Thermodynamically constrain a metabolic model

Author: Ronan Fleming, School of Medicine, University of Galway

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

23doguln
44

23dpg
45

2425dhvitd2
46

2425dhvitd3
47

24nph
48

25aics
49

25hvitd2
50

25hvitd3
51

2amac
52

2aobut
53

2c23dh56dhoxin
54

2ddecdicoa
55

2decdicoa
56

2docohexecoa
57

2docopencoa
58

2dodtricoa
59

2dp6mep
60

2dp6mobq
61

2dp6mobq_me
62

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

35diotyr
108

35dsmv
109

3aib
110

3aib_D
111

3bcrn
112

3ddcrn
113

3ddecdicoa
114

3deccrn
115

3decdicoa
116

3dhchol
117

3dhguln
118

3docopencoa
119

3dodtricoa
120

3dpdhb
121

3dpdhb_me
122

3dphb
123

3dsphgn
124

3h3mglt
125

3hadicoa
126

3hadpac
   127

3hanthrn
   128

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

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

3snpyr
   193

3spyr
   194

3tdcrn
   195

3tetd7ecoa
   196

3thexddcoa
   197

3ttetddcoa
   198

3uib
   199

3ump
   200

42A3HP24DB
   201

44mctr
   202

44mzym
   203

4aabutn
   204

4abut
   205

4abutn
   206

4aphdob
   207

4bhglz
   208

4fumacac
   209

4glu56dihdind
   210

4h2oglt
   211

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
339

CE0074
340

CE0233
341

CE0347
342

CE0693
343

CE0713
344

CE0737
345

CE0785
346

CE0849
347

CE0955
348

CE1243
349

CE1261
350

CE1273
351

CE1297
352

CE1310
353

CE1352
354

CE1401
355

CE1447
356

CE1556
357

CE1562
358

CE1589
359

CE1617
360

CE1918

361

CE1925
362

CE1926
363

CE1935
364

CE1936
365

CE1939
366

CE1940
367

CE1943
368

CE1944
369

CE1950
370

CE2006
371

CE2026
372

CE2028
373

CE2038
374

CE2047
375

CE2049
376

CE2053
377

CE2056
378

CE2084
379

CE2088
380

CE2089
381

CE2172
382

CE2176
383

CE2209
384

CE2211
385

CE2242
386

CE2243
387

CE2245
388

CE2246
389

CE2247
390

CE2248
391

CE2249
392

CE2250
393

CE2251
394

CE2253
395

CE2313
396

CE2314
397

CE2417
398

CE2418
399

CE2420
400

CE2421
401

CE2422
402

CE2424
403

CE2432
404

CE2433
405

CE2434
406

CE2437
407

CE2438
408

CE2439
409

CE2440
410

CE2441
411

CE2442
412

CE2445
413

CE2510
414

CE2537
415

CE2567
416

CE2576
417

CE2577
418

CE2705
419

CE2838
420

CE2839
421

CE2866
422

CE2870
423

CE2872
424

CE2873

425

CE2874
426

CE2875
427

CE2915
428

CE2916
429

CE2917
430

CE2934
431

CE3554
432

CE4633
433

CE4722
434

CE4723
435

CE4724
436

CE4790
437

CE4791
438

CE4792
439

CE4793
440

CE4794
441

CE4795
442

CE4796
443

CE4797
444

CE4798
445

CE4799
446

CE4800
447

CE4801
448

CE4802
449

CE4803
450

CE4804
451

CE4806
452

CE4807
453

CE4808
454

CE4810
455

CE4811
456

CE4812
457

CE4817
458

CE4819
459

CE4820
460

CE4821
461

CE4831
462

CE4832
463

CE4833
464

CE4834
465

CE4835
466

CE4838
467

CE4840
468

CE4841
469

CE4842
470

CE4843
471

CE4844
472

CE4845
473

CE4846
474

CE4847
475

CE4848
476

CE4849
477

CE4850
478

CE4851
479

CE4852
480

CE4853
481

CE4854
482

CE4855
483

CE4872
484

CE4874
485

CE4876
486

CE4877
487

CE4881
488

CE4888

489

CE4890
490

CE4968
491

CE4969
492

CE4970
493

CE4987
494

CE4988
495

CE4989
496

CE4990
497

CE5021
498

CE5022
499

CE5025
500

CE5026
501

CE5072
502

CE5114
503

CE5116
504

CE5117
505

CE5118
506

CE5119
507

CE5120
508

CE5125
509

CE5126
510

CE5144
511

CE5148
512

CE5150
513

CE5151
514

CE5152
515

CE5153
516

CE5154
517

CE5155
518

CE5156
519

CE5157
520

CE5158
521

CE5160
522

CE5161
523

CE5162
524

CE5166
525

CE5178
526

CE5236
527

CE5276
528

CE5304
529

CE5626
530

CE5629
531

CE5643
532

CE5665
533

CE5786
534

CE5787
535

CE5788
536

CE5789
537

CE5791
538

CE5797
539

CE5798
540

CE5853
541

CE5854
542

CE5867
543

CE5868
544

CE5869
545

CE5934
546

CE5944
547

CE5945
548

CE5946
549

CE5947
550

CE5986
551

CE6031
552

CE6205

553

CE6230
554

CE6232
555

CE6234
556

CE6246
557

CE6247
558

CE6252
559

CE6504
560

CE6506
561

CE6508
562

CE7047
563

CE7079
564

CE7081
565

CE7082
566

CE7083
567

CE7085
568

CE7088
569

CE7090
570

CE7091
571

CE7096
572

CE7097
573

CE7172
574

HC00250
575

HC00319
576

HC00342
577

HC00361
578

HC00460
579

HC00576
580

HC00591
581

HC00664
582

HC00682
583

HC00718
584

HC00822
585

HC00900
586

HC00955
587

HC01104
588

HC01118
589

HC01180
590

HC01223
591

HC01254
592

HC01361
593

HC01376
594

HC01377
595

HC01397
596

HC01405
597

HC01406
598

HC01407
599

HC01408
600

HC01412
601

HC01415
602

HC01434
603

HC01440
604

HC01441
605

HC01444
606

HC01446
607

HC01459
608

HC01496
609

HC01501
610

HC01522
611

HC01577
612

HC01609
613

HC01668
614

HC01672
615

HC01700
616

HC01842

617

HC02020
618

HC02021
619

HC02022
620

HC02023
621

HC02024
622

HC02025
623

HC02027
624

HC02110
625

HC02121
626

HC02180
627

HC02187
628

HC02191
629

HC02192
630

HC02193
631

HC02194
632

HC02195
633

HC02196
634

HC02197
635

HC02198
636

HC02200
637

HC02201
638

HC02202
639

HC02203
640

HC02204
641

HC02205
642

HC02206
643

HC02207
644

HC02208
645

HC02210
646

HC02213
647

HC02214
648

HC02216
649

HC02217
650

HC02220
651

HC02228
652

HC10856
653

HC10857
654

HC10858
655

HC10859
656

L2aadp
657

L2aadp6sa
658

L_dpchrm
659

Lcyst
660

Lcystin
661

Lfmkynr
662

Lhcystin
663

Lkynr
664

Lpipecol
665

M00003
666

M00004
667

M00006
668

M00008
669

M00010
670

M00011
671

M00012
672

M00017
673

M00018
674

M00019
675

M00020
676

M00021
677

M00022
678

M00023
679

M00044
680

M00046

```
   681

M00048
   682

M00049
   683

M00054
   684

M00056
   685

M00061
   686

M00063
   687

M00067
   688

M00069
   689

M00071
   690

M00100
   691

M00101
   692

M00115
   693

M00116
   694

M00117
   695

M00122
   696

M00123
   697

M00127
   698

M00129
   699

M00170
   700

M00172
   701

M00245
   702
```

M00260
703

M00261
704

M00263
705

M00265
706

M00285
707

M00315
708

M00341
709

M00342
710

M00343
711

M00406
712

M00429
713

M00579
714

M00603
715

M00605
716

M00606
717

M00615
718

M00625
719

M00658
720

M00673
721

M00699
722

M00702
723

```
M00707
   724

M00712
   725

M00715
   726

M00742
   727

M00743
   728

M00746
   729

M00753
   730

M00770
   731

M00778
   732

M00780
   733

M00782
   734

M00783
   735

M00790
   736

M00792
   737

M00795
   738

M00797
   739

M00804
   740

M00806
   741

M00839
   742

M00841
   743

M00843
   744

M00849
```

```
   745

M00852
   746

M00860
   747

M00862
   748

M00873
   749

M00875
   750

M00877
   751

M00879
   752

M00885
   753

M00887
   754

M00889
   755

M00897
   756

M00899
   757

M00907
   758

M00909
   759

M00911
   760

M00937
   761

M00938
   762

M00939
   763

M00940
   764

M00942
   765

M00960
   766
```

