Thermodynamically constrain a metabolic model

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Reviewers:

INTRODUCTION

In flux balance analysis of genome scale stoichiometric models of metabolism, the principal constraints are uptake or secretion rates, the steady state mass conservation assumption and reaction directionality. Von Bertylanffy [1,4] is a set of methods for (i) quantitative estimation of thermochemical parameters for metabolites and reactions using the component contribution method [3], (ii) quantitative assignment of reaction directionality in a multi-compartmental genome scale model based on an application of the second law of thermodynamics to each reaction [2], (iii) analysis of thermochemical parameters in a network context, and (iv) thermodynamically constrained flux balance analysis. The theoretical basis for each of these methods is detailed within the cited papers.

PROCEDURE

Configure the environment

All the installation instructions are in a separate .md file named vonBertalanffy.md in docs/source/installation

With all dependencies installed correctly, we configure our environment, verfy all dependencies, and add required fields and directories to the matlab path.

```
initVonBertalanffy
```

```
ChemAxon Marvin Beans is installed and working.
```

```
aPath = which('initVonBertalanffy');
basePath = strrep(aPath,'vonBertalanffy/initVonBertalanffy.m','');
addpath(genpath(basePath))
folderPattern=[filesep 'new'];
method = 'remove';
editCobraToolboxPath(basePath,folderPattern,method)
```

```
removing: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/componentContribution/ne
removing: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/new
removing: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/inchi/new
removing: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/molFiles/new
removing: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/protons/new
```

Select the model

This tutorial is tested for the E. coli model iAF1260 and the human metabolic model Recon3Dmodel. However, only the data for the former is provided within the COBRA Toolbox as it is used for testing von Bertylanffy.

However, the figures generated below are most suited to plotting results for Recon3D, so they may not be so useful for iAF1260. The Recon3D example uses values from literature for input variables where they are available.

```
%modelName = 'iAF1260';
%modelName='Ec_iAF1260_flux1';
%modelName='Recon3DModel_301';
%modelName='Recon3DModel_Dec2017';
modelName='Recon3.0model';
```

Load a model

Load a model, and save it as the original model in the workspace, unless it is already loaded into the workspace.

```
clear model
global CBTDIR
modelFileName = [modelName '.mat']
```

```
modelFileName =
'Recon3.0model.mat'
```

```


switch modelName
    case 'Ec_iAF1260_flux1'
        modelDirectory = getDistributedModelFolder(modelFileName); %Look up
the folder for the distributed Models.
        modelFileName= [modelDirectory filesep modelFileName]; % Get the
full path. Necessary to be sure, that the right model is loaded

        modelFileName = [modelName '.xml']
        model = readCbModel(modelFileName);
        if model.S(952, 350)==0
            model.S(952, 350)=1; % One reaction needing mass balancing in
iAF1260
        end
        model.metCharges(strcmp('asntrna[Cytosol]', model.mets))=0; % One
reaction needing charge balancing

    case 'iAF1260'
        modelDirectory = getDistributedModelFolder(modelFileName); %Look up
the folder for the distributed Models.
        modelFileName= [modelDirectory filesep modelFileName]; % Get the
full path. Necessary to be sure, that the right model is loaded

        model = readCbModel(modelFileName);
        model.mets = cellfun(@(mets)
strrep(mets,'_c','[c]'),model.mets,'UniformOutput',false);
        model.mets = cellfun(@(mets)
strrep(mets,'_e','[e]'),model.mets,'UniformOutput',false);
```

```
        model.mets = cellfun(@(mets)
strrep(mets,'_p','[p]'),model.mets,'UniformOutput',false);
        bool = strcmp(model.mets,'lipa[c]old[c]');
        model.mets{bool}='lipa_old_[c]';
        bool = strcmp(model.mets,'lipa[c]old[e]');
        model.mets{bool}='lipa_old_[e]';
        bool = strcmp(model.mets,'lipa[c]old[p]');
        model.mets{bool}='lipa_old_[p]';
        if model.S(952, 350)==0
            model.S(952, 350)=1; % One reaction needing mass balancing in
iAF1260
        end
        model.metCharges(strcmp('asntrna[c]', model.mets))=0; % One reaction
needing charge balancing

    case 'Recon3.0model'
        modelDirectory='~/work/sbgCloud/programReconstruction/projects/
recon2models/data/reconXComparisonModels';
        model = loadIdentifiedModel(modelName,modelDirectory);
        model.csense(1:size(model.S,1),1)='E';
        %Hack for thermodynamics
        model.metFormulas{strcmp(model.mets,'h[i]')}='H';
        model.metFormulas(cellfun('isempty',model.metFormulas)) = {'R'};
        if isfield(model,'metCharge')
            model.metCharges = double(model.metCharge);
            model=rmfield(model,'metCharge');
        end
        modelOrig = model;

    case 'Recon3DModel_Dec2017'
        modelDirectory = getDistributedModelFolder(modelFileName); %Look up
the folder for the distributed Models.
        modelFileName= [modelDirectory filesep modelFileName]; % Get the
full path. Necessary to be sure, that the right model is loaded

        model = readCbModel(modelFileName);
        model.csense(1:size(model.S,1),1)='E';
        %Hack for thermodynamics
        model.metFormulas{strcmp(model.mets,'h[i]')}='H';
        model.metFormulas(cellfun('isempty',model.metFormulas)) = {'R'};
        if isfield(model,'metCharge')
            model.metCharges = double(model.metCharge);
            model=rmfield(model,'metCharge');
        end
        modelOrig = model;
    case 'Recon3DModel_301'
        modelDirectory = getDistributedModelFolder(modelFileName); %Look up
the folder for the distributed Models.
        modelFileName= [modelDirectory filesep modelFileName]; % Get the
full path. Necessary to be sure, that the right model is loaded
```

```
        model = readCbModel(modelFileName);
        %Hack for thermodynamics
        model.metFormulas(cellfun('isempty',model.metFormulas)) = {'R'};
        modelOrig = model;
    otherwise
            error('setup specific parameters for your model')
end
```

```
Warning: fileName.mat and modelStructureName.mat did not match
```

Set the directory containing the results

```
switch modelName
    case 'Ec_iAF1260_flux1'
        resultsPath=which('tutorial_vonBertalanffy.mlx');
        resultsPath=strrep(resultsPath,'/tutorial_vonBertalanffy.mlx','');
        resultsPath=[resultsPath filesep modelName '_results'];
        resultsBaseFileName=[resultsPath filesep modelName '_results'];
    case 'iAF1260'
        resultsPath=which('tutorial_vonBertalanffy.mlx');
        resultsPath=strrep(resultsPath,'/tutorial_vonBertalanffy.mlx','');
        resultsPath=[resultsPath filesep modelName '_results'];
        resultsBaseFileName=[resultsPath filesep modelName '_results'];
    case 'Recon3.0model'
        basePath='~/work/sbgCloud';
        resultsPath=[basePath '/programReconstruction/projects/recon2models/
results/thermo/new2_' modelName];
        resultsBaseFileName=[resultsPath filesep modelName '_'
datestr(now,30) '_'];
     case 'Recon3DModel_Dec2017'
        basePath='~/work/sbgCloud';
        resultsPath=[basePath '/programReconstruction/projects/recon2models/
results/thermo/' modelName];
        resultsBaseFileName=[resultsPath filesep modelName '_'
datestr(now,30) '_'];
    case 'Recon3DModel_301'
        basePath='~/work/sbgCloud';
        resultsPath=which('tutorial_vonBertalanffy.mlx');
        resultsPath=strrep(resultsPath,'/tutorial_vonBertalanffy.mlx','');
        resultsPath=[resultsPath filesep modelName '_results'];
        resultsBaseFileName=[resultsPath filesep modelName '_results'];
    otherwise
        error('setup specific parameters for your model')
end
```

Set the directory containing molfiles

```
switch modelName
    case 'Ec_iAF1260_flux1'
```

```
        molfileDir = 'iAF1260Molfiles';
    case 'iAF1260'
        molfileDir = 'iAF1260Molfiles';
    case 'Recon3DModel_Dec2017'
        molfileDir = [basePath '/data/metDatabase/explicit/molFiles'];
        %molfileDir = [basePath '/programModelling/projects/atomMapping/
results/molFilesDatabases/DBimplicitHMol'];
        %molfileDir = [basePath '/programModelling/projects/atomMapping/
results/molFilesDatabases/DBexplicitHMol'];
    case {'Recon3DModel_301','Recon3.0model'}
        molfileDir = [basePath '/data/metDatabase/explicit/molFiles'];
        molfileDir = [basePath '/code/fork-ctf/mets/molFiles'];
    otherwise
        error('setup specific parameters for your model')
end
```

