

Extract a thermodynamically consistent subnetwork from a given model (Part 2 _ 2025)

1. Identify the largest subset of a model that admits a thermodynamically consistent flux
2. Specify a random subset of active/inactive reactions and present/absent metabolites
3. Remove absent metabolites and inactive reactions, then recalculate the largest subset of a model that admits a thermodynamically consistent flux
4. Compute the smallest thermodynamically consistent subnetwork containing a list of present metabolites and active reactions

```
[solverOK,solverInstalled]=changeCobraSolver('ibm_cplex','all');
```

```
> changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.  
> ibm_cplex (version 1210) is compatible and fully tested with MATLAB R2019a on your operating system.  
> changeCobraSolver: Solver for LP problems has been set to ibm_cplex.  
  
> changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.  
> ibm_cplex (version 1210) is compatible and fully tested with MATLAB R2019a on your operating system.  
> changeCobraSolver: Solver for MILP problems has been set to ibm_cplex.  
  
> changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.  
> ibm_cplex (version 1210) is compatible and fully tested with MATLAB R2019a on your operating system.  
> changeCobraSolver: Solver for QP problems has been set to ibm_cplex.  
  
> changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.  
> ibm_cplex (version 1210) is compatible and fully tested with MATLAB R2019a on your operating system.  
> changeCobraSolver: Solver for MIQP problems has been set to ibm_cplex.  
> changeCobraSolver: Solver ibm_cplex not supported for problems of type NLP. Currently used: matlab
```

```
%[solverOK,solverInstalled]=changeCobraSolver('gurobi','all');  
%[solverOK,solverInstalled]=changeCobraSolver('ibm_cplex','QP');
```

Load model

```
modelToLoad='circularToy';  
modelToLoad='ecoli_core';  
modelToLoad='modelRecon3MitoOpen';  
modelToLoad='Recon3DModel';  
%modelToLoad='iDopa';
```

Load a model

```
driver_thermoModelLoad
```

```
Model loaded: Recon3DModel  
lower bounds greater than zero  
Internal stoichiometric nullspace computed in 1.5352 seconds.
```

Remove forced reaction rates

```
forcedRxnBool = model.lb>0 | model.ub<0;  
nForcedRxn = nnz(forcedRxnBool)
```

```
nForcedRxn =
    1
```

```
printConstraints(model,[],[],forcedRxnBool)
```

Forward_Reaction	Name	lb	ub	
'biomass_reaction'	'Generic Human Biomass Reaction'	1	1000	'20.6508 h2o[c] + 20.7045 atp[

```
model.lb(strcmp(model.rxns,'biomass_reaction'))=0;
```

Stoichiometric consistency

```
if ~isfield(model,'SConsistentRxnBool') ||
~isfield(model,'SConsistentMetBool')
    massBalanceCheck=0;
    %massBalanceCheck=1;
    printLevel=2;
    [SConsistentMetBool, SConsistentRxnBool,
SInConsistentMetBool, SInConsistentRxnBool, unknownSConsistencyMetBool,
unknownSConsistencyRxnBool, model,stoichConsistModel]...
        = findStoichConsistentSubset(model, massBalanceCheck, printLevel);
else
    %Extract stoich consistent submodel
    if any(~model.SConsistentMetBool)
        rxnRemoveMethod='inclusive';%maintains stoichiometric consistency
        [stoichConsistModel, rxnRemoveList] = removeMetabolites(model,
model.mets(~model.SConsistentMetBool),rxnRemoveMethod);
        SConsistentRxnBool2=~ismember(model.rxns,rxnRemoveList);
        if ~all(model.SConsistentRxnBool==SConsistentRxnBool2)
            error('inconsistent reaction removal')
        end
        try
            stoichConsistModel = removeUnusedGenes(stoichConsistModel);
        catch ME
            disp(ME.message)
        end
    else
        stoichConsistModel = model;
    end
end

[nMet,nRxn]=size(stoichConsistModel.S)
```

```
nMet =
    5835
nRxn =
    10600
```

Flux consistency

```

fluxConsistentParam.method='fastcc';%can handle additional constraints
fluxConsistentParam.printLevel=1;
[~,~,~,~,stoichConsistModel]=
findFluxConsistentSubset(stoichConsistModel,fluxConsistentParam);

```

Extract flux consistent submodel

```

if any(~stoichConsistModel.fluxConsistentRxnBool)
    rxnRemoveList =
stoichConsistModel.rxns(~stoichConsistModel.fluxConsistentRxnBool);
    stoichFluxConsistModel = removeRxns(stoichConsistModel,
rxnRemoveList,'metRemoveMethod','exclusive','ctrsRemoveMethod','inclusive');
    try
        stoichFluxConsistModel = removeUnusedGenes(stoichFluxConsistModel);
    catch ME
        disp(ME.message)
    end
else
    stoichFluxConsistModel = stoichConsistModel;
end
[nMet,nRxn]=size(stoichFluxConsistModel.S)

```

```

nMet =
    5835
nRxn =
    10600

```

Thermodynamic consistency

```

%save('debug_prior_to_findThermoConsistentFluxSubset.mat')
%return
param.printLevel = 1;
[thermoFluxConsistentMetBool,thermoFluxConsistentRxnBool,stoichFluxConsistModel,stoichFluxThermoConsistModel] =
findThermoConsistentFluxSubset(stoichFluxConsistModel,param);

```

```

--- findThermoFluxConsistentSubset START ----
        printLevel: 1
                n: 200
normalizeZeroNormWeights: 0
                epsilon: 1e-06
            formulation: 'pqzw'
        iterationMethod: 'random'
                nMax: 20
            relaxBounds: 1
        acceptRepairedFlux: 1
            warmStartMethod: 'random'
            thetaMultiplier: 1.5
                theta: 0.5
            regularizeOuter: 0
thermoConsistencyMethod: 'cycleFreeFlux'
                bigNum: 10000
                debug: 0

```

optCardThermo objective data:

0.1 = beta, the global weight on one-norm of internal reaction rate.
 -5 = min(g0), the local weight on zero-norm of internal reaction rate.
 -0 = max(g0), the local weight on zero-norm of internal reaction rate.
 0 = min(h0), the local weight on zero-norm of metabolite production rate.
 0 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

0 min cardinality variables:

NaN mean(c(p))	NaN min(c(p))	NaN max(c(p))
1 lambda0	NaN min(k)	NaN max(k)
1 lambda1	NaN min(o(p))	NaN max(o(p))

5358 max cardinality variables:

-0 mean(c(q))	-0 min(c(q))	-0 max(c(q))
1 delta0	5 min(d)	5 max(d)
0 delta1	0 min(o(q))	0 max(o(q))

22824 cardinality free variables:

0.077 mean(c(r))	-0 min(c(r))	0.1 max(c(r))
0 alphas	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y
1	0.50	7.6672e+05	-8.8e+06	-2.2e+04	1.6e+03	0	0	0	-237
2	0.75	161.49	-7.9e+02	-2.3e+04	1.1e+03	0	0	0	-238
3	1.12	90.057	-4.3e+02	-2.3e+04	7.3e+02	0	0	0	-238
4	1.69	59.684	-2.6e+02	-2.3e+04	4.9e+02	0	0	0	-238
5	2.53	38.202	-1.6e+02	-2.4e+04	3.2e+02	0	0	0	-238
6	3.80	25.75	-1.1e+02	-2.4e+04	2.2e+02	0	0	0	-238
7	5.70	17.391	-72	-2.4e+04	1.4e+02	0	0	0	-238
8	8.54	12.147	-48	-2.4e+04	97	0	0	0	-238
9	12.81	13.536	-53	-2.4e+04	67	0	0	0	-238
10	19.22	7.1044	-23	-2.4e+04	45	0	0	0	-238
11	28.83	5.0586	-15	-2.4e+04	30	0	0	0	-238
12	43.25	3.3766	-10	-2.4e+04	20	0	0	0	-238
13	64.87	2.2681	-17	-2.4e+04	13	0	0	0	-238
14	97.31	1.59	-4.4	-2.4e+04	8.9	0	0	0	-238
15	145.96	1.0555	-3	-2.4e+04	5.9	0	0	0	-238
16	218.95	0.6324	-2	-2.4e+04	3.9	0	0	0	-238
17	328.42	0.46083	-1.3	-2.4e+04	2.6	0	0	0	-238
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

iter	card(y)	nz	%feas int.nz.	tot %feas int.nz.	tot
1	5358	7593	1.00	0.67	
2	1467	5506	1.00	0.85	
3	706	5006	1.00	0.92	
4	352	3403	1.00	0.95	
5	218	4480	1.00	0.97	
6	126	2147	1.00	0.97	
7	118	1301	1.00	0.98	
8	110	1095	1.00	0.98	
9	113	639	1.00	0.98	
10	94	2	NaN	0.98	
11	93	1739	1.00	0.98	
12	87	2	NaN	0.98	
13	92	7	1.00	0.98	
14	107	2	NaN	0.98	
15	101	2	NaN	0.98	
16	93	342	1.00	0.98	
17	91	1014	1.00	0.98	
18	76	2	NaN	0.98	
iter	card(y)	nz	%feas int.nz.	tot %feas int.nz.	tot

```
findThermoConsistentFluxSubset terminating early: no progress on % internal reactions thermodynamically fl
--- findThermoFluxConsistentSubset END ---
```

Size of the largest flux, stoich and thermo consistent submodel

```
[nMet,nRxn]=size(stoichFluxThermoConsistModel.S)
```

```
nMet =
      5756
nRxn =
     10447
```

Nullspace

Nullspace is necessary for backup check of thermodynamic consistency using thermoFlux2QNty

```
[stoichFluxThermoConsistModel,rankK,nnzK,timeTaken] =
internalNullspace(stoichFluxThermoConsistModel);
rankK
```

```
rankK =
      5522
```

Minimal thermodynamically consistent submodel

Compute the minimal thermodynamically consistent submodel

```
[minimalModel, modelThermoMetBool, modelThermoRxnBool] =
thermoKernel(stoichFluxThermoConsistModel);
```

```
--- thermoKernel START ---
      warmStartMethod: 'random'
      formulation: 'pqzwrS'
      thetaMultiplier: 1.5
      theta: 0.5
      regularizeOuter: 1
      epsilon: 1e-06
      printLevel: 3
      relaxBounds: 0
      acceptRepairedFlux: 1
      thermoConsistencyMethod: 'cycleFreeFlux'
      bigNum: 10000
      debug: 0

optCardThermo objective data:
      1 = beta, the global weight on one-norm of internal reaction rate.
      1 = min(g0), the local weight on zero-norm of internal reaction rate.
      1 = max(g0), the local weight on zero-norm of internal reaction rate.
      1 = min(h0), the local weight on zero-norm of metabolite production rate.
      1 = max(h0), the local weight on zero-norm of metabolite production rate.
```

optimizeCardinality objective data:

```
16203 min cardinality variables:
      0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
      1 lambda0             1 min(k)              1 max(k)
      0 lambda1             0 min(o(p))            0 max(o(p))
```

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8642e+05	-8.7e+07	0	0	0	0	0	
2	0.75	0	0	0	0	0	0	0	
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

iter.	nz.flux.	%it.feas.int.flux.	%feas.inc.flux.	nz.prod.	%it.feas.nz.prod.	%feas.inc.prod.
1	2	NaN	NaN	0	NaN	NaN

warmStartMethod: 'random'
 formulation: 'pqzwrns'
 thetaMultiplier: 1.5
 theta: 0.5
 regularizeOuter: 1
 epsilon: 1e-06
 printLevel: 2
 relaxBounds: 0
 acceptRepairedFlux: 1
 thermoConsistencyMethod: 'cycleFreeFlux'
 bigNum: 10000
 debug: 0

optCardThermo objective data:

1 = beta, the global weight on one-norm of internal reaction rate.
 1 = min(g0), the local weight on zero-norm of internal reaction rate.
 1 = max(g0), the local weight on zero-norm of internal reaction rate.
 1 = min(h0), the local weight on zero-norm of metabolite production rate.
 1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8153e+05	-8.7e+07	0	0	0	0	0	
2	0.75	0	0	0	0	0	0	0	
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

