Metabolic visualisation in ReconMap (Minerva)

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Reviewer(s):

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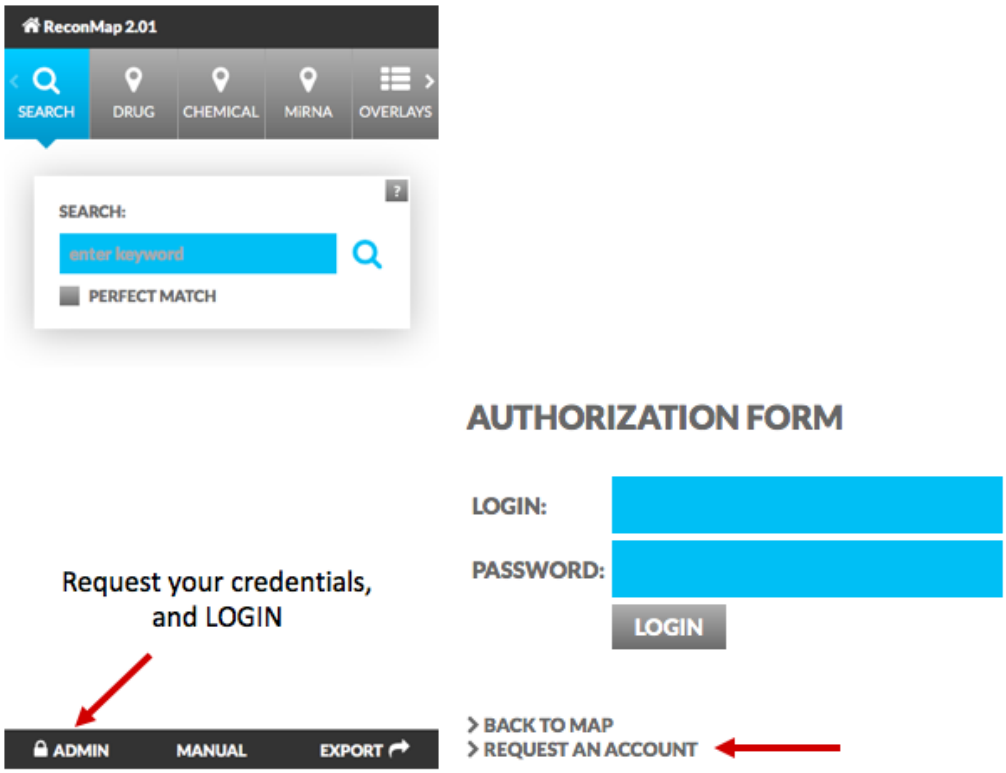
INTRODUCTION

The visualisation of metabolic pathways is an essential tool to understand the biological meaning underlying COBRA metabolic models. This would allow the user to visualise what can not be appreciated at first sight by directly looking to the model outputs. Here we present a visualisation through ReconMap [noronha_reconmap:_2017], a virtual visualisation of human metabolism derived from Recon 2.04 [thiele_community-driven_2013]. Diverse models can be found in the website http://vmh.uni.lu.

EQUIPMENT SETUP

In order to access remotely to ReconMap, the user has to be registered. To obtain your credentials, you must access the ADMIN area and request an account. To access ReconMap follow the link: http://vmh.uni.lu.



Then, use your credentials to remotely access to http://vmh.uni.lu.

```
load('minerva.mat')
minerva.minervaURL = 'http://vmh.uni.lu/minerva/galaxy.xhtml';
```

```
minerva.login = 'user_name';
minerva.password = 'user_password';
minerva.model = 'ReconMap-2.01';
```

