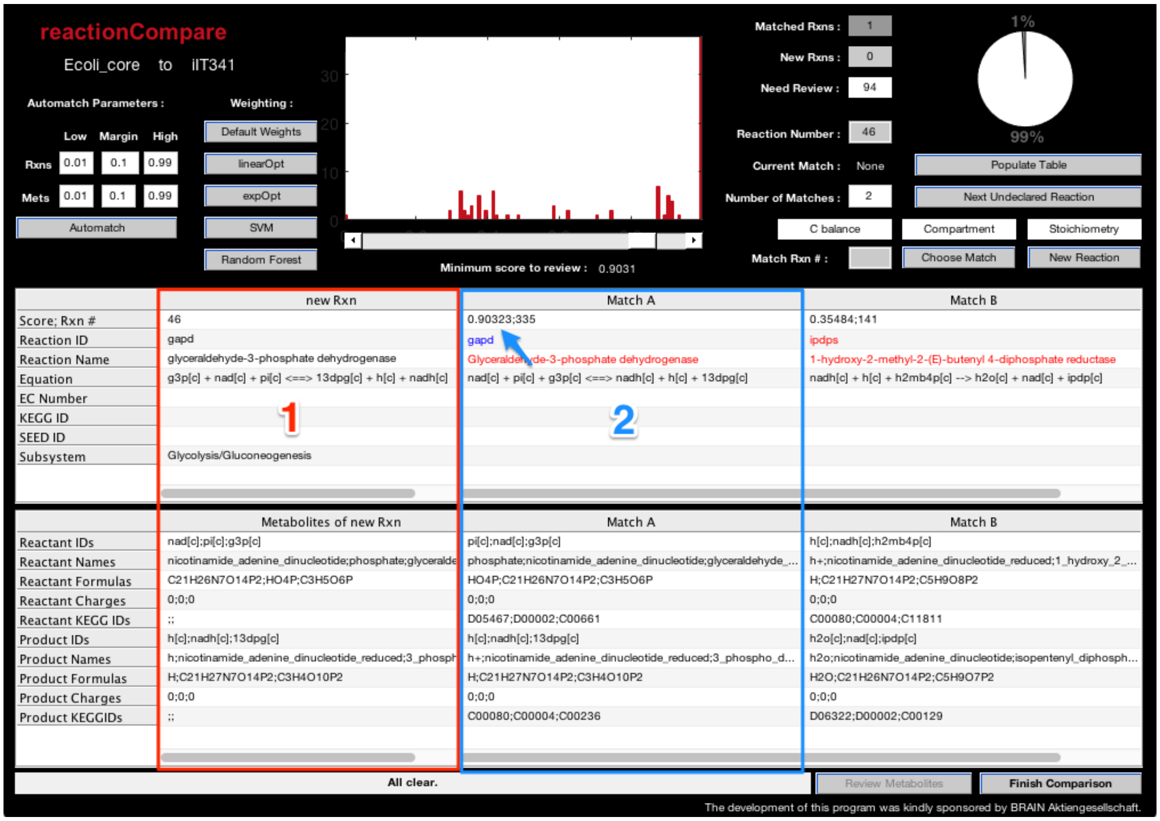
5. Match models

reactionCompare is the major step in the comparison process. It will launch a GUI that facilitates reaction-by-reaction comparision between Cmodel and Tmodel. This section will outline the different functions of the GUI.