M00964
767

M00976
768

M00977
769

M00978
770

M00979
771

M01067
772

M01068
773

M01075
774

M01076
775

M01077
776

M01079
777

M01080
778

M01081
779

M01082
780

M01083
781

M01084
782

M01141
783

M01165
784

M01191
785

M01197
786

M01207
787

M01235
788

M01236
789

M01237
790

M01238
791

M01389
792

M01454
793

M01456
794

M01458
795

M01461
796

M01462
797

M01465
798

M01466
799

M01468
800

M01475
801

M01476
802

M01487
803

M01490
804

M01491
805

M01492
806

M01495
807

M01498
808

M01501

809

M01502
810

M01506
811

M01573
812

M01582
813

M01724
814

M01726
815

M01727
816

M01729
817

M01770
818

M01775
819

M01776
820

M01777
821

M01966
822

M01989
823

M02035
824

M02051
825

M02052
826

M02053
827

M02102
828

M02103
829

M02107
830

M02108
831

M02112
832

M02155
833

M02186
834

M02447
835

M02451
836

M02457
837

M02467
838

M02490
839

M02491
840

M02611
841

M02612
842

M02613
843

M02616
844

M02637
845

M02638
846

M02694
847

M02745
848

M02760
849

M02761
850

M02837
851

M02973
852

M02976
853

M02977
854

M03005
855

M03006
856

M03008
857

M03011
858

M03014
859

M03016
860

M03018
861

M03019
862

M03022
863

M03024
864

M03045
865

M03047
866

M03050
867

M03051
868

M03116
869

M03117
870

M03131
871

M03134
872

M03153

873

M03167
874

M03168
875

N1aspmd
876

Nacasp
877

Nacsertn
878

Sfglutth
879

Ssq23epx
880

T4hcinnm
881

aacoa
882

aact
883

abt
884

abt_D
885

ac
886

acac
887

acald
888

accoa
889

acetol
890

acetone
891

acgal
892

acgal1p
893

acgam
894

acgam1p
   895

acgam6p
   896

acgbgbside_hs
   897

acglc13galacglcgal14acglcgalgluside_hs
   898

acglu
   899

acgly
   900

ach
   901

achom_L
   902

acile_L
   903

acleu_L
   904

aclys
   905

acmana
   906

acmanap
   907

acmp
   908

acmpglu
   909

acmpglut
   910

acnacngal14acglcgalgluside_hs
   911

acnam
   912

acnamp
   913

acorn
   914

acrn
   915

937

air
938

akg
939

ala_B
940

ala_D
941

ala_L
942

alaala
943

alaargcys
944

alaarggly
945

alaasnleu
946

alaglylys
947

alahisala
948

alalysthr
949

aldstrn
950

allop
951

alltn
952

alpa_hs
953

alpam
954

am19cs
955

am1a4ncs
956

am1accs
957

am1acs
958

am1alcs
   959

am1c4n9cs
   960

am1c9cs
   961

am1ccs
   962

am1cglc
   963

am1csa
   964

am4n9cs
   965

am4ncs
   966

am6sa
   967

am9csa
   968

amet
   969

ametam
   970

amp
   971

amuco
   972

and19one
   973

andrstandn
   974

andrstndn
   975

andrstrn
   976

andrstrnglc
   977

anth
   978

antipyrene
   979

apnnox
   980

appnn
   981

aprgstrn
   982

aprut
   983

aps
   984

arab_L
   985

arach
   986

arachcoa
   987

arachcrn
   988

arachd
   989

arachdcoa
   990

arachdcrn
   991

aracheth
   992

arg_D
   993

arg_L
   994

argalaala
   995

argalaphe
   996

argalathr
   997

argarg
   998

argarglys
   999

argargmet
        1000

argcysgly

1001

argcysser
1002

arggluglu
1003

argglupro
1004

argglygly
1005

arghisthr
1006

argleuphe
1007

arglysasp
1008

argphearg
1009

argpromet
1010

argprothr
1011

argserser
1012

argsuc
1013

argtyrval
1014

argvalcys
1015

argvaltrp
1016

ascb_L
1017

asn_L
1018

asnasnarg
1019

asncyscys
1020

asnmetpro
1021

asnpheasp
1022

asnphecys
1023

asntyrgly
1024

asntyrphe
1025

asntyrthr
1026

asp_D
1027

asp_L
1028

aspalaarg
1029

aspasnglu
1030

aspglu
1031

aspglupro
1032

aspglutrp
1033

asphiscys
1034

asphispro
1035

asplysglu
1036

asplyshis
1037

aspmetasp
1038

aspprolys
1039

aspvalasn
1040

atp
1041

atvacid
1042

atvacylgluc
1043

atvethgluc
	1044

atvlac
	1045

atvlacgluc
	1046

avite1
	1047

avite2
	1048

b2coa
	1049

bamppald
	1050

betald
	1051

bgly
	1052

bhb
	1053

bildglcur
	1054

bilglcur
	1055

bilirub
	1056

biliverd
	1057

biocyt
	1058

btamp
	1059

btcoa
	1060

btn
	1061

but
	1062

bvite
	1063

bz
	1064

bzcoa

1065

c101crn
1066

c10crn
1067

c10dc
1068

c12dc
1069

c12dccoa
1070

c14dccoa
1071

c16dc
1072

c226coa
1073

c226crn
1074

c3dc
1075

c4crn
1076

c4dc
1077

c51crn
1078

c5dc
1079

c6crn
1080

c6dc
1081

c81coa
1082

c81crn
1083

c8crn
1084

c8dc
1085

ca2
1086

```
cala
        1087

camp
        1088

caproic
        1089

caribup_R
        1090

caribup_s
        1091

caribupglu_S
        1092

carn
        1093

caro
        1094

carveol
        1095

cbasp
        1096

cbp
        1097

cdp
        1098

cdpchol
        1099

cdpea
        1100

cgly
        1101

chlstol
        1102

chol
        1103

cholate
        1104

cholcoa
        1105

cholcoads
        1106

cholcoaone
        1107
```

```
cholcoar
        1108

cholcoas
        1109

cholp
        1110

chsterol
        1111

chsterols
        1112

chtn
        1113

cit
        1114

citmcoa_L
        1115

citr_L
        1116

cl
        1117

clpnd
        1118

clpndcoa
        1119

clpndcrn
        1120

cmp
        1121

cmpacna
        1122

cmusa
        1123

co
        1124

co2
        1125

coa
        1126

coke
        1127

coprost
        1128

cortsn
```

```
        1129

coucoa
        1130

coumarin
        1131

cpppg1
        1132

cpppg3
        1133

creat
        1134

crglz
        1135

crn
        1136

crtn
        1137

crtsl
        1138

crtstrn
        1139

crvnc
        1140

crvs
        1141

csa
        1142

csasulp
        1143

csn
        1144

ctdecdcoa
        1145

ctp
        1146

cyan
        1147

cynt
        1148

cys_L
        1149

cysacmp
        1150
```

```
cysam
        1151

cysasnmet
        1152

cysaspphe
        1153

cyscys
        1154

cysglnmet
        1155

cysgluhis
        1156

cysglutrp
        1157

cysleuthr
        1158

cyssermet
        1159

cyst_L
        1160

cystyrasn
        1161

cytd
        1162

dad_2
        1163

dadp
        1164

dag_hs
        1165

damp
        1166

datp
        1167

dc2coa
        1168

dca
        1169

dcacoa
        1170

dcamp
        1171
```