Initialise the Cobra Toolbox.

```
initCobraToolbox
```

```
      _____   _____   _____   _____     _____     |
     / ___| / _   \ |  _  \ |  _  \   / ___ \    |   COnstraint-Based Reconstruction and Analysis
    | |     | | | | | |_| | | |_| |  | |___| |   |   The COBRA Toolbox - 2017
    | |     | | | | |  _  { |  _  /  |  ___  |   |
    | |___  | |_| | | |_| | | | \ \  | |   | |   |   Documentation:
    \_____| \_____/ |_____/ |_|  \_\ |_|   |_|   |   http://opencobra.github.io/cobratoolbox
                                                 |

 > Checking if git is installed ...  Done.
 > Checking if the repository is tracked using git ...  Done.
 > Checking if curl is installed ...  Done.
 > Checking if remote can be reached ...  Done.
 > Initializing and updating submodules ... Done.
 > Adding all the files of The COBRA Toolbox ...  Done.
 > Define CB map output... set to svg.
 > Retrieving models ...   Done.
 > TranslateSBML is installed and working properly.
 > Configuring solver environment variables ...
   - [----] ILOG_CPLEX_PATH :  --> set this path manually after installing the solver ( see instructions
   - [-*--] GUROBI_PATH: /opt/gurobi652
   - [----] TOMLAB_PATH :  --> set this path manually after installing the solver ( see instructions )
   - [----] MOSEK_PATH :  --> set this path manually after installing the solver ( see instructions )
   Done.
 > Checking available solvers and solver interfaces ... Done.
 > Setting default solvers ... Done.
 > Saving the MATLAB path ... Done.
   - The MATLAB path was saved as ~/pathdef.m.

 > Summary of available solvers and solver interfaces

   Support      LP   MILP     QP   MIQP    NLP
 ----------------------------------------------------------------------
 cplex_direct  full              0      0      0      0      -
 dqqMinos      full              0      -      -      -      -
 glpk          full              1      1      -      -      -
 gurobi        full              1      1      1      1      -
 ibm_cplex     full              0      0      0      -      -
 matlab        full              1      -      -      -      1
 mosek         full              0      0      0      -      -
 pdco          full              1      -      1      -      -
 quadMinos     full              0      -      -      -      0
 tomlab_cplex  full              0      0      0      0      -
 qpng          experimental      -      -      1      -      -
 tomlab_snopt  experimental      -      -      -      -      0
 gurobi_mex    legacy            0      0      0      0      -
 lindo_old     legacy            0      -      -      -      -
 lindo_legacy  legacy            0      -      -      -      -
 lp_solve      legacy            1      -      -      -      -
 opti          legacy            0      0      0      0      0
 ----------------------------------------------------------------------
 Total         -                 5      2      3      1      1

 + Legend: - = not applicable, 0 = solver not compatible or not installed, 1 = solver installed.


 > You can solve LP problems using: 'glpk' - 'gurobi' - 'matlab' - 'pdco' - 'lp_solve'
```

```
> You can solve MILP problems using: 'glpk' - 'gurobi'
> You can solve QP problems using: 'gurobi' - 'pdco' - 'qpng'
> You can solve MIQP problems using: 'gurobi'
> You can solve NLP problems using: 'matlab'

> Checking for available updates ...
> There are 87 new commit(s) on <master> and 0 new commit(s) on <develop> [e26f2b @ master]
> You can update The COBRA Toolbox by running updateCobraToolbox() (from within MATLAB).
```

A specific solver might be required (depending on the analysis you want to realise in the COBRA model).

```
changeCobraSolver('gurobi','QP');
```

```
> Gurobi interface added to MATLAB path.
ans =
   1
```

```
changeCobraSolver('gurobi', 'LP');
```

```
> Gurobi interface added to MATLAB path.
ans =
   1
```

Load your generic metabolic model. Recon's most recent version "Recon2.04" can be freely downloaded from http://vmh.uni.lu.

```
model = readCbModel('Recon2.v04.mat')
```

```
model =
                     S: [5063×7440 double]
                     b: [5063×1 double]
                csense: [5063×1 char]
                    lb: [7440×1 double]
                    ub: [7440×1 double]
                     c: [7440×1 double]
                osense: -1
                  rxns: {7440×1 cell}
                  mets: {5063×1 cell}
                 genes: {2140×1 cell}
                 rules: {7440×1 cell}
            metCharges: [5063×1 double]
           metFormulas: {5063×1 cell}
              metNames: {5063×1 cell}
             metHMDBID: {5063×1 cell}
        metInChIString: {5063×1 cell}
             metKEGGID: {5063×1 cell}
           metPubChemID: {5063×1 cell}
            description: 'Recon2.v04.mat'
                grRules: {7440×1 cell}
             rxnGeneMat: [7440×2140 double]
    rxnConfidenceScores: [7440×1 double]
               rxnNames: {7440×1 cell}
               rxnNotes: {7440×1 cell}
          rxnECNumbers: {7440×1 cell}
         rxnReferences: {7440×1 cell}
             rxnKEGGID: {7440×1 cell}
            subSystems: {7440×1 cell}
```

```
              DMRxnBool: [7440×1 logical]
              EXRxnBool: [7440×1 logical]
            ExchRxnBool: [7440×1 logical]
            SIntRxnBool: [7440×1 logical]
            SinkRxnBool: [7440×1 logical]
             metCHEBIID: {5063×1 cell}
              metEHMNID: {5063×1 cell}
          metHepatoNetID: {5063×1 cell}
     rxnConfidenceEcoIDA: {7440×1 cell}
              rxnsboTerm: {7440×1 cell}
```

PROCEDURE

1. Overlay a flux distribution

As an example of layout, we would like to see the the fluxes when maximizing ATP production through complex V (ATP synthase) in the Electron Transport Chain. To do so, we use Flux Balance Analysis (FBA) and set as an objective function the reaction responsible of this process (`'ATPS4m'`).