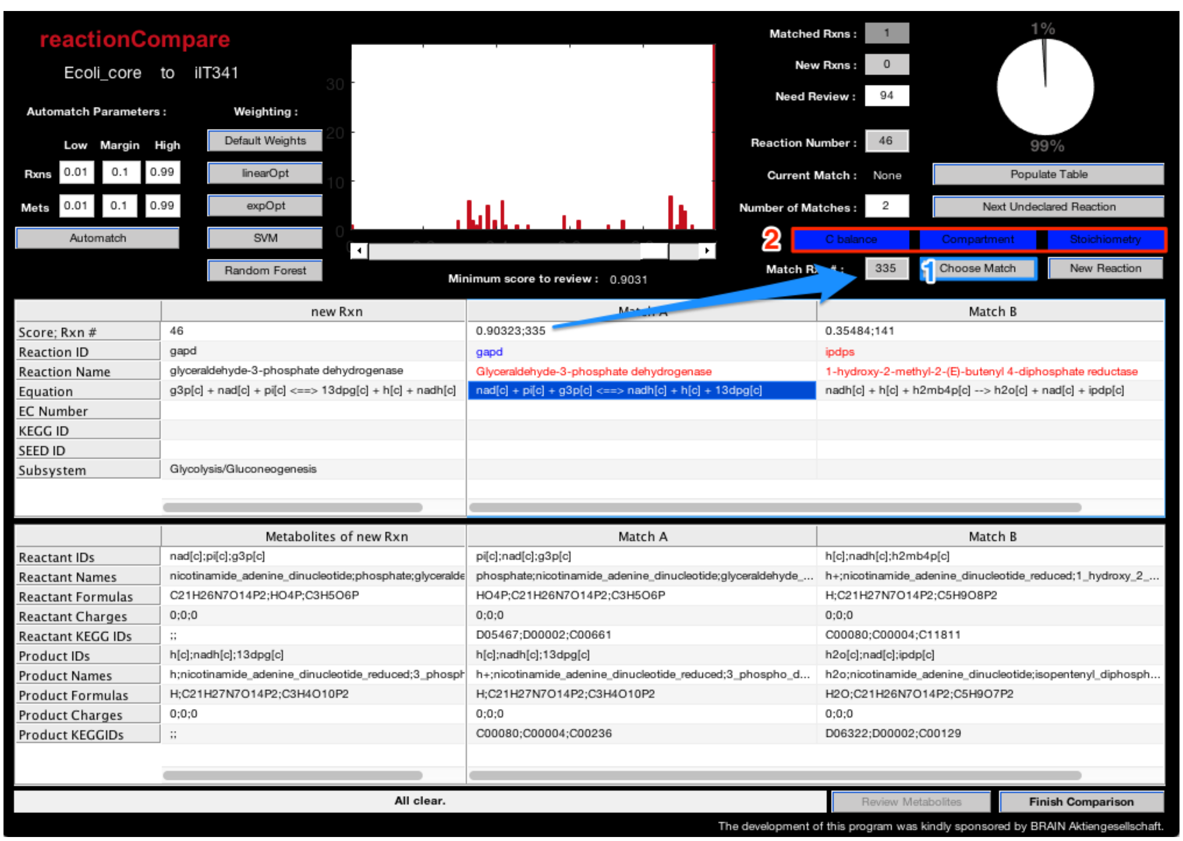
NOTE: You must run reactionCompare in the Command Window, as GUIs are not proprely rendered within the Matlab Live script.

```
if ~exist('rxnsList', 'var') || ~exist('metList', 'var') || ~exist('Stats', 'var')
    rxnList = [];
    metList = [];
    Stats = [];
end

% Initial comparison and matching.
% [rxnList, metList, Stats] = reactionCompare(Cmodel, Tmodel, score);

% Subsequent comparisons and matching.
% [rxnList, metList, Stats] = reactionCompare(Cmodel, Tmodel, score, rxnList, metList, Stats);
```