Set the thermochemical parameters for the model

```
switch modelName
    case 'Ec_iAF1260_flux1'
        T = 310.15; % Temperature in Kelvin
        compartments = {'Cytosol'; 'Extra_organism'; 'Periplasm'}; % Cell
compartment identifiers
        ph = [7.7; 7.7; 7.7]; % Compartment specific pH
        is = [0.25; 0.25; 0.25]; % Compartment specific ionic strength in
mol/L
        chi = [0; 90; 90]; % Compartment specific electrical potential
relative to cytosol in mV
    case 'iAF1260'
        T = 310.15; % Temperature in Kelvin
        compartments = ['c'; 'e'; 'p']; % Cell compartment identifiers
        ph = [7.7; 7.7; 7.7]; % Compartment specific pH
        is = [0.25; 0.25; 0.25]; % Compartment specific ionic strength in
mol/L
        chi = [0; 90; 90]; % Compartment specific electrical potential
relative to cytosol in mV
    case 'Recon3DModel_Dec2017'
        % Temperature in Kelvin
        T = 310.15;
        % Cell compartment identifiers
        compartments = ['c'; 'e'; 'g'; 'l'; 'm'; 'n'; 'r'; 'x';'i'];
        % Compartment specific pH
        ph = [7.2; 7.4; 6.35; 5.5; 8; 7.2; 7.2; 7; 7.2];
        % Compartment specific ionic strength in mol/L
        is = 0.15*ones(length(compartments),1);
        % Compartment specific electrical potential relative to cytosol in mV
        chi = [0; 30; 0; 19; -155; 0; 0;
-2.303*8.3144621e-3*T*(ph(compartments == 'x') - ph(compartments == 'c'))/
(96485.3365e-6); 0];
    case {'Recon3DModel_301','Recon3.0model'}
```

```
        % Temperature in Kelvin
        T = 310.15;
        % Cell compartment identifiers
        compartments = ['c'; 'e'; 'g'; 'l'; 'm'; 'n'; 'r'; 'x';'i'];
        % Compartment specific pH
        ph = [7.2; 7.4; 6.35; 5.5; 8; 7.2; 7.2; 7; 7.2];
        % Compartment specific ionic strength in mol/L
        is = 0.15*ones(length(compartments),1);
        % Compartment specific electrical potential relative to cytosol in mV
        chi = [0; 30; 0; 19; -155; 0; 0;
-2.303*8.3144621e-3*T*(ph(compartments == 'x') - ph(compartments == 'c'))/
(96485.3365e-6); 0];
    otherwise
        error('setup specific parameters for your model')
end
```

Set the default range of metabolite concentrations

```
switch modelName
    case 'Ec_iAF1260_flux1'
        concMinDefault = 1e-5; % Lower bounds on metabolite concentrations
in mol/L
        concMaxDefault = 0.02; % Upper bounds on metabolite concentrations
in mol/L
        metBoundsFile=[];
    case 'iAF1260'
        concMinDefault = 1e-5; % Lower bounds on metabolite concentrations
in mol/L
        concMaxDefault = 0.02; % Upper bounds on metabolite concentrations
in mol/L
        metBoundsFile=[];
    case 'Recon3DModel_Dec2017'
        concMinDefault=1e-5; % Lower bounds on metabolite concentrations in
mol/L
        concMaxDefault=1e-2; % Upper bounds on metabolite concentrations in
mol/L
        metBoundsFile=which('HumanCofactorConcentrations.txt');%already in
the COBRA toolbox
    case {'Recon3DModel_301','Recon3.0model'}
        concMinDefault=1e-5; % Lower bounds on metabolite concentrations in
mol/L
        concMaxDefault=1e-2; % Upper bounds on metabolite concentrations in
mol/L
        metBoundsFile=which('HumanCofactorConcentrations.txt');%already in
the COBRA toolbox
    otherwise
        error('setup specific parameters for your model')
end
```

Set the desired confidence level for estimation of thermochemical parameters

The confidence level for estimated standard transformed reaction Gibbs energies is used to quantitatively assign reaction directionality.

```
switch modelName
    case 'Ec_iAF1260_flux1'
        confidenceLevel = 0.95;
        DrGt0_Uncertainty_Cutoff = 20; %KJ/KMol
    case 'iAF1260'
        confidenceLevel = 0.95;
        DrGt0_Uncertainty_Cutoff = 20; %KJ/KMol
    case {'Recon3DModel_301','Recon3.0model'}
        confidenceLevel = 0.95;
        DrGt0_Uncertainty_Cutoff = 20; %KJ/KMol
    otherwise
        confidenceLevel = 0.95;
        DrGt0_Uncertainty_Cutoff = 20; %KJ/KMol
end
```

Prepare folder for results

```
if ~exist(resultsPath,'dir')
    mkdir(resultsPath)
end
cd(resultsPath)
```

Set the print level and decide to record a diary or not (helpful for debugging)

```
printLevel=2;

diary([resultsPath filesep 'diary.txt'])
```

Setup a thermodynamically constrained model

Read in the metabolite bounds

```
setDefaultConc=1;
setDefaultFlux=0;
rxnBoundsFile=[];
model=readMetRxnBoundsFiles(model,setDefaultConc,setDefaultFlux,concMinDefaul
t,concMaxDefault,metBoundsFile,rxnBoundsFile,printLevel);
```

```
Reading metabolite conc bounds from: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/ther
             adp[c]         1e-07        0.0019
             adp[m]        0.0026        0.0094
             amp[c]         1e-07        0.0012
             atp[c]       0.00129        0.0049
             atp[m]        0.0028        0.0204
             coa[c]      2.92e-05     0.0001168
```

```
coa[m]        0.0022        0.0039
na1[c]         1e-07         0.025
na1[e]        0.1326        0.1554
nad[c]    0.00010546     0.0007572
nad[m]        0.0005        0.0075
nadh[c]    9.2574e-07    0.00038294
nadh[m]         1e-07        0.0011
nadp[c]         1e-07    5.8284e-06
nadp[m]         1e-07        0.0015
nadph[c]        1e-07    0.00037523
nadph[m]        1e-07        0.0042
nh4[c]         0.0007        0.0009
pi[c]           0.001        0.0063
ppi[c]         0.0021        0.0076
udp[g]       1.4e-06       0.00014
```

Check inputs

```
model =
configureSetupThermoModelInputs(model,T,compartments,ph,is,chi,concMinDefault
,concMaxDefault,confidenceLevel);
```

```
Field metCompartments is missing from model structure. Attempting to create it.
Attempt to create field metCompartments successful.

Warning: Setting temperature to a value other than 298.15 K may introduce error, since enthalpies and heat
```

Check elemental balancing of metabolic reactions

```
ignoreBalancingOfSpecifiedInternalReactions=1;
if ~exist('massImbalance','var')
    if isfield(model,'Srecon')
        model.S=model.Srecon;
    end
    % Check for imbalanced reactions
    fprintf('\nChecking mass and charge balance.\n');
    %Heuristically identify exchange reactions and metabolites exclusively
involved in exchange reactions
    if ~isfield(model,'SIntMetBool')  ||  ~isfield(model,'SIntRxnBool') ||
ignoreBalancingOfSpecifiedInternalReactions
        %finds the reactions in the model which export/import from the model
        %boundary i.e. mass unbalanced reactions
        %e.g. Exchange reactions
        %     Demand reactions
        %     Sink reactions
        model = findSExRxnInd(model,[],printLevel);
    end

    if ignoreBalancingOfSpecifiedInternalReactions
        [nMet,nRxn]=size(model.S);
        ignoreBalancingMetBool=false(nMet,1);
        for m=1:nMet
%             if strcmp(model.mets{m},'Rtotal3coa[m]')
%                 pause(0.1);
```

```
%             end
            if ~isempty(model.metFormulas{m})

ignoreBalancingMetBool(m,1)=numAtomsOfElementInFormula(model.metFormulas{m},'
FULLR');
            end
        end

ignoreBalancingRxnBool=getCorrespondingCols(model.S,ignoreBalancingMetBool,mo
del.SIntRxnBool,'inclusive');
        SIntRxnBool=model.SIntRxnBool;
        model.SIntRxnBool=model.SIntRxnBool & ~ignoreBalancingRxnBool;
    end

    printLevelcheckMassChargeBalance=-1;  % -1; % print problem reactions to
a file
    %mass and charge balance can be checked by looking at formulas

[massImbalance,imBalancedMass,imBalancedCharge,imBalancedRxnBool,Elements,mis
singFormulaeBool,balancedMetBool]...
        =
checkMassChargeBalance(model,printLevelcheckMassChargeBalance,resultsBaseFile
Name);
    model.balancedRxnBool=~imBalancedRxnBool;
    model.balancedMetBool=balancedMetBool;
    model.Elements=Elements;
    model.missingFormulaeBool=missingFormulaeBool;

    %reset original boolean vector
    if ignoreBalancingOfSpecifiedInternalReactions
        model.SIntRxnBool=SIntRxnBool;
    end
end
```

```
Checking mass and charge balance.
Found multiple possible biomass reactions: biomass_reaction
Found multiple possible biomass reactions: biomass_maintenance
Found multiple possible biomass reactions: biomass_maintenance_noTrTr
ATP demand reaction is not considered an exchange reaction by default. It should be mass balanced:
DM_atp_c_    h2o[c] + atp[c]     ->    h[c] + adp[c] + pi[c]
There are mass imbalanced reactions, see ~/work/sbgCloud/programReconstruction/projects/recon2models/resul
There are mass balanced, but charge imbalanced reactions, see ~/work/sbgCloud/programReconstruction/projec
```

