Entropic flux balance analysis

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INTRODUCTION

Entropic flux balance analysis [1] maximises the (unnormalised) entropy of unidirectional fluxes (v_f and v_r) and optionally a linear function of external net fluxes w, subject to mass balance constraints, optionally coupling constraints, box constraints on net flux, and zero lower bounds on unidirectional fluxes. This ensures that predicted steady state fluxes are thermodynamically feasible, assuming one is given a model that admits a thermodynamically feasible flux. A method for finding the largest subset of a given model that admits a thermodynamically feasible flux is described in this paper [3] and this tutorial [4]. Given a generic model of metabolism and context-specific omics data, this paper [5] and this tutorial [6] explain how to extract a context-specific model that admits a thermodynamically feasible internal net flux vector, using the XomicsToModel protocol [5].

Entropic flux balance analysis is mathematically represented by the optimisation problem

$$\min_{v_f, v_r, w} v_f^T \cdot (\log(v_f) - 1) + v_r^T \cdot (\log(v_r) - 1) + c_e^T \cdot w$$

subject to

$$\begin{aligned}
& v = [v_f - v_r; w] \\
& N \cdot (v_f - v_r) + B \cdot w = b, && : y_N \\
& C \cdot (v_f - v_r) \leq d, && : y_C \\
& l \leq v \leq u, && : z_v \\
& 0 \leq v_{f,} && : z_{v_f} \\
& 0 \leq v_r, && : z_{v_r}
\end{aligned}$$

where N is the internal reaction stoichiometric matrix (all reactions bass balanced), B is the external reaction stoichiometric matrix (all reactions mass imbalanced), b may be used to represent any known fixed input (negative) or output (positive) of molecular species from the system, and zero otherwise. The variables to the right of the : are the corresponding dual variables to each constraint.

A variation of this is quadratically constrained entropic flux balance analysis [2], which allows one to penalise deviation of predicted net flux from experimentally measured net flux. This is represented by the following optimisation problem

$$\min_{v_f, v_r, w} v_f^T \cdot (\log(v_f) - 1) + v_r^T \cdot (\log(v_r) - 1) + c_e^T \cdot w + \frac{1}{2}(v - h)^T \cdot H \cdot (v - h)$$

subject to

$$\begin{aligned}
& v = [v_f - v_r; w] \\
& N \cdot (v_f - v_r) + B \cdot w = b, && : y_N \\
& C \cdot (v_f - v_r) \leq d, && : y_C \\
& l \leq v \leq u, && : z_v \\
& 0 \leq v_{f,} && : z_{v_f} \\
& 0 \leq v_r, && : z_{v_r}
\end{aligned}$$

where H may be used to add penalties, e.g., $H_{j,j} = \frac{1}{(1 + \sigma_{exp}^2)}$ where $\sigma_{exp} \in \mathbb{R}^n_{\geq 0}$ is the standard deviation in measured net flux h.

MATERIALS - EQUIPMENT SETUP

Mosek installation required

PROCEDURE

Set the directory for results

```
basePath='~/work/sbgCloud';
resultsDirectory=[basePath '/programModelling/projects/thermoModel/results/
entropicFBA'];
```

Set the model to load

```
modelToUse='iDopaNeuro';
%modelToUse='ecoli_core';
%modelToUse = 'fork';
%modelToUse = 'single';
%modelToUse='recon3';

if ~exist('model','var')
    switch modelToUse
        case 'single'
            driver_singleModel
        case 'fork'
            driver_forkModel

        case 'ecoli_core'
            dataDirectory=[basePath '/data'];
            load([dataDirectory '/models/published/e_coli_core.mat']);
```

```
            if ~isfield(model,'SConsistentMetBool') ||
~isfield(model,'SConsistentRxnBool')
                massBalanceCheck=0;
                [~, ~, ~, ~, ~, ~, model, ~] =
findStoichConsistentSubset(model, massBalanceCheck, 0);
            end
            model.lb(ismember(model.rxns,'BIOMASS_Ecoli_core_w_GAM'))=0.1;

        case 'recon3'
            %COBRA.models/mat/Recon3DModel_301_xomics_input.mat
            load(which('Recon3DModel_301_xomics_input.mat'))

            %change onto uMol/gDW/hr
            model.lb = model.lb;
            model.ub = model.ub;
        case 'iDopaNeuro'
            %load('~/drive/sbgCloud/projects/iDopaNeuro/results/codeResults/
iDN1/iDopaNeuroC/iDopaNeuroC.mat')
            load('~/drive/sbgCloud/projects/variationalKinetics/data/
iDopaNeuro/iDopaNeuroC.mat')
            model = iDopaNeuroC;
            clear iDopaNeuroC
            model.lb(ismember(model.rxns,'ATPM')) =
model.lb(ismember(model.rxns,'ATPM'))/2;

            %problematic reactions
%             {'34DHPHEt'}      {'3, 4-Dihydroxy-L-Phenylalanine
Transport' }      -0.53635    0     {'34dhphe[e]  <=> 34dhphe[c] '}
%             {'URAt'    }      {'Uracil Transport via Faciliated
Diffusion'}    -0.0013626    0     {'ura[e]  <=> ura[c] '        }
            model.lb(ismember(model.rxns,'34DHPHEt'))=-1e4;
            model.ub(ismember(model.rxns,'34DHPHEt'))= 1e4;
            model.lb(ismember(model.rxns,'URAt'))=-1e4;
            model.ub(ismember(model.rxns,'URAt'))= 1e4;
    end
end
```

Examine the constraints on the model

```
printConstraints(model,-1e4,1e4,model.SIntRxnBool)
```

Forward_Reaction, 0 bound	Name	lb
{'10FTHF6GLUtl' }	{'6-Glutamyl-10Fthf Transport, Lysosomal' }	0
{'1PPDCRp' }	{'Delta1-Piperideine-2-Carboxylate Reductase, Perixosomal' }	0
{'2OXOADOXm' }	{'2-Oxoadipate:Lipoamde 2-Oxidoreductase (Decarboxylating And '}	0
{'34DHPHAMT' }	{'3, 4-Dihydroxyphenylacetate:Amet O-Methyltransferase' }	0
{'34DHPLACOX' }	{'3, 4-Dihydroxyphenylacetaldehyde:NAD+ Oxidoreductase' }	0
{'34DHXMANDACOX' }	{'3, 4-Dihydroxymandelaldehyde:NAD+ Oxidoreductase' }	0
{'34HPLFM' }	{'3- (4-Hydroxyphenyl-)Lactate Formation' }	0
{'3DSPHR' }	{'3-Dehydrosphinganine Reductase' }	0

{'3HLYTCL' }	{'3-Hydroxy-L-Tyrosine Carboxy-Lyase' }	0
{'3SALACBOXL' }	{'3-Sulfino-L-Alanine Carboxy-Lyase' }	0
{'3SALAOX' }	{'Cysteinesulfinic Acid Oxidase' }	0
{'3SALATAi' }	{'3-Sulfino-Alanine Transaminase (Irreversible)' }	0
{'3SPYRSP' }	{'3-Sulfinopyruvate Hydrolase (Spotaneous Reaction)' }	0
{'41R1H2MAE12BOOX' }	{'4-[(1R)-1-Hydroxy-2- (Methylamino)Ethyl]-1, 2-Benzenediol:O'}	0
{'42A12BOOX' }	{'4- (2-Aminoethyl)-1, 2-Benzenediol:Oxygen Oxidoreductase (De'}	0
{'4HBZCOAFm' }	{'4-Hydroxybenzoyl Coenzyme A Formation' }	0
{'4HBZFm' }	{'4-Hydroxybenzoate Formation' }	0
{'4MOPt2im' }	{'4-Methyl-2-Oxopentanoate Mitochondrial Transport via Proton '}	0
{'7DHFtl' }	{'7-Glutamyl-Dhf Transport, Lysosomal' }	0
{'AASAD3m' }	{'L-Aminoadipate-Semialdehyde Dehydrogenase (NADH), Mitochondr'}	0
{'ACACT1x' }	{'Acetyl Coenzyme A C-Acetyltransferase' }	0
{'ACGALK' }	{'N-Acetylgalactosamine Kinase' }	0
{'ACGALK2' }	{'N-Acetylgalactosamine Kinase (ITP)' }	0
{'ACGAM6PSi' }	{'N-Acetylglucosamine-6-Phosphate Synthase' }	0
{'ACGAMK' }	{'N-Acetylglucosamine Kinase' }	0
{'ACGAMtly' }	{'N-Acetyl-Glucosamine Lysosomal Efflux' }	0
{'ACITL' }	{'ATP-Citrate Lyase' }	0
{'ACNAM9PL2' }	{'N-Acetylneuraminate 9-Phosphate Pyruvate-Lyase (Pyruvate-Pho'}	0
{'ACOAD8m' }	{'Acyl Coenzyme A Dehydrogenase (Isovaleryl Coenzyme A), Mitoc'}	0
{'ACP1_FMN_' }	{'Acid Phosphatase (FMN)' }	0
{'ADMDC' }	{'Adenosylmethionine Decarboxylase' }	0
{'ADNCYC' }	{'Adenylate Cyclase' }	0
{'ADRNLPVESSEC' }	{'Adrenaline Secretion via Secretory Vesicle (ATP Driven)' }	0
{'ADSK' }	{'Adenylyl-Sulfate Kinase' }	0
{'ADSL1' }	{'Adenylosuccinate Lyase' }	0
{'ADSL2' }	{'Adenylosuccinate Lyase' }	0
{'AGPAT1' }	{'1-Acylglycerol-3-Phosphate O-Acyltransferase 1' }	0
{'AGTim' }	{'Alanine-Glyoxylate Transaminase (Irreversible), Mitochondria'}	0
{'AKGDm' }	{'2-Oxoglutarate Dehydrogenase' }	0
{'ALAASNNaEx' }	{'L-Alanine/L-Asparagine Na-Dependent Exchange (Ala-L In)' }	0
{'ALAGLNNaEx' }	{'L-Alanine/L-Glutamine Na-Dependent Exchange (Ala-L In)' }	0
{'ALASm' }	{'5-Aminolevulinate Synthase' }	0
{'ALAt4' }	{'Alanine-Sodium Symporter' }	0
{'ALCD21_L' }	{'Alcohol Dehydrogenase (L-1, 2-Propanediol)' }	0
{'ALDD2xm' }	{'Aldehyde Dehydrogenase (Acetylaldehyde, NAD), Mitochondrial' }	0
{'ALDD2y' }	{'Aldehyde Dehydrogenase (Acetaldehyde, NADP)' }	0
{'ALOX5' }	{'Arachidonate 5-Lipoxygenase' }	0
{'ALOX52' }	{'Arachidonate 5-Lipoxygenase' }	0
{'ALR2' }	{'Aldose Reductase (Methylglyoxal)' }	0
{'ALR3' }	{'Aldose Reductase (Acetol)' }	0
{'AMPDA' }	{'Adenosine Monophosphate Deaminase' }	0
{'APRTO2' }	{'N-Acetylputrescine: Oxygen Oxireductase (Deaminating)' }	0
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{'ARGSS' }	{'Argininosuccinate Synthase' }	0
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{'ASNS1' }	{'Asparagine Synthase (Glutamine-Hydrolysing)' }	0
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{'ASNtm' }	{'L-Asparagine Transport, Mitochondrial' }	0
{'ASPDt6' }	{'D-Aspartate Transport via Na, H Symport And K Antiport' }	0
{'ASPGLUm' }	{'Aspartate-Glutamate Mitochondrial Shuttle' }	0
{'ASPNATm' }	{'Aspartate N-Acetyltransferase, Mitochondrial' }	0
{'ASPt6' }	{'L-Aspartate Transport via Na, H Symport And K Antiport' }	0
{'ATPasel' }	{'V-Type ATPase, H+ Transporting, Lysosomal' }	0
{'ATPH1e' }	{'ATP Diphosphohydrolase' }	0
{'ATPtm' }	{'ADP/ATP Transporter, Mitochondrial' }	0
{'BAMPPALDOX' }	{'Beta-Aminopropion Aldehyde:NAD+ Oxidoreductase' }	0
{'BPNT2' }	{'3', 5'-Bisphosphate Nucleotidase (Paps)' }	0
{'CAATPS' }	{'Ca ATPase' }	0