dcdp
	1172

dchac
	1173

dcholcoa
	1174

dcmp
	1175

dcsptn1
	1176

dcsptn1coa
	1177

dcsptn1crn
	1178

dctp
	1179

dcyt
	1180

dd2coa
	1181

dd3coa
	1182

dd5ecoa
	1183

ddca
	1184

ddcacoa
	1185

ddeccrn
	1186

ddece1crn
	1187

ddsmsterol
	1188

debrisoquine
	1189

dec24dicoa
	1190

dec47dicoa
	1191

decdicoa
	1192

decdicrn

1193

decdp
1194

dece3coa
1195

dece4coa
1196

dectricoa
1197

dedoldp_L
1198

dedolp_L
1199

dgchol
1200

dgcholcoa
1201

dgdp
1202

dgmp
1203

dgsn
1204

dgtp
1205

dha
1206

dhap
1207

dhbpt
1208

dhcholestanate
1209

dhcholestancoa
1210

dhcholoylcoa
1211

dhdascb
1212

dhea
1213

dheas
1214

dhf
	1215

dhglz
	1216

dhlam
	1217

dhmtp
	1218

dhor_S
	1219

didecaeth
	1220

didp
	1221

diholineth
	1222

dimp
	1223

din
	1224

ditp
	1225

dkmpp
	1226

dlnlcg
	1227

dlnlcgcoa
	1228

dlnlcgcrn
	1229

dmantipyrine
	1230

dmgly
	1231

dmhptcoa
	1232

dmhptcrn
	1233

dmnoncoa
	1234

dmnoncrn
	1235

dmpp
	1236

dnad
	1237

doco13ac
	1238

doco13ecoa
	1239

docohepcoa
	1240

docohexcoa
	1241

docohxeth
	1242

docosac
	1243

docosahexcoa
	1244

docoscoa
	1245

docosdiac
	1246

doctеteth
	1247

dodecanac
	1248

doldp_L
	1249

dolglcp_L
	1250

dolmanp_U
	1251

dolp_L
	1252

dolp_U
	1253

dopa
	1254

dopa3glcur
	1255

dopa4glcur
	1256

dopa4sf

1257

dopaqn
1258

dopasf
1259

dpcoa
1260

drib
1261

dsT_antigen
1262

dsmsterol
1263

dtdp
1264

dtmp
1265

dttp
1266

dudp
1267

dump
1268

duri
1269

dutp
1270

e4hglu
1271

e4p
1272

eaflatoxin
1273

eandrstrn
1274

ebastine
1275

ebastineoh
1276

egme
1277

ei11ecoa
1278

eic21114tr
1279

eicostet
1280

eicostetcoa
1281

eicostetcrn
1282

eidi1114ac
1283

eipencoa
1284

eitetcoa
1285

elaid
1286

elaidcrn
1287

epoxtac
1288

estradiol
1289

estradiolglc
1290

estriol
1291

estriolglc
1292

estrone
1293

estroneglc
1294

estrones
1295

etha
1296

ethamp
1297

ethmalac
1298

ethmalcoa
1299

etoh
	1300

f1p
	1301

f26bp
	1302

f6p
	1303

fad
	1304

fadh2
	1305

fald
	1306

fdp
	1307

fe2
	1308

fe3
	1309

fgam
	1310

fmn
	1311

fna5moxam
	1312

fol
	1313

for
	1314

forglu
	1315

formcoa
	1316

fpram
	1317

fprica
	1318

frdp
	1319

fru
	1320

fuc132galacglcgal14acglcgalgluside_hs

```
        1321

fuc13galacglcgal14acglcgalgluside_hs
        1322

fuc1p_L
        1323

fuc_L
        1324

fucacngal14acglcgalgluside_hs
        1325

fum
        1326

fvs
        1327

g1p
        1328

g3p
        1329

g3pc
        1330

g6p
        1331

gal
        1332

gal1p
        1333

galacglc13galacglcgal14acglcgalgluside_hs
        1334

galam
        1335

galgluside_hs
        1336

galt
        1337

gam
        1338

gam6p
        1339

gar
        1340

gcald
        1341

gchola
        1342
```

```
gdp
        1343

gdpddman
        1344

gdpfuc
        1345

gdpmann
        1346

glac
        1347

glc3meacp
        1348

glc_D
        1349

glcn
        1350

glcr
        1351

glcur
        1352

glcur1p
        1353

gln_L
        1354

glnasngln
        1355

glnhishis
        1356

glnhislys
        1357

glnlyslys
        1358

glnlystrp
        1359

glnproglu
        1360

glntrpglu
        1361

glntyrleu
        1362

glu5p
        1363
```

glu5sa
	1364

glu_L
	1365

gluargleu
	1366

gluasnleu
	1367

glucys
	1368

gluglu
	1369

gluilelys
	1370

gluleu
	1371

glumet
	1372

glumethis
	1373

glutacoa
	1374

glutar
	1375

glutcoa
	1376

glutcon
	1377

gluthr
	1378

gluthrlys
	1379

glutrpala
	1380

glx
	1381

gly
	1382

glyald
	1383

glyb
	1384

glyc

```
        1385

glyc2p
        1386

glyc3p
        1387

glyc_R
        1388

glyc_S
        1389

glyclt
        1390

glygly
        1391

glyhisasn
        1392

glyhislys
        1393

glyleu
        1394

glylyscys
        1395

glylysphe
        1396

glyphe
        1397

glypro
        1398

glysar
        1399

glytyrlys
        1400

glyvalhis
        1401

glz
        1402

gmp
        1403

grdp
        1404

gsn
        1405

gthox
        1406
```

gthrd
	1407

gtp
	1408

gua
	1409

gudac
	1410

gullac
	1411

guln
	1412

h2co3
	1413

h2o
	1414

h2o2
	1415

hLkynr
	1416

ha_pre1
	1417

hco3
	1418

hcoumarin
	1419

hcys_L
	1420

hdca
	1421

hdcea
	1422

hdcecrn
	1423

hdcoa
	1424

hdd2coa
	1425

hdd2crn
	1426

hepcoa
	1427

hepdeceth
1428

hestratriol
1429

hexc
1430

hexccoa
1431

hexddcoa
1432

hexde7coa
1433

hexdeceeth
1434

hexdectecoa
1435

hexdiac
1436

hexdicoa
1437

hexdpencoa
1438

hexdtr
1439

hexdtrcoa
1440

hexe3coa
1441

hexgly
1442

hgentis
1443

hhxdcal
1444

his_L
1445

hisargcys
1446

hisargser
1447

hisasp
1448

hiscyscys

1449

hisglnala
1450

hisglu
1451

hisglugln
1452

hisglylys
1453

hishislys
1454

hislysala
1455

hislysglu
1456

hislysile
1457

hislysthr
1458

hislysval
1459

hismet
1460

hismetgln
1461

hisphearg
1462

hisprolys
1463

hista
1464

histrphis
1465

hmbil
1466

hmcarn
1467

hmcr
1468

hmgcoa
1469

hnifedipine
1470

```
hom_L
        1471

homoval
        1472

hpdca
        1473

hpdcacoa
        1474

hpdcacrn
        1475

hpdece
        1476

hpdececoa
        1477

hpyr
        1478

hretn
        1479

htaxol
        1480

hx2coa
        1481

hxa
        1482

hxan
        1483

hxcoa
        1484

hxdcal
        1485

hyochol
        1486

hyptaur
        1487

i
        1488

ibcoa
        1489

ibup_R
        1490

ibup_S
        1491
```

ibupcoa_S
	1492

ibupgluc
	1493

icdchol
	1494

icit
	1495

id3acald
	1496

idour
	1497

idp
	1498

ile_L
	1499

ileargile
	1500

ileasnhis
	1501

ileasp
	1502

ileglnglu
	1503

ileglyarg
	1504

ileprolys
	1505

ileserarg
	1506

iletrptyr
	1507

im4ac
	1508

im4act
	1509

imp
	1510

ind3ac
	1511

ind56qn
	1512

inost

```
        1513

ins
        1514

iodine
        1515

ipdp
        1516

isochol
        1517

isolvstacid
        1518

isomal
        1519

itaccoa
        1520

itacon
        1521

itp
        1522

ivcoa
        1523

ivcrn
        1524

k
        1525

kdn
        1526

kdnp
        1527

ksii_core2
        1528

ksii_core2_pre1
        1529

ksii_core2_pre10
        1530

ksii_core2_pre2
        1531

ksii_core2_pre3
        1532

ksii_core2_pre4
        1533

ksii_core2_pre5
        1534
```

```
ksii_core2_pre6
        1535

ksii_core2_pre7
        1536

ksii_core2_pre8
        1537

ksii_core2_pre9
        1538

ksii_core4
        1539

ksii_core4_pre1
        1540

ksii_core4_pre10
        1541

ksii_core4_pre2
        1542

ksii_core4_pre3
        1543

ksii_core4_pre4
        1544

ksii_core4_pre5
        1545

ksii_core4_pre6
        1546

ksii_core4_pre7
        1547

ksii_core4_pre8
        1548

ksii_core4_pre9
        1549

kynate
        1550

lac_D
        1551

lac_L
        1552

lald_D
        1553

lald_L
        1554

lanost
        1555
```