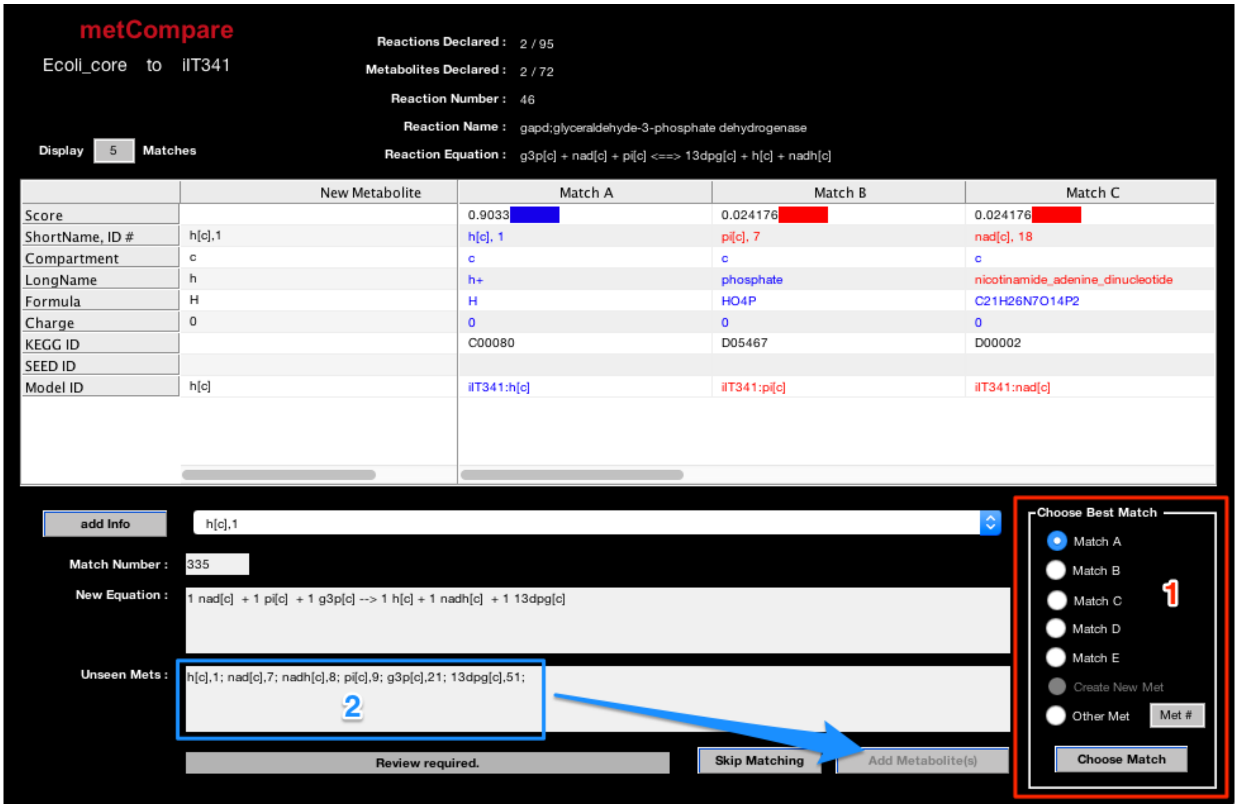
i. Comparing similarity of reactions. Reactions from Cmodel (Ecoli_core) are displayed 1-by-1 along with the best matches from Tmodel. Information about the current reaction (gapd, reaciton #46) can be seen in the red box labeled 1. Information about the best match from Tmodel (gapd, reaction #335) is the blue box labeled 2. The score of this reaction is indicated by the blue arrow. The subsequent best reactions are to the right (Match B).



ii. <u>Choose a matching reaction or declare a new reaction</u>. To pair a reaction from Cmodel to a reaction in Tmodel, put the reaction number of the match into the box and press "Choose Match" (indicated by the arrow and the blue box labeled 1). If there is no appropriate match then click "New Reaction". By clicking on any of the information in the match table (such as the highlighted reaction equation under Match A), the blocks in the red box labeled 2 will indicated if this reaction matches the current reaction from Cmodel in terms of carbon balance, compartment, and metabolite stoichiometry.