Check that the input data necessary for the component contribution method is in place

```
save('modelNew_prior_to_setupComponentContribution','model')
model = setupComponentContribution(model,molfileDir);
```

```
Creating MetStructures.sdf from molfiles.
Percentage of metabolites without mol files: 9.1%
Converting SDF to InChI strings.
```

```
Estimating metabolite pKa values.
     1

10fthf
     2

10fthf5glu
     3

10fthf6glu
     4

10fthf7glu
     5

11docrtsl
     6

11docrtstrn
     7

12HPET
     8

12harachd
     9

12htacr
    10

12ppd_R
    11

12ppd_S
    12

1331tacr
    13

13_cis_oretn
    14

13_cis_retn
    15

13_cis_retnglc
    16

13dampp
    17

13dmt
    18

13dpg
    19

14hmdz
    20

1513tacr
    21

1531tacr
```

22

15HPET
23

15dmt
24

15kprostgf2
25

17ahprgnlone
26

17ahprgstrn
27

18harachd
28

1a2425thvitd2
29

1a25dhvitd2
30

1a25dhvitd3
31

1hibup_S
32

1hibupglu_S
33

1hmdgluc
34

1mncam
35

1ohmdz
36

1p3h5c
37

1pipdn2c
38

1pyr5c
39

20ahchsterol
40

21hprgnlone
41

23cump
42

23dh1i56dio
43

2dr5p
    65

2h3mv
    66

2hatvacid
    67

2hatvacidgluc
    68

2hatvlac
    69

2hatvlacgluc
    70

2hb
    71

2hexdtetcoa
    72

2hexdtricoa
    73

2hibup_R
    74

2hibup_S
    75

2hibupglu_S
    76

2hiv
    77

2hydog
    78

2hyoxplac
    79

2kmb
    80

2m3hbu
    81

2m3hvac
    82

2m3ovac
    83

2m3ovcoa
    84

2maacoa
    85

2mb2coa

86

2mbcoa
87

2mcit
88

2mop
89

2mp2coa
90

2mpdhl
91

2obut
92

2octdectecoa
93

2octpencoa
94

2oxoadp
95

2pg
96

31dmt
97

34dhmald
98

34dhoxmand
99

34dhoxpeg
100

34dhpac
101

34dhpe
102

34dhpha
103

34dhphe
104

34hpl
105

34hpp
106

35cgmp
107

3hbcoa
   129

3hbcoa_R
   130

3hdcoa
   131

3hddcoa
   132

3hdeccoa
   133

3hdececrn
   134

3hexdcoa
   135

3hexdcrn
   136

3hexdtetcoa
   137

3hexdtricoa
   138

3hglutcoa
   139

3hibup_R
   140

3hibup_S
   141

3hibutcoa
   142

3hivac
   143

3hlvst
   144

3hmbcoa
   145

3hmp
   146

3hodcoa
   147

3hpcoa
   148

3hpp
   149

3hpppn

150

3hsmv
151

3hsmvacid
152

3htdcoa
153

3htmelys
154

3ityr_L
155

3ivcoa
156

3ivcrn
157

3m4hpga
158

3mb2coa
159

3mgcoa
160

3mglutac
161

3mglutr
162

3mhis
163

3mlda
164

3mldz
165

3mob
166

3mop
167

3mox4hoxm
168

3mox4hpac
169

3moxtyr
170

3mtp
171

3ocddcoa
   172

3octdec2crn
   173

3octdeccrn
   174

3octdece1coa
   175

3octdece1crn
   176

3octdectecoa
   177

3octpencoa
   178

3odcoa
   179

3oddcoa
   180

3ohdcoa
   181

3ohglutac
   182

3ohodcoa
   183

3ohsebac
   184

3ohsebcoa
   185

3ohsubac
   186

3ohsubcoa
   187

3ohxccoa
   188

3otdcoa
   189

3pg
   190

3php
   191

3sala
   192

214

4hbzcoa
215

4hdebrisoquine
216

4hexdtetcoa
217

4hexdtricoa
218

4hglusa
219

4hmdgluc
220

4hoxpacd
221

4hphac
222

4hpro_LT
223

4izp
224

4mlacac
225

4mop
226

4mptnl
227

4mtob
228

4mtolbutamide
229

4mzym_int1
230

4mzym_int2
231

4nph
232

4nphsf
233

4ohbut
234

4ohmdz
235

278

6hddopaqn
279

6hlvst
280

6hlvstacid
281

6hmsmv
282

6hmsmvacid
283

6hoxmelatn
284

6hsmv
285

6hsmvacid
286

6htststerone
287

6melvacid
288

6melvst
289

6msmv
290

6pgc
291

6pgl
292

6pthp
293

6thf
294

7bhglz
295

7bhglzglc
296

7dhchsterol
297

7dhf
298

7klitchol
299

7ohocata
   300

7thf
   301

C01041
   302

C01601
   303

C01747
   304

C02356
   305

C02470
   306

C02528
   307

C02712
   308

C03681
   309

C04717
   310

C04805
   311

C04849
   312

C05109
   313

C05279
   314

C05280
   315

C05298
   316

C05299
   317

C05300
   318

C05301
   319

C05302
   320

C05767
321

C05769
322

C05770
323

C05957
324

C06314
325

C06315
326

C07297
327

C08261
328

C09642
329

C10164
330

C11695
331

C11821
332

C13856
333

C14768
334

C14769
335

C14770
336

C14771
337

C14825
338

C14826
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CE0074
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	2046

thrtyrmet
	2047

thsacmp
	2048

thym
	2049

thymd
	2050

thyochol
	2051

thyox_L
	2052

tiggly
	2053

tmacmp
	2054

tmd
	2055

tmdm1
	2056

tmdm3
	2057

tmdm5
	2058

tmlys
	2059

tmndnc
	2060

tmndnccoa
	2061

tmndnccrn
	2062

tmtrdcoa
	2063

tmuncoa
	2064

tolbutamide
	2065

tre
	2066

tridcoa
	2067

trideceth
	2068

triodthy
	2069

triodthysuf

2070

trp_L
2071

trpalapro
2072

trpargala
2073

trpaspasp
2074

trpglngln
2075

trpglugly
2076

trpgluleu
2077

trpglupro
2078

trpglutyr
2079

trpglyasp
2080

trpglyleu
2081

trpglyphe
2082

trpglyval
2083

trphismet
2084

trpilelys
2085

trpiletrp
2086

trpleuval
2087

trplys
2088

trpmetarg
2089

trpmetval
2090

trpphe
2091

trpprogly
	2092

trpproleu
	2093

trpproval
	2094

trpsertyr
	2095

trpthrglu
	2096

trpthrile
	2097

trpthrtyr
	2098

trptyrgln
	2099

trptyrtyr
	2100

trpvalasp
	2101

trypta
	2102

ts3
	2103

tsacmgluc
	2104

tsacmsul
	2105

tststerone
	2106

tststeroneglc
	2107

tststerones
	2108

tsul
	2109

ttc_ggdp
	2110

ttccoa
	2111

ttdca
	2112

ttdcea
	2113

ttdcrn
	2114

ttetddcoa
	2115

txa2
	2116

txb2
	2117

tym
	2118

tymsf
	2119

tyr_L
	2120

tyrala
	2121

tyralaphe
	2122

tyrargglu
	2123

tyrargser
	2124

tyrasparg
	2125

tyrcysgly
	2126

tyrcysthr
	2127

tyrglu
	2128

tyrleuarg
	2129

tyrphetyr
	2130

tyrthr
	2131

tyrtrpphe
	2132

tyrtyr
	2133

tyrvalmet

2134

uacgam
2135

uchol
2136

udp
2137

udpacgal
2138

udpg
2139

udpgal
2140

udpglcur
2141

udprib
2142

udpxyl
2143

ump
2144

undcoa
2145

uppg3
2146

ura
2147

urate
2148

urcan
2149

urea
2150

uri
2151

urscholcoa
2152

utp
2153

vacc
2154

vacccoa
2155

vacccrn
2156

val_L
2157

valarggly
2158

valhisasn
2159

valleuphe
2160

vallystyr
2161

valphearg
2162

valprotrp
2163

valserarg
2164

valtrpphe
2165

valtrpval
2166

valval
2167

vanillac
2168

vanilpyr
2169

vitd3
2170

wharachd
2171

whddca
2172

whhdca
2173

whtststerone
2174

whttdca
2175

xan
2176

xmp
	2177

xol24oh
	2178

xol25oh
	2179

xol27oh
	2180

xol7a
	2181

xol7ah
	2182

xol7ah2
	2183

xol7ah2al
	2184

xol7ah3
	2185

xol7aone
	2186

xoldiolone
	2187

xoldioloneh
	2188

xolest181_hs
	2189

xolest182_hs
	2190

xolest183_hs
	2191

xolest204_hs
	2192

xolest205_hs
	2193

xolest226_hs
	2194

xoltetrol
	2195

xoltri24
	2196

xoltri25
	2197

xoltri27

```
        2198

xoltriol
        2199

xtsn
        2200

xu1p_D
        2201

xu5p_D
        2202

xyl_D
        2203

xylt
        2204

xylu_D
        2205

xylu_L
        2206

yvite
        2207

zn2
        2208

zym_int2
        2209

zymst
        2210

zymstnl

ChemAxon's pKa calculator plugin returned an error for metabolites:
CE6252
pchol2ste_hs
Assuming that metabolite species in model.metFormulas are representative for metabolites where pKa could n
```

```
save('modelNew_after_setupComponentContribution','model')
```

