Visualise conserved moieties in dopaminergic neuronal metabolism

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INTRODUCTION

Given a set of conserved moieties, this tutorial generates metabolic maps corresponding to different conserved moieties.

These tutorials should generally be used in the following order:

1. Initialise and set the paths to inputs and outputs

COBRA.tutorials/driver_initConservedMoietyPaths.mlx

2. Build an atom transition graph

tutorial_buildAtomTransitionMultigraph.mlx

3. Identify conserved moieties, given an atom transition graph

tutorial_identifyConservedMoieties.mlx

4. Analyse the output of #3

tutorial_analyseConservedMoieties.mlx

5. Prepare for visualisation of individual conserved moieties (beta)

tutorial_visualiseConservedMoieties.mlx

```
tutorial_initConservedMoietyPaths
```

```
modelName =
'DAS'
projectDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties'
dataDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties/data/models/'
softwareDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties/software/'
visDataDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties/data/visualisation/'
resultsDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties/results/DAS_ConservedMo
rxnfileDir =
'/home/rfleming/work/sbgCloud/code/fork-COBRA.tutorials/analysis/conservedMoieties/data/mini-ctf/rxns/atom
```

```
% if ~recompute
%     load([resultsDir  modelName '_ConservedMoietiesAnalysis.mat'])
%     return
% end
```

Load the dopaminergic neuronal metabolic model

```
load([dataDir modelName '.mat'])
```

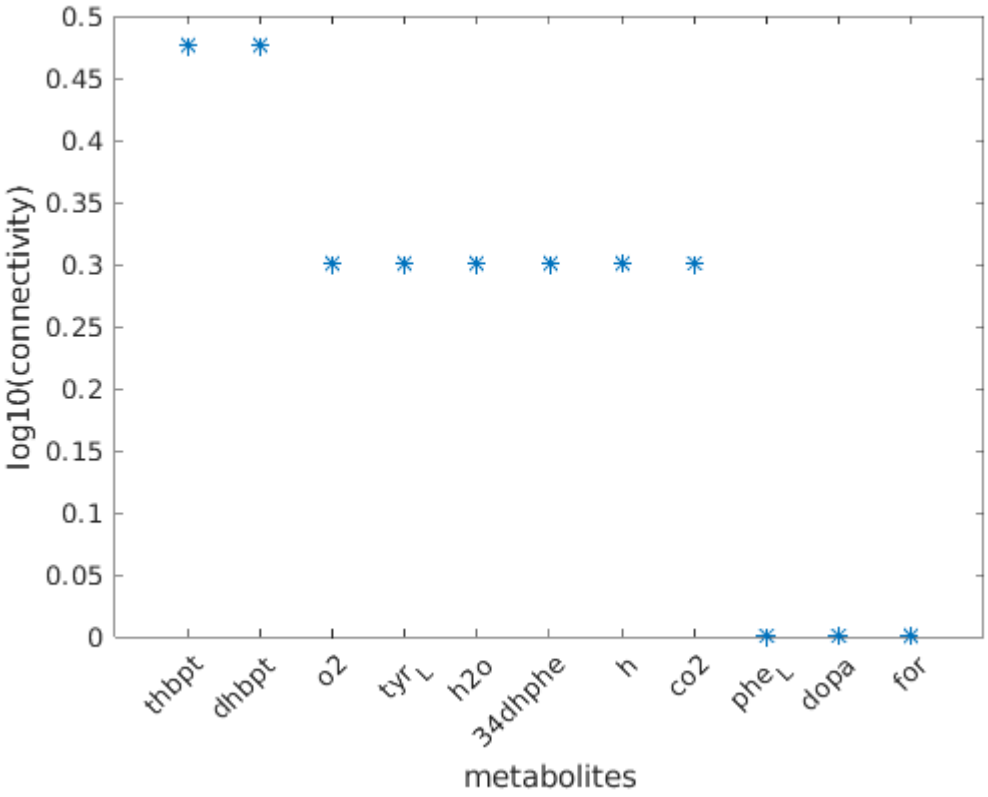
Identify the stoichiometrically consistent subset of the model

```
massBalanceCheck=1;
printLevel=1;
[SConsistentMetBool, SConsistentRxnBool, SInConsistentMetBool,
SInConsistentRxnBool, unknownSConsistencyMetBool,
unknownSConsistencyRxnBool, model]...
    = findStoichConsistentSubset(model,massBalanceCheck,printLevel);
```

```
--- findStoichConsistentSubset START ----
--- Summary of stoichiometric consistency ----
    11        11     totals.
     0         7     heuristically external.
    11         4     heuristically internal:
    11         4     ... of which are stoichiometrically consistent.
     0         0     ... of which are stoichiometrically inconsistent.
     0         0     ... of which are of unknown consistency.
---
     0         0     heuristically internal and stoichiometrically inconsistent or unknown consistency.
     0         0     ... of which are elementally imbalanced (inclusively involved metabolite).
     0         0     ... of which are elementally imbalanced (exclusively involved metabolite).
    11         4     Confirmed stoichiometrically consistent by leak/siphon testing.
--- findStoichConsistentSubset END ----
Warning: Model did not contain a genes field. Building it along with the rules field
Warning: This function can be only be used on a model that has grRules field!\n
```