lcts
	1556

leu_L
	1557

leualaarg
	1558

leuasnasp
	1559

leuasplys
	1560

leugly
	1561

leuktrA4
	1562

leuktrB4
	1563

leuktrB4wcooh
	1564

leuktrB4woh
	1565

leuktrC4
	1566

leuktrD4
	1567

leuktrE4
	1568

leuktrF4
	1569

leuleu
	1570

leuleutrp
	1571

leupro
	1572

leuproarg
	1573

leusertrp
	1574

leutrp
	1575

leutrparg
	1576

leutyrtyr

1577

leuval
1578

lgnc
1579

lgt_S
1580

limnen
1581

lineth
1582

lipoate
1583

lneldc
1584

lneldccoa
1585

lneldccrn
1586

lnlc
1587

lnlccoa
1588

lnlccrn
1589

lnlnca
1590

lnlncacoa
1591

lnlncacrn
1592

lnlncg
1593

lnlncgcoa
1594

lnlncgcrn
1595

lpam
1596

lst4exp
1597

lstn
1598

lstn1gluc
1599

lstnm1
1600

lstnm2
1601

lstnm4
1602

lstnm5
1603

lstnm7
1604

lthstrl
1605

lvst
1606

lvstacid
1607

lxser
1608

lys_L
1609

lysargleu
1610

lyscyshis
1611

lysglnphe
1612

lysgluglu
1613

lyslyslys
1614

lyspheile
1615

lystrparg
1616

lystyrile
1617

lysvalphe
1618

lysvaltrp
1619

m2mn
	1620

magarachi_hs
	1621

maglinl_hs
	1622

magole_hs
	1623

magpalm_hs
	1624

magste_hs
	1625

mal_L
	1626

malcoa
	1627

malt
	1628

malthp
	1629

malthx
	1630

maltpt
	1631

malttr
	1632

maltttr
	1633

man
	1634

man1p
	1635

man6p
	1636

mdz
	1637

mdzglc
	1638

melanin
	1639

melatn
	1640

meoh

1641

mepi
1642

meracmp
1643

mercplac
1644

mercplaccys
1645

mercppyr
1646

mescoa
1647

mescon
1648

metargleu
1649

metasntyr
1650

metglntyr
1651

metglyarg
1652

methf
1653

methislys
1654

methsucc
1655

methsuccoa
1656

metmetile
1657

metphearg
1658

mettrpphe
1659

mev_R
1660

mhglz
1661

mhista
1662

```
mi1345p
        1663

mi134p
        1664

mi13p
        1665

mi145p
        1666

mi14p
        1667

mi1p_D
        1668

mi34p
        1669

mi3p_D
        1670

mi4p_D
        1671

minohp
        1672

mlthf
        1673

mma
        1674

mmcoa_R
        1675

mmcoa_S
        1676

mn
        1677

mqn10
        1678

mqn11
        1679

mqn7
        1680

mqn8
        1681

mqn9
        1682

msa
        1683
```

mthgxl
	1684

mvlac
	1685

n4abutn
	1686

n8aspmd
	1687

na1
	1688

nac
	1689

nacvanala
	1690

nad
	1691

nadh
	1692

nadp
	1693

nadph
	1694

napqi
	1695

ncam
	1696

nfd
	1697

nformanth
	1698

nh4
	1699

nicrns
	1700

nicrnt
	1701

nifedipine
	1702

nmn
	1703

no
	1704

no2

1705

noncoa
1706

normete_L
1707

npthl
1708

nrpphr
1709

nrpphrsf
1710

nrvnc
1711

nrvnccoa
1712

nwharg
1713

o2
1714

oaa
1715

oagd3_hs
1716

occoa
1717

ocdca
1718

ocdcea
1719

ocde9ecoa
1720

ocdececrn
1721

octa
1722

octd11ecoa
1723

octdececoa
1724

octdececrn
1725

octe5coa
1726

od2coa
	1727

odecoa
	1728

odecrn
	1729

oh1
	1730

oleth
	1731

omeprazole
	1732

omhdecacid
	1733

omhdocosac
	1734

onpthl
	1735

oretn
	1736

orn
	1737

orn_D
	1738

orot
	1739

orot5p
	1740

oxa
	1741

oxy1rb
	1742

oxy7rb
	1743

oxyp
	1744

pac
	1745

pacald
	1746

pailar_hs
	1747

pailpalm_hs
	1748

pailste_hs
	1749

pan4p
	1750

pap
	1751

paps
	1752

pchol2linl_hs
	1753

pchol2ole_hs
	1754

pchol2palm_hs
	1755

pchol2ste_hs
	1756

pcholar_hs
	1757

pcholdoc_hs
	1758

pcholeic_hs
	1759

pcholet_hs
	1760

pchollinl_hs
	1761

pcholn15_hs
	1762

pcholn1836_hs
	1763

pcholn183_hs
	1764

pcholn19_hs
	1765

pcholn201_hs
	1766

pcholn203_hs
	1767

pcholn205_hs
	1768

pcholn224_hs

```
        1769

pcholn2254_hs
        1770

pcholn225_hs
        1771

pcholn226_hs
        1772

pcholn261_hs
        1773

pcholn281_hs
        1774

pcholn28_hs
        1775

pcholpalm_hs
        1776

pcholpalme_hs
        1777

pcollg5hlys
        1778

pcreat
        1779

pcresol
        1780

pcrn
        1781

pcs
        1782

pd3
        1783

pdx5p
        1784

pe12_hs
        1785

pe13_hs
        1786

pe14_hs
        1787

pe15_hs
        1788

pe161_hs
        1789

pe17_hs
        1790
```

pe203_hs
	1791

pe224_hs
	1792

pe2linl_hs
	1793

peamn
	1794

pear_hs
	1795

pedh203_hs
	1796

pelinl_hs
	1797

pendecaeth
	1798

pentcoa
	1799

peole_hs
	1800

pep
	1801

pepalm_hs
	1802

perillyl
	1803

peste_hs
	1804

phaccoa
	1805

phacgly
	1806

phe_L
	1807

pheacgln
	1808

pheacgly
	1809

pheasnmet
	1810

pheasp
	1811

pheglnphe
	1812

pheleu
	1813

pheleuasp
	1814

pheleuhis
	1815

phelysala
	1816

phelyspro
	1817

phephe
	1818

phepheasn
	1819

phephethr
	1820

pheproarg
	1821

phesertrp
	1822

phethrlys
	1823

phetrpleu
	1824

phetyr
	1825

phetyrgln
	1826

phetyrlys
	1827

phlac
	1828

phom
	1829

phpyr
	1830

phsph1p
	1831

phsphings
	1832

phyQ

```
        1833

phyt
        1834

phyt2ohcoa
        1835

phytcoa
        1836

pi
        1837

pmeth
        1838

pmtcoa
        1839

pmtcrn
        1840

pnto_R
        1841

ppa
        1842

ppbng
        1843

ppcoa
        1844

ppi
        1845

ppiogly
        1846

ppmi12346p
        1847

ppp9
        1848

pppg9
        1849

pppi
        1850

pram
        1851

prgnlone
        1852

prgnlones
        1853

prgstrn
        1854
```

prist
	1855

pristanal
	1856

pristcoa
	1857

pro_D
	1858

pro_L
	1859

proargasp
	1860

proargcys
	1861

proasncys
	1862

procys
	1863

proglnpro
	1864

proglulys
	1865

progly
	1866

prohis
	1867

prohistyr
	1868

proleuarg
	1869

prolyspro
	1870

prophe
	1871

proproarg
	1872

propropro
	1873

prostgd2
	1874

prostge1
	1875

prostge2
	1876

prostgf2
	1877

prostgh2
	1878

prostgi2
	1879

protrplys
	1880

protrpthr
	1881

provalgln
	1882

prpp
	1883

pser_L
	1884

ptdca
	1885

ptdcacoa
	1886

ptdcacrn
	1887

ptrc
	1888

ptth
	1889

ptvst
	1890

pvs
	1891

pyam5p
	1892

pydam
	1893

pydx
	1894

pydx5p
	1895

pydxn
	1896

pyr

```
        1897

q10
        1898

q10h2
        1899

quln
        1900

r1p
        1901

r5p
        1902

rbl_D
        1903

rbt
        1904

retinal
        1905

retinal_11_cis
        1906

retinal_cis_13
        1907

retinal_cis_9
        1908

retinol
        1909

retinol_9_cis
        1910

retinol_cis_11
        1911

retinol_cis_13
        1912

retn
        1913

retnglc
        1914

rib_D
        1915

ribflv
        1916

rnam
        1917

ru5p_D
        1918
```