Prepare the training data for the component contribution method

```
training_data = prepareTrainingData(model,printLevel);
```

```
Successfully added 3914 values from TECRDB
Successfully added 223 formation energies
Successfully added 13 redox potentials
Loading the InChIs for the training data from: /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/ana
Successfully created balanced training-data structure: 672 compounds and 4138 reactions
Loading the pKa values for the training data from: cache/kegg_pkas.mat
Warning: Estimation inaccuracy may result from missing stereo in InChI for:
1.    2hydog
2.    fum
3.    mescon
4.    retinal
```

```
5.    retinal_11_cis
6.    retinal_cis_13
7.    retinal_cis_9
Mapping model metabolites to nist compounds
Creating group incidence matrix
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H14N3O8P/c10-5-1-2-12(9(15)11-5)8-7(14)6(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H16N3O14P3/c10-5-1-2-12(9(15)11-5)8-7(14)6
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H15N3O11P2/c10-5-1-2-12(9(15)11-5)8-7(14)6
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H14N3O7P/c10-7-1-2-12(9(14)11-7)8-3-5(13)6
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C14H26N4O11P2/c1-18(2,3)6-7-26-30(22,23)29-3
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H22O2/c1-18-9-8-14-13-5-3-12(19)10-11(13)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H13N3O5/c10-5-1-2-12(9(16)11-5)8-7(15)6(14
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C11H20N4O11P2/c12-2-4-23-27(19,20)26-28(21,2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H15N3O10P2/c10-7-1-2-12(9(14)11-7)8-3-5(13
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H24O2/c1-18-9-8-14-13-5-3-12(19)10-11(13)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C12H17N4O4PS/c1-8-11(3-4-20-21(17,18)19)22-7
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C3H9NO/c1-4(2,3)5/h1-3H3
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/Na/q+1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C17H19N3O4S/c1-10-15(18-7-11(8-21)16(10)24-3
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C39H51N11O18/c40-20(33(59)60)5-9-24(51)19(13
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C44H54N12O21/c45-21(36(66)67)5-10-26(57)43(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C44H54N12O21/c45-21(36(66)67)5-10-26(57)43(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C49H63N13O24/c50-22(39(71)72)5-11-28(63)34(4
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C49H64N13O24/c50-22(39(71)72)5-11-28(63)34(4
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C17H12O6/c1-20-10-6-11-14(8-4-5-21-17(8)22-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C72H119N7O54S/c1-18(89)74-35-25(95)7-72(71(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C80H132N8O59S/c1-20(99)82-39-28(106)8-80(79(
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C70H116N6O54S/c1-17(86)72-33-23(91)6-70(69(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C78H129N7O59S/c1-19(96)80-37-26(102)7-78(77(
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O4/c1-2-3-4-5-10-13-16-19(24-23)17-14-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O4/c1-2-3-13-16-19(24-23)17-14-11-9-7-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O4/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C11H12N2O/c1-9-8-11(14)13(12(9)2)10-6-4-3-5-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/K/q+1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
```

```
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/Ca/q+2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/ClH/h1H/p-1/fCl/h1h/q-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/HI/h1H/p-1/fI/h1h/q-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H31N4O16P/c1-7(26)22-12-8(27)4-20(18(32)3
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C4H5N3O/c5-3-1-2-6-4(8)7-3/h1-2H,(H3,5,6,7,8
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H16N3O13P3/c10-7-1-2-12(9(14)11-7)8-3-5(13
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H13N3O4/c10-7-1-2-12(9(15)11-7)8-3-5(14)6(
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H13N5O3/c1-3(15)6(16)4-2-11-7-5(12-4)8(17)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C10H10N2O/c1-8-7-10(13)12(11-8)9-5-3-2-4-6-9
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C17H12O7/c1-20-7-4-8-11(12-14-17(23-14)24-16
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C24H32O8/c1-24-9-8-14-13-5-3-12(10-11(13)2-4
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C24H32O9/c1-24-7-6-13-12-5-3-11(25)8-10(12)2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H24O3/c1-18-7-6-13-12-5-3-11(19)8-10(12)2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C24H30O8/c1-24-9-8-14-13-5-3-12(10-11(13)2-4
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H22O5S/c1-18-9-8-14-13-5-3-12(23-24(20,21
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H24O3/c1-18-9-8-11-10-4-6-15(19)17(21)13(
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C84H139N7O70S3/c1-20(103)86-39-27(109)7-84(8
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C86H142N8O70S3/c1-21(106)88-41-29(113)8-86(8
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/NO/c1-2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C17H19N3O3S/c1-10-8-18-15(11(2)16(10)23-4)9-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C10H8O/c1-2-4-8-7(3-1)5-6-9-10(8)11-9/h1-6,9
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C12H19N4O10P3S/c1-8-11(30-7-16(8)6-10-5-14-9
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/H2O3S2/c1-5(2,3)4/h(H2,1,2,3,4)/p-2/fO3S2/q-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C34H34N4O4/c1-7-21-17(3)25-13-26-19(5)23(9-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C80H132N8O62S2/c1-20(99)82-39-28(106)8-80(79
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C86H142N8O67S2/c1-21(106)88-41-29(113)8-86(8
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C78H129N7O62S2/c1-19(96)80-37-26(102)7-78(77
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C84H139N7O67S2/c1-20(103)86-39-27(109)7-84(8
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/I2/c1-2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/H5O10P3/c1-11(2,3)9-13(7,8)10-12(4,5)6/h(H,7
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C5H11NO2Se/c1-9-3-2-4(6)5(7)8/h4H,2-3,6H2,1H
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C12H18N4O7P2S/c1-8-11(3-4-22-25(20,21)23-24(
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
```

```
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C12H17N4OS/c1-8-11(3-4-17)18-7-16(8)6-10-5-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C6H6NO6P/c8-7(9)5-1-3-6(4-2-5)13-14(10,11)12
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/H2O3S2/c1-5(2,3)4/h(H2,1,2,3,4)/p-1/fHO3S2/h
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/Zn/q+2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O6/c1-2-3-6-9-15(24-23)12-13-17-16(18-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/CH2NO2S/c2-1-5(3)4/h3-4H
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C3H3O2/c4-2-1-3-5/h1-3H/q-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H22O3/c1-18-7-6-11-12(14(18)4-5-17(18)21)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H24O3/c1-18-7-6-11-12(14(18)4-5-17(18)21)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C19H24O3/c1-19-8-7-12-13(15(19)5-6-18(19)21)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H13N5O3/c1-3-5(15)4-2-11-6-9(14-4,17-3)7(1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H22O3/c1-18-7-6-13-12-5-3-11(19)8-10(12)2
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H16O3/c1-2-3-4-6-9(12-11)7-5-8-10/h5,7-9,1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C19H26O3/c1-19-8-7-12-13(15(19)5-6-18(19)21)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/ClHO/c1-2/h2H
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/ClNO2/c1-4-2-3
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/HNO3/c2-1-4-3/h3H/p-1/fNO3/h3h/q-1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C28H47O2/c1-20(2)11-8-12-21(3)13-9-14-22(4)1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O6/c21-17(11-6-2-1-3-9-15-19(23)24)12-
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C20H32O7/c21-17(11-6-2-1-5-9-16-20(25,26)27)
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C36H38N4O8/c1-17-21(5-9-33(41)42)29-14-26-19
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C36H38N4O8/c1-17-21(5-9-33(41)42)29-14-27-19
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C9H5NO4/c11-7-2-4-1-6(9(13)14)10-5(4)3-8(7)1
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C27H48O5/c1-15(6-5-7-16(2)25(31)32)19-8-9-20
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H32O4/c1-2-3-11-14-17(22-21)15-12-9-7-5-4
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
Warning: getGroupVectorFromInchi did not succeed for: InChI=1/C18H32O6/c1-2-3-7-10-15-16(23-15)13-14-22-18
python2 /home/rfleming/work/sbgCloud/code/fork-cobratoolbox/src/analysis/thermo/groupContribution/old/inch
```

```
save('training_dataNew_after_prepareTrainingData','training_data')
```

Call the component contribution method

```
if ~isfield(model,'DfG0')
    [model,~] = componentContribution(model,training_data);
end
```

```
Running Component Contribution method
```

Setup a thermodynamically constrained model

```
if ~isfield(model,'DfGt0')
    model = setupThermoModel(model,confidenceLevel);
end
```

```
Estimating standard transformed Gibbs energies of formation.

Estimating bounds on transformed Gibbs energies.
Additional effect due to possible change in chemical potential of Hydrogen ions for transport reactions.
Additional effect due to possible change in electrical potential for transport reactions.
```

Generate a model with reactants instead of major microspecies

```
if ~isfield(model,'Srecon')
    printLevel_pHbalanceProtons=-1;


model=pHbalanceProtons(model,massImbalance,printLevel_pHbalanceProtons,result
sBaseFileName);
end
```

```
Warning: vonBertalanffy:pHbalanceProtons 'Hydrogen unbalanced reconstruction reactions exist!
```