Metabolite connectity

```
param.n=20;
[rankMetConnectivity,rankMetInd,rankConnectivity] =
rankMetabolicConnectivity(model,param);
```



Load atomically resolved models & conserved moiety analysis

Load the atomically resolved models derived from identifyConservedMoieties.m

```
if 0
    load([resultsDir 'iDopaMoieties_noChecks.mat'])
else
    load([resultsDir  modelName '_ConservedMoietiesAnalysis.mat'])
end
```

Transitive moiety, of sufficient mass, with moderate incidence

```
isTransititiveMoiety= strcmp('Transitive',moietyTypes);
isModerateIncidence = moietyIncidence>=10 & moietyIncidence<=100;
isSufficientMass = moietyMasses > 2;
isSufficientMinimalMassFraction = minimalMassFraction > 0.1;
interestingMoiety = isTransititiveMoiety & isModerateIncidence &
isSufficientMass & isSufficientMinimalMassFraction;
C = cell(nnz(interestingMoiety),9);
n=1;
for i=1:size(arm.L,1)
    if interestingMoiety(i)
        ind = find(strcmp(minimalMassMetabolite{i},model.mets));
        C(n,1:9) =
{i,nnz(arm.L(i,:)),nnz(model.S((arm.L(i,:)~=0)',:)~=0),moietyFormulae{i},moie
```

```
tyMasses(i),minimalMassMetabolite{i},model.metNames{ind},model.metFormulas{in
d},minimalMassFraction(i)};
        n=n+1;
    end
end

C=sortrows(C,9,'descend');
T=cell2table(C);
T.Properties.VariableNames={'index','metabolites','rxns','moiety_formula','ma
ss','Minimal_mass_metabolite','Name','Formula','Mass_fraction'};
size(T,1)
```

```
ans = 0
```

```
disp(T)
```

Recon3Map

Import Recon3Map

```
if ~exist('Recon3xml','var')
    [Recon3xml, Recon3map] = transformXML2Map([visDataDir
'reconMap3d_allin.xml']);
end
if 0
    transformMap2XML(Recon3xml,Recon3map,[resultsDir 'Recon3map.xml']);
end
```

Compare the reactions in the specified metabolic model and Recon3Map

The function `checkCDerrors` gives four outputs summarising all possible discrepancies between model and map.

```
printLevel=0;
[diffReactions, diffMetabolites, diffReversibility, diffFormula] =
checkCDerrors(Recon3map, model,printLevel);
```

Four outputs are obtained from this function:

"`diffReactions`" summarises present and absent reactions between model and map.