s2l2fn2m2masn
	1919

s3meacmp
	1920

s7p
	1921

saccrp_L
	1922

sarcs
	1923

sbcoa
	1924

sbt_D
	1925

sebacid
	1926

sebcoa
	1927

selmeth
	1928

ser_D
	1929

ser_L
	1930

serargala
	1931

serargtrp
	1932

sercysarg
	1933

serglyglu
	1934

serlyshis
	1935

serphelys
	1936

sertrphis
	1937

simvgluc
	1938

sl_L
	1939

slfcys
	1940

smv
	1941

smvacid
	1942

so3
	1943

so4
	1944

spc_hs
	1945

sph1p
	1946

sphgn
	1947

sphings
	1948

sphmyln180241_hs
	1949

sphmyln18114_hs
	1950

sphmyln18115_hs
	1951

sphmyln181161_hs
	1952

sphmyln18116_hs
	1953

sphmyln18117_hs
	1954

sphmyln181181_hs
	1955

sphmyln18118_hs
	1956

sphmyln181201_hs
	1957

sphmyln18120_hs
	1958

sphmyln18121_hs
	1959

sphmyln181221_hs
	1960

sphmyln18122_hs

```
        1961

sphmyln18123_hs
        1962

sphmyln1824_hs
        1963

sphmyln1825_hs
        1964

sphmyln_hs
        1965

sphs1p
        1966

spmd
        1967

sprm
        1968

sql
        1969

srtn
        1970

stcoa
        1971

stcrn
        1972

steeth
        1973

strch1
        1974

strch2
        1975

strdnc
        1976

strdnccoa
        1977

strdnccrn
        1978

subeac
        1979

subgly
        1980

sucacetat
        1981

sucaceto
        1982
```