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{'CATp'	}	{'Catalase A, Peroxisomal'	} 0
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{'CEPTC'	}	{'Choline Phosphotransferase'	} 0
{'CERK'	}	{'Ceramide Kinase'	} 0
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{'CHLPCTD'	}	{'Choline Phosphate Cytididyltransferase'	} 0
{'CHOLK'	}	{'Choline Kinase'	} 0
{'CHSTEROLtg'	}	{'Cholesterol Efflux (ATP Depedent), Golgi Apparatus'	} 0
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{'CSm'	}	{'Citrate Synthase'	} 0
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{'DESAT16_2'	}	{'Palmitoyl Coenzyme A Desaturase (N-C16:0CoA -> N-C16:1CoA)'	} 0
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{'DHCRD1'	}	{'Dihydroceramide Desaturase'	} 0
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{'DHPR2'	}	{'6, 7-Dihydropteridine Reduction'	} 0
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{'DOLPMT4_Ler'	}	{'Dolichyl-Phosphate-Mannose-Glycolipid Alpha-Mannosyltransfer'	} 0
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{'FAS80COA_L'	}	{'Fatty Acyl Coenzyme A Synthase (N-C8:0CoA), Lumped Reaction'	} 0
{'FBP26'	}	{'Fructose-2, 6-Bisphosphate 2-Phosphatase'	} 0
{'FKYNH'	}	{'N-Formyl-L-Kynurenine Amidohydrolase'	} 0
{'FOLR2'	}	{'Folate Reductase'	} 0
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{'FPGS8'	}	{'Folylpolyglutamate Synthetase (10Fthf)'	} 0
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{'GLNTHRNaEx'	}	{'L-Threonine/L-Glutamine Na-Dependent Exchange (Gln-L In)'	} 0
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{'GLYCLTDy'	}	{'Glycolate Dehydrogenase (NADP)'	} 0
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{'HAS1'	}	{'Hyaluronan Synthase'	} 0
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{'KYNAKGAT'	}	{'L-Kynurenine:2-Oxoglutarate Aminotransferase'	} 0
{'KYNATESYN'	}	{'4- (2-Aminophenyl)-2, 4-Dioxobutanoate Dehydratase'	} 0
{'LAPCOAl'	}	{'Lysosomal Acid Phosphorylase (CoA)'	} 0
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{'L_LACtcm'	}	{'Transport of L-Lactate via Diffusion, Mitochondrial'	} 0
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{'LYStip'	}	{'Transport of L-Lysine, Peroxisomal (Irreversible)'	} 0
{'MACOXO'	}	{'3-Methylimidazole Acetaldehyde:NAD+ Oxidoreductase'	} 0
{'MAOX'	}	{'Methylamine Oxidase'	} 0
{'MDRPD'	}	{' 5-Methylthio-5-Deoxy-D-Ribulose 1-Phosphate Dehydratase'	} 0
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{'ME2'	}	{'Malic Enzyme (NADP)'	} 0
{'ME2m'	}	{'Malic Enzyme (NADP), Mitochondrial'	} 0
{'METLEUex'	}	{'Methionine/Leucine Exchange (Met In)'	} 0
{'METS'	}	{'Methionine Synthase'	} 0
{'METt4'	}	{'L-Methionine Transport in via Sodium Symport'	} 0
{'MEVK1x'	}	{'Mevalonate Kinase (ATP)'	} 0
{'MGSA'	}	{'Methylglyoxal Synthase'	} 0
{'MGSA2'	}	{'Methyglyoxylate Synthase 2 (from G3P)'	} 0
{'MHISOR'	}	{'N-Methylhistamine:Oxygen Oxidoreductase (Deaminating)'	} 0
{'MI1345PP'	}	{'Inositol-1, 3, 4, 5-Trisphosphate 5-Phosphatase'	} 0
{'MI1PS'	}	{'Myo-Inositol-1-Phosphate Synthase'	} 0
{'MMSAD3m'	}	{'Methylmalonate-Semialdehyde Dehydrogenase (Malonic Semialdeh'	} 0
{'MTAP'	}	{'5'-Methylthioadenosine Phosphorylase'	} 0
{'NABTNO'	}	{'N4-Acetylaminobutanal:NAD+ Oxidoreductase'	} 0
{'NACASPtm'	}	{'N-Acetyl-L-Aspartate Transport (Mitochondria to Cytosol)'	} 0
{'NACHEX27ly'	}	{'Beta-N-Acetylhexosaminidase, Lysosomal'	} 0
{'NADHtpu'	}	{'NADH Transporter, Peroxisome'	} 0
{'NADPHtru'	}	{'Transport of NADPH, Endoplasmic Reticulum'	} 0
{'NADPHtxu'	}	{'Transport of NADPH, Peroxisome'	} 0
{'NADPtru'	}	{'Transport of NADP, Endoplasmic Reticulum'	} 0
{'NADPtxu'	}	{'Transport of NADP, Peroxisome'	} 0
{'NaKt'	}	{'Na+/K+ Exchanging ATPase'	} 0
{'NDP6'	}	{'Nucleoside-Diphosphatase (dCDP)'	} 0
{'NDP7er'	}	{'Nucleoside-Diphosphatase (UDP), Endoplasmic Reticulum'	} 0
{'NDP8'	}	{'Nucleoside-Diphosphatase (dUDP)'	} 0
{'NICRNS'	}	{'Nicotinate D-Ribonucleoside Kinase'	} 0
{'NMNATn'	}	{'Nicotinamide-Nucleotide Adenylyltransferase'	} 0
{'NMNS'	}	{'Nicotinamide Ribotide (NMN) Synthetase'	} 0
{'NORANMT'	}	{'Noradrenaline N-Methyltransferase'	} 0
{'NP1'	}	{'Nucleotide Phosphatase'	} 0
{'NTD2e'	}	{'5'-Nucleotidase (UMP), Extracellular'	} 0
{'NTD7e'	}	{'5'-Nucleotidase (AMP), Extracellular'	} 0
{'OCCOAtm'	}	{'Octanoyl Coenzyme A Transport, Diffusion'	} 0
{'OIVD1m'	}	{'2-Oxoisovalerate Dehydrogenase (Acylating'	} 0
{'ORNtiDF'	}	{'Ornithine Transport via Diffusion (Extracellular to Cytosol)'	} 0
{'P45027A12m'	}	{'5-Beta-Cholestane-3-Alpha, 7-Alpha, 12-Alpha-Triol 27-Hydrox'	} 0
{'P45027A13m'	}	{'5-Beta-Cholestane-3-Alpha, 7-Alpha, 12-Alpha-Triol 27-Hydrox'	} 0

{'P45027A15m'	}	{'5-Beta-Cytochrome P450, Family 27, Subfamily A, Polypeptide '}	0
{'P45027A16m'	}	{'Cytochrome P450 27'	}	0
{'P45027A1m'	}	{'Cytochrome P450 27'	}	0
{'P450LTB4r'	}	{'Cytochrome P450 Leukotriene B4'	}	0
{'PAFH'	}	{'Platelet-Activating Factor Acetylhydrolase'	}	0
{'PAFS'	}	{'Alkyl Glycerol Phosphocholine Acetyl Transferase'	}	0
{'PAN4PP'	}	{'Phosphatase (Pan4P)'	}	0
{'PCFLOPm'	}	{'Phosphatidylcholine Flippase'	}	0
{'PCHOLP_hs'	}	{'Choline Phosphatase'	}	0
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{'PCREATtmdiffir'	}	{'Phosphocreatine Transport To/from Mitochondria via Diffusion'}	0
{'PDE1'	}	{'3', 5'-Cyclic-Nucleotide Phosphodiesterase'	}	0
{'PDE4'	}	{'3', 5'-Cyclic-Nucleotide Phosphodiesterase'	}	0
{'PEFLIPm'	}	{'Phosphatidylethanolamine Flippase'	}	0
{'PETOHMm_hs'	}	{'Phosphatidylethanolamine N-Methyltransferase'	}	0
{'PFK26'	}	{'6-Phosphofructo-2-Kinase'	}	0
{'PGCD'	}	{'Phosphoglycerate Dehydrogenase'	}	0
{'PGLer'	}	{'6-Phosphogluconolactonase, Endoplasmic Reticulum'	}	0
{'PHEt4'	}	{'Transport of L-Phenylalanine via Sodium Symport'	}	0
{'PHYQt'	}	{'Transport of Phylloquinone '	}	0
{'PI345P3P'	}	{'Phosphatidylinositol-3, 4, 5-Trisphosphate 3-Phosphatase'	}	0
{'PI345P5P'	}	{'Phosphatidylinositol-3, 4, 5-Trisphosphate 5-Phosphatase'	}	0
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{'PI3P5K'	}	{'Phosphatidylinositol 3-Phosphate 5-Kinase'	}	0
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{'PI4PP'	}	{'Phosphatidylinositol-4-Phosphate 4-Phosphatase'	}	0
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{'PIK5'	}	{'Phosphatidylinositol 5-Kinase'	}	0
{'PIPLC'	}	{'Phosphatidylinositol Phospholipase C'	}	0
{'PItg'	}	{'Phosphate Transport, Golgi Apparatus'	}	0
{'PLA2_2'	}	{'Phospholipase A2'	}	0
{'PMEVKx'	}	{'Phosphomevalonate Kinase'	}	0
{'PMI12346PH'	}	{'5-Diphosphoinositol-1, 2, 3, 4, 6-Pentakisphosphate Diphosph'}	0
{'PNTOt5'	}	{'Pantothenate Sodium Symporter Ii'	}	0
{'PPA2'	}	{'Inorganic Triphosphatase'	}	0
{'PPAer'	}	{'Inorganic Diphosphatase, Endoplasmic Reticulum'	}	0
{'PPAm'	}	{'Inorganic Diphosphatase'	}	0
{'PPAn'	}	{'Inorganic Diphosphatase, Nuclear'	}	0
{'PPAP'	}	{'Phosphatidic Acid Phosphatase'	}	0
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{'PRASCS'	}	{'Phosphoribosylaminoimidazolesuccinocarboxamide Synthase'	}	0
{'PRDX'	}	{'Peroxidase (Multiple Substrates)'	}	0
{'PROt4'	}	{'Na+/Proline-L Symporter'	}	0
{'PSFLIPm'	}	{'Phosphatidylserine Flippase'	}	0
{'PTE2x'	}	{'Peroxisomal Acyl Coenzyme A Thioesterase'	}	0
{'PTHPS'	}	{'6-Pyruvoyltetrahydropterin Synthase'	}	0
{'PTRCAT1'	}	{'Putrescine Acetyltransferase'	}	0
{'PTRCOX1'	}	{'Putrescine:Oxygen Oxidoreductase (Deaminating)'	}	0
{'PYRt2m'	}	{'Pyruvate Mitochondrial Transport via Proton Symport'	}	0
{'RDH3a'	}	{'Retinol Dehydrogenase (11-Cis, NADPH)'	}	0
{'SACCD3m'	}	{'Saccharopine Dehydrogenase (NADP, L-Lysine Forming), Mitocho'}	0
{'SADT'	}	{'Sulfate Adenylyltransferase'	}	0
{'SAMHISTA'	}	{'S-Adenosyl-L-Methionine:Histamine N-Tele-Methyltransferase'	}	0
{'SBTD_D2'	}	{'D-Sorbitol Dehydrogenase (D-Fructose Producing)'	}	0
{'SBTR'	}	{'D-Sorbitol Reductase'	}	0
{'SERCYSNaEx'	}	{'L-Serine/L-Cysteine Na-Dependent Exchange (Ser-L In)'	}	0
{'SERPT'	}	{'Serine C-Palmitoyltransferase'	}	0
{'SERt4'	}	{'L-Serine via Sodium Symport'	}	0
{'SFGTH'	}	{'S-Formylglutathione Hydralase'	}	0
{'SMS'	}	{'Sphingomyelin Synthase (Homo Sapiens)'	}	0

{'SO4HCOtex' }	{'Sulfate Transport via Bicarbonate Antiport' }	0
{'SPODMm' }	{'Superoxide Dismutase' }	0
{'SPR' }	{'Sepiapterin Reductase' }	0
{'SPRMS' }	{'Spermine Synthase' }	0
{'SULFOX' }	{'Sulfite Oxidase' }	0
{'T4HCINNMFM' }	{'4-Hydroxycinnamate Formation' }	0
{'THBPT4ACAMDASE' }	{'Tetrahydrobiopterin-4A-Carbinolamine Dehydratase' }	0
{'THD1m' }	{'NAD (P) Transhydrogenase' }	0
{'THMTP' }	{'Thiamine-Triphosphatase' }	0
{'THRALANaEx' }	{'L-Alanine/L-Threonine Na-Dependent Exchange (Thr-L In)' }	0
{'THRCYSNaEx' }	{'L-Cysteine/L-Threonine Na-Dependent Exchange (Thr-L In)' }	0
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{'THYMDt1' }	{'Thymd Transport' }	0
{'TMDK1m' }	{'Thymidine Kinase (ATP:Thymidine)' }	0
{'TMDPPK' }	{'Thiamine-Diphosphate Kinase' }	0
{'TRDR' }	{'Thioredoxin Reductase (NADPH)' }	0
{'TRPO2' }	{'L-Tryptophan:Oxygen 2, 3-Oxidoreductase (Decyclizing)' }	0
{'TYR3MO2' }	{'Tyrosine 3-Monooxygenase' }	0
{'TYRCBOX' }	{'L-Tyrosine Carboxy-Lyase' }	0
{'UAG2EMAi' }	{'UDP-N-Acetyl-D-Glucosamine 2-Epimerase (Hydrolysis)' }	0
{'UAGALDP' }	{'UDP-N-Acetylgalactosamine Diphosphorylase' }	0
{'UDPDOLPT_L' }	{'UDPglucose:Dolichyl-Phosphate Beta-D-Glucosyltransferase (Li'}	0
{'UDPGD' }	{'UDPglucose 6-Dehydrogenase' }	0
{'UDPGNP' }	{'UDPglucuronate Uridine-Diphosphohydrolase' }	0
{'UDPGP' }	{'UDPglucose Pyrophosphohydrolase' }	0
{'URIK1' }	{'Uridine Kinase (ATP:Uridine)' }	0
{'r0023' }	{'NADH:Ferricytochrome-B5 Oxidoreductase' }	0
{'r0047' }	{'Adenosine 5-Monophosphate Phosphohydrolase' }	0
{'r0085' }	{'2-Oxoglutaramate Amidohydrolase' }	0
{'r0086' }	{'2-Oxoglutaramate Amidohydrolase' }	0
{'r0119' }	{'Guanosine 5-Triphosphate Pyrophosphohydrolase' }	0
{'r0142' }	{'Sulfite:Oxygen Oxidoreductase' }	0
{'r0145' }	{'L-Arginine, NADPH:Oxygen Oxidoreductase (Nitric-Oxide-Formin'}	0
{'r0153' }	{'CTP:Pyruvate O2-Phosphotransferase' }	0
{'r0156' }	{'L-Glutamine:Pyruvate Aminotransferase' }	0
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{'r0160' }	{'L-Serine:Pyruvate Aminotransferase' }	0
{'r0165' }	{'UTP:Pyruvate O2-Phosphotransferase' }	0
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{'r0179' }	{'Succinate-Semialdehyde:NADP+ Oxidoreductase' }	0
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{'r0280' }	{'DATP:Pyruvate O2-Phosphotransferase' }	0
{'r0281' }	{'Putrescine:Oxygen Oxidoreductase (Deaminating)' }	0
{'r0301' }	{'Xanthosine-5-Phosphate:Ammonia Ligase (AMP-Forming)' }	0
{'r0354' }	{'Hexokinase' }	0
{'r0357' }	{'Hexokinase' }	0
{'r0365' }	{'3-Hydroxypropanoate:NAD+ Oxidoreductase ' }	0
{'r0377' }	{'ATP:Deoxycitidine 5-Phosphotransferase' }	0
{'r0383' }	{'Pyruvate:[Dihydrolipoyllysine-Residue Acetyltransferase]-Lip'}	0
{'r0399' }	{'L-Phenylalanine, Tetrahydrobiopterin:Oxygen Oxidoreductase ('}	0
{'r0413' }	{'DATP:Pyruvate O2-Phosphotransferase' }	0
{'r0423' }	{'Isocitrate:NADP+ Oxidoreductase (Decarboxylating)' }	0
{'r0426' }	{'Isocitrate Hydro-Lyase ' }	0
{'r0438' }	{'Palmitoyl Coenzyme A:L-Carnitine O-Palmitoyltransferase' }	0
{'r0451' }	{'2-Oxoadipate:Lipoamde 2-Oxidoreductase (Decarboxylating And '}	0
{'r0456' }	{'ATP:Deoxyguanosine 5-Phosphotransferase' }	0
{'r0509' }	{'Succinate:Ubiquinone Oxidoreductase' }	0
{'r0511' }	{'Steroyl Coenzyme A, Hydrogen-Donor:Oxygen Oxidoreductase Pol'}	0
{'r0555' }	{'Acetyl Coenzyme A:Enzyme N6- (Dihydrolipoyl)Lysine S-Acetylt'}	0
{'r0557' }	{'Glutaryl Coenzyme A:Dihydrolipoamide S-Succinyltransferase L'}	0
{'r0568' }	{' (5-L-Glutamyl)-L-Amino-Acid 5-Glutamyltransferase (Cyclizin'}	0
{'r0578' }	{'ATP:Pantothenate 4-Phosphotransferase' }	0
{'r0594' }	{'L-2-Aminoadipate-6-Semialdehyde:NAD+ 6-Oxidoreductase Lysine'}	0