Display the internal reactions in the model that are not present in the map.

```
bool=ismember(diffReactions.extraRxnModel,model.rxns(model.SConsistentRxnBool
));
nnz(bool)
```

```
ans = 4
```

```
disp(diffReactions.extraRxnModel(bool))
```

```
    {'R1'}
    {'R2'}
    {'R3'}
    {'R4'}
```

"`diffMetabolites`" summarises present and absent metabolites.

NOTE! *Note that having more metabolites and reactions in the COBRA model is normal since the model can contain more elements than the map. On the other hand, the map should only contain elements present in the model.*

"`diffReversibility`" summarises discrepancies in defining the reversibility of reactions.

The last output "`diffFormula`" summarises discrepancies in reactions formulae (kinetic rates) and also lists duplicated reactions.

Create a map of the model

Remove some reactions from the map

```
rxnRemoveList = diffReactions.extraRxnsMap;
```

Remove non-dopaminergic neuronal reactions from the map

```
[modelNameXml,modelNameMap] = removeMapReactions(Recon3xml,
Recon3map,rxnRemoveList);
```

Remove pathway labels from the map

```
specRemoveType='UNKNOWN';
specRemoveList=[];
printLevel=0;
[modelNameXml,modelNameMap,specNotInMap] =
removeMapSpecies(modelNameXml,modelNameMap,specRemoveList,specRemoveType,prin
tLevel);
```

Remove highly connected metabolites from the map

```
specRemoveList={'h[c]';'h[l]';'h[e]';'h[r]';'h2o[c]';'h2o[l]';'h20[e]';'pi[c]
';'adp[c]';'nadph[c]';'nadh[c]';'nadph[m]';'nadh[m]'};
[xmlStruct,map,specNotInMap] =
removeMapSpeciesOnly(modelNameXml,modelNameMap,specRemoveList,specRemoveType,
printLevel);
```

Export the model map

```
transformMap2XML(modelNameXml,modelNameMap,[resultsDir modelName '_CD.xml']);
```

```
Elapsed time is 0.030606 seconds.
```

Nicotinate moiety

```
ind = 9;% Nicotinate moiety
mBool=arm.L(min(ind,size(arm.L,1)),:)~=0;
nnz(mBool)
```

```
ans = 5
```

```
rBool = getCorrespondingCols(model.S, mBool, true(size(model.S,2),1),
'inclusive');
nnz(rBool)
```

```
ans = 6
```

Metabolites

```
bool=mBool;
C = cell(nnz(bool),5);
n=1;
for i=1:size(model.S,1)
    if bool(i)
        C(n,1:5) =
{i,model.mets{i},model.metNames{i},model.metFormulas{i},metMasses(i)};
        n=n+1;
    end
end
C=sortrows(C,5,'descend');
T=cell2table(C);
T.Properties.VariableNames={'index','met','name','formula','mass'};
disp(T)
```

index	met	name	formula	mass
7	{'34dhphe'}	{'34dhphe'}	{'C9H11NO4'}	197.07
4	{'tyr_L'}	{'tyr_L'}	{'C9H11NO3'}	181.07
9	{'dopa'}	{'dopa'}	{'C8H12NO2'}	154.09
3	{'o2'}	{'o2'}	{'O2'}	31.99
6	{'h2o'}	{'h2o'}	{'H2O'}	18.011

Reactions

```
formulas = printRxnFormula(model, model.rxns(rBool));
```

```
R1    phe_L + thbpt + o2     ->    tyr_L + dhbpt + h2o
R2    thbpt + o2 + tyr_L     ->    dhbpt + h2o + 34dhphe
R3    34dhphe + h     ->    dopa + co2
EX_o2    o2     <=>
EX_h2o    h2o     ->
EX_dopa    dopa     ->
```

Map of nicotinate subnetwork

This code is specific to the dopaminergic neuronal metabolic model. Export the dopaminergic neuronal model as an sbml file

```
if 0
    nicotinateRxnRemoveList=model.rxns(~rBool);
    [iDopaNicotinateXml,iDopaNicotinateMap] =
removeMapReactions(iDopaXml,iDopaMap,nicotinateRxnRemoveList);
    transformMap2XML(iDopaNicotinateXml,iDopaNicotinateMap,[resultsDir
modelName '_Nicotinate_CD.xml']);
    outmodel = writeCbModel(model, 'format','sbml','fileName', [resultsDir
'iDopaNeuro_SBML.xml']);
end
```