`ChangeObjective` function, changes the objective function of a constraint-based model

`optimizeCbModel` function solves a flux balance analysis problem.

```
formula = printRxnFormula(model, 'ATPS4m')
```

```
ATPS4m 4 h[c] + adp[m] + pi[m]  -> 3 h[m] + h2o[m] + atp[m]
```

```
formula =
    '4 h[c] + adp[m] + pi[m]  -> 3 h[m] + h2o[m] + atp[m] '
```

```
model_atp_production = model  % re-name the model to do not modify the original one.
```

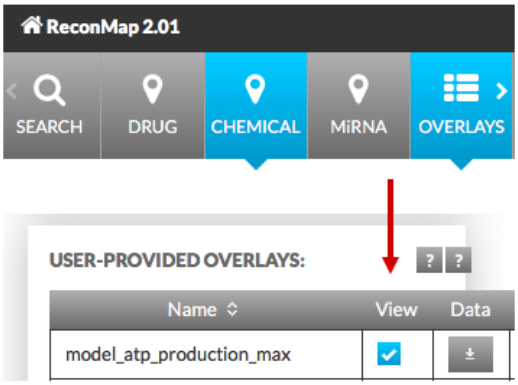
```
model_atp_production =
                      S: [5063×7440 double]
                      b: [5063×1 double]
                 csense: [5063×1 char]
                     lb: [7440×1 double]
                     ub: [7440×1 double]
                      c: [7440×1 double]
                 osense: -1
                   rxns: {7440×1 cell}
                   mets: {5063×1 cell}
                  genes: {2140×1 cell}
                  rules: {7440×1 cell}
             metCharges: [5063×1 double]
            metFormulas: {5063×1 cell}
               metNames: {5063×1 cell}
             metHMDBID: {5063×1 cell}
          metInChIString: {5063×1 cell}
               metKEGGID: {5063×1 cell}
            metPubChemID: {5063×1 cell}
             description: 'Recon2.v04.mat'
                 grRules: {7440×1 cell}
             rxnGeneMat: [7440×2140 double]
     rxnConfidenceScores: [7440×1 double]
                rxnNames: {7440×1 cell}
                rxnNotes: {7440×1 cell}
           rxnECNumbers: {7440×1 cell}
          rxnReferences: {7440×1 cell}
```

```
              rxnKEGGID: {7440×1 cell}
             subSystems: {7440×1 cell}
              DMRxnBool: [7440×1 logical]
              EXRxnBool: [7440×1 logical]
            ExchRxnBool: [7440×1 logical]
            SIntRxnBool: [7440×1 logical]
            SinkRxnBool: [7440×1 logical]
             metCHEBIID: {5063×1 cell}
              metEHMNID: {5063×1 cell}
         metHepatoNetID: {5063×1 cell}
    rxnConfidenceEcoIDA: {7440×1 cell}
             rxnsboTerm: {7440×1 cell}
```

```
model_atp_production = changeObjective(model_atp_production, 'ATPS4m');
model_atp_production_max = optimizeCbModel(model_atp_production, 'max');
```

ANTICIPATED RESULTS

The `buildFluxDistLayout` function, create a layout that is automatically sent to ReconMap website. After this, you can visualise your layout in http://vmh.uni.lu. Use your credentials to log in as it is previously explained. Select your input map (minerva.model) and go to "overlays" section to find your layout.




```
buildFluxDistLayout(minerva, model, model_atp_production_max, 'atp_production_max')
```