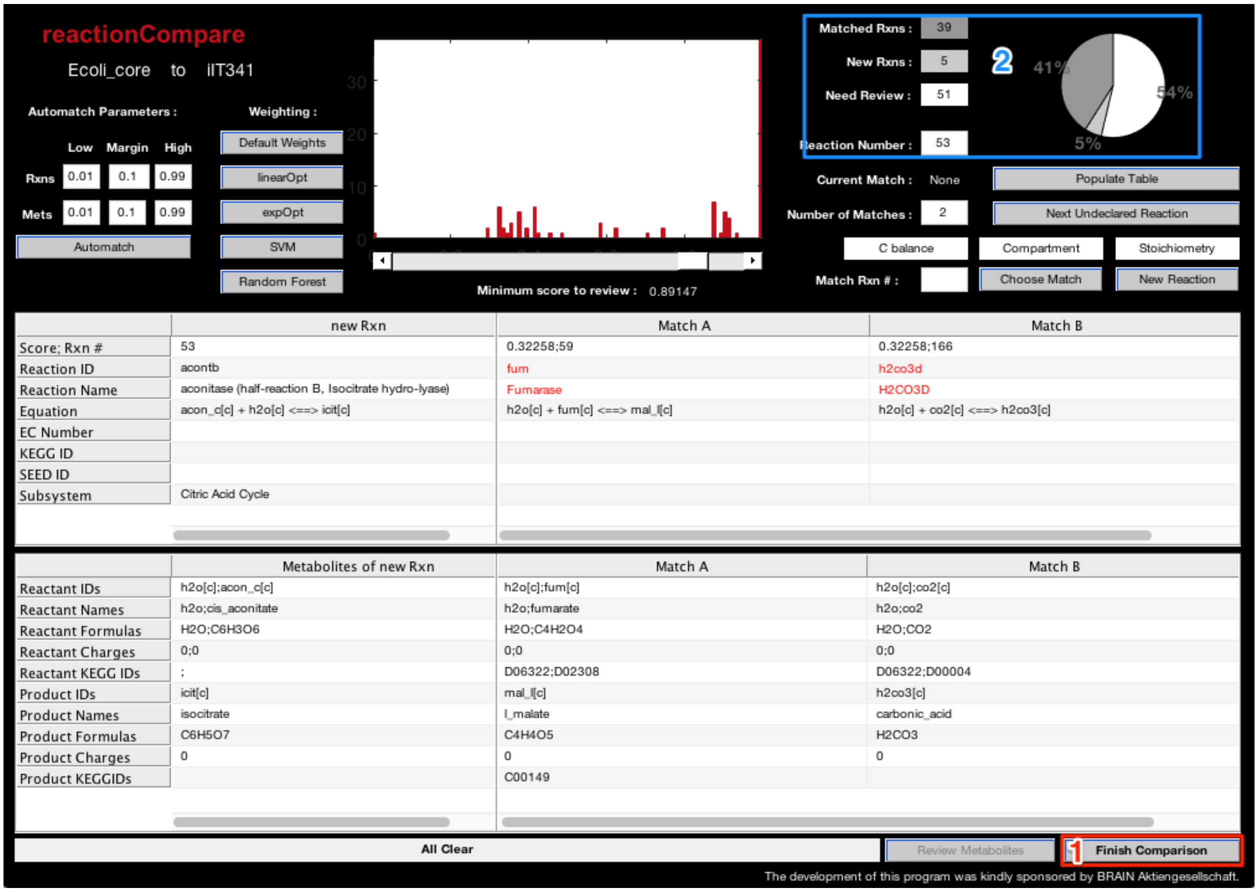


iii. Compare metabolites. When a reaction from Cmodel has been matched or declared as new, its metabolites are then reviewed in an analogous GUI. Choose the best matching metabolite from the table (Match A, Match B, ...), with the radio buttons in the red box labeled 1. You are only allowed to declare a new metabolite if the reaction itself was delcared new. After all metabolites have been reviewed (in the blue box labeled 2), you can press the button "Add Metabolite(s)" (blue arrow), and resume comparing reactions. Alternatively, you can postpone matching metabolites by pressing "Skip Matching." However, matching metabolites facilitates determining the fate of as of yet unreviewed reactions.