2	2	NaN	NaN	0	NaN	NaN
---	---	-----	-----	---	-----	-----

warmStartMethod: 'random'
 formulation: 'pqzwrns'
 thetaMultiplier: 1.5
 theta: 0.5

```

        regularizeOuter: 1
        epsilon: 1e-06
        printLevel: 2
        relaxBounds: 0
        acceptRepairedFlux: 1
        thermoConsistencyMethod: 'cycleFreeFlux'
        bigNum: 10000
        debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0             1 min(k)              1 max(k)
    0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))        NaN min(c(q))          NaN max(c(q))
    1 delta0             NaN min(d)             NaN max(d)
    0 delta1             NaN min(o(q))          NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))       0 min(c(r))           1 max(c(r))
    0 alpha1             0 min(o(r))           0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
  1    0.50  9.8337e+05  -8.7e+07   0       0         0         0         0
  2    0.75      0      0       0       0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  3      2      NaN      NaN      0      NaN      NaN      NaN      gre
    warmStartMethod: 'random'
    formulation: 'pqzwrS'
    thetaMultiplier: 1.5
    theta: 0.5
    regularizeOuter: 1
    epsilon: 1e-06
    printLevel: 2
    relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
    bigNum: 10000
    debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0             1 min(k)              1 max(k)

```

```

0 lambda1          0 min(o(p))          0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))          NaN min(c(q))          NaN max(c(q))
    1 delta0          NaN min(d)          NaN max(d)
    0 delta1          NaN min(o(q))          NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))          0 min(c(r))          1 max(c(r))
    0 alpha1          0 min(o(r))          0 max(o(r))

itn    theta    ||dx||    del_obj    obj    linear    ||x||0    a(x)    ||x||1    ||y||
  1    0.50    9.7839e+05    -8.6e+07    0        0        0        0        0
  2    0.75        0        0        0        0        0        0        0
itn    theta    ||dx||    del_obj    obj    linear    ||x||0    a(x)    ||x||1    ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  4        2        NaN        NaN        0        NaN        NaN        NaN        gre
    warmStartMethod: 'random'
    formulation: 'pqzwrS'
    thetaMultiplier: 1.5
    theta: 0.5
    regularizeOuter: 1
    epsilon: 1e-06
    printLevel: 2
    relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
    bigNum: 10000
    debug: 0

optCardThermo objective data:
  1 = beta, the global weight on one-norm of internal reaction rate.
  1 = min(g0), the local weight on zero-norm of internal reaction rate.
  1 = max(g0), the local weight on zero-norm of internal reaction rate.
  1 = min(h0), the local weight on zero-norm of metabolite production rate.
  1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0          1 min(k)          1 max(k)
    0 lambda1          0 min(o(p))          0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))          NaN min(c(q))          NaN max(c(q))
    1 delta0          NaN min(d)          NaN max(d)
    0 delta1          NaN min(o(q))          NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))          0 min(c(r))          1 max(c(r))
    0 alpha1          0 min(o(r))          0 max(o(r))

itn    theta    ||dx||    del_obj    obj    linear    ||x||0    a(x)    ||x||1    ||y||
  1    0.50    9.8617e+05    -8.7e+07    0        0        0        0        0
  2    0.75        0        0        0        0        0        0        0
itn    theta    ||dx||    del_obj    obj    linear    ||x||0    a(x)    ||x||1    ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  5        2        NaN        NaN        0        NaN        NaN        NaN        gre
    warmStartMethod: 'random'
    formulation: 'pqzwrS'
    thetaMultiplier: 1.5

```



```

        theta: 0.5
    regularizeOuter: 1
        epsilon: 1e-06
        printLevel: 2
        relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
        bigNum: 10000
        debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0             1 min(k)              1 max(k)
    0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))        NaN min(c(q))          NaN max(c(q))
    1 delta0             NaN min(d)             NaN max(d)
    0 delta1             NaN min(o(q))          NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))       0 min(c(r))           1 max(c(r))
    0 alpha1             0 min(o(r))           0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||_0   a(x)   ||x||_1   ||y||_1
  1    0.50  9.8379e+05  -8.6e+07   0       0         0         0         0         0
  2    0.75    0         0         0       0         0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||_0   a(x)   ||x||_1   ||y||_1
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  6      2      NaN      NaN      0      NaN      NaN      NaN      NaN      gre
    warmStartMethod: 'random'
    formulation: 'pqzwrS'
    thetaMultiplier: 1.5
    theta: 0.5
    regularizeOuter: 1
    epsilon: 1e-06
    printLevel: 2
    relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
        bigNum: 10000
        debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))

```

```

1 lambda0          1 min(k)          1 max(k)
0 lambda1          0 min(o(p))        0 max(o(p))

0 max cardinality variables:
NaN mean(c(q))      NaN min(c(q))      NaN max(c(q))
1 delta0            NaN min(d)          NaN max(d)
0 delta1            NaN min(o(q))       NaN max(o(q))

23034 cardinality free variables:
0.75 mean(c(r))      0 min(c(r))        1 max(c(r))
0 alpha1             0 min(o(r))        0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
1     0.50   9.8185e+05 -8.6e+07   0       0         0         0         0
2     0.75      0         0         0       0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
7      2      NaN      NaN      0      NaN      NaN      NaN      NaN      gre
warmStartMethod: 'random'
formulation: 'pqzwr'
thetaMultiplier: 1.5
theta: 0.5
regularizeOuter: 1
epsilon: 1e-06
printLevel: 2
relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
bigNum: 10000
debug: 0

optCardThermo objective data:
1 = beta, the global weight on one-norm of internal reaction rate.
1 = min(g0), the local weight on zero-norm of internal reaction rate.
1 = max(g0), the local weight on zero-norm of internal reaction rate.
1 = min(h0), the local weight on zero-norm of metabolite production rate.
1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
1 lambda0             1 min(k)             1 max(k)
0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
NaN mean(c(q))      NaN min(c(q))      NaN max(c(q))
1 delta0            NaN min(d)          NaN max(d)
0 delta1            NaN min(o(q))       NaN max(o(q))

23034 cardinality free variables:
0.75 mean(c(r))      0 min(c(r))        1 max(c(r))
0 alpha1             0 min(o(r))        0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
1     0.50   9.8498e+05 -8.7e+07   0       0         0         0         0
2     0.75      0         0         0       0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
8      2      NaN      NaN      0      NaN      NaN      NaN      NaN      gre
warmStartMethod: 'random'
formulation: 'pqzwr'