Determine quantitative directionality assignments

```
if ~exist('directions','var')
    fprintf('Quantitatively assigning reaction directionality.\n');
    [modelThermo, directions] =
thermoConstrainFluxBounds(model,confidenceLevel,DrGt0_Uncertainty_Cutoff,prin
tLevel);
end
```

```
Quantitatively assigning reaction directionality.
9/10600 reactions with DrGtMin=DrGtMax~=0
4/10600 reactions with DrGtMin=DrGtMax=0
The following reactions have DrGtMax=DrGtMin=0:
H2Oter    h2o[c]     <=>    h2o[r]
H2Otn    h2o[n]     <=>    h2o[c]
Htr    h[c]     <=>    h[r]
HMR_1095    h[c]     <=>    h[n]
ACYP
```

Analyse thermodynamically constrained model

Choose the cutoff for probablity that reaction is reversible

```
cumNormProbCutoff=0.2;
```

Build Boolean vectors with reaction directionality statistics

```
[modelThermo,directions]=directionalityStats(modelThermo,directions,cumNormPr
obCutoff,printLevel);
```

```
9/10600 reactions with DrGtMin=DrGtMax~=0
4/10600 reactions with DrGtMin=DrGtMax=0
Qualitative internal reaction directionality:
      8791     internal reconstruction reaction directions.
      5208     forward reconstruction assignment.
         4     reverse reconstruction assignment.
      3579     reversible reconstruction assignment.

Quantitative internal reaction directionality:
      8791     internal reconstruction reaction directions.
      7155     of which have a thermodynamic assignment.
      1632     of which have no thermodynamic assignment.
       871     forward thermodynamic only assignment.
       325     reverse thermodynamic only assignment.
      5959     reversible thermodynamic only assignment.

Qualitiative vs Quantitative:
      2992     Reversible -> Reversible
       159     Reversible -> Forward
       185     Reversible -> Reverse
       239     Reversible -> Uncertain
       712     Forward -> Forward
       140     Forward -> Reverse
      2965     Forward -> Reversible
      1391     Forward -> Uncertain
         2     Reverse -> Reverse
         0     Reverse -> Forward
         2     Reverse -> Reversible
         2     Reversible -> Uncertain

Breakdown of relaxation of reaction directionality, Qualitiative vs Quantitative:
      2965     qualitatively forward reactions that are quantitatively reversible (total).
      1499     of which are quantitatively reversible by range of dGt0. P(\Delta_{r}G^{\primeo}<0) > 0.7
       130     of which are quantitatively reversible by range of dGt0. 0.3< P(\Delta_{r}G^{\primeo}<0) <
      1336     of which are quantitatively reversible by range of dGt0. P(\Delta_{r}G^{\primeo}<0) < 0.3
        65     of which are quantitatively forward by fixed dGr0t, but reversible by concentration alone (
         0     of which are quantitatively reverse by dGr0t, but reversible by concentration (negative fix
         0     of which are quantitatively forward by dGr0t, but reversible by concentration (positve fixe
       424     of which are quantitatively reverse by dGr0t, but reversible by concentration (uncertain ne
       873     of which are quantitatively forward by dGr0t, but reversible by concentration (uncertain po
```

```
% directions    a structue of boolean vectors with different directionality
%               assignments where some vectors contain subsets of others
%
% qualtiative -> quantiative changed reaction directions
%   .forward2Forward
%   .forward2Reverse
%   .forward2Reversible
%   .forward2Uncertain
%   .reversible2Forward
%   .reversible2Reverse
%   .reversible2Reversible
%   .reversible2Uncertain
%   .reverse2Forward
%   .reverse2Reverse
%   .reverse2Reversible
```

```
%   .reverse2Uncertain
%   .tightened
%
% subsets of qualtiatively forward  -> quantiatively reversible
%   .forward2Reversible_bydGt0
%   .forward2Reversible_bydGt0LHS
%   .forward2Reversible_bydGt0Mid
%   .forward2Reversible_bydGt0RHS
%
%   .forward2Reversible_byConc_zero_fixed_DrG0
%   .forward2Reversible_byConc_negative_fixed_DrG0
%   .forward2Reversible_byConc_positive_fixed_DrG0
%   .forward2Reversible_byConc_negative_uncertain_DrG0
%   .forward2Reversible_byConc_positive_uncertain_DrG0
```

Write out reports on directionality changes for individual reactions to the results folder.

```
fprintf('%s\n','directionalityChangeReport...');
```

```
directionalityChangeReport...
```

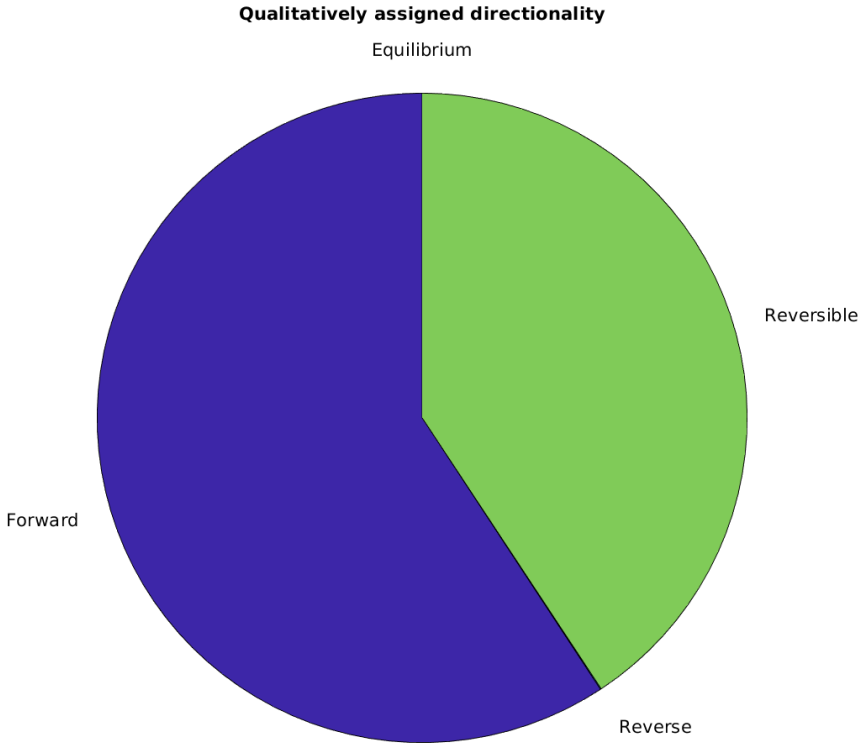
```
directionalityChangeReport(modelThermo,directions,cumNormProbCutoff,printLeve
l,resultsBaseFileName)
```

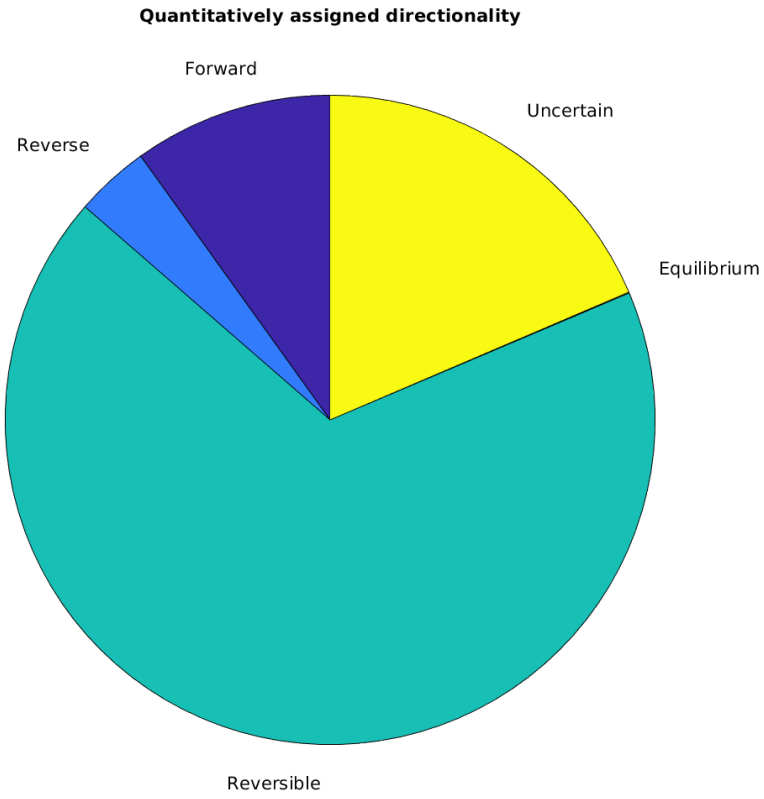
Generate pie charts with proportions of reaction directionalities and changes in directionality