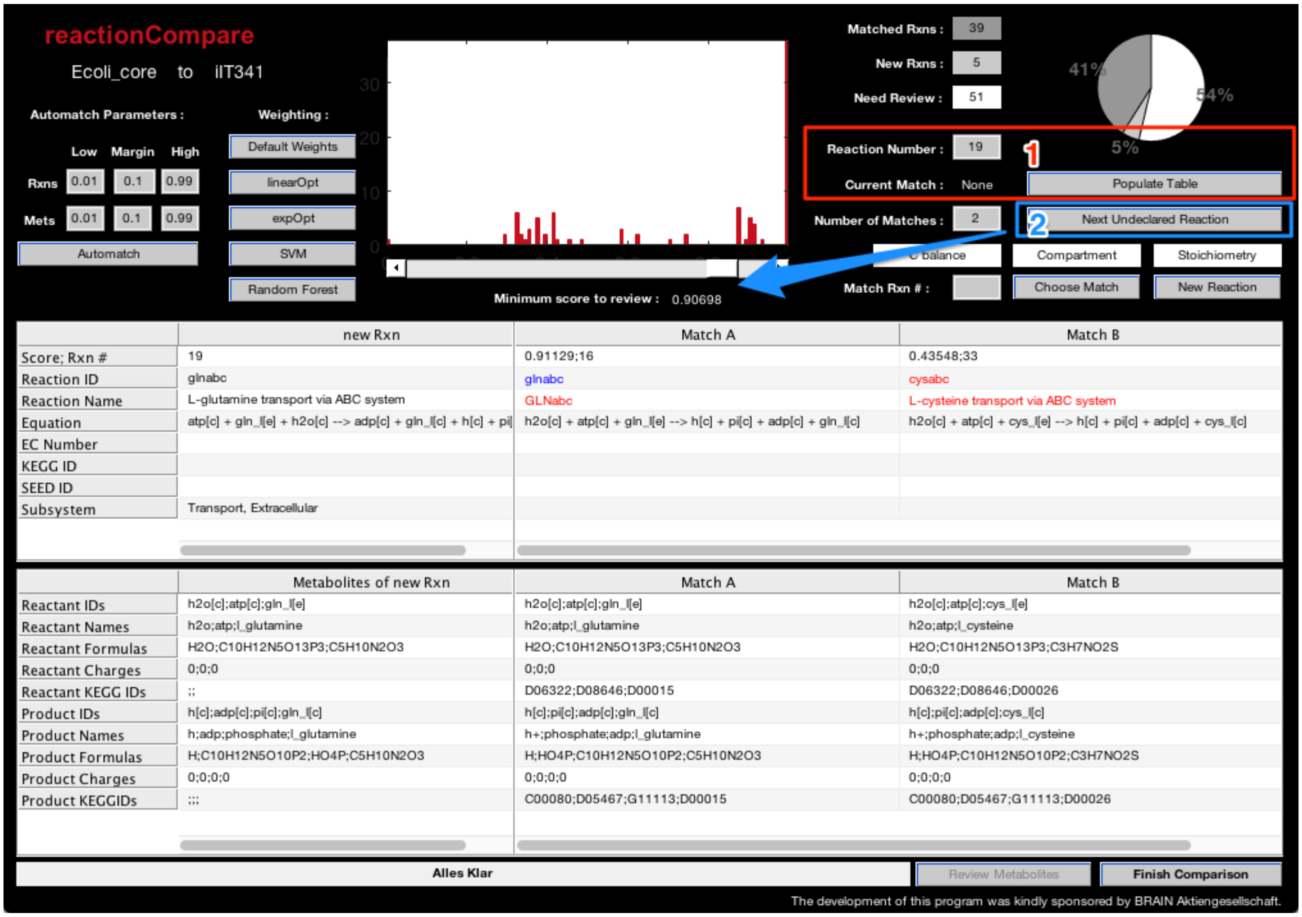


iv. Finish/pause comparison. You can quit comparision and save your work at any time by pressing "Finish Comparison" in the red box labeled 1. The number of reactions which have been reviewed, matched, or declared new is located is presented in blue box labeled 2. Finishing comparision produces two arrays, "rxnList" and "metList," which indicated to which reaction or metabolite in Tmodel matches a reaction or metabolite in Cmodel, respectively. New reactions are given a designation "-1," while new metabolites are given new metabolite numbers immediately (such numbers will be higher than the total number of metabolites in Tmodel). Unreviewed reactions and metabolites have the designation "0."