```

```

        thetaMultiplier: 1.5
            theta: 0.5
        regularizeOuter: 1
            epsilon: 1e-06
            printLevel: 2
            relaxBounds: 0
        acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
            bigNum: 10000
            debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0             1 min(k)                1 max(k)
    0 lambda1             0 min(o(p))             0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))        NaN min(c(q))          NaN max(c(q))
    1 delta0             NaN min(d)              NaN max(d)
    0 delta1             NaN min(o(q))            NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))       0 min(c(r))            1 max(c(r))
    0 alpha1             0 min(o(r))            0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
  1    0.50  9.8335e+05  -8.7e+07    0     0         0         0         0
  2    0.75    0         0         0     0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  9      2      NaN      NaN      0      NaN      NaN      NaN      gre
    warmStartMethod: 'random'
    formulation: 'pqzwrns'
    thetaMultiplier: 1.5
        theta: 0.5
    regularizeOuter: 1
        epsilon: 1e-06
        printLevel: 2
        relaxBounds: 0
    acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
        bigNum: 10000
        debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:

```

```

0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
1 lambda0             1 min(k)              1 max(k)
0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
NaN mean(c(q))        NaN min(c(q))        NaN max(c(q))
1 delta0              NaN min(d)            NaN max(d)
0 delta1              NaN min(o(q))         NaN max(o(q))

23034 cardinality free variables:
0.75 mean(c(r))       0 min(c(r))          1 max(c(r))
0 alpha1              0 min(o(r))          0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
1     0.50   9.8281e+05 -8.7e+07   0       0         0         0         0
2     0.75    0         0         0       0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
10      2      NaN      NaN      0      NaN      NaN      NaN      gre
warmStartMethod: 'random'
formulation: 'pqzwrS'
thetaMultiplier: 1.5
theta: 0.5
regularizeOuter: 1
epsilon: 1e-06
printLevel: 2
relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
bigNum: 10000
debug: 0

optCardThermo objective data:
1 = beta, the global weight on one-norm of internal reaction rate.
1 = min(g0), the local weight on zero-norm of internal reaction rate.
1 = max(g0), the local weight on zero-norm of internal reaction rate.
1 = min(h0), the local weight on zero-norm of metabolite production rate.
1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
1 lambda0             1 min(k)              1 max(k)
0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
NaN mean(c(q))        NaN min(c(q))        NaN max(c(q))
1 delta0              NaN min(d)            NaN max(d)
0 delta1              NaN min(o(q))         NaN max(o(q))

23034 cardinality free variables:
0.75 mean(c(r))       0 min(c(r))          1 max(c(r))
0 alpha1              0 min(o(r))          0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
1     0.50   9.7854e+05 -8.6e+07   0       0         0         0         0
2     0.75    0         0         0       0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
11      2      NaN      NaN      0      NaN      NaN      NaN      gre
warmStartMethod: 'random'

```

```

        formulation: 'pqzwrns'
        thetaMultiplier: 1.5
            theta: 0.5
        regularizeOuter: 1
            epsilon: 1e-06
            printLevel: 2
            relaxBounds: 0
        acceptRepairedFlux: 1
        thermoConsistencyMethod: 'cycleFreeFlux'
            bigNum: 10000
            debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0             1 min(k)              1 max(k)
    0 lambda1             0 min(o(p))            0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))        NaN min(c(q))          NaN max(c(q))
    1 delta0              NaN min(d)              NaN max(d)
    0 delta1              NaN min(o(q))           NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))        0 min(c(r))          1 max(c(r))
    0 alpha1              0 min(o(r))            0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
  1    0.50  9.8416e+05  -8.6e+07   0     0         0         0         0
  2    0.75    0         0         0     0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  12      2      NaN      NaN      0      NaN      NaN      NaN      gre
        warmStartMethod: 'random'
        formulation: 'pqzwrns'
        thetaMultiplier: 1.5
            theta: 0.5
        regularizeOuter: 1
            epsilon: 1e-06
            printLevel: 2
            relaxBounds: 0
        acceptRepairedFlux: 1
        thermoConsistencyMethod: 'cycleFreeFlux'
            bigNum: 10000
            debug: 0

optCardThermo objective data:
    1 = beta, the global weight on one-norm of internal reaction rate.
    1 = min(g0), the local weight on zero-norm of internal reaction rate.
    1 = max(g0), the local weight on zero-norm of internal reaction rate.
    1 = min(h0), the local weight on zero-norm of metabolite production rate.
    1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

```

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8362e+05	-8.6e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

13	2	NaN	NaN	0	NaN	NaN	NaN	gre
----	---	-----	-----	---	-----	-----	-----	-----

```

warmStartMethod: 'random'
formulation: 'pqzwrns'
thetaMultiplier: 1.5
theta: 0.5
regularizeOuter: 1
epsilon: 1e-06
printLevel: 2
relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
bigNum: 10000
debug: 0

```

optCardThermo objective data:

```

1 = beta, the global weight on one-norm of internal reaction rate.
1 = min(g0), the local weight on zero-norm of internal reaction rate.
1 = max(g0), the local weight on zero-norm of internal reaction rate.
1 = min(h0), the local weight on zero-norm of metabolite production rate.
1 = max(h0), the local weight on zero-norm of metabolite production rate.

```

optimizeCardinality objective data:

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8003e+05	-8.6e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

14	2	NaN	NaN	0	NaN	NaN	NaN	gre
----	---	-----	-----	---	-----	-----	-----	-----

```

warmStartMethod: 'random'
  formulation: 'pqzwrS'
thetaMultiplier: 1.5
  theta: 0.5
regularizeOuter: 1
  epsilon: 1e-06
  printLevel: 2
  relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
  bigNum: 10000
  debug: 0

optCardThermo objective data:
  1 = beta, the global weight on one-norm of internal reaction rate.
  1 = min(g0), the local weight on zero-norm of internal reaction rate.
  1 = max(g0), the local weight on zero-norm of internal reaction rate.
  1 = min(h0), the local weight on zero-norm of metabolite production rate.
  1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
  0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
  1 lambda0             1 min(k)              1 max(k)
  0 lambda1             0 min(o(p))           0 max(o(p))

0 max cardinality variables:
  NaN mean(c(q))        NaN min(c(q))          NaN max(c(q))
  1 delta0              NaN min(d)              NaN max(d)
  0 delta1              NaN min(o(q))           NaN max(o(q))

23034 cardinality free variables:
  0.75 mean(c(r))       0 min(c(r))            1 max(c(r))
  0 alpha1              0 min(o(r))            0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||1
  1   0.50  9.8108e+05  -8.7e+07   0       0         0         0         0         0
  2   0.75      0         0         0       0         0         0         0         0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||1
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
  15      2      NaN      NaN      0      NaN      NaN      NaN      NaN      gre
    warmStartMethod: 'random'
    formulation: 'pqzwrS'
    thetaMultiplier: 1.5
    theta: 0.5
    regularizeOuter: 1
    epsilon: 1e-06
    printLevel: 2
    relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
    bigNum: 10000
    debug: 0

optCardThermo objective data:
  1 = beta, the global weight on one-norm of internal reaction rate.
  1 = min(g0), the local weight on zero-norm of internal reaction rate.
  1 = max(g0), the local weight on zero-norm of internal reaction rate.
  1 = min(h0), the local weight on zero-norm of metabolite production rate.
  1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