succ
	1983

succoa
	1984

sucr
	1985

sucsal
	1986

sulpacmp
	1987

tacr
	1988

tag1p_D
	1989

tagat_D
	1990

taur
	1991

tauribup_S
	1992

taxol
	1993

tchola
	1994

tcynt
	1995

td2glutrcoa
	1996

tdchola
	1997

tdcoa
	1998

tddedi2coa
	1999

tddedicoa
	2000

tdec4ecoa
	2001

tdechola
	2002

tetd7ecoa
	2003

tetde5coa
	2004

tetdec2crn
	2005

tetdeca511ac
	2006

tetdecaeth
	2007

tetdecdicoa
	2008

tetdece1coa
	2009

tetdece1crn
	2010

tethex3
	2011

tethex3coa
	2012

tetpent3
	2013

tetpent3coa
	2014

tetpent3crn
	2015

tetpent6
	2016

tetpent6coa
	2017

tetpent6crn
	2018

tettet6
	2019

tettet6coa
	2020

tettet6crn
	2021

thbpt
	2022

thbpt4acam
	2023

thcholoylcoa
	2024

thcholst

2025

thcholstoic
2026

thexdd
2027

thexddcoa
2028

thf
2029

thm
2030

thmmp
2031

thmpp
2032

thmtp
2033

thp2c
2034

thr_L