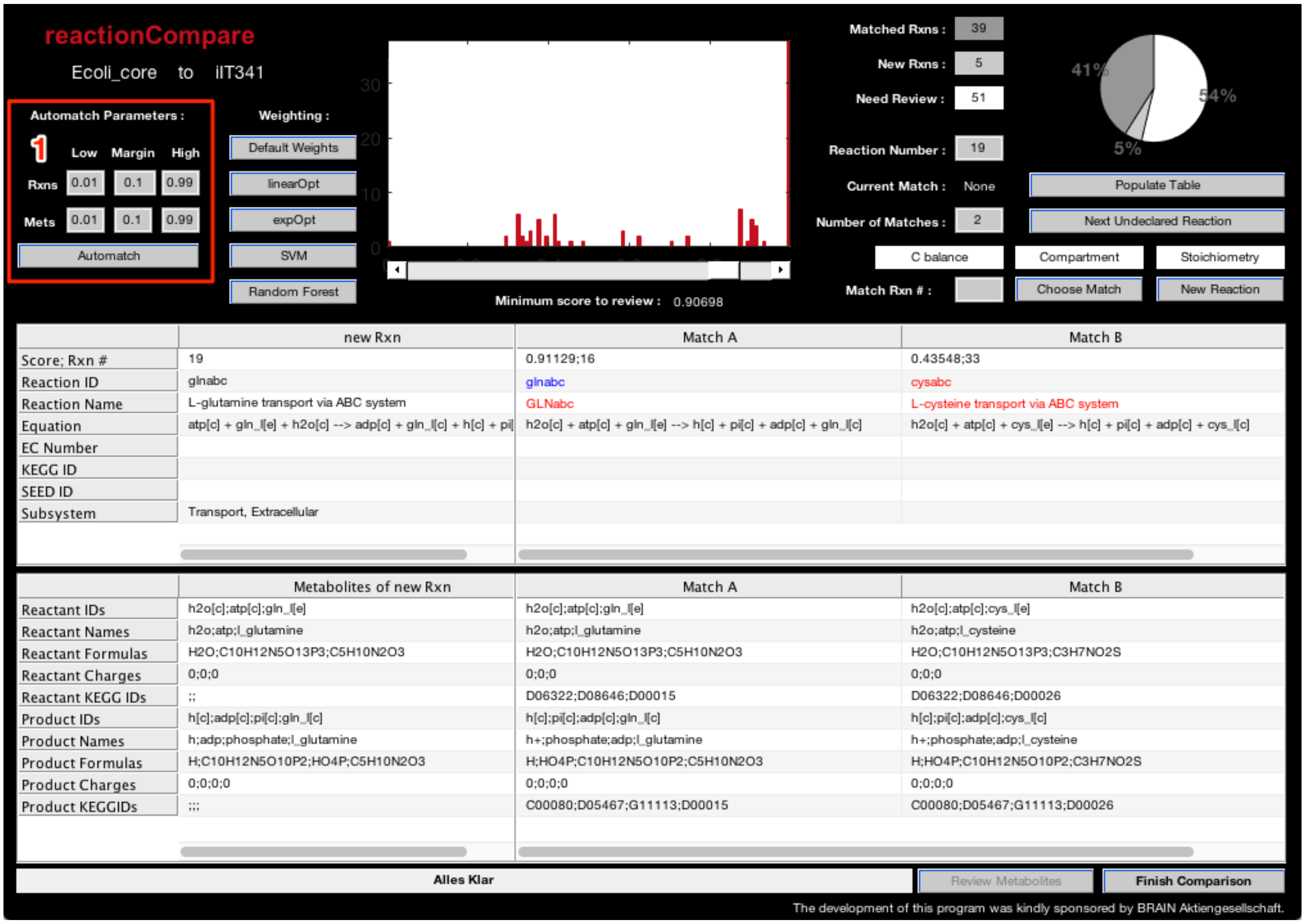
When you resuming comparison, give rxnList and metList as arguments to reactionCompare (see above).