{'r0596'	}	{'3-Hydroxyisobutyryl Coenzyme A Hydrolase '	} 0
{'r0655'	}	{'3-Methylbutanoyl Coenzyme A: (Acceptor) 2, 3-Oxidoreductase '}	0
{'r0666'	}	{'2- (Formamido)-N1- (5-Phosphoribosyl)Acetamidine Cyclo-Ligas'}	0
{'r0698'	}	{'Propanoyl Coenzyme A:Acetyl Coenzyme A C-Acyltransferase Bil'}	0
{'r0853'	}	{'Facilitated Diffusion'	} 0
{'r0924'	}	{'ATP-Binding Cassette (ABC) Tcdb:3.A.1.204.5'	} 0
{'r0986'	}	{'Vesicular Transport'	} 0
{'r1002'	}	{'Facilitated Diffusion'	} 0
{'r1078'	}	{'Vesicular Transport'	} 0
{'r1109'	}	{'Citrate Oxaloacetate-Lyase ((Pro-3S)-Ch2Coo- ->Acetate)'	} 0
{'r1150'	}	{'Facilitated Diffusion'	} 0
{'r1164'	}	{'Sterol O-Acyltransferase'	} 0
{'r1168'	}	{'Sterol O-Acyltransferase'	} 0
{'r1170'	}	{'Sterol O-Acyltransferase'	} 0
{'r1171'	}	{'Sterol O-Acyltransferase'	} 0
{'r1179'	}	{'Sterol Esterase'	} 0
{'r1182'	}	{'Sterol Esterase'	} 0
{'r1183'	}	{'Sterol Esterase'	} 0
{'r1253'	}	{'Long-Chain-Fatty-Acid---Coa Ligase'	} 0
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{'r1298'	}	{'Vesicular Transport'	} 0
{'r1299'	}	{'Vesicular Transport'	} 0
{'r1382'	}	{'Folylpolyglutamyl Synthetase'	} 0
{'r1383'	}	{'Gamma-Glutamyl Hydrolase'	} 0
{'r1423'	}	{'Facilitated Diffusion'	} 0
{'r1434'	}	{'Transport Reaction'	} 0
{'r1435'	}	{'Transport Reaction'	} 0
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{'r1515'	}	{'ATP-Binding Cassette (ABC) Tcdb:3.A.1.211.1'	} 0
{'r1517'	}	{'ATP-Binding Cassette (ABC) Tcdb:3.A.1.211.1'	} 0
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{'r1530'	}	{'ATP-Binding Cassette (ABC) Tcdb:3.A.1.208.15'	} 0
{'r1674'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1725'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1726'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1735'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1790'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1810'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1815'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1834'	}	{'Y+Lat2 Utilized Transport'	} 0
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{'r1928'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1944'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1954'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1962'	}	{'Y+Lat2 Utilized Transport'	} 0
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{'r1975'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1982'	}	{'Y+Lat2 Utilized Transport'	} 0
{'r1989'	}	{'Y+Lat2 Utilized Transport'	} 0
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{'r2381'	}	{'Mitochondrial Carrier (Mc) Tcdb:2.A.29.7.2'	} 0
{'r2419'	}	{'Mitochondrial Carrier (Mc) Tcdb:2.A.29.2.7'	} 0
{'r2471'	}	{'Major Facilitator (Mfs) Tcdb:2.A.18.8.1'	} 0
{'r2473'	}	{'Major Facilitator (Mfs) Tcdb:2.A.1.4.5'	} 0
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{'RE0565C'	}	{'RE0565C'	} 0
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{'RE1836X' }	{'Propionyl Coenzyme A C2-Trimethyltridecanoyltransferase' }	0
{'RE2666C' }	{'RE2666C' }	0
{'RE2717L' }	{'Galactosylceramidase' }	0
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{'RE3052C' }	{'RE3052C' }	0
{'RE3095C' }	{'Peroxidase' }	0
{'RE3201C' }	{'Tyrosinase' }	0
{'RE3251M' }	{'RE3251M' }	0
{'RE3346M' }	{'Aldehyde Dehydrogenase (NAD+)' }	0
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{'RE3525R' }	{'Arachidonate 12-Lipoxygenase' }	0
{'RE3624M' }	{'Acyl Coenzyme A Oxidase' }	0
{'RE3637C' }	{'RE3637C' }	0
{'FAOXC101C102x' }	{'Fatty Acid Beta Oxidation (C10:1->C10:2), Peroxisomal' }	0
{'FAOXC16C14m' }	{'Fatty Acid Beta Oxidation (C16->C14), Mitochondrial' }	0
{'FAOXC4C2m' }	{'Fatty Acid Beta Oxidation (C4->C2), Mitochondrial' }	0
{'FAOXC5C5OHm' }	{'Fatty Acid Beta Oxidation (C5->C5Oh), Mitochondrial' }	0
{'FAOXC6C4m' }	{'Fatty Acid Beta Oxidation (C6->C4), Mitochondrial' }	0
{'FAOXC8C6m' }	{'Fatty Acid Beta Oxidation (C8->C6), Mitochondrial' }	0
{'HEXCOAACBP' }	{'Transport of Hexanoyl Coenzyme A (N-C6:0CoA) from Mitochondr'}	0
{'PRISTCOAtcx' }	{'Transport of Pristanoylcoa from Cytosol to Peroxisomes.' }	0
{'SCP21cx' }	{'Transport of Phytanoylcoa from Cytosol to Peroxisomes.' }	0
{'SUCCACT' }	{'Activation of Succinate' }	0
{'TDCRNe' }	{'Transport of Myristoyl Carnitine into Extra Cellular Space' }	0
{'34DHPHELAT1tc' }	{'Transport of 3, 4-Dihydroxy-L-Phenylalanine by Lat1 in Assoc'}	0
{'ASCBSVCTtc' }	{'Transport of L-Ascorbate by Svct1 Or Svct2 Transporter' }	0
{'FOLTle' }	{'Transport of Folate' }	0
{'GLNyLATthc' }	{'Transport of Glutamine by Y+Lat1 Or Y+Lat2 with Symporter of'}	0
{'HISyLATtc' }	{'Transport of L-Histidine by Y+Lat1 Or Y+Lat2 Transporters' }	0
{'LEUyLAThtc' }	{'Transport of Leucine by Y+Lat1 Or Y+Lat2 with Symporter of H'}	0
{'LINOFATPtc' }	{'Uptake of Linoleic Acid' }	0
{'PALFATPtc' }	{'Transport of Hexadecanoate' }	0
{'PNTORDe' }	{'Release of Pantothenate' }	0
{'TAUPAT1c' }	{'Transport of Taurine by Pat1' }	0
{'VITKtl' }	{'Transport of Vitamin K into Lymph' }	0
{'4HPROLTASCT1' }	{'Transport of Hydroxy-Proline ' }	0
{'ASPPROASCT1' }	{'Aspartate Intake by System Asct-1 Transporter' }	0
{'CHOLESACATc' }	{'Esterification of Cholesterol to Cholesterol Ester' }	0
{'DPMVDc' }	{'Diphosphomevalonate Decarboxylase, Cytosol' }	0
{'FADH2ETC' }	{'Complex Ii Reaction for Respiratory Chain' }	0
{'G6PDH2c' }	{'Glucose 6-Phosphate Dehydrogenase' }	0

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printConstraints(model,-1e4,1e4,~model.SIntRxnBool)
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Forward_Reaction, 0 bound	Name	lb	u
{'EX_34dhoxpeg[e]' }	{'Exchange of 3, 4-Dihydroxyphenylethyleneglycol ' }	0	10
{'EX_3mlda[e]' }	{'Exchange of 3-Methylimidazoleacetic Acid ' }	0	10
{'EX_adrnl[e]' }	{'Exchange of Adrenaline ' }	0	10
{'EX_amp[e]' }	{'Exchange of AMP ' }	0	10
{'EX_creat[e]' }	{'Exchange of Creatine ' }	0	10
{'EX_dag_hs[e]' }	{'Exchange of Diglyceride' }	0	10
{'EX_gsn[e]' }	{'Exchange of Guanosine' }	0	10
{'EX_gthox[e]' }	{'Exchange of Oxidized Glutathione ' }	0	10
{'EX_hista[e]' }	{'Exchange of Histamine ' }	0	10
{'EX_imp[e]' }	{'Exchange of IMP ' }	0	10
{'EX_leuktrB4[e]' }	{'Exchange of Leukotriene B4 ' }	0	10

{'EX_mag_hs[e]'	}	{'Exchange of Monoacylglycerol 2 (Homo Sapiens) '	}	0 10
{'EX_no[e]'	}	{'Exchange of Nitric Oxide'	}	0 10
{'EX_nrpphr[e]'	}	{'Exchange of Norepinephrine '	}	0 10
{'EX_xolest2_hs[e]'	}	{'Exchange of Cholesterol Ester (from FullR2) '	}	0 10
{'EX_4abutn[e]'	}	{'Exchange of 4-Ammoniobutanal'	}	0 10
{'EX_fad[e]'	}	{'Exchange of Flavin Adenine Dinucleotide Oxidized'	}	0 10
{'EX_fald[e]'	}	{'Exchange of Formaldehyde'	}	0 10
{'EX_HC02213[e]'	}	{'Exchange of Prostaglandin-E3 '	}	0 10
{'EX_4hpro[e]'	}	{'Exchange of Hydroxy Proline'	}	0 10
{'EX_leuleu[e]'	}	{'Exchange of Leucylleucine'	}	0 10
{'EX_34hpp[e]'	}	{'Exchange of 3- (4-Hydroxyphenyl)Pyruvate'	}	0 10
{'EX_3mob[e]'	}	{'Exchange of 3-Methyl-2-Oxobutanoate'	}	0 10
{'EX_3mop[e]'	}	{'Exchange of 3-Methyl-2-Oxopentanoate'	}	0 10
{'EX_4mop[e]'	}	{'Exchange of 4-Methyl-2-Oxopentanoate'	}	0 10
{'EX_5mta[e]'	}	{'Exchange of 5-S-Methyl-5-Thioadenosine'	}	0 10
{'EX_5oxpro[e]'	}	{'Exchange of 5-Oxoprolinate'	}	0 10
{'EX_ahcys[e]'	}	{'Exchange of S-Adenosyl-L-Homocysteine'	}	0 10
{'EX_cbasp[e]'	}	{'Exchange of N-Carbamoyl-L-Aspartate'	}	0 10
{'EX_crtn[e]'	}	{'Exchange of Creatinine'	}	0 10
{'EX_cyst_L[e]'	}	{'Exchange of L-Cystathionine'	}	0 10
{'EX_ethamp[e]'	}	{'Exchange of Ethanolamine Phosphate'	}	0 10
{'EX_gudac[e]'	}	{'Exchange of Guanidinoacetic Acid'	}	0 10
{'EX_kynate[e]'	}	{'Exchange of Kynurenic Acid'	}	0 10
{'EX_xmp[e]'	}	{'Exchange of Xanthylic Acid'	}	0 10
{'EX_argsuc[e]'	}	{'Exchange of L-Arginosuccinic Acid'	}	0 10
{'EX_3mtp[e]'	}	{'Exchange of 3-Methyl-Thio-Propionate'	}	0 10
{'EX_34hpl[e]'	}	{'Exchange of 3- (4-Hydroxyphenyl)Lactate'	}	0 10
{'EX_4aabutn[e]'	}	{'Exchange of 4-Acetamidobutanoate'	}	0 10
{'EX_aclys[e]'	}	{'Exchange of Acetyl-Lysine'	}	0 10
{'EX_C02712[e]'	}	{'Exchange of N-Acetylmethionine'	}	0 10
{'EX_C04805[e]'	}	{'Exchange of 5(S)-HETE'	}	0 10
{'EX_leuktrB4wcooh[e]'	}	{'Exchange of W-Carboxy Leukotriene B4'	}	0 10
{'EX_Lpipecol[e]'	}	{'Exchange of L-Pipecolic Acid'	}	0 10
{'EX_magole_hs[e]'	}	{'Exchange of 1-Oleoylglycerol'	}	0 10
{'EX_mi1p_D[e]'	}	{'Exchange of Myo-Inositol 1-Phosphate'	}	0 10
{'EX_urcan[e]'	}	{'Exchange of Urocanate'	}	0 10
{'EX_dhbpt[e]'	}	{'Exchange of 6,7-Dihydrobiopterin'	}	0 10
{'EX_thbpt[e]'	}	{'Exchange of 5,6,7,8-Tetrahydrobiopterin'	}	0 10
{'EX_argglygly[e]'	}	{'Exchange of ArgGlyGly'	}	0 10
{'EX_gluleu[e]'	}	{'Exchange of GluLeu'	}	0 10
{'EX_hisglylys[e]'	}	{'Exchange of HisGlyLys'	}	0 10
{'EX_leuleutrp[e]'	}	{'Exchange of LeuLeuTrp'	}	0 10
{'EX_leuval[e]'	}	{'Exchange of LeuVal'	}	0 10
{'EX_lysvaltrp[e]'	}	{'Exchange of LysValTrp'	}	0 10
{'EX_phetrpleu[e]'	}	{'Exchange of PheTrpLeu'	}	0 10
{'EX_trpglyleu[e]'	}	{'Exchange of TrpGlyLeu'	}	0 10
{'EX_trpglyval[e]'	}	{'Exchange of TrpGlyVal'	}	0 10
{'EX_homoval[e]'	}	{'Exchange of Homovanillate'	}	0 10
{'EX_acgal[e]'	}	{'Exchange of N-Acetylgalactosamine '	}	0 10
{'EX_acnam[e]'	}	{'Exchange of N-Acetylneuraminate '	}	0 10
{'EX_pcreat[e]'	}	{'Exchange of Phosphocreatine'	}	0 10
{'EX_2obut[e]'	}	{'Exchange of 2-Oxobutanoate'	}	0 10
{'EX_glcn[e]'	}	{'Exchange of D-Gluconate'	}	0 10
{'EX_adn[e]'	}	{'Exchange of Adenosine'	}	0 10
{'EX_cgly[e]'	}	{'Exchange of Cysteinyl-Glycine '	}	0 10
{'EX_co2[e]'	}	{'Exchange of Carbon Dioxide '	}	0 10
{'EX_cytd[e]'	}	{'Exchange of Cytidine'	}	0 10
{'EX_glypro[e]'	}	{'Exchange of Glypro'	}	0 10
{'EX_ppi[e]'	}	{'Exchange of Ppi'	}	0 10
{'EX_for[e]'	}	{'Exchange of Formate '	}	0 10
{'EX_ac[e]'	}	{'Exchange of Acetate '	}	0 10
{'EX_fru[e]'	}	{'Exchange of D-Fructose'	}	0 10
{'EX_glcur[e]'	}	{'Exchange of D-Glucuronate '	}	0 10
{'EX_xan[e]'	}	{'Exchange of Xanthine '	}	0 10