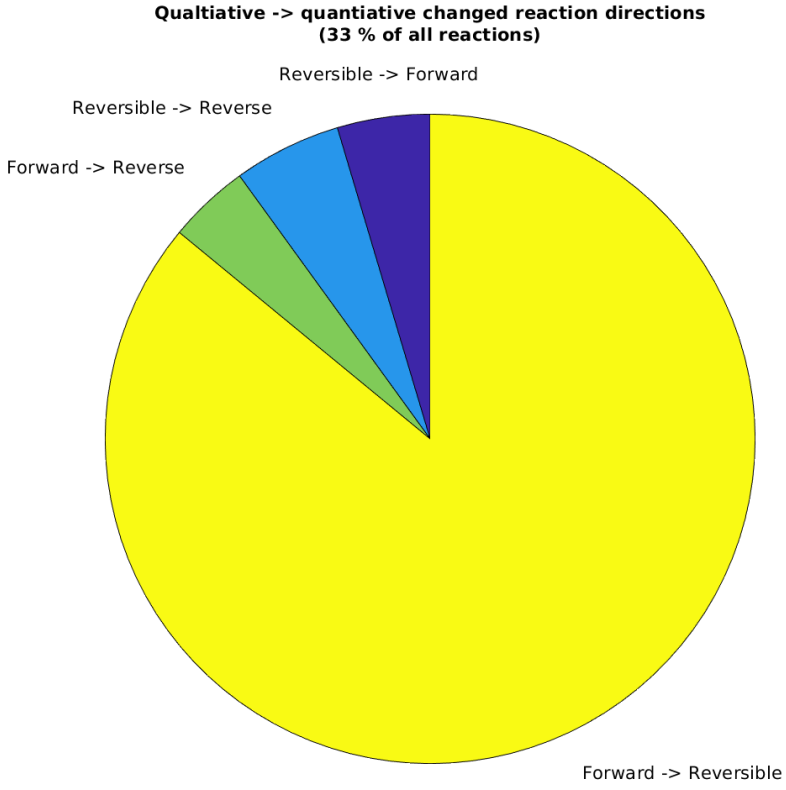
```
fprintf('%s\n','directionalityStatFigures...');
```

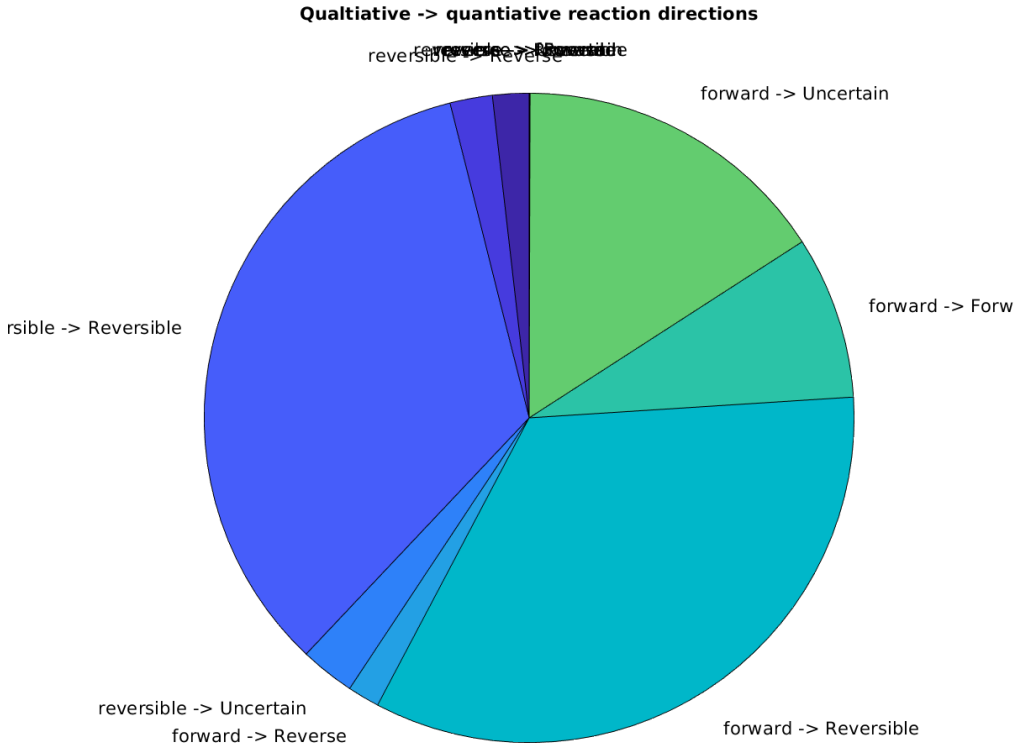
```
directionalityStatFigures...
```

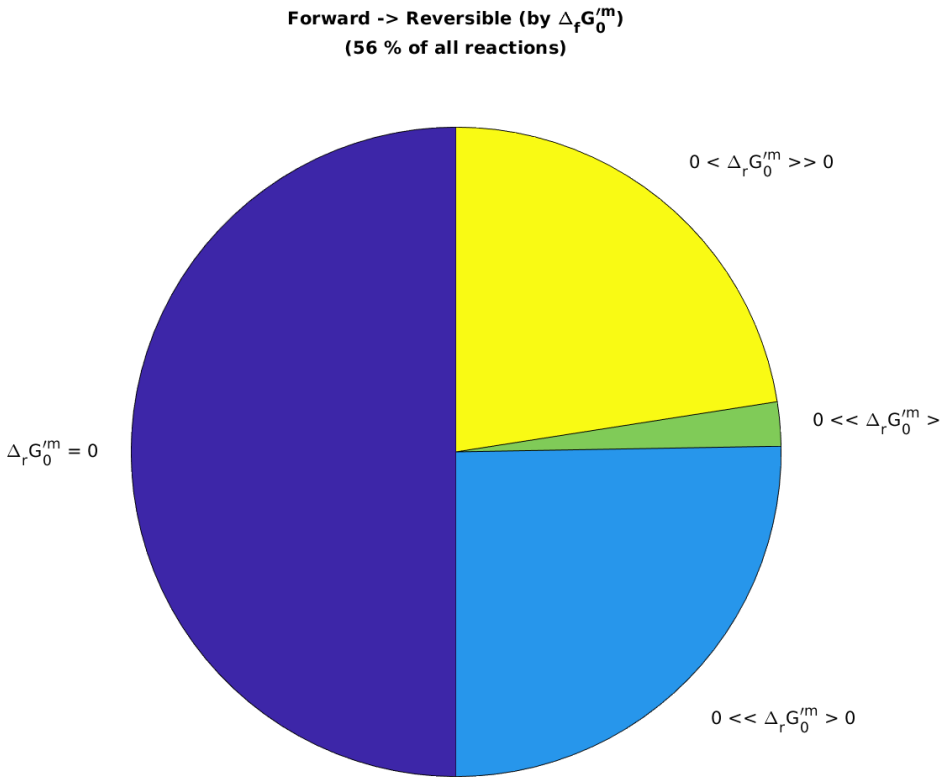
```
directionalityStatsFigures(directions,resultsBaseFileName)
```

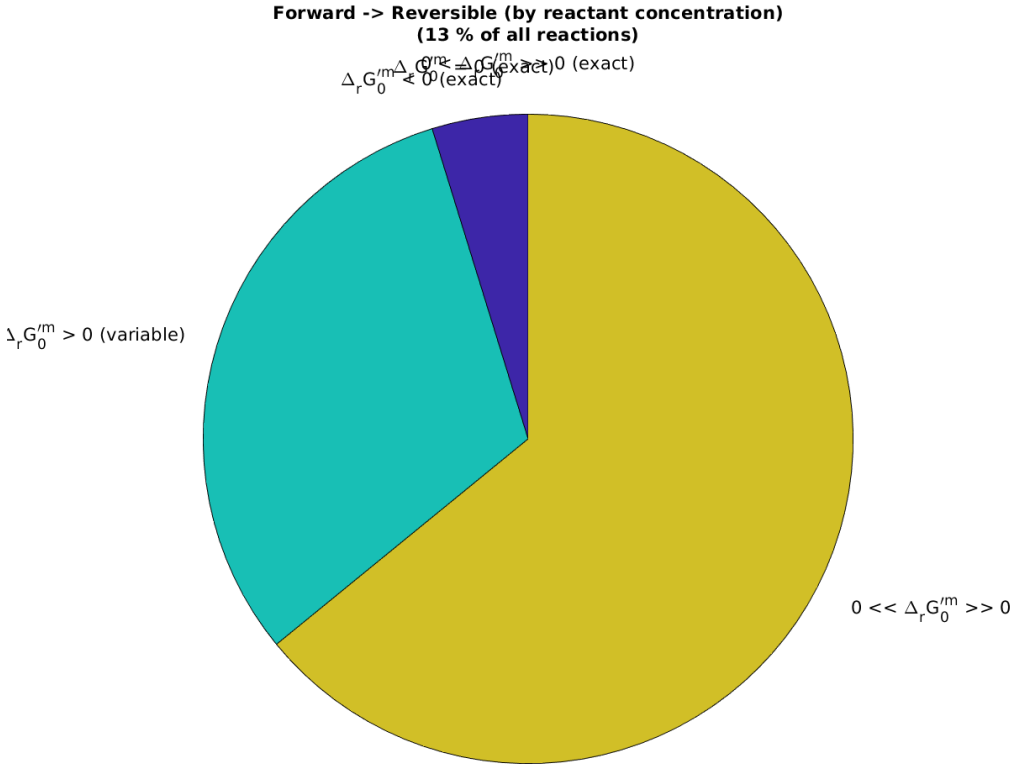

Qualitatively assigned directionality
Equilibrium
Reversible
Forward
Reverse


Quantitatively assigned directionality
Forward
Uncertain
Reverse
Equilibrium
Reversible