Generate a set of submodels of the interesting moieties

Get abbreviations, without compartments for each metabolite in the model, then generate a results directory for each interesting moiety

```
[compartments, uniqueCompartments, minimalMassMetaboliteAbbr, uniqueAbbr]=
getCompartment(minimalMassMetabolite);
extractSubnetwork=1;
matFile=0;
sbmlFile=1;
moietyData=1;
CDFile=0;
n=1;
for i=1:size(arm.L,1)
    if interestingMoiety(i)
        metSampleName = minimalMassMetaboliteAbbr{i};
        disp(metSampleName)
        [SUCCESS,MESSAGE,MESSAGEID] = mkdir(resultsDir,metSampleName);
        cd([resultsDir filesep metSampleName])
        mBool = arm.L(i,:)~=0;
        rBool = getCorrespondingCols(model.S, mBool,
true(size(model.S,2),1), 'inclusive');
        if extractSubnetwork
            modelNameInterestingSubModel{n,1} = extractSubNetwork(model,
model.rxns(rBool), model.mets(mBool), 1);
        end
        mBoolModel =
ismember(model.mets,modelNameInterestingSubModel{n,1}.mets);
        modelNameInterestingSubModel{n,2}=i;
        modelNameInterestingSubModel{n,3}=minimalMassMetabolite{i};

        if matFile
            outmodel = writeCbModel(modelNameInterestingSubModel{n,1},
'format','mat','fileName', [resultsDir metSampleName filesep modelName '_'
metSampleName '.mat']);
        end

        if sbmlFile
```

```
            outmodel = writeCbModel(modelNameInterestingSubModel{n,1},
'format','sbml','fileName', [resultsDir metSampleName filesep modelName '_'
metSampleName '_SBML.xml']);
        end

        if moietyData

            moietyIncidence =
arm.L(modelNameInterestingSubModel{n,2},ismember(model.mets,modelNameInterest
ingSubModel{n,1}.mets))';

            fileName = [resultsDir metSampleName filesep modelName '_'
metSampleName '_moietyData.txt'];
            param.name = [modelName '_' metSampleName 'MoietySubnetwork'];
            param.description = [modelName '_' metSampleName ' moiety
incidence'];
            param.color.minValue = -1;
            param.color.minColor = '#FF0000';
            param.color.zeroValue = 0;
            param.color.zeroColor = '#FFFFFF';
            param.color.maxValue =  full(max(moietyIncidence));
            param.color.maxColor = '#87CEFA';

writeNewtExperiment(modelNameInterestingSubModel{n,1},moietyIncidence,metSamp
leName,fileName,param);
        end

        if CDFile

[modelNameInterestingXml{n},modelNameInterestingMap{n},modelNameRxnNotInMap{n
}] = removeMapReactions(modelNameXml,modelNameMap,model.rxns(~rBool));

transformMap2XML(modelNameInterestingXml{n},modelNameInterestingMap{n},
[resultsDir metSampleName filesep modelName '_' metSampleName '_CD.xml']);
        end
        n=n+1;
        cd('../')
    end
end
```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REFERENCES

1. Ghaderi, S., Haraldsdóttir, H. S., Ahookhosh, M., Arreckx, S., & Fleming, R. M. T. (2020). Structural conserved moiety splitting of a stoichiometric matrix. Journal of Theoretical Biology, 499, 110276. https://doi.org/10.1016/j.jtbi.2020.110276
2. Rahou, H., Haraldsdóttir, H. S., Martinelli, F., Thiele, I., & Fleming, R. M. T. (2026). Characterisation of conserved and reacting moieties in chemical reaction networks. Journal of Theoretical Biology, 112348. https://doi.org/10.1016/j.jtbi.2025.112348