```

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8477e+05	-8.7e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

16	2	NaN	NaN	0	NaN	NaN	gre
----	---	-----	-----	---	-----	-----	-----

```

warmStartMethod: 'random'
formulation: 'pqzwrS'
thetaMultiplier: 1.5
theta: 0.5
regularizeOuter: 1
epsilon: 1e-06
printLevel: 2
relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
bigNum: 10000
debug: 0

```

optCardThermo objective data:

```

1 = beta, the global weight on one-norm of internal reaction rate.
1 = min(g0), the local weight on zero-norm of internal reaction rate.
1 = max(g0), the local weight on zero-norm of internal reaction rate.
1 = min(h0), the local weight on zero-norm of metabolite production rate.
1 = max(h0), the local weight on zero-norm of metabolite production rate.

```

optimizeCardinality objective data:

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.7946e+05	-8.7e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).


```

17          2          NaN          NaN          0          NaN          NaN          gre
    warmStartMethod: 'random'
      formulation: 'pqzwrS'
    thetaMultiplier: 1.5
      theta: 0.5
    regularizeOuter: 1
      epsilon: 1e-06
      printLevel: 2
      relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
      bigNum: 10000
      debug: 0

optCardThermo objective data:
  1 = beta, the global weight on one-norm of internal reaction rate.
  1 = min(g0), the local weight on zero-norm of internal reaction rate.
  1 = max(g0), the local weight on zero-norm of internal reaction rate.
  1 = min(h0), the local weight on zero-norm of metabolite production rate.
  1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:
    0 mean(c(p))          -0 min(c(p))          -0 max(c(p))
    1 lambda0            1 min(k)              1 max(k)
    0 lambda1            0 min(o(p))            0 max(o(p))

0 max cardinality variables:
    NaN mean(c(q))          NaN min(c(q))          NaN max(c(q))
    1 delta0              NaN min(d)              NaN max(d)
    0 delta1              NaN min(o(q))            NaN max(o(q))

23034 cardinality free variables:
    0.75 mean(c(r))          0 min(c(r))          1 max(c(r))
    0 alpha1                0 min(o(r))            0 max(o(r))

itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
  1   0.50  9.7824e+05  -8.6e+07   0       0       0       0       0
  2   0.75      0      0       0       0       0       0       0
itn   theta   ||dx||   del_obj   obj   linear   ||x||0   a(x)   ||x||1   ||y||
Optimise cardinality reached the stopping criterion. Finished.
100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).
18          2          NaN          NaN          0          NaN          NaN          gre
    warmStartMethod: 'random'
      formulation: 'pqzwrS'
    thetaMultiplier: 1.5
      theta: 0.5
    regularizeOuter: 1
      epsilon: 1e-06
      printLevel: 2
      relaxBounds: 0
    acceptRepairedFlux: 1
    thermoConsistencyMethod: 'cycleFreeFlux'
      bigNum: 10000
      debug: 0

optCardThermo objective data:
  1 = beta, the global weight on one-norm of internal reaction rate.
  1 = min(g0), the local weight on zero-norm of internal reaction rate.
  1 = max(g0), the local weight on zero-norm of internal reaction rate.
  1 = min(h0), the local weight on zero-norm of metabolite production rate.
  1 = max(h0), the local weight on zero-norm of metabolite production rate.

```

optimizeCardinality objective data:

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8468e+05	-8.7e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

19	2	NaN	NaN	0	NaN	NaN	NaN	gre
----	---	-----	-----	---	-----	-----	-----	-----

```

warmStartMethod: 'random'
formulation: 'pqzwrS'
thetaMultiplier: 1.5
theta: 0.5
regularizeOuter: 1
epsilon: 1e-06
printLevel: 2
relaxBounds: 0
acceptRepairedFlux: 1
thermoConsistencyMethod: 'cycleFreeFlux'
bigNum: 10000
debug: 0

```

optCardThermo objective data:

1 = beta, the global weight on one-norm of internal reaction rate.
1 = min(g0), the local weight on zero-norm of internal reaction rate.
1 = max(g0), the local weight on zero-norm of internal reaction rate.
1 = min(h0), the local weight on zero-norm of metabolite production rate.
1 = max(h0), the local weight on zero-norm of metabolite production rate.

optimizeCardinality objective data:

16203 min cardinality variables:

0 mean(c(p))	-0 min(c(p))	-0 max(c(p))
1 lambda0	1 min(k)	1 max(k)
0 lambda1	0 min(o(p))	0 max(o(p))

0 max cardinality variables:

NaN mean(c(q))	NaN min(c(q))	NaN max(c(q))
1 delta0	NaN min(d)	NaN max(d)
0 delta1	NaN min(o(q))	NaN max(o(q))