Qualtiative -> quantiative changed reaction directions
(33 % of all reactions)
Reversible -> Forward
Reversible -> Reverse
Forward -> Reverse
Forward -> Reversible


Qualtiative -> quantiative reaction directions
forward -> Uncertain
forward -> Forw
rsible -> Reversible
reversible -> Uncertain
forward -> Reverse
forward -> Reversible


Forward -> Reversible (by $\Delta_f G_0'^m$)
(56 % of all reactions)
$0 < \Delta_r G_0'^m >> 0$
$0 << \Delta_r G_0'^m >$
$\Delta_r G_0'^m = 0$
$0 << \Delta_r G_0'^m > 0$

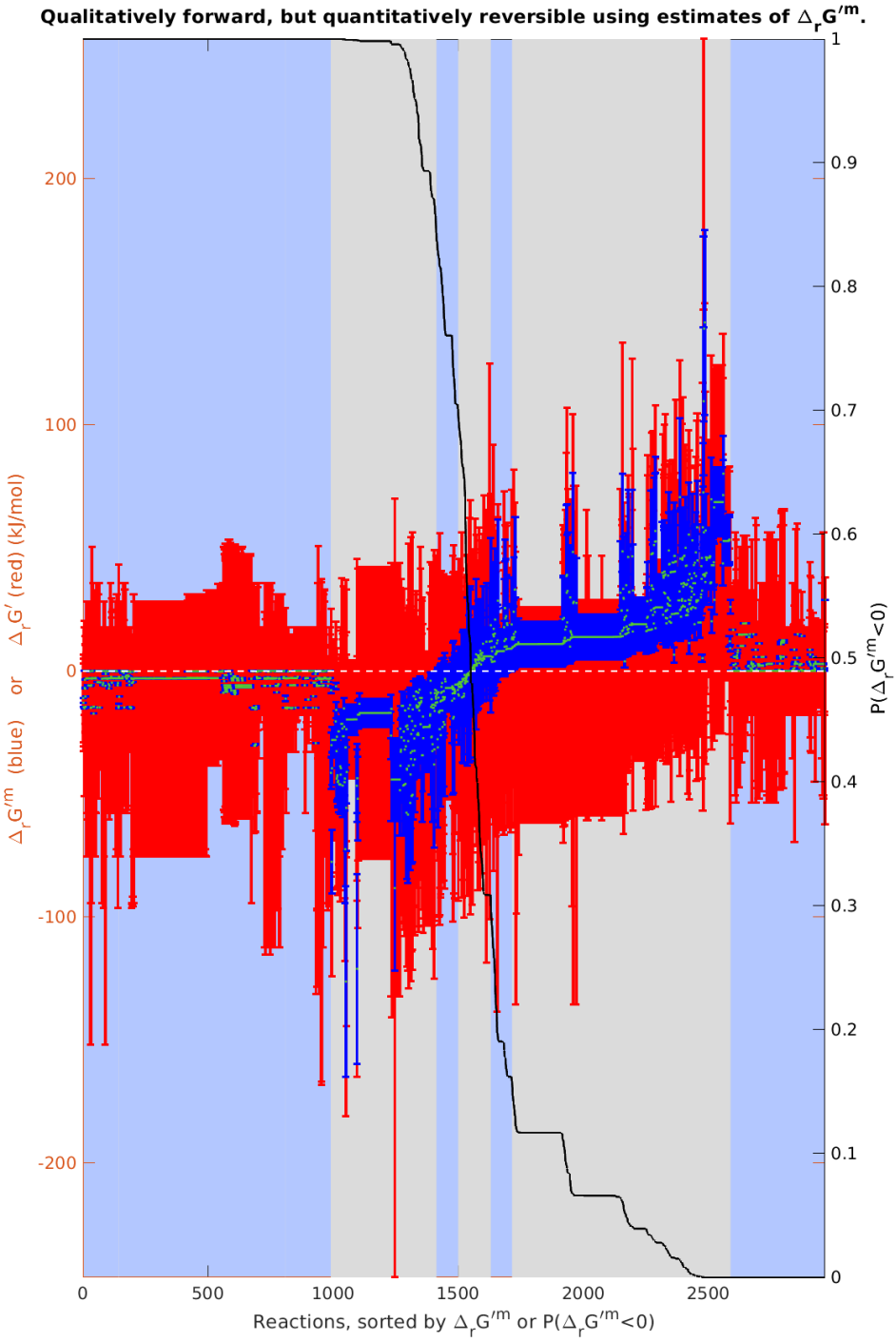


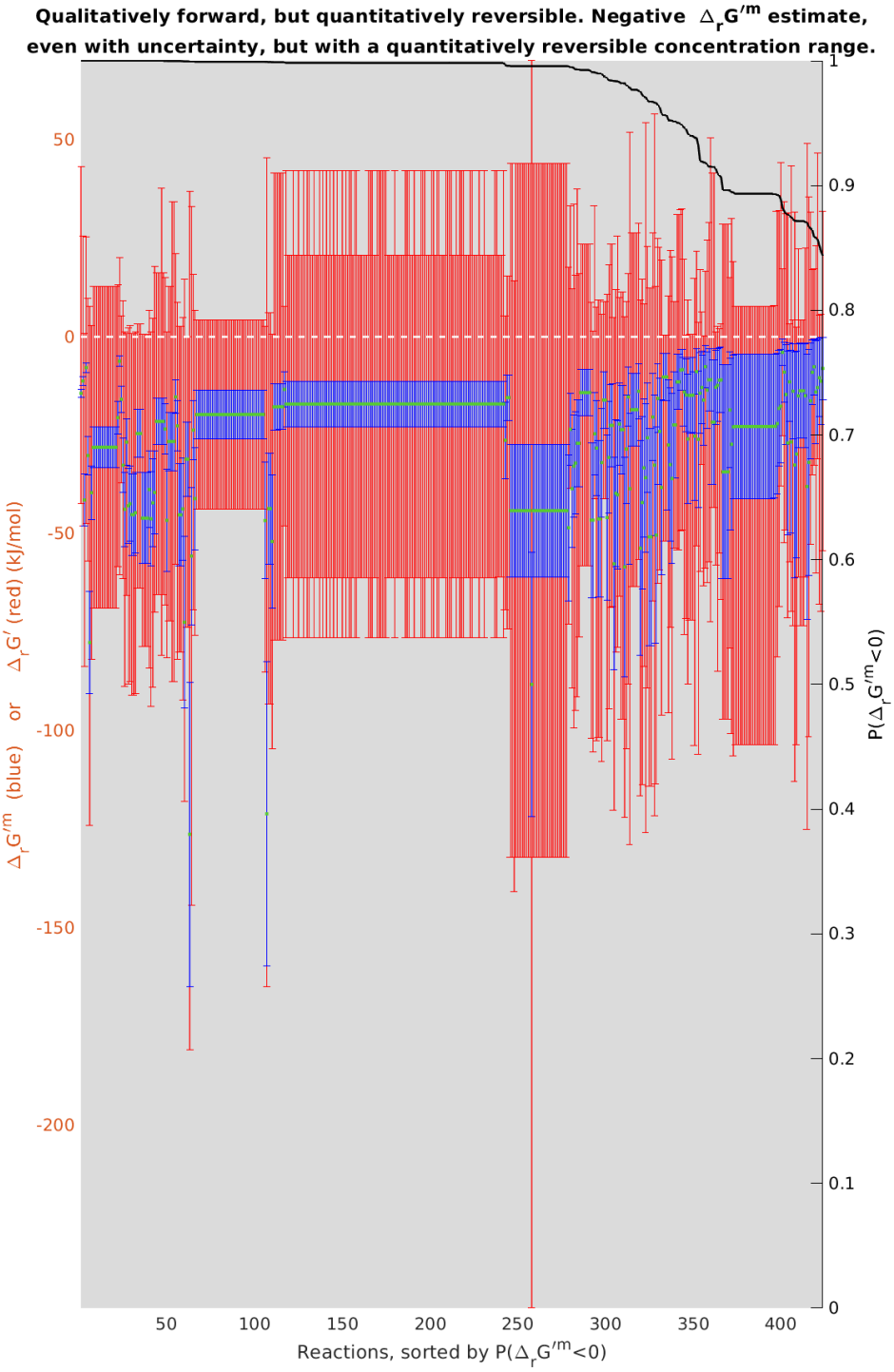
Generate figures to interpret the overall reasons for reaction directionality changes for the qualitatively forward now quantiatiavely reversible reactions