2035

thrargtyr
2036

thrasntyr
2037

thrglnglu
2038

thrglntyr
2039

thrhishis
2040

thrilearg
2041

thrmetarg
2042

thrnt
2043

thrphearg
2044

thrserarg
2045

thrthrarg
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...
```

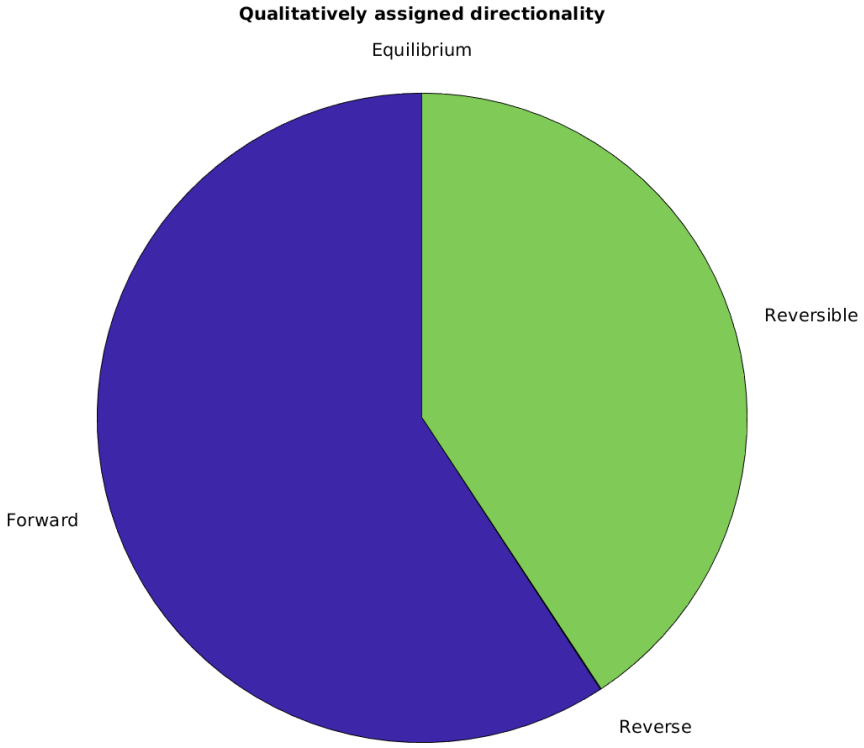
```
directionalityChangeReport(modelThermo,directions,cumNormProbCutoff,printLeve
l,resultsBaseFileName)
```

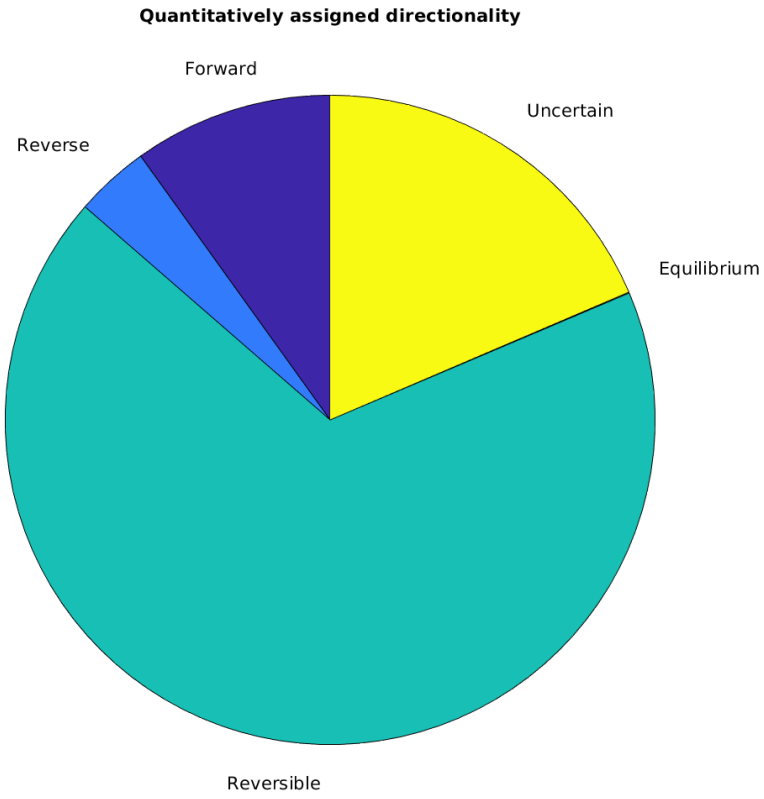
Generate pie charts with proportions of reaction directionalities and changes in directionality

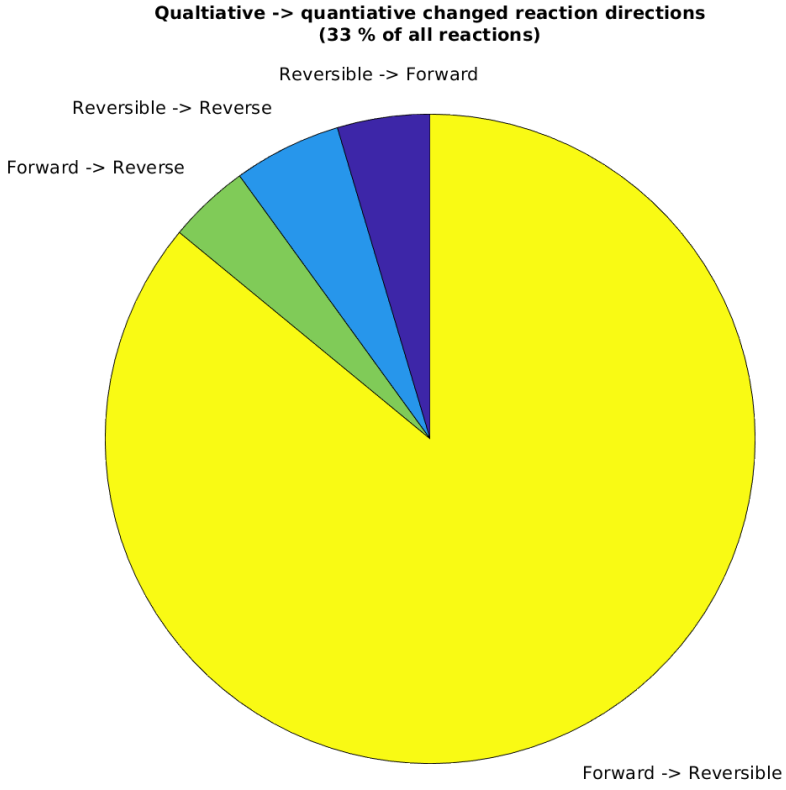
```
fprintf('%s\n','directionalityStatFigures...');
```

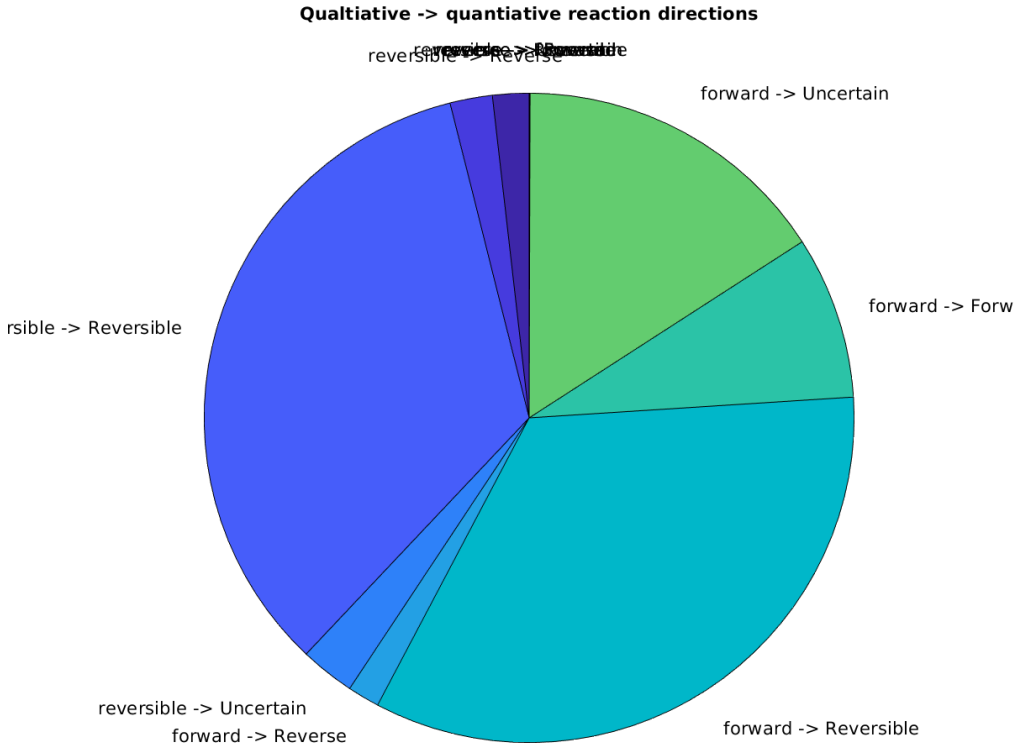
```
directionalityStatFigures...
```

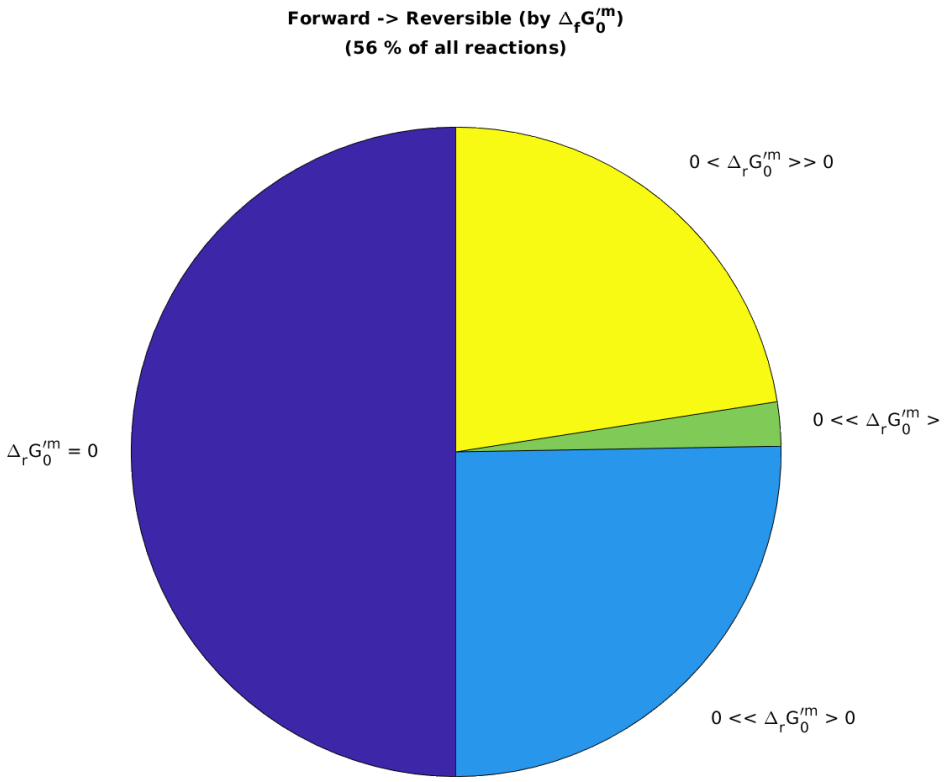
```
directionalityStatsFigures(directions,resultsBaseFileName)
```