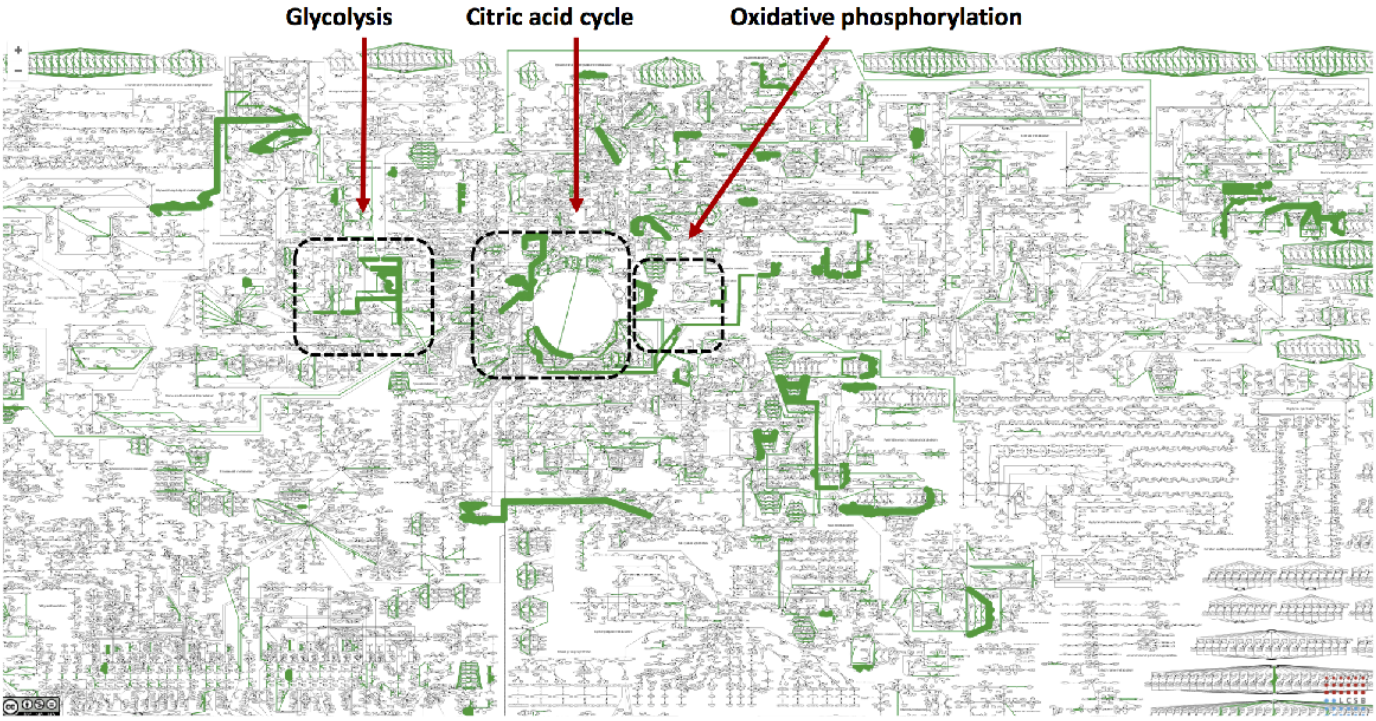
```
ans =
    [1]    'Overlay was sucessfully sent to ReconMap!'
```

If everything is correctly defined you should get a structure with 2 values. If everything works fine, the output of this function should be:

`[1] 'Overlay was successfully sent to ReconMap!'`

If there is any error, the message obtained will display:

`[0] 'Explanation of the obtained error'`



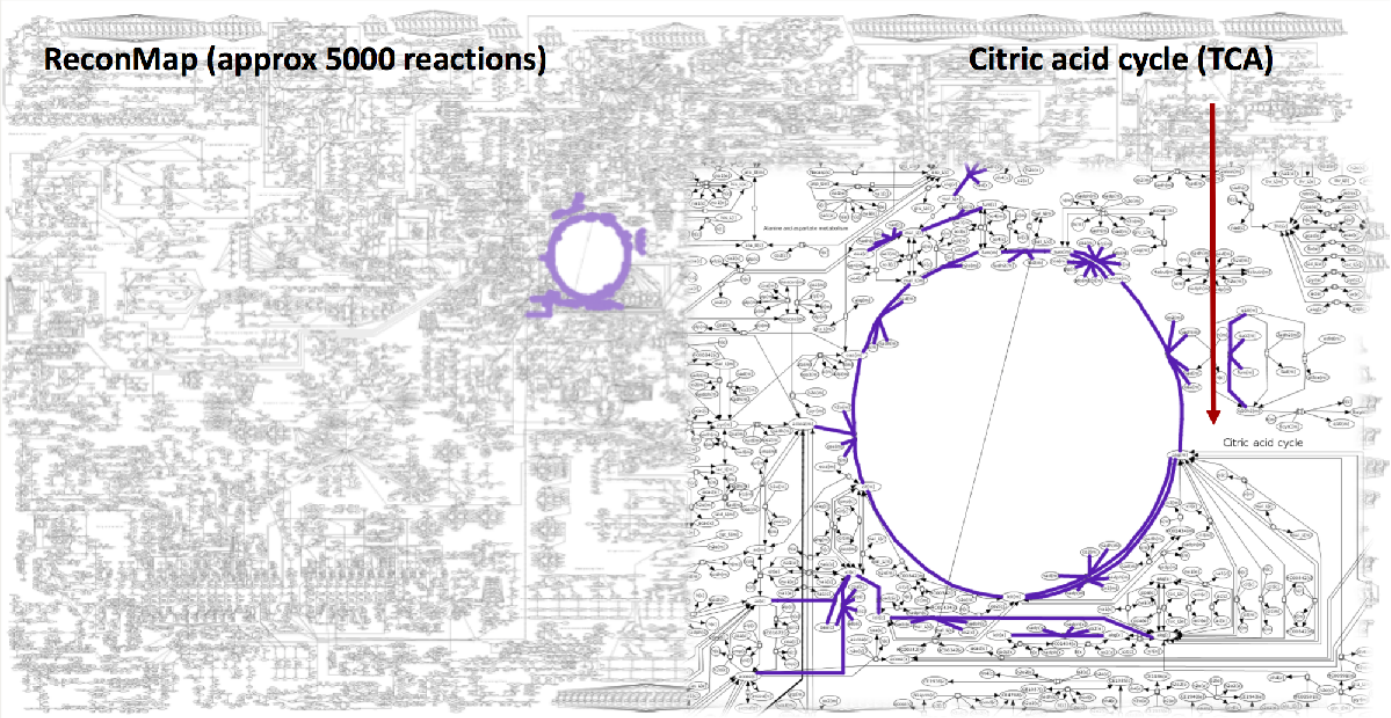
Note: If the "layout name" selected has been already given, an error might appear. Please, try to give a new layout name each time you run the code.

```
[0] 'ERROR. Layout with given identifier ("model_atp_productio…'
```

2. Overlay a SubSystem

There is also the possibility to highlight a specific subSystems by using the function `generateSubsytemsLayout.` A subSystem is a group of metabolic reactions involved in the same metabolic pathway, such as glycolysis, Oxidative phosphorylation, citric acid cycle, etc. Add the name of a specific subSystem you want to highlight from the COBRA model (see the example, TCA cycle), and the color reference.

```
generateSubsytemsLayout(minerva, model, 'Citric acid cycle', '#6617B5');
```



Alternatively, the user can generate a layout of all common subSystems between model and map using the function `generateSubsystemLayouts.`

Note: every single layout can be observed individually, or merged with other layouts. Therefore, making possible the visualization of several layouts at the same time.

REFERENCES:

[1] Alberto Noronha, Anna Dröfn Daníelsdóttir, Piotr Gawron, Freyr Jóhannsson, Sofía Jónsdóttir, Sindri Jarlsson, Jón Pétur Gunnarsson, Sigurður Brynjólfsson, Reinhard Schneider, Ines Thiele, and Ronan M. T. Fleming. ReconMap: an interactive visualization of human metabolism. Bioinformatics , 33(4):605607, February 2017.

[2] Ines Thiele, Neil Swainston, Ronan M. T. Fleming, Andreas Hoppe, Swagatika Sahoo, Maike K. Aurich, Hulda Haraldsdottir, Monica L. Mo, Ottar Rolfsson, Miranda D. Stobbe, Stefan G. Thorleifsson, Rasmus Agren, Christian Bölling, Sergio Bordel, Arvind K. Chavali, Paul Dobson, Warwick B. Dunn, Lukas Endler, David Hala, Michael Hucka, Duncan Hull, Daniel Jameson, Neema Jamshidi, Jon J. Jonsson, Nick Juty, Sarah Keating, Intawat Nookaew, Nicolas Le Novère, Naglis Malys, Alexander Mazein, Jason A. Papin, Nathan D. Price, Evgeni Selkov Sr, Martin I. Sigurdsson, Evangelos Simeonidis, Nikolaus Sonnenschein, Kieran Smallbone, Anatoly Sorokin, Johannes H. G. M. van Beek, Dieter Weichart, Igor Goryanin, Jens Nielsen, Hans V. Westerho, Douglas B. Kell, Pedro Mendes, and Bernhard Ø Palsson. A community-driven global reconstruction of human metabolism. 5 Nat Biotech , 31(5):419425, May 2013.