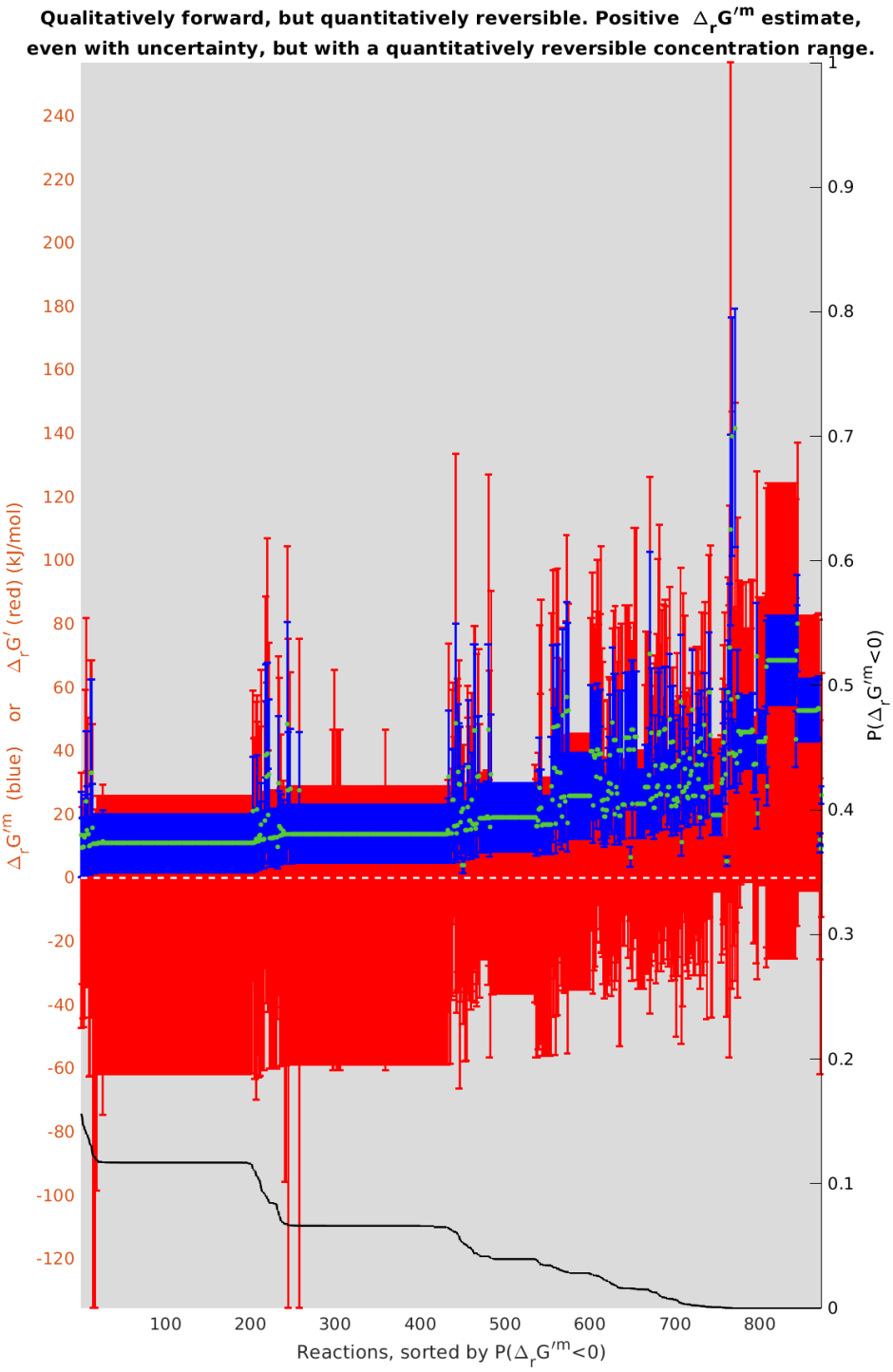
```
if any(directions.forward2Reversible)
```

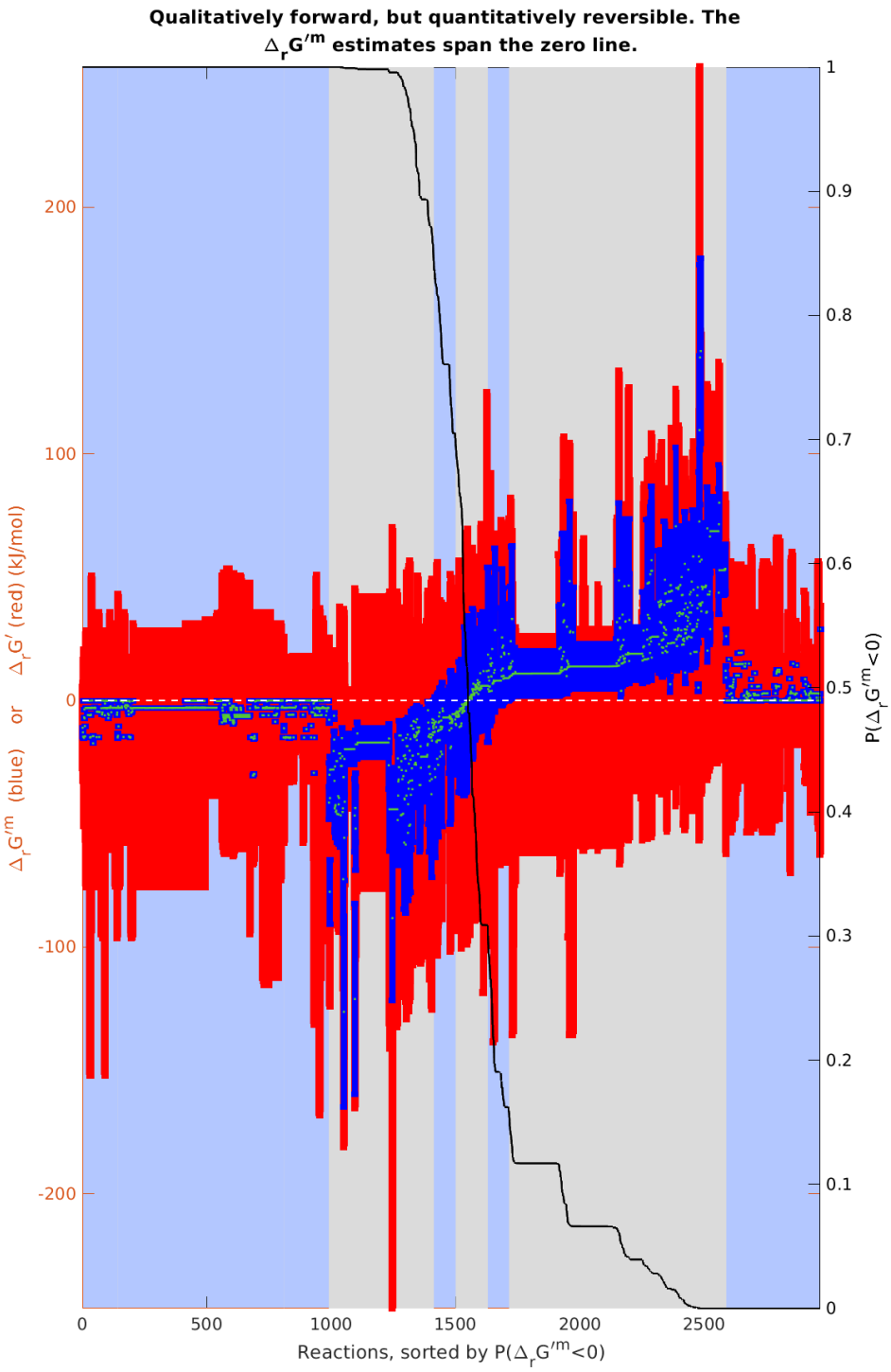
```
    fprintf('%s\n','forwardReversibleFigures...');
    forwardReversibleFigures(modelThermo,directions,confidenceLevel)
end
```

```
forwardReversibleFigures...
```




Qualitatively forward, but quantitatively reversible. Negative $\Delta_r G'^m$ estimate,
even with uncertainty, but with a quantitatively reversible concentration range.
50
0
-50
-100
-150
-200
$\Delta_r G'^m$ (blue) or $\Delta_r G'$ (red) (kJ/mol)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
$P(\Delta_r G'^m<0)$
50
100
150
200
250
300
350
400
Reactions, sorted by $P(\Delta_r G'^m<0)$


Qualitatively forward, but quantitatively reversible. Positive $\Delta_r G'^m$ estimate, even with uncertainty, but with a quantitatively reversible concentration range.
$\Delta_r G'^m$ (blue) or $\Delta_r G'$ (red) (kJ/mol)
$P(\Delta_r G'^m<0)$
Reactions, sorted by $P(\Delta_r G'^m<0)$
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
100
200
300
400
500
600
700
800



Write out tables of experimental and estimated thermochemical parameters for the model

```
generateThermodynamicTables(modelThermo,resultsBaseFileName);
```

REFERENCES

[1] Fleming, R. M. T. & Thiele, I. von Bertalanffy 1.0: a COBRA toolbox extension to thermodynamically constrain metabolic models. Bioinformatics 27, 142–143 (2011).

[2] Haraldsdóttir, H. S., Thiele, I. & Fleming, R. M. T. Quantitative assignment of reaction directionality in a multicompartmental human metabolic reconstruction. Biophysical Journal 102, 1703–1711 (2012).

[3] Noor, E., Haraldsdóttir, H. S., Milo, R. & Fleming, R. M. T. Consistent Estimation of Gibbs Energy Using Component Contributions. PLoS Comput Biol 9, e1003098 (2013).

[4] Fleming, R. M. T. , Predicat, G., Haraldsdóttir, H. S., Thiele, I. von Bertalanffy 2.0 (in preparation).