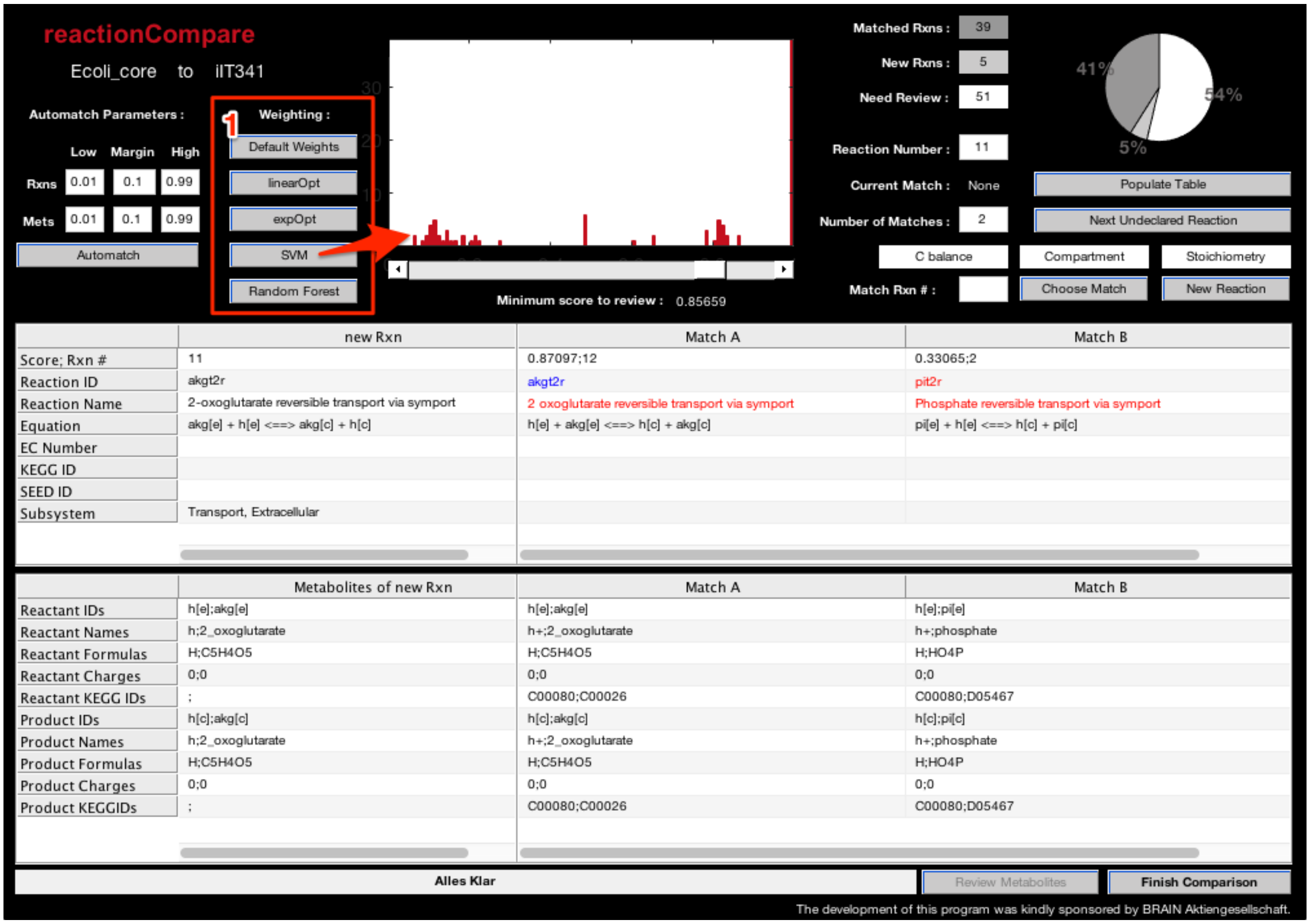
v. Review additional reacitons. You can control which reactions you review in two ways. You can review any arbitrary reaction from Cmodel by putting in the reaction number and pressing "Populate Table," indicated by the red box labeled 1. Alternatively, you can press the button "Next Undeclared Reaction," which will go to the next undeclared reaction in Cmodel with the lowest reaction number (blue box labeled 2). You can require that reactions presented by "Next Undeclared Reaction have at least one match above a give score by moving the slider indicated by the arrow.