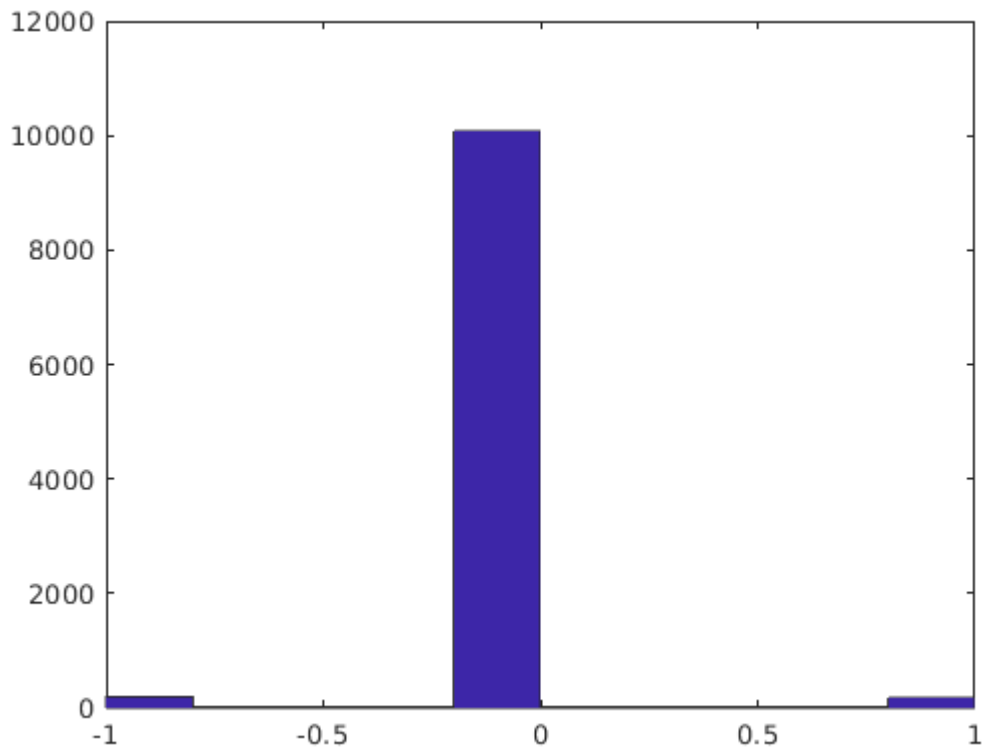
23034 cardinality free variables:

0.75 mean(c(r))	0 min(c(r))	1 max(c(r))
0 alpha1	0 min(o(r))	0 max(o(r))

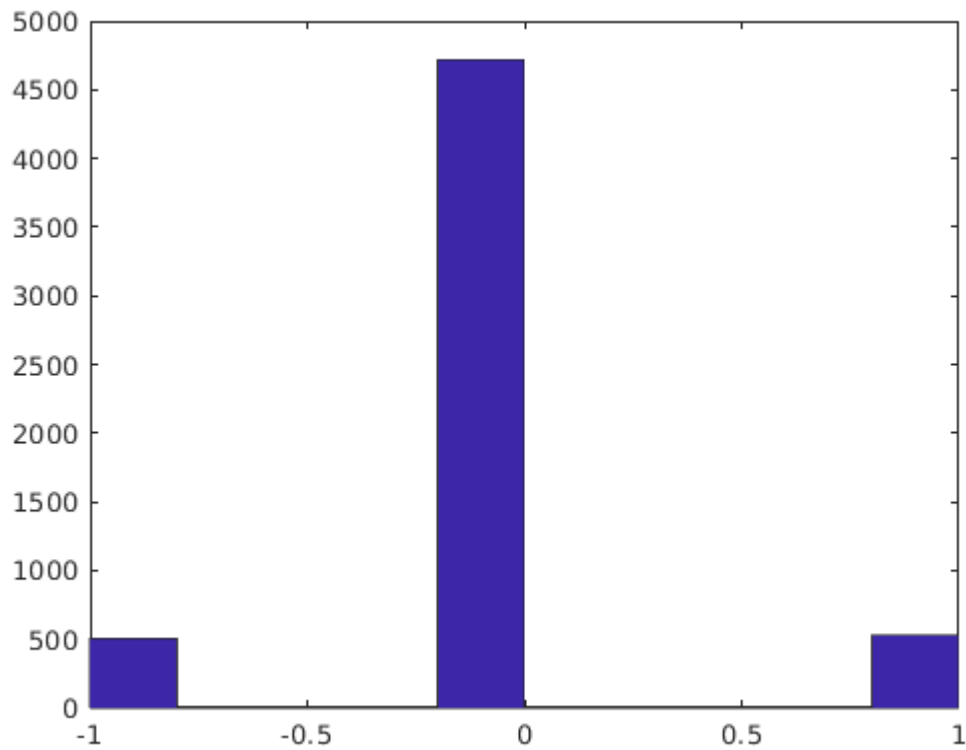
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1
1	0.50	9.8464e+05	-8.6e+07	0	0	0	0	0	0
2	0.75	0	0	0	0	0	0	0	0
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y 1

Optimise cardinality reached the stopping criterion. Finished.


```
rxnWeights(rxnWeights>0.4)=1;
rxnWeights(rxnWeights<-0.4)=-1;
rxnWeights(rxnWeights>=-0.4 & rxnWeights<=0.4)=0;
hist(rxnWeights)
```



```
metWeights=rand(nMet,1)-0.5;
metWeights(rankMetInd(1:200))=0;
coreMetBool=metWeights<0.45;
removeMetBool=metWeights>0.5;
metWeights(metWeights>0.4)=1;
metWeights(metWeights<-0.4)=-1;
metWeights(metWeights>=-0.4 & metWeights<=0.4)=0;
hist(metWeights)
```



Remove inactive reactions and absent metabolites

```
param.printLevel = 1;
[solverOK,solverInstalled]=changeCobraSolver('gurobi','QP');
```

```
> changeCobraSolver: Gurobi interface added to MATLAB path.
> gurobi (version 811) is compatible and fully tested with MATLAB R2019a on your operating system.
```

```
[thermoFluxConsistentMetBool,thermoFluxConsistentRxnBool,stoichFluxThermoConsistModel,stoichFluxThermoConsistModelRed] =
findThermoConsistentFluxSubset(stoichFluxThermoConsistModel, param,
removeMetBool, removeRxnBool);
```

```
--- findThermoFluxConsistentSubset START ----
46 flux inconsistent metabolites
48 flux inconsistent reactions
      printLevel: 1
          n: 200
normalizeZeroNormWeights: 0
          epsilon: 1e-06
      formulation: 'pqzw'
    iterationMethod: 'random'
          nMax: 20
      relaxBounds: 1
acceptRepairedFlux: 1
    warmStartMethod: 'random'
    thetaMultiplier: 1.5
          theta: 0.5
    regularizeOuter: 0
thermoConsistencyMethod: 'cycleFreeFlux'
```

```
bigNum: 10000
debug: 0
```

optCardThermo objective data:

```
0.1 = beta, the global weight on one-norm of internal reaction rate.
-5 = min(g0), the local weight on zero-norm of internal reaction rate.
-0 = max(g0), the local weight on zero-norm of internal reaction rate.
0 = min(h0), the local weight on zero-norm of metabolite production rate.
0 = max(h0), the local weight on zero-norm of metabolite production rate.
```

optimizeCardinality objective data:

0 min cardinality variables:

```
NaN mean(c(p))      NaN min(c(p))      NaN max(c(p))
1 lambda0           NaN min(k)      NaN max(k)
1 lambda1           NaN min(o(p))    NaN max(o(p))
```

5046 max cardinality variables:

```
-0 mean(c(q))      -0 min(c(q))      -0 max(c(q))
1 delta0           5 min(d)        5 max(d)
0 delta1           0 min(o(q))      0 max(o(q))
```

22498 cardinality free variables:

```
0.076 mean(c(r))    -0 min(c(r))      0.1 max(c(r))
0 alpha1            0 min(o(r))      0 max(o(r))
```

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y
1	0.50	7.5581e+05	-8.5e+06	-2e+04	1.5e+03	0	0	0	-221
2	0.75	159.51	-9.2e+02	-2.1e+04	1e+03	0	0	0	-223
3	1.12	105.52	-4.4e+02	-2.2e+04	7e+02	0	0	0	-224
4	1.69	65.094	-2.5e+02	-2.2e+04	4.7e+02	0	0	0	-224
5	2.53	39.738	-1.7e+02	-2.2e+04	3.1e+02	0	0	0	-224
6	3.80	26.358	-1.1e+02	-2.2e+04	2.1e+02	0	0	0	-224
7	5.70	17.391	-69	-2.2e+04	1.4e+02	0	0	0	-224
8	8.54	38.487	-73	-2.2e+04	1e+02	0	0	0	-225
9	12.81	15.112	-48	-2.2e+04	67	0	0	0	-225
10	19.22	10.09	-32	-2.2e+04	44	0	0	0	-225
11	28.83	6.7343	-15	-2.3e+04	30	0	0	0	-225
12	43.25	4.4555	-9.9	-2.3e+04	20	0	0	0	-225
13	64.87	2.9919	-6.6	-2.3e+04	13	0	0	0	-225
14	97.31	1.9934	-4.4	-2.3e+04	8.8	0	0	0	-225
15	145.96	1.3302	-2.9	-2.3e+04	5.8	0	0	0	-225
16	218.95	0.89203	-1.9	-2.3e+04	3.9	0	0	0	-225
17	328.42	0.59077	-1.3	-2.3e+04	2.6	0	0	0	-225
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y

Optimise cardinality reached the stopping criterion. Finished.

100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

iter	card(y)	nz	%feas int.nz.	tot %feas int.nz.	tot
1	5046	7439	1.00	0.68	
2	1459	5243	1.00	0.84	
3	677	5398	1.00	0.93	
4	310	3769	1.00	0.96	
5	190	1675	1.00	0.97	
6	150	2816	1.00	0.97	
7	118	2522	1.00	0.98	
8	81	3234	1.00	0.98	
9	75	153	1.00	0.98	
10	77	275	1.00	0.98	
11	71	135	1.00	0.98	
12	68	1	NaN	0.98	
13	69	1162	1.00	0.98	
14	85	1537	1.00	0.98	
15	81	2	NaN	0.98	
16	66	2	NaN	0.98	

```

17          72          2          NaN          0.98
18          63          2          NaN          0.98
iter      card(y)      nz      %feas int.nz.  tot %feas int.nz.  tot
findThermoConsistentFluxSubset terminating early: no progress on % internal reactions thermodynamically fl
--- findThermoFluxConsistentSubset END ---

```

```
[nMet,nRxn]=size(stoichFluxThermoConsistModelRed.S)
```

```

nMet =
    5633
nRxn =
    10225

```

Remove the corresponding entries from the weights

```

bool = coreRxnBool & ~thermoFluxConsistentRxnBool;
if any(bool)
    fprintf('%u%s\n',nnz(bool), ' core reactions inconsistent due to removed
reactions')
    if nnz(bool)<0
        stoichFluxThermoConsistModel.rxns{bool}
    end
end
end

```

```
183 core reactions inconsistent due to removed reactions
```

```

bool = coreMetBool & ~thermoFluxConsistentMetBool;
if any(bool)
    fprintf('%u%s\n',nnz(bool),' core metabolites inconsistent due to
removed metabolites')
    if nnz(bool)<10
        stoichFluxThermoConsistModel.mets{bool}
    end
end
end

```

```
117 core metabolites inconsistent due to removed metabolites
```

```

rxnWeightsRed = rxnWeights(thermoFluxConsistentRxnBool);
metWeightsRed = metWeights(thermoFluxConsistentMetBool);
coreRxnBoolRed = coreRxnBool(thermoFluxConsistentRxnBool);
coreMetBoolRed = coreMetBool(thermoFluxConsistentMetBool);

```

Compute the smallest thermodynamically consistent subnetwork containing a list of present metabolites and active reactions

```

activeInactiveRxn=coreRxnBoolRed;
presentAbsentMet=coreMetBoolRed;
activeInactiveRxn(:)=0;
presentAbsentMet(:)=0;
activeInactiveRxn(~stoichFluxThermoConsistModelRed.SConsistentRxnBool)=0;

```

```
param.normalizeZeroNormWeights=0;
```

```
[tissueModel, thermoModelMetBool, thermoModelRxnBool] =  
thermoKernel(stoichFluxThermoConsistModelRed, activeInactiveRxn,  
rxnWeightsRed, presentAbsentMet, metWeightsRed,param);
```

```
--- thermoKernel START ---  
    warmStartMethod: 'random'  
    formulation: 'pqzwrS'  
    thetaMultiplier: 1.5  
    theta: 0.5  
    regularizeOuter: 1  
        epsilon: 1e-06  
        printLevel: 1  
        relaxBounds: 0  
    acceptRepairedFlux: 1  
    thermoConsistencyMethod: 'cycleFreeFlux'  
        bigNum: 10000  
        debug: 0
```

optCardThermo objective data:

```
1 = beta, the global weight on one-norm of internal reaction rate.  
-1 = min(g0), the local weight on zero-norm of internal reaction rate.  
1 = max(g0), the local weight on zero-norm of internal reaction rate.  
-1 = min(h0), the local weight on zero-norm of metabolite production rate.  
1 = max(h0), the local weight on zero-norm of metabolite production rate.
```

optimizeCardinality objective data:

649 min cardinality variables:

```
0 mean(c(p))          -0 min(c(p))          -0 max(c(p))  
1 lambda0             1 min(k)              1 max(k)  
0 lambda1             0 min(o(p))           0 max(o(p))
```

1188 max cardinality variables:

```
0 mean(c(q))          -0 min(c(q))          -0 max(c(q))  
1 delta0             1 min(d)              1 max(d)  
0 delta1             0 min(o(q))           0 max(o(q))
```

36568 cardinality free variables:

```
0.46 mean(c(r))       -0 min(c(r))          1 max(c(r))  
0 alpha1             0 min(o(r))           0 max(o(r))
```

itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y
1	0.50	9.6816e+05	-8.5e+07	-18	67	14	9.1	0	-1
2	0.75	20.361	-25	-43	52	13	9.2	0	-1
3	1.12	16.927	-19	-63	38	11	7.9	0	-1
4	1.69	11.532	-13	-76	26	11	7.8	0	-1
5	2.53	8.2997	-9.9	-86	19	10	7.3	0	-1
6	3.80	5.7142	-7.1	-93	14	9	6.9	0	-1
7	5.70	3.85	-4.5	-97	9.1	9	6.9	0	-1
8	8.54	2.2986	-3	-1e+02	6.1	9	6.9	0	-1
9	12.81	1.7613	-2	-1e+02	4	9	6.9	0	-1
10	19.22	1.3692	-1.3	-1e+02	2.7	9	6.9	0	-1
11	28.83	0.86665	-0.9	-1e+02	1.8	9	6.9	0	-1
12	43.25	0.49273	-0.6	-1.1e+02	1.2	9	6.9	0	-1
13	64.87	0.41444	-0.4	-1.1e+02	0.8	9	6.9	0	-1
14	97.31	0.21692	-0.27	-1.1e+02	0.53	9	6.9	0	-1
15	145.96	0.14927	-0.18	-1.1e+02	0.35	9	6.9	0	-1
16	218.95	0.097833	-0.12	-1.1e+02	0.24	9	6.9	0	-1
17	328.42	0.065178	-0.079	-1.1e+02	0.16	9	6.9	0	-1
itn	theta	dx	del_obj	obj	linear	x 0	a(x)	x 1	y

Optimise cardinality reached the stopping criterion. Finished.
 100.00% thermodynamically feasible internal fluxes (checked by cycleFreeFlux method).

iter.	nz.flux.%it.feas.int.flux.	%feas.inc.flux.	nz.prod.%it.feas.nz.prod.	%feas.inc.prod.
1	1578	1.00	0.23	893
2	3929	1.00	0.47	1936
3	1162	1.00	0.55	814
4	1108	1.00	0.69	810
5	879	1.00	0.79	538

```
[nMet,nRxn]=size(tissueModel.S)
```

Compare the target versus predicted model

```
plotThermoKernelExtractStats(stoichFluxThermoConsistModelRed,  
activeInactiveRxn, rxnWeightsRed, presentAbsentMet, metWeightsRed,  
thermoModelMetBool, thermoModelRxnBool);
```

Save weights

```
rxnWeightsRedTmp=rxnWeightsRed;  
metWeightsRedTmp=metWeightsRed;  
return
```

Submodel with just metabolites specified

```
metWeightsRed=metWeightsRedTmp;  
rxnWeightsRed(:)=0;  
[tissueModel, thermoModelMetBool, thermoModelRxnBool] =  
thermoKernel(stoichFluxThermoConsistModelRed, activeInactiveRxn,  
rxnWeightsRed, presentAbsentMet, metWeightsRed,param);  
[nMet,nRxn]=size(tissueModel.S)
```

Compare the target versus predicted model

```
plotThermoKernelExtractStats(stoichFluxThermoConsistModelRed,  
activeInactiveRxn, rxnWeightsRed, presentAbsentMet, metWeightsRed,  
thermoModelMetBool, thermoModelRxnBool)
```

Submodel with just reactions specified

```
rxnWeightsRed=rxnWeightsRedTmp;  
metWeightsRed(:)=0;  
[tissueModel, thermoModelMetBool, thermoModelRxnBool] =  
thermoKernel(stoichFluxThermoConsistModelRed, activeInactiveRxn,  
rxnWeightsRed, presentAbsentMet, metWeightsRed,param);  
  
[nMet,nRxn]=size(tissueModel.S)
```

Compare the target versus predicted model

```
plotThermoKernelExtractStats(stoichFluxThermoConsistModelRed,  
activeInactiveRxn, rxnWeightsRed, presentAbsentMet, metWeightsRed,  
thermoModelMetBool, thermoModelRxnBool)
```

Submodel with just active metabolites specified

```
metWeightsRed=metWeightsRedTmp;  
rxnWeightsRed(:)=0;  
metWeightsRed(metWeightsRed>=0)=0;
```

```
[tissueModel, thermoModelMetBool, thermoModelRxnBool] =  
thermoKernel(stoichFluxThermoConsistModelRed, activeInactiveRxn,  
rxnWeightsRed, presentAbsentMet, metWeightsRed,param);  
[nMet,nRxn]=size(tissueModel.S)
```

Compare the target versus predicted model

```
plotThermoKernelExtractStats(stoichFluxThermoConsistModelRed,  
activeInactiveRxn, rxnWeightsRed, presentAbsentMet, metWeightsRed,  
thermoModelMetBool, thermoModelRxnBool)
```

Submodel with just active reactions specified

```
rxnWeightsRed=rxnWeightsRedTmp;  
metWeightsRed(:)=0;  
rxnWeightsRed(rxnWeightsRed>=0)=0;  
[tissueModel, thermoModelMetBool, thermoModelRxnBool] =  
thermoKernel(stoichFluxThermoConsistModelRed, activeInactiveRxn,  
rxnWeightsRed, presentAbsentMet, metWeightsRed,param);  
  
[nMet,nRxn]=size(tissueModel.S)
```

Compare the target versus predicted model

```
plotThermoKernelExtractStats(stoichFluxThermoConsistModelRed,  
activeInactiveRxn, rxnWeightsRed, presentAbsentMet, metWeightsRed,  
thermoModelMetBool, thermoModelRxnBool)
```