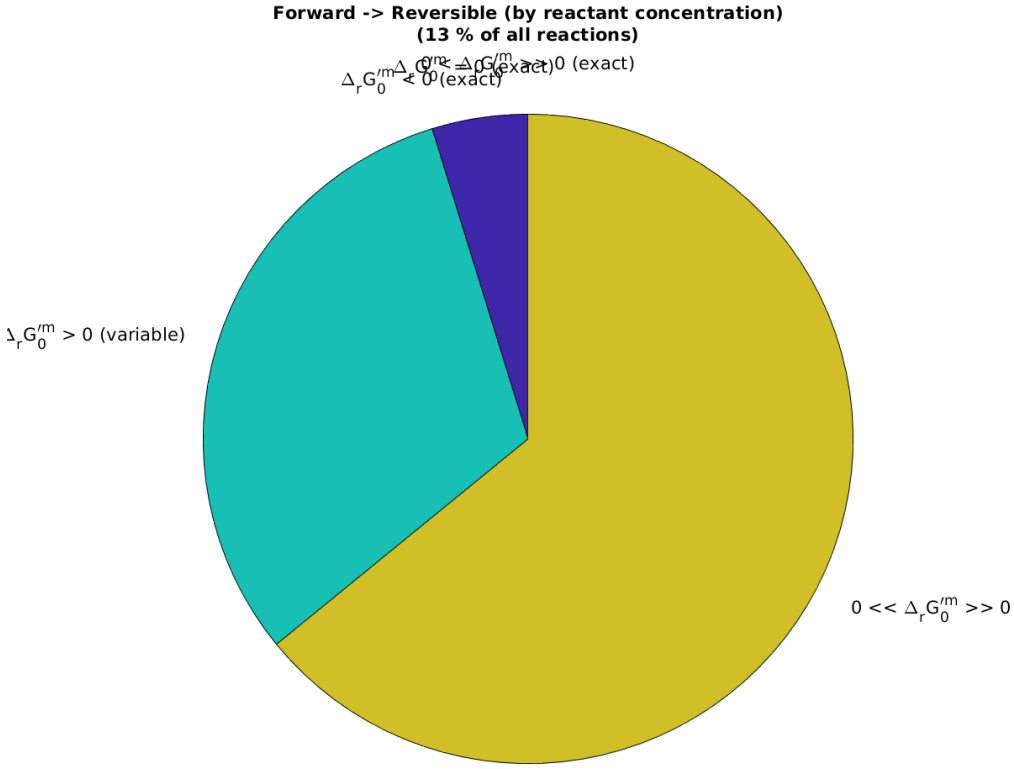

Qualitatively assigned directionality
Equilibrium
Reversible
Forward
Reverse


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)
$0 < \Delta_r G_0'^m >> 0$
$0 << \Delta_r G_0'^m >$
$\Delta_r G_0'^m = 0$
$0 << \Delta_r G_0'^m > 0$

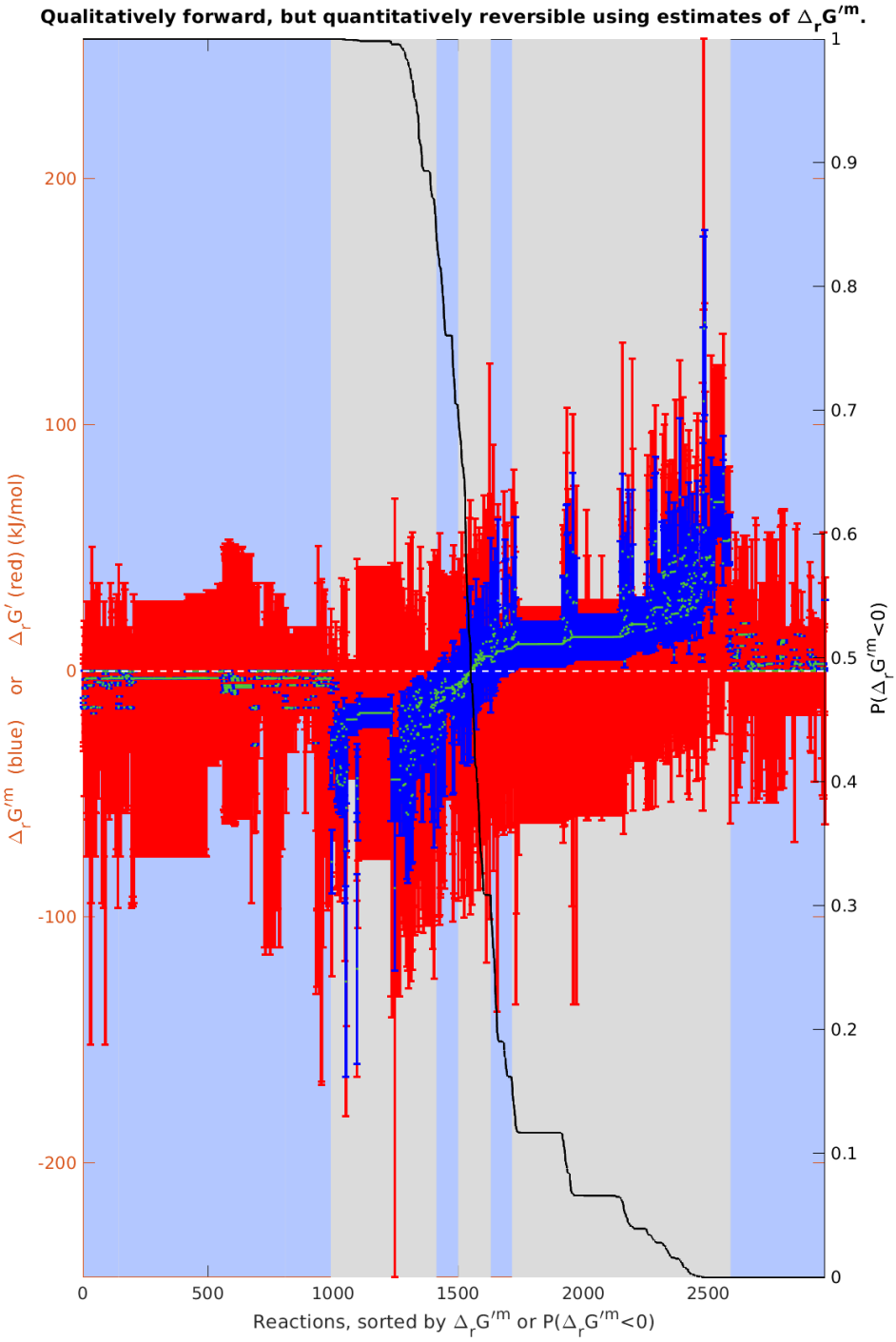


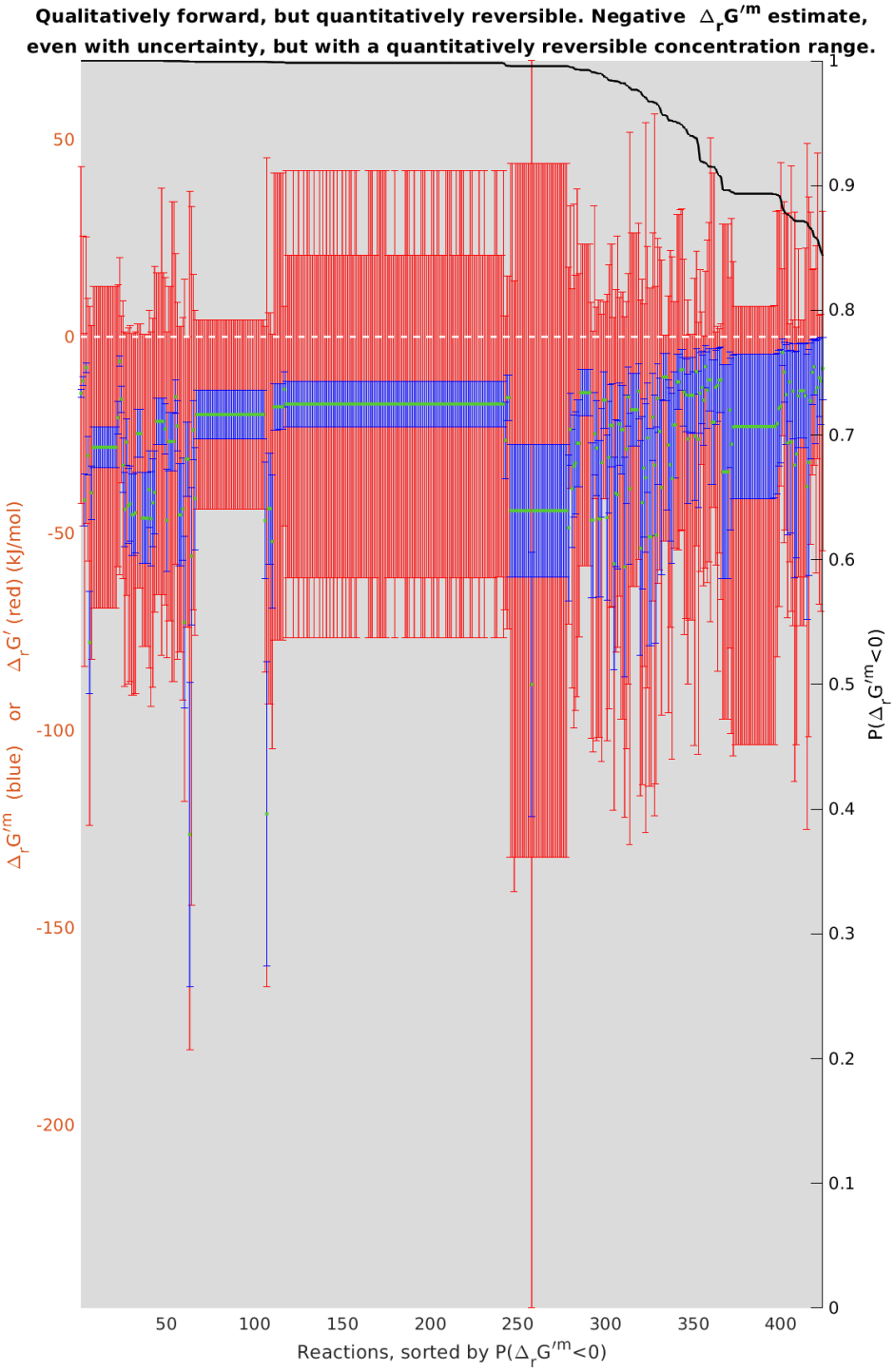
Generate figures to interpret the overall reasons for reaction directionality changes for the qualitatively forward now quantiatiavely reversible reactions

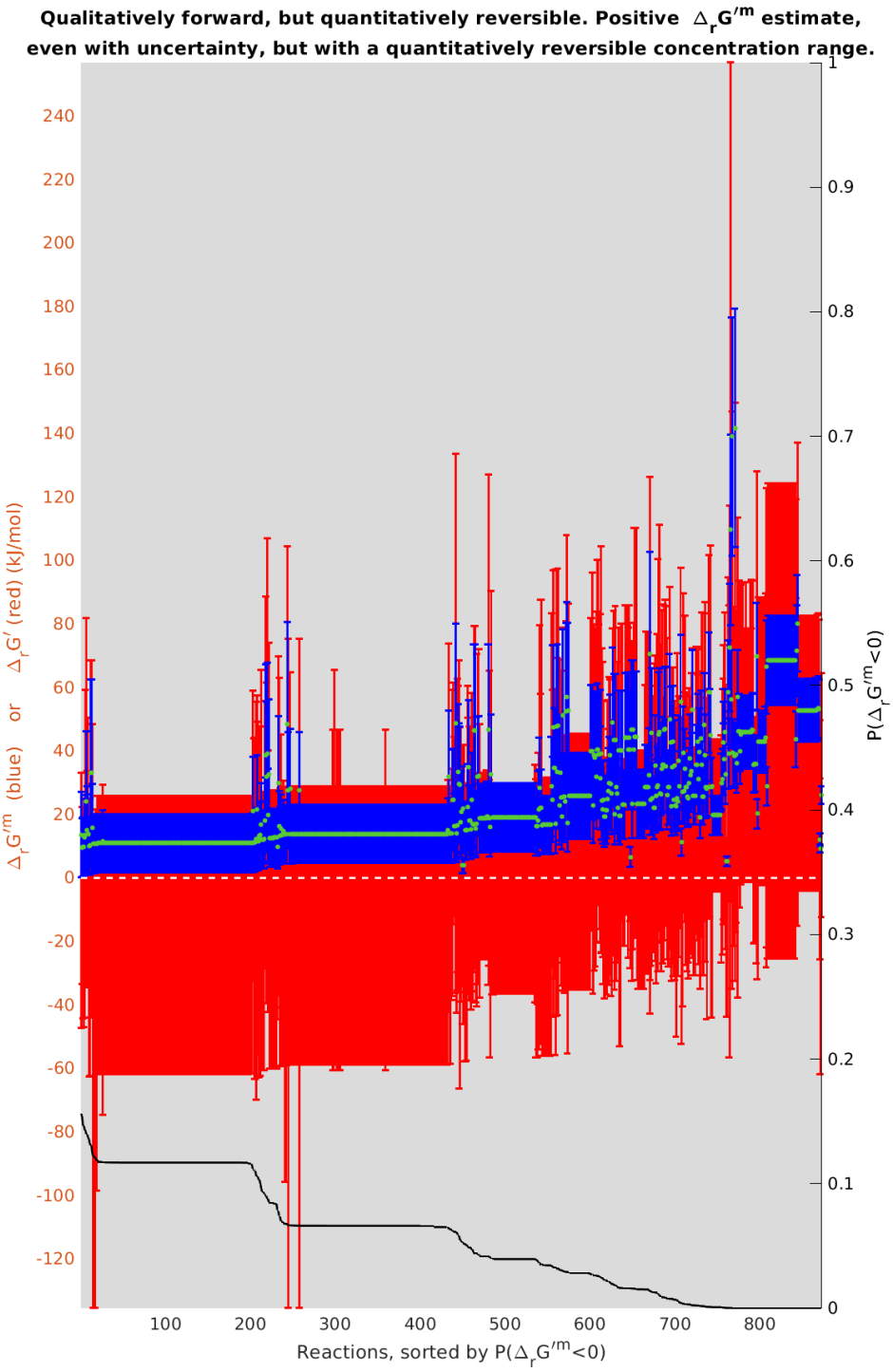
```
if any(directions.forward2Reversible)
```

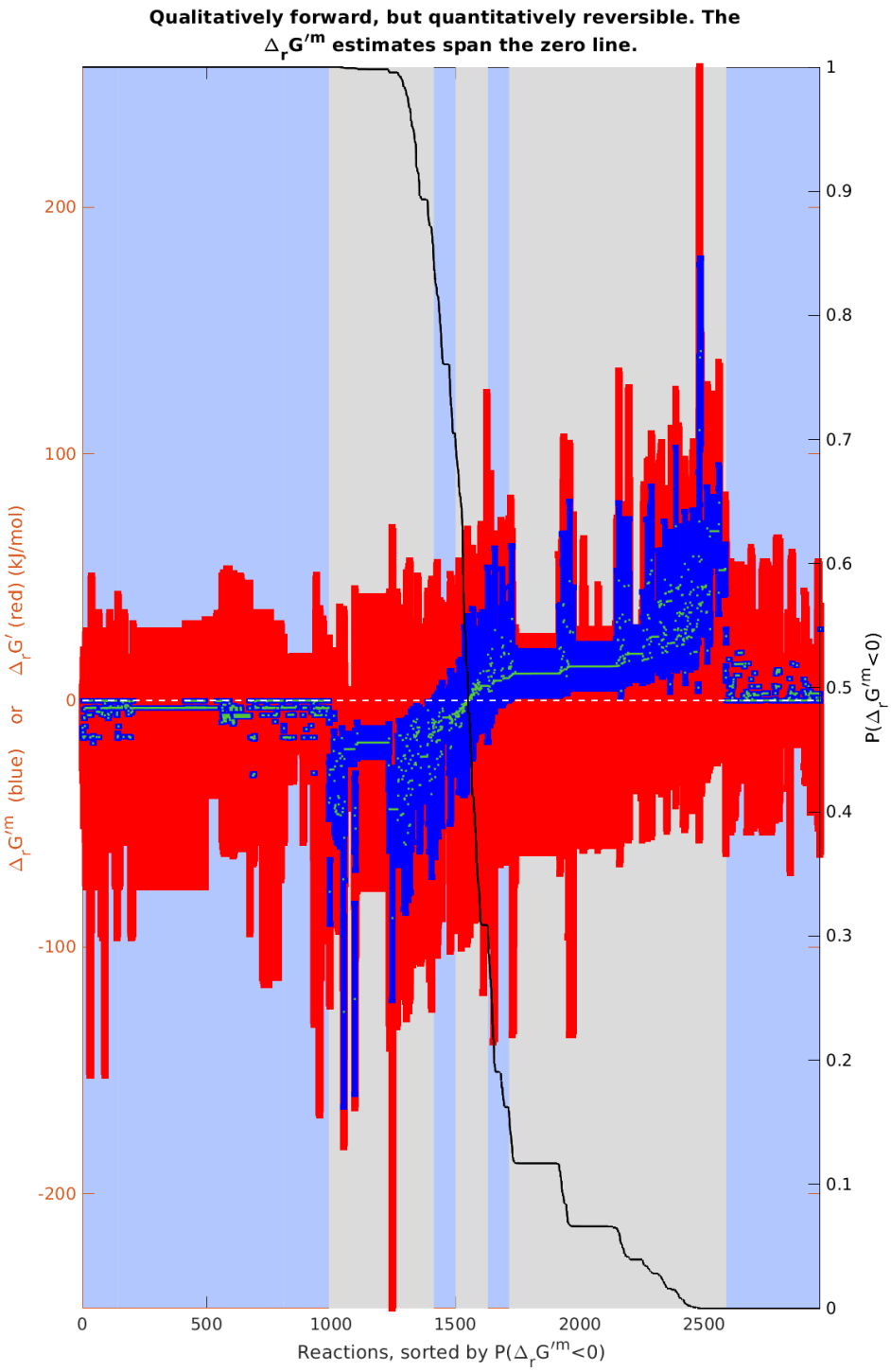
```
    fprintf('%s\n','forwardReversibleFigures...');
    forwardReversibleFigures(modelThermo,directions,confidenceLevel)
end
```

```
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).