vi. Automatch reactions and metabolites. High and low scoring reactions may be safely matched or declared new, respectively. This is done with the options in the red box labeled 1. Reactions or metabolites above the score in the box "High" will be matched with their best match from Tmodel, as long as the score of the best match from Tmodel is better than the second best match by the value in "Margin." Reactions and metabolites whose matches are not above the score in "Low" will be declared as new. When a metabolite is declared as new, then all reactions in Cmodel containing that metabolite are also declared new.



vii. Score weighting. Once you have manually compared some reactions, this information can be used to determine which scoring parameters are most informative and can be weighted accordingly. Four weighting functions/algorithms are provided in addition to the default weighting scheme (red box labeled 1). There is a linear optimization, an exponential optimization, a support vector machine (SVM) learning method, and a random forest algorithm. See the script "optimalScores.m" for more information. The image below shows the scores under SVM weighing. Automatching should be used in conjunction with score weighting to reduce manual intervention.



6. Merge models

mergeModels will combine Cmodel into Tmodel and return it as TmodelC. It will iteratively check the fidelity of the merging and will prompt the user if errors are found. It will also produce a copy of Cmodel which has been extracted from TmodelC (see next step).

Merge models and test results.

```
if ~isempty(rxnsList) && ~isempty(metList) && ~isempty(Stats)
    [TmodelC, Cspawn, Stats] = mergeModels(Cmodel, Tmodel, rxnList, metList, Stats, 'Verbose')
end
```

The structure Stats contains informationa about the number of unique and shared metabolites between the models, as well as the completeness of annotations.

```
if ~isempty(rxnsList) && ~isempty(metList) && ~isempty(Stats)
    % Shared reaction between the models. Values along the diagonal how many reactions in the
    Stats.sharedRxns
    % Shared metabolites between models,
    Stats.sharedMets
    Stats.sharedMetsNoComp % does not consider differences in compartment.
end
```

7. Extract a model

A model can be extracted from the combined model with the funtion readCbTmodel and referencing its name. Extracted models should be mathematically identical to the model that went in, but will contain additional annotation information garnered from the comparison. For example, the extracted Ecoli_core model now contains KEGG IDs for its metabolites.

```
%% Extract both models
if ~isempty(rxnsList) && ~isempty(metList) && ~isempty(Stats)
    Ecoli_core = readCbTmodel('Ecoli_core', TmodelC, 'Verbose');
    iIT341 = readCbTmodel('iIT341', TmodelC, 'Verbose');
end
```

8. Save work

Finally, you should save your combined model to be used for future comparison. Subsequent comparisons become easier a Tmodel gains information.

```
%     save([filesep 'Tmodel_' datestr(now,'yyyy.mm.dd') '.mat'], 'TmodelC')
```

REFERENCES

1. Sauls, J. T., & Buescher, J. M. (2014). Assimilating genome-scale metabolic reconstructions with modelBorgifier. *Bioinformatics* (Oxford, England), 30(7), 1036–8. http://doi.org/10.1093/bioinformatics/btt747
2. Thiele, I., Vo, T. D., Price, N. D., & Palsson, B. Ø. (2005). Expanded metabolic reconstruction of *Helicobacter pylori* (*i*IT341 GSM/GPR): an *in silico* genome-scale characterization of single- and double-deletion mutants. *Journal of Bacteriology*, *187*(16), 5818–5830. http://doi.org/10.1128/JB.187.16.5818