{'EX_xyl_D[e]' }	{'Exchange of D-Xylose ' }	0	10
{'EX_4hbz[e]' }	{'Exchange of 4-Hydroxybenzoate' }	0	10
{'EX_3mox4hoxm[e]' }	{'Exchange of 3-Methoxy-4-Hydroxymandelate' }	0	10
{'EX_2h3mv[e]' }	{'Exchange of 2-Hydroxy-3-Methyl-Valerate' }	0	10
{'EX_2hiv[e]' }	{'Exchange of 2-Hydroxy-Isovalerate' }	0	10
{'EX_2m3hbu[e]' }	{'Exchange of 2-Methyl-3-Hydroxy-Butyrate' }	0	10
{'EX_2m3hvac[e]' }	{'Exchange of 2-Methyl-3-Hydroxy-Valerate' }	0	10
{'EX_3h3mglt[e]' }	{'Exchange of 3-Hydroxy-3-Methyl-Glutarate' }	0	10
{'EX_3mglutac[e]' }	{'Exchange of 3-Methyl-Glutaconate' }	0	10
{'EX_mvlac[e]' }	{'Exchange of Mevalonate-Lactone' }	0	10
{'EX_3ohglutac[e]' }	{'Excahnge of 3-Hydroxy-Glutarate' }	0	10
{'EX_glutcon[e]' }	{'Exchange of Glutaconate' }	0	10
{'EX_sql[e]' }	{'Exchange of Squalene' }	0	10
{'EX_HC02020[e]' }	{'Exchange of Cholesterol-Ester-Palm' }	0	10
{'EX_xol24oh[e]' }	{'Exchange of (24S)-24-Hydroxycholesterol' }	0	10
{'EX_xol27oh[e]' }	{'Exchange of 26-Hydroxycholesterol' }	0	10
{'EX_34dhoxmand[e]' }	{'Exchange of 3,4-Dihydroxymandelate' }	0	10
{'EX_C05767[e]' }	{'Exchange of Uroporphyrin I' }	0	10
{'EX_C05770[e]' }	{'Exchange of Coproporphyrin Iii' }	0	10
{'EX_mhista[e]' }	{'Exchange of N(Tele)-Methylhistaminium' }	0	10
{'EX_ppbng[e]' }	{'Exchange of Porphobilinogen' }	0	10
{'EX_ametam[e]' }	{'Exchange of S-Adenosylmethioninamine' }	0	10
{'EX_xylu_D[e]' }	{'Exchange of Xylu_D' }	0	10
{'EX_sphings[e]' }	{'Exchange of Sphingosine' }	0	10
{'EX_im4ac[e]' }	{'Exchange of Imidazol-4-Ylacetate' }	0	10
{'EX_mlthf[e]' }	{'Exchange of 5,10-Methylenetetrahydrofolate' }	0	10
{'EX_CE2705[e]' }	{'Exchange of Quinonoid Dihydrobiopterin' }	0	10
{'EX_fdp[e]' }	{'Exchange of D-Fructose 1,6-Bisphosphate' }	0	10
{'EX_34dhpe[c]' }	{'Exchange of 3, 4-Dihydroxyphenylethanol ' }	0	10
{'EX_pail_hs[e]' }	{'Exchange of 1-Phosphatidyl-1D-Myo-Inositol' }	0	10
{'EX_caproic[e]' }	{'Exchange for Caproic Acid' }	0	10
{'EX_M01966[e]' }	{'Exchange for D-Glucose 1,6-Bisphosphate' }	0	10
{'EX_kdn[e]' }	{'Exchange for 2-Keto-3-Deoxy-D-Glycero-D-Galactononic Acid'}	0	10
{'DM_CE5026[c]' }	{'Demand for 5-S-Glutathionyl-L-Dopa' }	0	10
{'DM_CE1261[c]' }	{'Demand for 5-S-Cysteinyldopa' }	0	10
{'DM_4glu56dihdind[c]'}	{'Demand for 4-S-Glutathionyl-5,6-Dihydroxyindoline' }	0	10
{'DM_CE1562[c]' }	{'Demand for 5,6-Indolequinone-2-Carboxylate' }	0	10
{'DM_ind56qn[c]' }	{'Demand for Indole-5,6-Quinone' }	0	10
{'DM_5cysdopa[c]' }	{'Demand for 5-S-Cysteinyldopamine' }	0	10
{'DM_CE5025[c]' }	{'Demand for 5-S-Glutathionyl-Dopamine' }	0	10
{'DM_CE4888[c]' }	{'Demand for Dopaminochrome' }	0	10

Reverse_Reaction, 0 bound	**Name**	**lb**	**ub**	**equation**
{'EX_lys_L[e]'}	{'Exchange of L-Lysine ' }	-100.23	0	{'lys_L[e] <=> '}
{'EX_met_L[e]'}	{'Exchange of L-Methionine ' }	-1.8909	0	{'met_L[e] <=> '}
{'EX_o2[e]' }	{'Exchange of Oxugen' }	-1516.9	0	{'o2[e] <=> ' }
{'EX_his_L[e]'}	{'Exchange of L-Histidine' }	-27.05	0	{'his_L[e] <=> '}
{'EX_thr_L[e]'}	{'Exchange of L-Threonine ' }	-96.44	0	{'thr_L[e] <=> '}
{'EX_phe_L[e]'}	{'Exchange of L-Phenylalanine'}	-47.547	0	{'phe_L[e] <=> '}
{'EX_trp_L[e]'}	{'Exchange of L-Tryptophan ' }	-0.83573	0	{'trp_L[e] <=> '}

Forward_Reaction, non-0 bound	**Name**	**lb**
{'EX_2hb[e]' }	{'Exchange of 2-Hydroxybutyrate ' }	0.032705
{'EX_bhb[e]' }	{'Transport of (R)-3-Hydroxybutanoate via H+ Symport'}	0.053865
{'EX_3hpp[e]' }	{'Exchange of 3-Hydroxypropionate' }	0.02363
{'EX_Nacasp[e]'}	{'Exchange of N-Acetyl-L-Aspartate' }	0.32205
{'EX_glyc_R[e]'}	{'Exchange of D-Glycerate' }	0.28767
{'EX_glyclt[e]'}	{'Exchange of Glycolate' }	0.10791
{'EX_akg[e]' }	{'Exchange of 2-Oxoglutarate ' }	0.1022
{'EX_asn_L[e]' }	{'Exchange of L-Asparagine' }	0.48669

{'EX_fum[e]' }	{'Exchange of Fumarate' }	0.06551
{'EX_lac_L[e]' }	{'Exchange of L-Lactate ' }	196.46
{'EX_mal_L[e]' }	{'Exchange of L-Malate' }	0.054241
{'EX_orn[e]' }	{'Exchange of Ornithine ' }	25.366
{'EX_pro_L[e]' }	{'Exchange of L-Proline ' }	0.96137
{'EX_ser_L[e]' }	{'Exchange of L-Serine' }	2.79
{'EX_succ[e]' }	{'Exchange of Succinate ' }	0.15368
{'EX_ala_L[e]' }	{'Exchange of L-Alanine' }	8.6953
{'EX_cit[e]' }	{'Exchange of Citrate ' }	0.254
{'EX_ura[e]' }	{'Exchange of Uracil ' }	0.0070234
{'EX_taur[e]' }	{'Exchange of Taurine ' }	0.0022509
{'EX_actyr[e]' }	{'Exchange of N-Acetyl-Tyrosine' }	0.00018472
{'EX_3hivac[e]'}	{'Exchange of 3-Hydroxy-Isovalerate' }	0.92259

Reverse_Reaction, non-0 bound	Name	lb	ub	
{'EX_acglu[e]'}	{'Exchange of N-Acetyl-L-Glutamate'}	-0.27082	-0.18228	{'acg
{'EX_ile_L[e]'}	{'Exchange of L-Isoleucine ' }	-19.49	-8.4975	{'ile
{'EX_leu_L[e]'}	{'Exchange of L-Leucine ' }	-18.323	-8.3021	{'leu
{'EX_val_L[e]'}	{'Exchange of L-Valine ' }	-11.719	-2.6654	{'val
{'EX_gly[e]' }	{'Exchange of Glycine' }	-25.654	-14.496	{'gly
{'EX_cys_L[e]'}	{'Exchange of L-Cysteine' }	-1.6574	-0.57181	{'cys
{'EX_gln_L[e]'}	{'Exchange of L-Glutamine' }	-60.556	-3.9021	{'gln
{'EX_arg_L[e]'}	{'Exchange of L-Arginine ' }	-6.0387	-1.8685	{'arg
{'EX_etha[e]' }	{'Exchange of Ethanolamine ' }	-0.56504	-0.35439	{'eth
{'EX_glc_D[e]'}	{'Exchange of D-Glucose ' }	-298.95	-126.74	{'glc

Reversible_Reaction	Name	lb
{'EX_34dhphe[e]' }	{'Exchange of 3, 4-Dihydroxy-L-Phenylalanine ' }	-1
{'EX_ala_B[e]' }	{'Exchange of Beta-Alanine ' }	-0.1
{'EX_arachd[e]' }	{'Exchange of Nc20:4 ' }	-1
{'EX_atp[e]' }	{'Exchange of ATP ' }	-1
{'EX_chol[e]' }	{'Exchange of Choline' }	-7.
{'EX_chsterol[e]' }	{'Exchange of Cholesterol' }	-1
{'EX_dopa[e]' }	{'Exchange of Dopamine ' }	-1
{'EX_dopasf[e]' }	{'Exchange of Dopamine 3-O-Sulfate ' }	-1
{'EX_gthrd[e]' }	{'Exchange of Reduced Glutathione ' }	-0.2
{'EX_h2o2[e]' }	{'Exchange of Hydrogen Peroxide ' }	-1
{'EX_hco3[e]' }	{'Exchange of Bicarbonate ' }	-42
{'EX_inost[e]' }	{'Exchange of Myo-Inositol ' }	-8.
{'EX_Lcystin[e]' }	{'Exchange of L-Cystine ' }	-7.
{'EX_lneldc[e]' }	{'Exchange of Linoelaidic Acid ' }	-1
{'EX_lnlc[e]' }	{'Exchange of Linoleic Acid (All Cis C18:2) ' }	-0.01
{'EX_lnlncg[e]' }	{'Exchange of Gamma-Linolenic Acid ' }	-1
{'EX_octa[e]' }	{'Exchange of Octanoate (N-C8:0)' }	-0.03
{'EX_strdnc[e]' }	{'Exchange of Stearidonic Acid ' }	-1
{'EX_citr_L[e]' }	{'Exchange of L-Citrulline ' }	-0.001
{'EX_Lkynr[e]' }	{'Exchange of L-Kynurenine' }	-0.0009
{'EX_CE2028[e]' }	{'Exchange of Beta-Hydroxy-Beta-Methylbutyrate' }	-1
{'EX_acile_L[e]' }	{'Exchange of Acetyl Isoleucine' }	-0.009
{'EX_acleu_L[e]' }	{'Exchange of Acetyl Leucine' }	-0.007
{'EX_asp_L[e]' }	{'Exchange of L-Aspartate ' }	-3.
{'EX_gal[e]' }	{'Exchange of D-Galactose' }	-1
{'EX_glu_L[e]' }	{'Exchange of L-Glutamate ' }	-3.
{'EX_h[e]' }	{'Exchange of Proton' }	-1
{'EX_h2o[e]' }	{'Exchange of Water ' }	-1
{'EX_pi[e]' }	{'Exchange of Phosphate ' }	-14
{'EX_ribflv[e]' }	{'Exchange of Riboflavin' }	-0.1
{'EX_so4[e]' }	{'Exchange of Sulfate ' }	-31
{'EX_thymd[e]' }	{'Exchange of Thymidine ' }	-0.
{'EX_tyr_L[e]' }	{'Exchange of L-Tyrosine ' }	-5.

```
    {'EX_nh4[e]'          }    {'Exchange of Ammonia '                                          }    -0.0001
    {'EX_fol[e]'          }    {'Exchange of Folate'                                            }        -1.
    {'EX_ptrc[e]'         }    {'Exchange of 1, 4-Butanediammonium'                             }       -0.1
    {'EX_34dhpha[e]'      }    {'Exchange of 34Dhpha'                                           }         -1
    {'EX_pyr[e]'          }    {'Exchange of Pyruvate '                                         }       -0.7
    {'EX_4abut[e]'        }    {'Exchange of 4-Aminobutanoate '                                 }    -0.0002
    {'EX_C09642[e]'       }    {'Exchange of (-)-Salsolinol'                                    }         -1
    {'EX_dopa4sf[e]'      }    {'Exchange of Dopamine 4-O-Sulfate '                             }         -1
    {'EX_dopa4glcur[e]'   }    {'Exchange of Dopamine 4-O-Glucuronide '                         }         -1
    {'EX_dopa3glcur[e]'   }    {'Exchange of Dopamine 3-O-Glucuronide '                         }         -1
    {'EX_4glu56dihdind[e]'}    {'Exchange of 4-S-Glutathionyl-5, 6-Dihydroxyindoline '          }         -1
    {'EX_5cysdopa[e]'     }    {'Exchange of 5-S-Cysteinyldopamine '                            }         -1
    {'EX_CE5025[e]'       }    {'Exchange of 5-S-Glutathionyl-Dopamine '                        }         -1
    {'EX_CE5629[e]'       }    {'Exchange of 6, 7-Dihydroxy-1, 2, 3, 4-Tetrahydroisoquinoline'}         -1
    {'EX_CE5026[e]'       }    {'Exchange of 5-S-Glutathionyl-L-Dopa'                           }         -1
    {'EX_CE1261[e]'       }    {'Exchange of 5-S-Cysteinyldopa'                                 }         -1
    {'EX_CE1554[e]'       }    {'Exchange of Acetyl-Alanine'                                    }         -1
    {'DM_ps_hs[c]'        }    {'Phosphatidylserine demand'                                     }         -1
```

```
printCouplingConstraints(model,1);
```

```
        coupledRxnId                                  constraints
    ____________________    ____________________________________________________________________

    {'Phosphatidylcholine'    }    {'PCHOLP_hs + PLA2_2 + SMS >= 2.025'
    {'Adenosine Monophosphate'}    {'AMPDA + NTD7 >= 0.2265'
    {'Glutamate'              }    {'- ALATA_L + GLUCYS + GLUDxm + GLUDym - ASPTA - ILETA - LEUTA - VALTA
    {'Aspartate'              }    {'ARGSS + ASPTA >= 1.1925'
    {'Serine'                 }    {'GHMT2r + r0060 >= 0.8625'
    {'Arginine'               }    {'GLYAMDTRc + r0145 >= 0.7245'
    {'Tyrosine'               }    {'TYR3MO2 + TYRTA + HMR_6728 + HMR_6874 >= 0.55875'
    {'Histidine'              }    {'HISDC + HISD >= 1.095'
    {'Leucine + Isoleucine'   }    {'ILETA + LEUTA >= 1.305'
    {'Valine + Methionine'    }    {'METAT + VALTA >= 0.705'
    {'Glycine'                }    {'GTHS - GHMT2r >= 0.7725'
```

Set the data parameters for the entropic flux balance analysis problem

Linear optimisation direction

```
model.osenseStr = 'min';
```

Reaction parameters

```
model.cf=0.1;
model.cr=0.1;
model.g=2;
if 0
    quad = zeros(size(model.S,2),1);
    quad(~model.SIntRxnBool)=1;
    model.Q=diag(quad);
end
```

Reaction parameters

Setting the bounds on reaction direction is important, because certain bounds may be incompatible with the existence of a thermodynamically feasible steady state

`param.internalNetFluxBounds = 'original'` maintains direction and magnitude of internal net flux from model.lb & model.ub

`param.internalNetFluxBounds = 'directional'` maintains direction of internal net flux from model.lb & model.ub but not magnitude

`param.internalNetFluxBounds = 'none'` removes lower and upper bounds on internal net flux

`param.internalNetFluxBounds = 'random'` random internal net flux direction, replacing constraints from model.lb & model.ub

```
param.internalNetFluxBounds='directional';
%param.internalNetFluxBounds='original';
%param.internalNetFluxBounds='none';
```

Maximum permitted internal flux

```
param.maxUnidirectionalFlux=100;
%model.vfl = [0;0;0]
```

Method parameters

```
param.method='fluxes';
%param.method='fluxConc';%param.method='fluxConcNorm';
```

Metabolite parameters (only relevant if a concentration method chosen)

Standard chemical potential

```
model.u0 = ones(1,size(model.S,1))*0;
```

Strictly positive weight on concentration entropy maximisation

```
model.f=1;
```

Scalar maximum permitted metabolite concentration

```
param.maxConc=1;
```

Solver parameters

Set the solver

```
%param.solver='pdco';
param.solver='mosek';
```

Minimum permitted internal flux required for exponential cone reformulation

```
if strcmp(param.solver,'mosek')
    param.minUnidirectionalFlux=0;
end
```

Tolerances

```
param.feasTol=1e-7;
```

Printing level

```
param.printLevel=2;
param.debug = 1;
```

Entropic flux balance analysis

```
[solution,modelOut] = entropicFluxBalanceAnalysis(model,param);
```

```
Using directional internal net flux bounds only.
Using existing external net flux bounds without modification.

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Platform: Linux/64-X86


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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : LO (linear optimization problem)
  Constraints            : 2965
  Affine conic cons.     : 0
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 3625
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Eliminator started.
Freed constraints in eliminator : 1219
Eliminator terminated.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 141
Eliminator terminated.
Eliminator - tries                  : 2                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 9                 dual deps.             : 0
Presolve terminated. Time: 0.02
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
```

```
Optimizer  - Constraints           : 512
Optimizer  - Cones                 : 0
Optimizer  - Scalar variables      : 1700              conic                  : 0
Optimizer  - Semi-definite variables: 0                scalarized             : 0
Factor     - setup time            : 0.01
Factor     - dense det. time       : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 5040             after factor           : 1.19e+04
Factor     - dense dim.            : 1                 flops                  : 5.13e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ               MU       TIME
0   8.1e+03  1.2e+03  2.7e+04  0.00e+00   2.524651910e+04   -1.187509009e+03  1.3e+02  0.03
1   3.5e+03  5.6e-01  1.1e+04  1.01e+00   9.340150454e+03   2.546036924e+03   5.5e+01  0.05
2   1.6e+03  2.6e-01  5.4e+03  1.21e+00   5.103765843e+03   2.145030639e+03   2.6e+01  0.05
3   6.0e+02  9.6e-02  2.0e+03  1.12e+00   2.290895208e+03   1.257801880e+03   9.4e+00  0.06
4   1.2e+02  1.9e-02  3.8e+02  1.05e+00   6.891441803e+02   4.922303657e+02   1.8e+00  0.06
5   4.0e+01  6.4e-03  1.3e+02  1.02e+00   4.330729771e+02   3.656226850e+02   6.3e-01  0.06
6   5.4e+00  8.8e-04  1.8e+01  1.02e+00   3.116637492e+02   3.025822720e+02   8.6e-02  0.06
7   1.8e+00  2.9e-04  5.9e+00  1.01e+00   2.971165650e+02   2.941345150e+02   2.8e-02  0.06
8   4.7e-01  7.6e-05  1.5e+00  1.00e+00   2.918325929e+02   2.910515001e+02   7.4e-03  0.07
9   3.4e-02  5.4e-06  1.1e-01  1.00e+00   2.900752738e+02   2.900195527e+02   5.3e-04  0.07
10  1.5e-02  2.5e-06  5.1e-02  9.93e-01   2.899968569e+02   2.899711094e+02   2.4e-04  0.07
11  9.4e-04  1.5e-07  3.1e-03  9.98e-01   2.899355375e+02   2.899339714e+02   1.5e-05  0.07
12  1.6e-05  2.6e-09  5.3e-05  1.00e+00   2.899307214e+02   2.899306947e+02   2.5e-07  0.08
13  1.1e-07  1.8e-11  3.7e-07  1.00e+00   2.899306171e+02   2.899306169e+02   1.7e-09  0.08
14  2.8e-08  1.2e-11  3.3e-08  1.00e+00   2.899306168e+02   2.899306168e+02   1.8e-13  0.08
Basis identification started.
Primal basis identification phase started.
Primal basis identification phase terminated. Time: 0.00
Dual basis identification phase started.
Dual basis identification phase terminated. Time: 0.00
Basis identification terminated. Time: 0.00
Optimizer terminated. Time: 0.09


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061675e+02    nrm: 2e+02    Viol.  con: 1e-07    var: 3e-09
  Dual.    obj: 2.8993061677e+02    nrm: 5e+00    Viol.  con: 0e+00    var: 6e-12

Basic solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061677e+02    nrm: 2e+02    Viol.  con: 7e-13    var: 1e-14
  Dual.    obj: 2.8993061677e+02    nrm: 7e+00    Viol.  con: 2e-14    var: 8e-10
Optimizer summary
  Optimizer                 -                        time: 0.09
    Interior-point          - iterations : 14        time: 0.09
      Basis identification  -                        time: 0.00
        Primal              - iterations : 37        time: 0.00
        Dual                - iterations : 95        time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00

solveCobraEP: LP part of EPproblem is feasible according to solveCobraLP with mosek.

MOSEK Version 10.2.5 (Build date: 2024-9-17 12:12:35)
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Platform: Linux/64-X86
```

```
MOSEK Version 10.2.5 (Build date: 2024-9-17 12:12:35)
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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : CONIC (conic optimization problem)
  Constraints            : 2965
  Affine conic cons.     : 3420 (10260 rows)
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 7046
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 0
Eliminator terminated.
Eliminator - tries                  : 1                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 25                dual deps.             : 0
Presolve terminated. Time: 0.03
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 1960
Optimizer  - Cones                  : 3420
Optimizer  - Scalar variables       : 11264             conic                  : 10260
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.02
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 1.19e+04          after factor           : 2.06e+04
Factor     - dense dim.             : 0                 flops                  : 7.95e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   1.0e+04  1.2e+00  1.0e+04  0.00e+00   5.937759534e+03   -4.414972768e+03  1.0e+00  0.06
1   7.8e+03  9.2e-01  9.2e+03  -9.99e-01  8.329038595e+03   -2.020744460e+03  7.8e-01  0.08
2   7.1e+03  8.3e-01  8.7e+03  -9.96e-01  9.584261566e+03   -7.537052715e+02  7.1e-01  0.08
3   5.2e+03  6.1e-01  7.4e+03  -9.87e-01  1.460992409e+04   4.361323650e+03   5.2e-01  0.09
4   1.7e+03  2.0e-01  4.1e+03  -9.66e-01  5.216178440e+04   4.235234708e+04   1.7e-01  0.10
5   7.4e+02  8.7e-02  2.4e+03  -8.64e-01  1.028563864e+05   9.397331223e+04   7.4e-02  0.11
6   4.0e+02  4.6e-02  1.4e+03  -6.03e-01  1.076676790e+05   1.004097991e+05   4.0e-02  0.12
7   2.8e+02  3.3e-02  9.7e+02  -1.71e-01  8.893218123e+04   8.290489716e+04   2.8e-02  0.13
8   1.6e+02  1.9e-02  4.9e+02  8.31e-02   6.300096522e+04   5.880765531e+04   1.6e-02  0.13
9   1.1e+02  1.2e-02  2.7e+02  4.17e-01   4.940899724e+04   4.640012206e+04   1.1e-02  0.14
10  4.5e+01  5.3e-03  8.2e+01  6.09e-01   3.123427143e+04   2.979941887e+04   4.5e-03  0.16
11  1.4e+01  1.7e-03  1.6e+01  8.34e-01   2.194998655e+04   2.146636309e+04   1.4e-03  0.16
12  4.4e+00  5.2e-04  2.8e+00  9.56e-01   1.845528587e+04   1.830414181e+04   4.4e-04  0.17
13  1.3e+00  1.6e-04  4.8e-01  9.89e-01   1.743922038e+04   1.739390618e+04   1.3e-04  0.18
14  3.6e-01  4.3e-05  7.2e-02  9.98e-01   1.714335346e+04   1.713092359e+04   3.6e-05  0.19
15  8.7e-02  1.0e-05  8.4e-03  1.00e+00   1.705275421e+04   1.704978384e+04   8.7e-06  0.20
16  1.5e-02  1.7e-06  6.2e-04  9.99e-01   1.703018296e+04   1.702967748e+04   1.5e-06  0.21
17  2.2e-03  2.5e-07  3.4e-05  1.00e+00   1.702611788e+04   1.702604409e+04   2.2e-07  0.22
18  1.2e-03  1.5e-07  1.5e-05  1.00e+00   1.702582068e+04   1.702577846e+04   1.2e-07  0.23
19  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548983e+04   1.702548272e+04   2.1e-08  0.24
20  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548982e+04   1.702548271e+04   2.1e-08  0.25
21  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548968e+04   1.702548258e+04   2.1e-08  0.25
22  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548967e+04   1.702548258e+04   2.1e-08  0.27
23  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548966e+04   1.702548257e+04   2.1e-08  0.28
```

```
24  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548948e+04   1.702548241e+04   2.1e-08  0.28
25  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548946e+04   1.702548239e+04   2.1e-08  0.29
26  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548944e+04   1.702548238e+04   2.1e-08  0.30
27  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548912e+04   1.702548208e+04   2.1e-08  0.31
28  2.1e-04  2.4e-08  1.0e-06  1.00e+00   1.702548909e+04   1.702548206e+04   2.1e-08  0.32
29  2.0e-04  2.3e-08  9.3e-07  1.00e+00   1.702548550e+04   1.702547886e+04   2.0e-08  0.33
30  1.9e-04  2.3e-08  9.3e-07  1.00e+00   1.702548537e+04   1.702547873e+04   1.9e-08  0.34
31  1.9e-04  2.2e-08  8.8e-07  1.00e+00   1.702548330e+04   1.702547689e+04   1.9e-08  0.35
32  1.9e-04  2.2e-08  8.8e-07  1.00e+00   1.702548321e+04   1.702547681e+04   1.9e-08  0.36
33  1.8e-04  2.2e-08  8.5e-07  1.00e+00   1.702548189e+04   1.702547563e+04   1.8e-08  0.37
34  1.8e-04  2.1e-08  8.3e-07  1.00e+00   1.702548076e+04   1.702547461e+04   1.8e-08  0.38
35  1.8e-04  2.1e-08  8.3e-07  1.00e+00   1.702548072e+04   1.702547458e+04   1.8e-08  0.39
36  1.8e-04  2.1e-08  8.2e-07  1.00e+00   1.702548061e+04   1.702547448e+04   1.8e-08  0.40
37  1.8e-04  2.1e-08  8.2e-07  1.00e+00   1.702548053e+04   1.702547441e+04   1.8e-08  0.41
38  1.7e-04  2.0e-08  7.9e-07  1.00e+00   1.702547900e+04   1.702547305e+04   1.7e-08  0.41
39  1.7e-04  2.0e-08  7.9e-07  1.00e+00   1.702547899e+04   1.702547303e+04   1.7e-08  0.42
40  1.7e-04  2.0e-08  7.9e-07  1.00e+00   1.702547899e+04   1.702547303e+04   1.7e-08  0.43
41  1.7e-04  2.0e-08  7.9e-07  1.00e+00   1.702547899e+04   1.702547303e+04   1.7e-08  0.44
42  3.8e-05  4.4e-09  7.9e-08  1.00e+00   1.702543493e+04   1.702543364e+04   3.8e-09  0.45
43  3.8e-05  4.4e-09  7.9e-08  1.00e+00   1.702543493e+04   1.702543364e+04   3.8e-09  0.47
44  3.8e-05  4.4e-09  7.9e-08  1.00e+00   1.702543493e+04   1.702543364e+04   3.8e-09  0.49
Optimizer terminated. Time: 0.51


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 1.7025434927e+04    nrm: 5e+02    Viol.  con: 3e-07    var: 2e-05    acc: 3e-08
  Dual.    obj: 1.7025433643e+04    nrm: 8e+03    Viol.  con: 8e-08    var: 1e-07    acc: 0e+00
Optimizer summary
  Optimizer                 -                        time: 0.51
    Interior-point          - iterations : 45        time: 0.50
      Basis identification  -                        time: 0.00
        Primal              - iterations : 0         time: 0.00
        Dual                - iterations : 0         time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00


 > [mosek] Primal optimality condition in solveCobraEP satisfied.
 > [mosek] Dual   optimality condition in solveCobraEP satisfied.

Optimality conditions (biochemistry)
 2.8e-07 || N*(vf - vr) + B*ve - b ||_inf
     Inf || C*(vf - vr) + s_C - d ||_inf, s_C = slack variable
 8.8e-08 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + k_vf + z_vf ||_inf
 8.8e-08 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + k_vr + z_vr ||_inf
 7.4e-13 || ce + B'*y_N  + z_ve ||_inf
       0 || k_e_1 + z_e_1 ||_inf
 1.5e-07 || -g + k_e_vf + z_e_vf||_inf
 1.5e-07 || -g + k_e_vr + z_e_vr||_inf
 2.1e-06 || e_vf + vf*log(vf) ||_inf
 3.4e-06 || e_vr + vr*log(vr) ||_inf

Derived optimality conditions (biochemistry)
      18 || g.*log(vf) + g - k_vf ||_inf
  0.0043 || g.*log(vr) + g - k_vr ||_inf
      18 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + g.*log(vf) + g + z_vf ||_inf
  0.0043 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + g.*log(vr) + g + z_vr ||_inf
```

```
Thermo conditions
 2.7e+02 || g.*log(vr/vf) - 2*N'*y_N - 2*C'*y_C ||_inf
      53 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi ||_inf
      88 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi - z_vr + z_vf ||_inf
-1.5e+02 min(slack)
     Inf max(slack)
```

```
model=modelOut;
```

Extract the fields of the solution structure

```
if solution.stat ~=1
    disp('No solution')
    return
end
[v,vf,vr,vt,y_N,z_v,z_dx,z_vf,z_vr,stat]=...

deal(solution.v,solution.vf,solution.vr,solution.vt,solution.y_N,solution.z_v
,solution.z_dx,solution.z_vf,solution.z_vr,solution.stat);
cf = model.cf;
cr = model.cr;

g=deal(model.g);
if isfield(solution,'x')
    [x, x0, z_x, z_x0, z_dx] = deal(solution.x, solution.x0, solution.z_x,
solution.z_x0, solution.z_dx);
    [u0,f]=deal(model.u0,model.f);
    dx = x - x0;
end
```

Extract the internal (N) and exchange (B) stoichiometric matrices

```
N = model.S(:,model.SConsistentRxnBool);
B = model.S(:,~model.SConsistentRxnBool);
```

Extract the matrix of coupling constraints, if present

```
if isfield(model,'C')
    C = model.C(:,model.SConsistentRxnBool);
    y_C = solution.y_C;
end
```

Extract the objective on the internal reaction rates

```
e   = ones(length(vf),1);
ci = solution.osense*model.c(model.SConsistentRxnBool);
```

Extract the net internal reaction dual variable

```
z_vi = z_v(model.SConsistentRxnBool);
```

Compute the nullspace of the internal stoichiometric matrix

```
if 0
   %get nullspace of N
    [Z,rankS]=getNullSpace(N,0);
else
    Z=[];
end
```

ANTICIPATED RESULTS

Optimality conditions should be satisfied approximately to the feasibility (or optimality) tolerances of the numerical optimisation solver, typically 1e-6.

```
if param.printLevel>2 || 1
    v_detailed=1;
else
    v_detailed=0;
end
```

Biochemical optimality conditions: steady state

```
if isfield(solution,'x')
    fprintf('%8.2g %s\n',norm(N*(vf - vr) - x + x0 - model.b,inf), '|| N*(vf
- vr) - x + x0 - b ||_inf');
else
    fprintf('%8.2g %s\n',norm(model.S*v - model.b,inf), '|| S*v - b ||_inf');
end
```

```
 2.8e-07 || S*v - b ||_inf
```

Optionally, display detailed properties of flux related solution vector

```
if v_detailed
    fprintf('%8.2g %s\n',sum(vf)+sum(vr),'sum(vf)+sum(vr) >= 0');
    fprintf('%8.2g %s\n',norm(g.*reallog(vf),inf),'|| g*log(vf) ||_inf');
    fprintf('%8.2g %s\n',norm(g.*reallog(vr),inf),'|| g*log(vr) ||_inf');
    fprintf('%8.2g %s\n',norm(cr,inf),'|| cr ||_inf');
    fprintf('%8.2g %s\n',norm(cf,inf),'|| cf ||_inf');
    fprintf('%8.2g %s\n',norm(ci,inf),'|| ci ||_inf');
    fprintf('%8.2g %s\n',norm(N'*y_N,inf),'|| N''*y_N ||_inf');
    fprintf('%8.2g %s\n',norm(z_v,inf),'|| z_v ||_inf');
    fprintf('%8.2g %s\n',norm(z_vf,inf),'|| z_vf ||_inf');
    fprintf('%8.2g %s\n',norm(z_vr,inf),'|| z_vr ||_inf');
    if isfield(model,'C')
        fprintf('%8.2g %s\n',norm(C'*y_C,inf),'|| C''*y_C ||_inf');
    end
end
```

```
 4.1e+03 sum(vf)+sum(vr) >= 0
      31 || g*log(vf) ||_inf
```

```
      13 || g*log(vr) ||_inf
     0.1 || cr ||_inf
     0.1 || cf ||_inf
       0 || ci ||_inf
 1.4e+02 || N'*y_N ||_inf
 1.4e+02 || z_v ||_inf
   2e-07 || z_vf ||_inf
      35 || z_vr ||_inf
      37 || C'*y_C ||_inf
```

```
if isfield(model,'C')
    fprintf('%8.2g %s\n',norm(g.*reallog(vf) + ci + cf + N'*y_N + C'*y_C +
z_vi + z_vf,inf), '|| g*log(vf) + ci + cf + N''*y_N + C''*y_C + z_vi + z_vf
||_inf');
    fprintf('%8.2g %s\n',norm(g.*reallog(vr) - ci + cr - N'*y_N - C'*y_C -
z_vi + z_vr,inf),'|| g*log(vr) - ci + cr - N''*y_N - C''*y_C - z_vi + z_vr
||_inf');
    fprintf('%8.2g %s\n',norm(   C'*y_C + z_vi + z_vf,inf), '||  + C''*y_C +
z_vi + z_vf ||_inf');
    fprintf('%8.2g %s\n',norm( - C'*y_C - z_vi + z_vr,inf),'||  - C''*y_C -
z_vi + z_vr ||_inf');
else
    fprintf('%8.2g %s\n',norm(g.*reallog(vf) + ci + cf + N'*y_N + z_vi -
z_vf,inf), '|| g*log(vf) + ci + cf + N''*y_N + z_vi - z_vf ||_inf');
    fprintf('%8.2g %s\n',norm(g.*reallog(vr) - ci + cr - N'*y_N - z_vi -
z_vr,inf),'|| g*log(vr) - ci + cr - N''*y_N - z_vi - z_vr ||_inf');
end
```

```
      16 || g*log(vf) + ci + cf + N'*y_N + C'*y_C + z_vi + z_vf ||_inf
       2 || g*log(vr) - ci + cr - N'*y_N - C'*y_C - z_vi + z_vr ||_inf
 1.4e+02 ||  + C'*y_C + z_vi + z_vf ||_inf
 1.4e+02 ||  - C'*y_C - z_vi + z_vr ||_inf
```

Derived biochemical optimality conditions (fluxes)

```
if isfield(model,'C')
    res = g.*reallog(vr./vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*z_vi
- z_vr + z_vf;
    fprintf('%8.2g %s\n',norm(res,inf),'|| g*log(vr/vf) + cr - cf - 2*ci -
2*N''*y_N - 2*C''*y_C - 2*z_vi - z_vr + z_vf ||_inf');
else
    res = g.*reallog(vr./vf) + cr - cf - 2*ci - 2*N'*y_N - 2*z_vi - z_vr +
z_vf;
    fprintf('%8.2g %s\n',norm(res,inf),'|| g*log(vr/vf) + cr - cf - 2*ci -
2*N''*y_N - 2*z_vi - z_vr + z_vf ||_inf');
end
```

```
      88 || g*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*z_vi - z_vr + z_vf ||_inf
```

Optionally, display detailed properties of concentration related solution vector

```
if isfield(solution,'x')
    fprintf('\n%s\n','Optimality conditions (concentrations)')
    if v_detailed
```

```
        fprintf('%8.2g %s\n',norm(reallog(x),inf), '|| log(x)||_inf');
        fprintf('%8.2g %s\n',norm(u0,inf), '|| u0 ||_inf');
        fprintf('%8.2g %s\n',norm(y_N,inf), '|| y_N ||_inf');
        fprintf('%8.2g %s\n',norm(z_dx,inf), '|| z_dx ||_inf');
        fprintf('%8.2g %s\n',norm(z_x,inf), '|| z_x ||_inf');
        fprintf('%8.2g %s\n',norm(z_x0,inf), '|| z_x0 ||_inf');
    end
    fprintf('%8.2g %s\n',norm(f.*reallog(x) + u0 - y_N + z_dx + z_x,inf),
'|| f.*log(x) + u0 - y_N + z_dx + z_x ||_inf');
    fprintf('%8.2g %s\n',norm(f.*reallog(x0) + u0 + y_N - z_dx +
z_x0,inf),'|| f.*log(x0) + u0 + y_N - z_dx + z_x0 ||_inf');

    fprintf('\n%s\n','Derived biochemical optimality conditions
(concentrations)')
    fprintf('%8.2g %s\n',norm(f.*reallog(x./x0) - 2*y_N + 2*z_dx + z_x -
z_x0,inf),'|| f.*log(x/x0) - 2*y_N + 2*z_dx + z_x - z_x0 ||_inf');
    fprintf('%8.2g %s\n',norm(f.*reallog(x.*x0) + 2*u0 + z_x + z_x0,inf),'||
f.*log(x.*x0) + 2*u0 + z_x + z_x0 ||_inf');


    fprintf('\n%s\n','Derived biochemical optimality conditions (fluxes and
concentrations)')
    if isfield(model,'C')
        fprintf('%8.2g %s\n',norm(g.*reallog(vf) + cf + ci + N'*(u0 +
f.*reallog(x) + z_dx + z_x) + C'*y_C + z_v + z_vf,inf),'|| g*log(vf) + cf
+ ci + N''*(u0 + f*log(x) + z_dx + z_x) + C''*y_C + z_v + z_vf ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr) + cr - ci - N'*(u0 +
f.*reallog(x) + z_dx + z_x) - C'*y_C - z_v + z_vr,inf), '|| g*log(vr) + cr -
ci - N''*(u0 + f*log(x) + z_dx + z_x) - C''*y_C - z_v +  z_vr ||_inf');
    else
        fprintf('%8.2g %s\n',norm(g.*reallog(vf) + cf + ci + N'*(u0 +
f.*reallog(x) + z_dx + z_x) + z_v + z_vf,inf),'|| g*log(vf) + cf + ci +
N''*(u0 + f*log(x) + z_dx + z_x) + z_v + z_vf ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr) + cr - ci - N'*(u0 +
f.*reallog(x) + z_dx + z_x) - z_v + z_vr,inf),'|| g*log(vr) + cr - ci -
N''*(u0 + f*log(x) + z_dx + z_x) - z_v + z_vr ||_inf');
    end

    fprintf('\n%s\n','Derived biochemical optimality conditions (fluxes and
concentrations)')
    if isfield(model,'C')
        fprintf('%8.2g %s\n',norm(g.*reallog(vr./vf) + cr - cf - 2*ci -
2*N'*(u0 + f.*reallog(x) + z_dx + z_x) - 2*C'*y_C - 2*z_v - z_vf +
z_vr,inf),   '|| g.*reallog(vr./vf) + cr - cf - 2*(ci + N''*(u0 + f*log(x)
+ z_dx +   z_x) + C''*y_C + z_v) - z_vf + z_vr ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr./vf) + cr - cf - 2*ci +
2*N'*(u0 + f.*reallog(x0) - z_dx + z_x0) - 2*C'*y_C - 2*z_v - z_vf +
z_vr,inf),'|| g.*reallog(vr./vf) + cr - cf - 2*(ci - N''*(u0 + f*log(x0) -
z_dx + z_x0) + C''*y_C + z_v) - z_vf + z_vr ||_inf');
    else
```

```
        fprintf('%8.2g %s\n',norm(g.*reallog(vr./vf) + cr - cf - 2*ci -
2*N'*(u0 + f.*reallog(x) + z_dx + z_x) - 2*z_v - z_vf + z_vr,inf),   '||
g.*reallog(vr./vf) + cr - cf - 2*(ci + N''*(u0 + f*log(x)  + z_dx +   z_x) +
z_v) - z_vf + z_vr ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr./vf) + cr - cf - 2*ci +
2*N'*(u0 + f.*reallog(x0) - z_dx + z_x0) - 2*z_v - z_vf + z_vr,inf),'||
g.*reallog(vr./vf) + cr - cf - 2*(ci - N''*(u0 + f*log(x0) - z_dx + z_x0) +
z_v) - z_vf + z_vr ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr.*vf) + cr + cf - N'*(u0
+ f.*reallog(x) + z_dx + z_x) - 2*z_v - z_vf + z_vr,inf),   '||
g.*reallog(vr./vf) + cr - cf - 2*(ci + N''*(u0 + f*log(x)  + z_dx +   z_x) +
z_v) - z_vf + z_vr ||_inf');
        fprintf('%8.2g %s\n',norm(g.*reallog(vr./vf) + cr - cf - 2*ci +
2*N'*(u0 + f.*reallog(x0) - z_dx + z_x0) - 2*z_v - z_vf + z_vr,inf),'||
g.*reallog(vr./vf) + cr - cf - 2*(ci - N''*(u0 + f*log(x0) - z_dx + z_x0) +
z_v) - z_vf + z_vr ||_inf');
    end
end
```

```
fprintf('\n')
if isfield(solution,'v')
    vfpad = NaN*ones(size(model.S,2),1);
    vfpad(model.SConsistentRxnBool)=vf;
    vrpad = NaN*ones(size(model.S,2),1);
    vrpad(model.SConsistentRxnBool)=vr;
    zvfpad = NaN*ones(size(model.S,2),1);
    zvfpad(model.SConsistentRxnBool)=z_vr;
    zvrpad = NaN*ones(size(model.S,2),1);
    zvrpad(model.SConsistentRxnBool)=z_vr;
    T1 =
table(model.lb, v,model.ub,z_v,vfpad,zvfpad,vrpad,zvrpad,'VariableNames',
{'vl','v','vu','z_v','vf','z_vf','vr','z_vr'});
    if length(v)<=10
        disp(T1)
    end
end
```

```


if isfield(solution,'x')
    T2 =
table(model.xl,solution.x,model.xu,z_x,model.x0l,x0,model.x0u,z_x0,model.dxl,
dx,model.dxu,z_dx,...
        'VariableNames',{'xl' 'x' 'xu' 'z_x' 'x0l' 'x0' 'x0u' 'z_x0' 'dxl'
'dx' 'dxu' 'z_dx'});
    if length(solution.x)<=10
        disp(T2)
    end
end
```

TROUBLESHOOTING

Debugging satisfaction of constraints

Entropic Flux Balance Analysis will find a thermodynamically feasible steady state, provided one exists. That is, bounds on net fluxes, for example those causing net flux around a stoichiometrically balanced cycle, can preclude the existince of a thermodynamically feasible steady state. The following plots can be used to investigate deviation from thermodynamic feasibility for certain reactions, indicated by numerical tolerances beyond that considered satifactory (typically 1e-6 for a double precision solver). Setting the bounds on reaction direction is important, because certain bounds may be incompatible with the existence of a thermodynamically feasible steady state

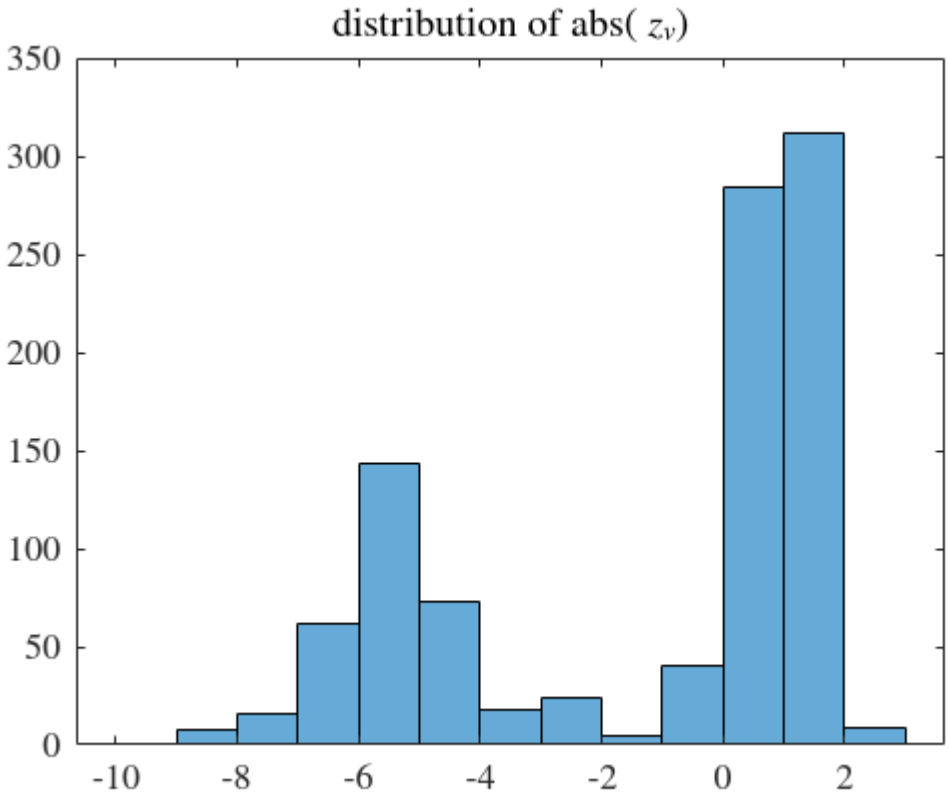
`param.internalNetFluxBounds = 'original'` maintains direction and magnitude of internal net flux from model.lb & model.ub

`param.internalNetFluxBounds = 'directional'` maintains direction of internal net flux from model.lb & model.ub but not magnitude

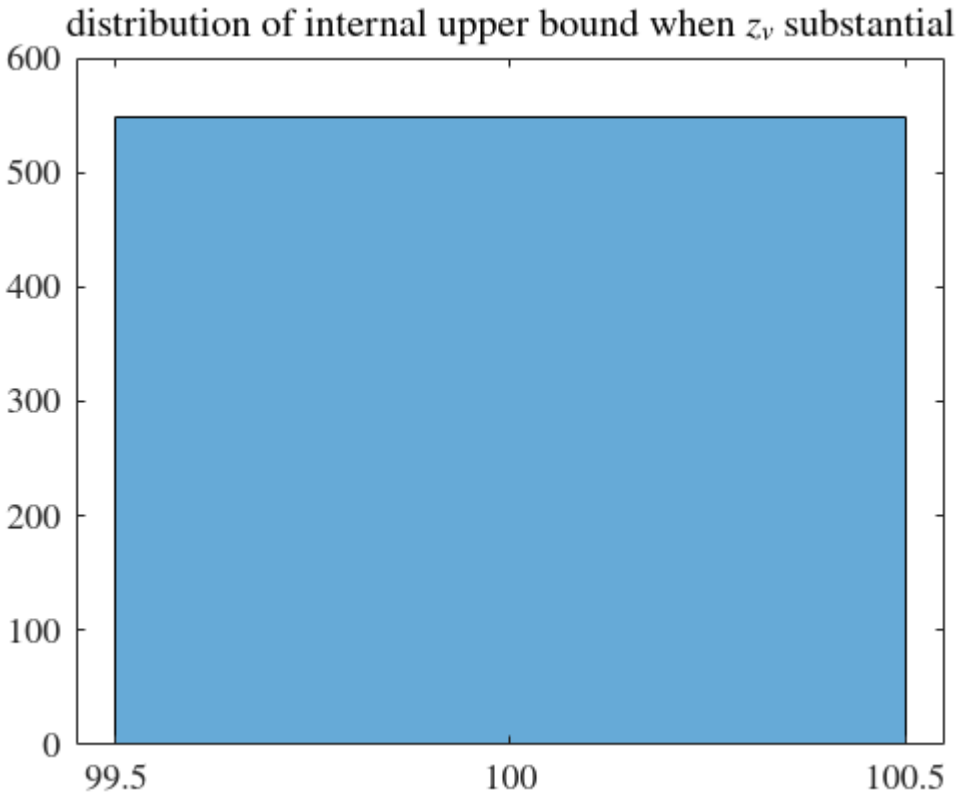
`param.internalNetFluxBounds = 'none'` removes lower and upper bounds on internal net flux

`param.internalNetFluxBounds = 'random'` random internal net flux direction, replacing constraints from model.lb & model.ub

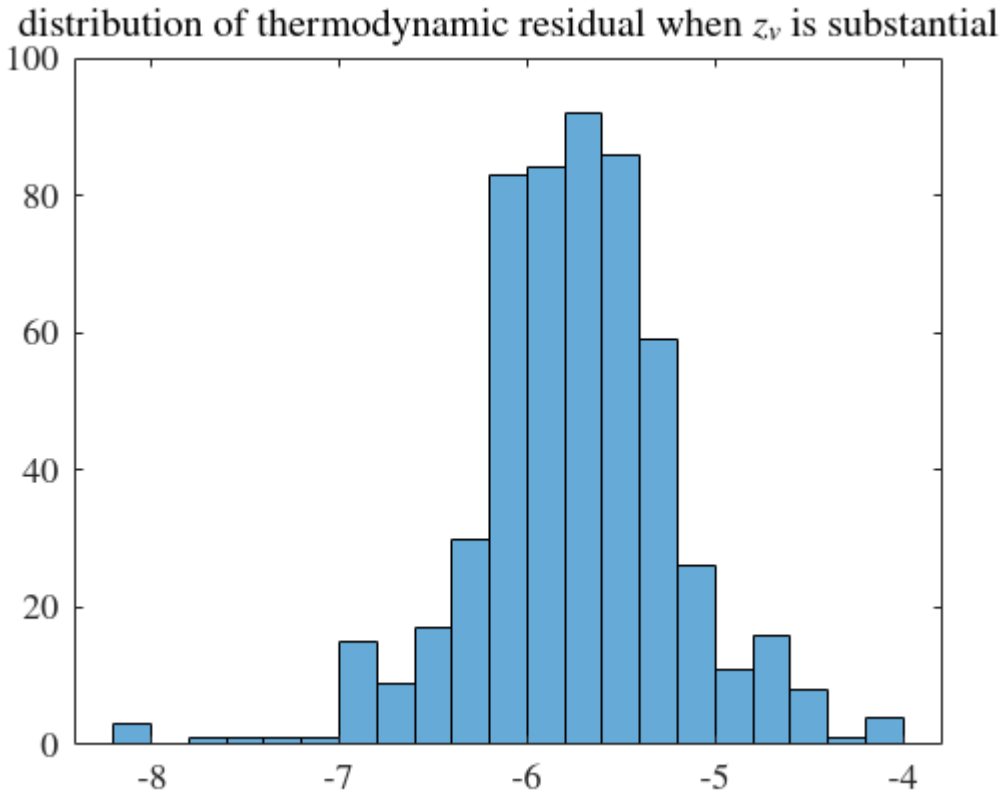
```
l = model.lb(model.SConsistentRxnBool);
u = model.ub(model.SConsistentRxnBool);
vi = vf - vr;
logvrvf = reallog(vr./vf);

figure
histogram(log10(abs(z_v)))
title('distribution of abs( $z_v$)')
```



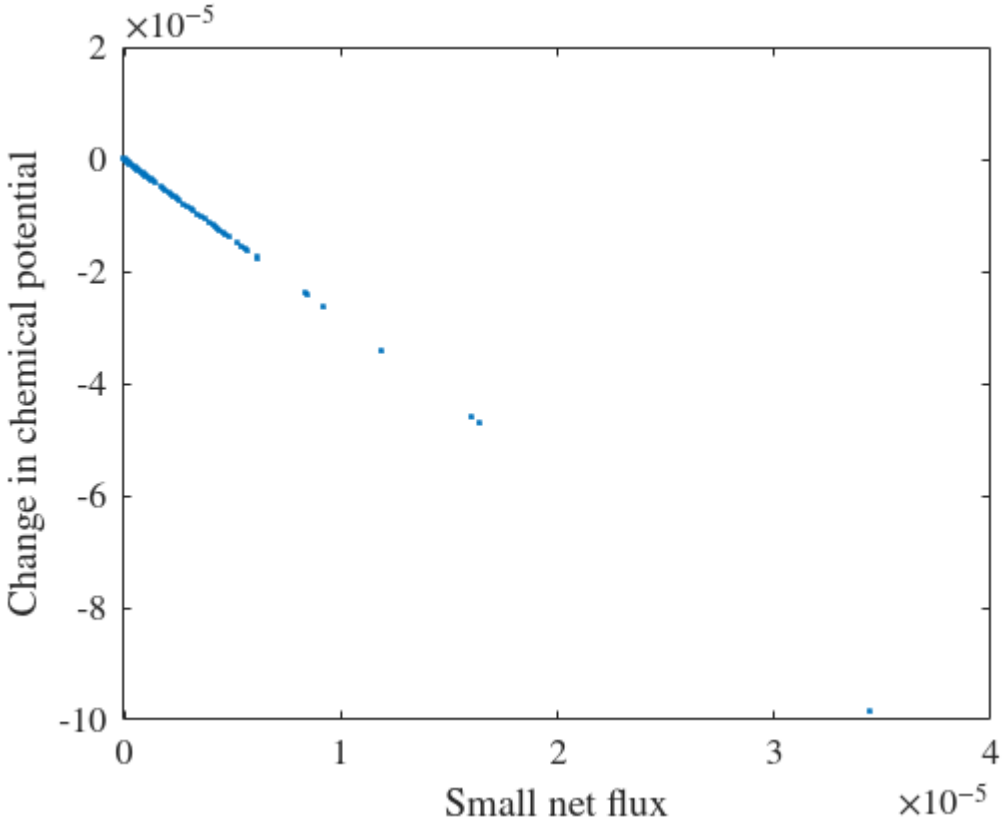

```
zBool = abs(z_vi)>0.1;
if any(l(zBool)~=0)
    figure
    histogram(l(zBool))
    title('distribution of internal lower bound when  $z_v$ substantial')
end
if any(u(zBool)~=inf)
    figure
    histogram(u(zBool))
    title('distribution of internal upper bound when $z_v$ substantial')
end
```



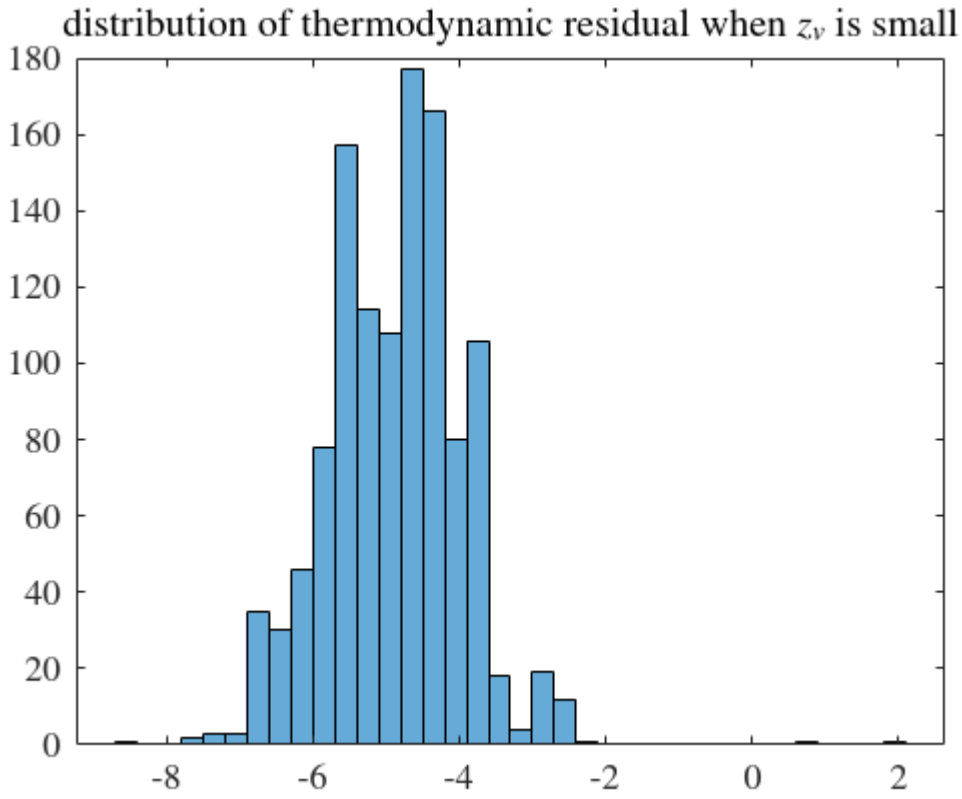

```
if any(zBool)
    figure
    histogram(log10(abs(res(zBool))))
    title('distribution of thermodynamic residual when $z_v$ is substantial')
end
```



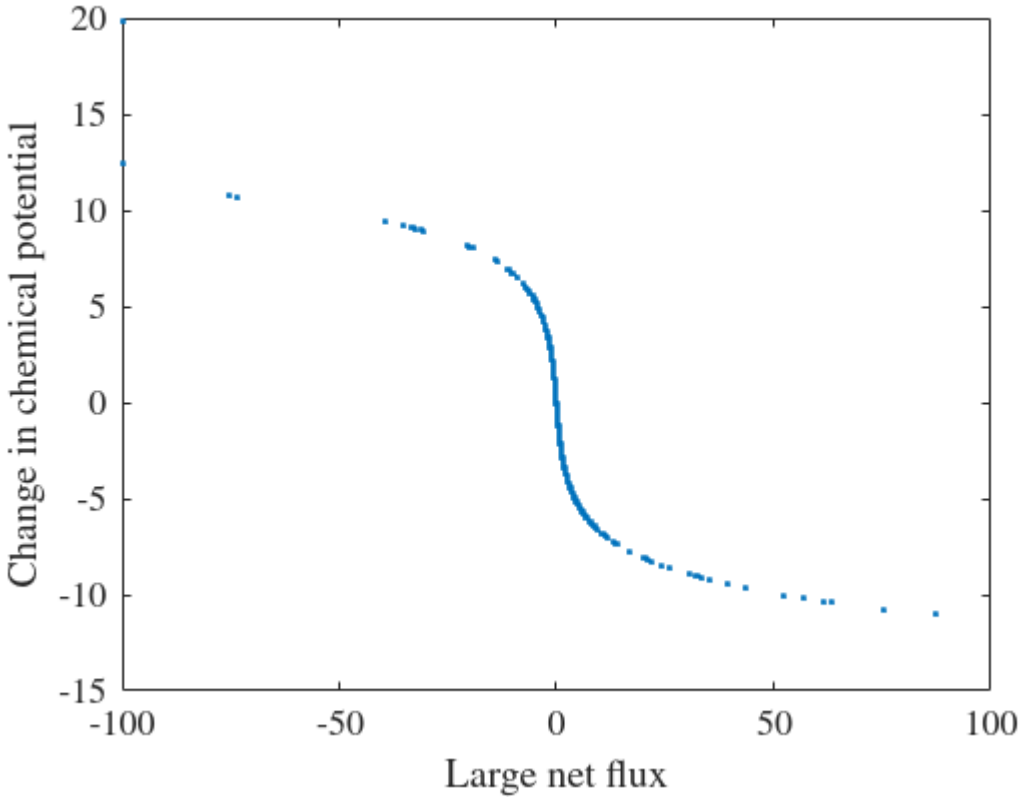

```
if any(zBool)
    figure
    plot(vi(zBool),logvrvf(zBool),'.')
    xlabel('Small net flux')
    ylabel('Change in chemical potential')
end
```



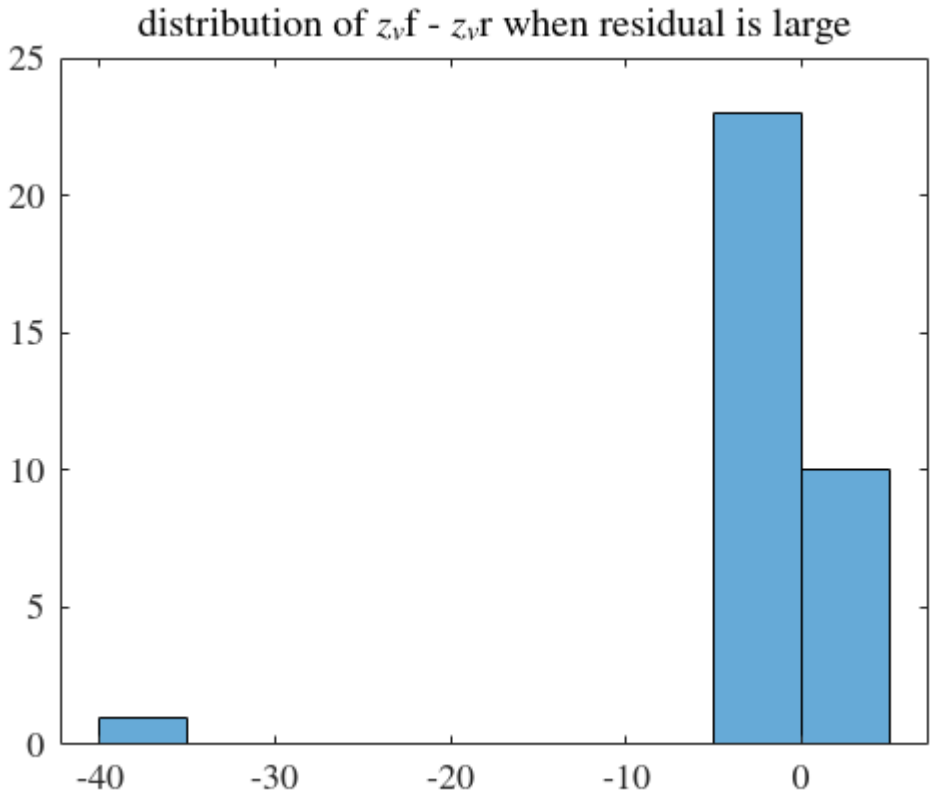

```
if any(~zBool)
    %thermo residual is large even when z_v is small
    figure
    histogram(log10(abs(res(~zBool))))
    title('distribution of thermodynamic residual when $z_v$ is small')
end
```



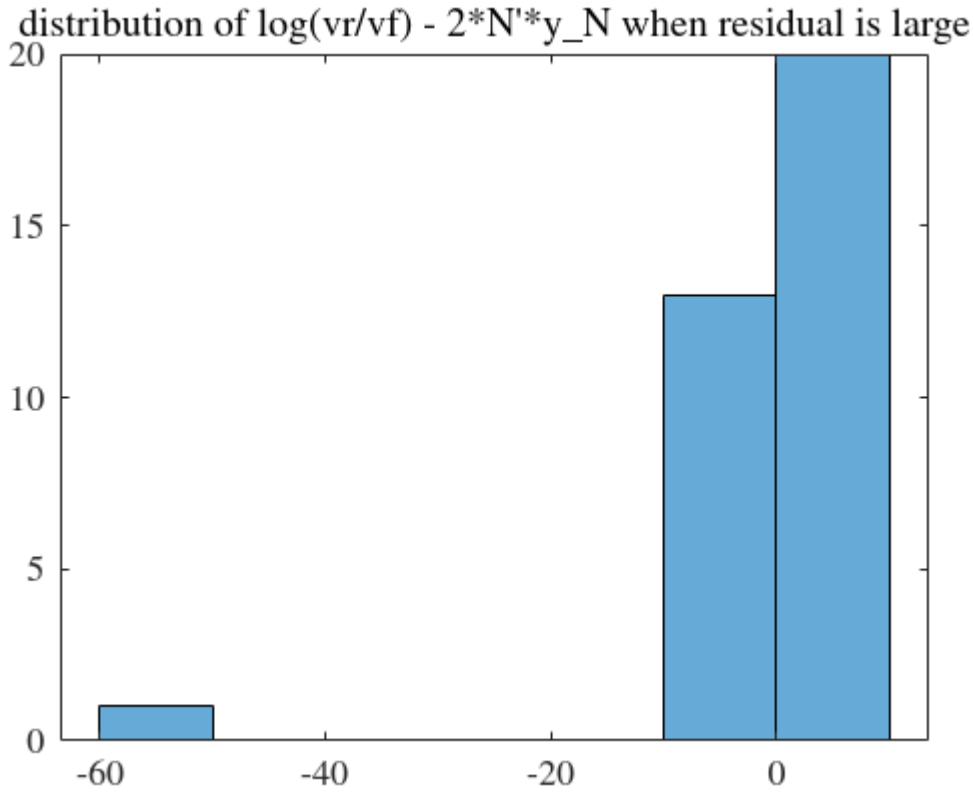

```
if any(~zBool)
    figure
    plot(vi(~zBool),logvrvf(~zBool),'.')
    xlabel('Large net flux')
    ylabel('Change in chemical potential')
end
```



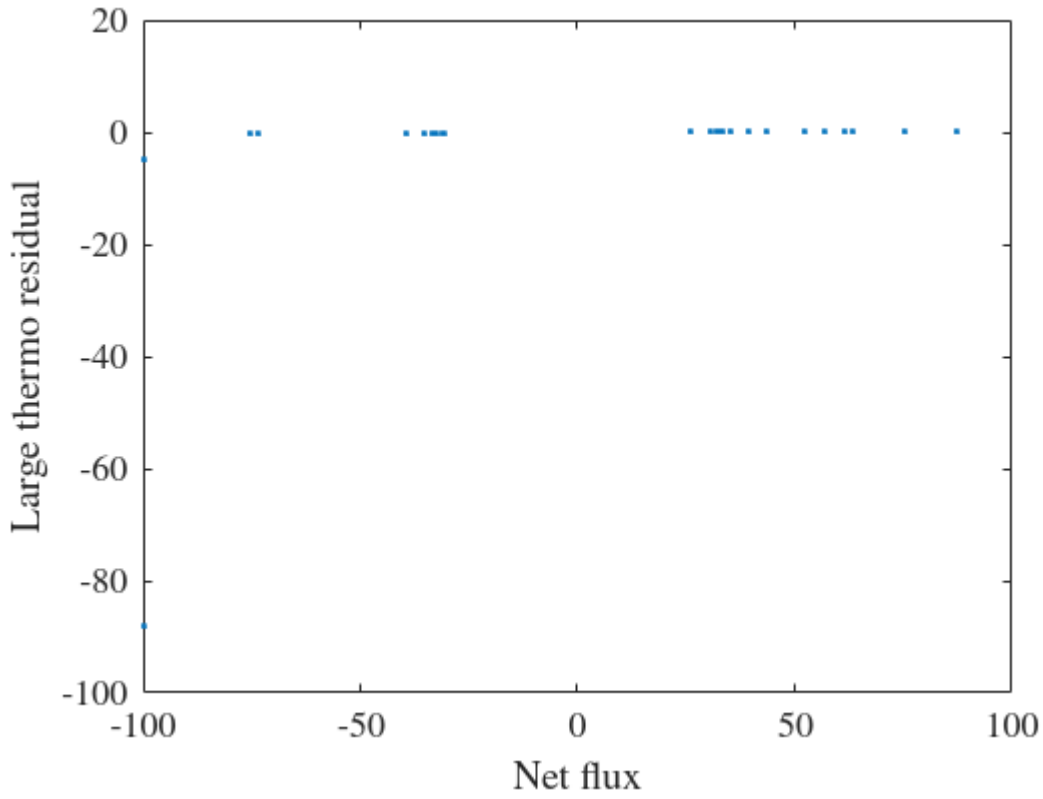

```
rBool = abs(res)>0.001;
fwdBool = vi>0;
if any(rBool)
    ab = z_vf - z_vr;
    figure
    histogram(ab(rBool))
    title('distribution of $z_v$f - $z_v$r when residual is large')
end
```



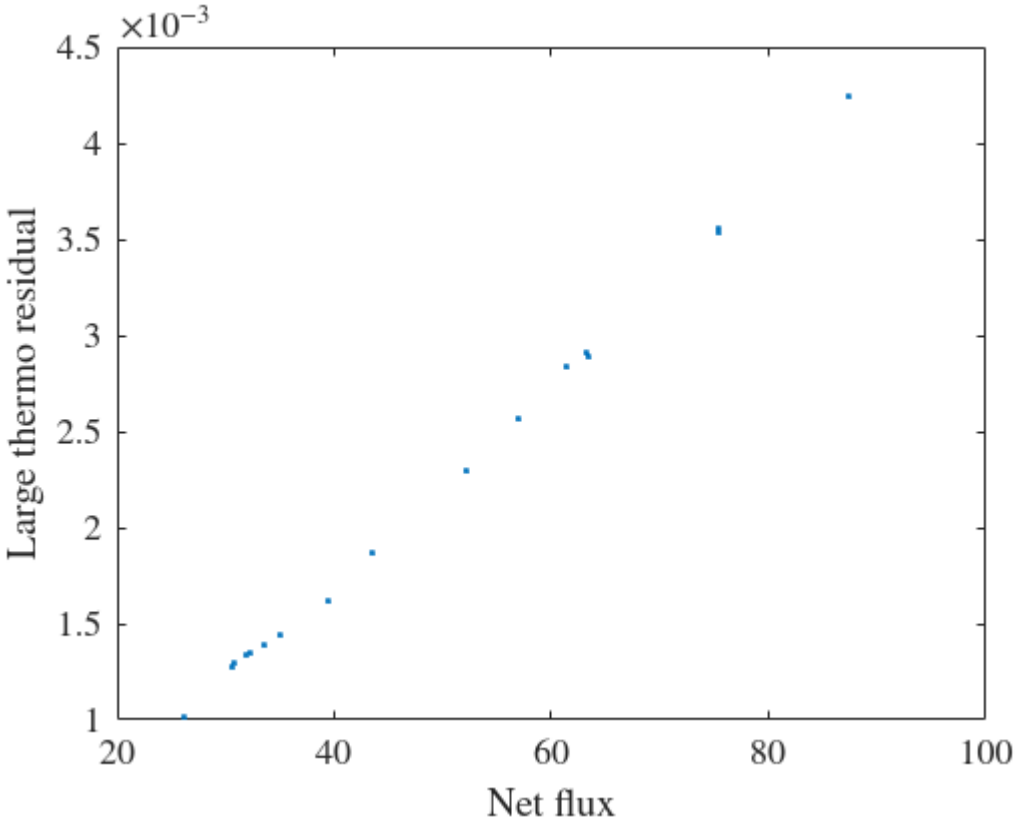

```
if any(rBool)
    %deviation from thermodynamic constraint occuring when net flux is
    %substantial
    figure
    res1 = g.*reallog(vr./vf) + cr - cf - 2*ci - 2*N'*y_N;
    histogram(res1(rBool))
    title('distribution of log(vr/vf) - 2*N''*y\_N when residual is large')
end
```




```
if any(rBool)
    figure
    plot(vi(rBool),res(rBool),'.')
    xlabel('Net flux')
    ylabel('Large thermo residual')
end
```

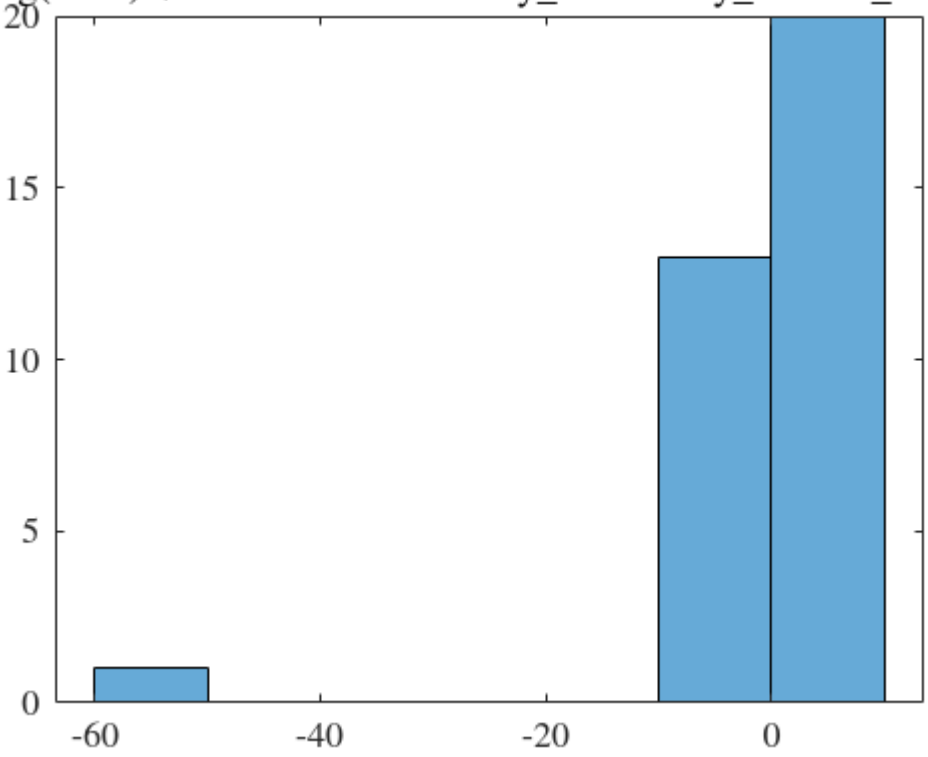



```
if any(rBool)
    figure
    plot(vi(rBool & fwdBool),res(rBool & fwdBool),'.')
    xlabel('Net flux')
    ylabel('Large thermo residual')
end
```

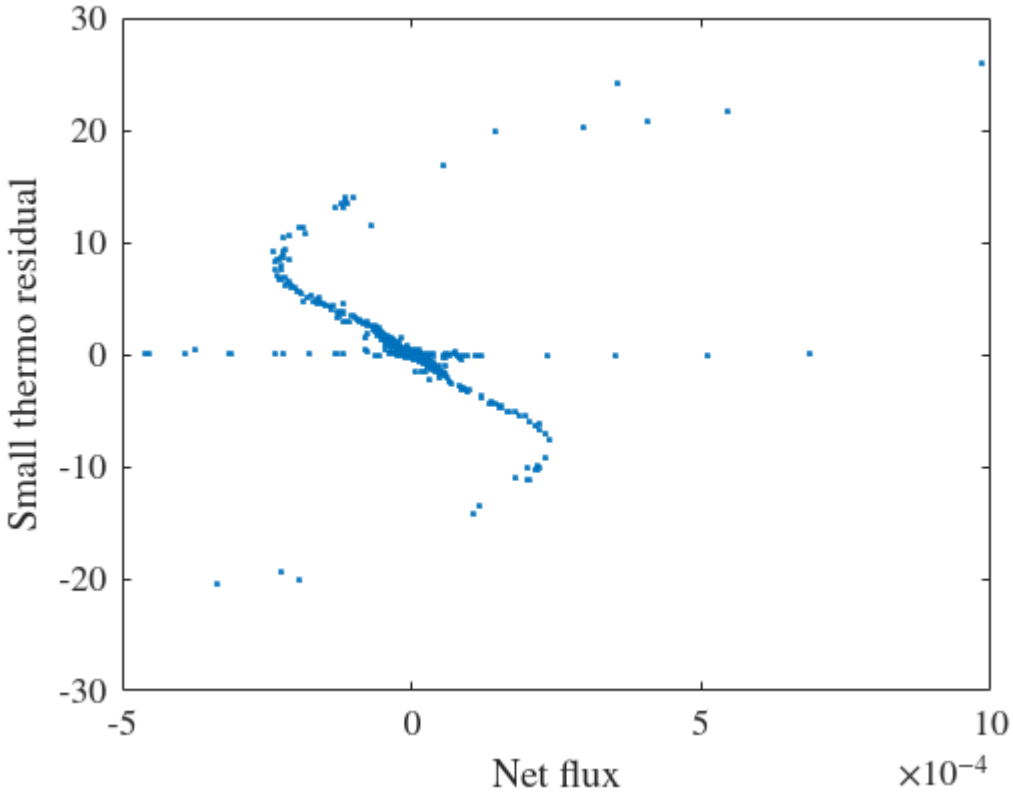



```
if any(rBool)
    figure
    if isfield(model,'C')
        res5 = g.*reallog(vr./vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C -
2*z_vi;
        histogram(res5(rBool))
        title('distribution of g.*log(vr/vf) + cr - cf - 2*ci - 2*N''*y\_N -
2*C''*y\_C - 2*z\_vi when residual is large')
    else
        res5 = g.*reallog(vr./vf) + cr - cf - 2*ci - 2*N'*y_N - 2*z_vi;
        histogram(res5(rBool))
        title('distribution of g.*log(vr/vf) + cr - cf - 2*ci - 2*N''*y\_N -
2*z\_vi when residual is large')
    end
end
```

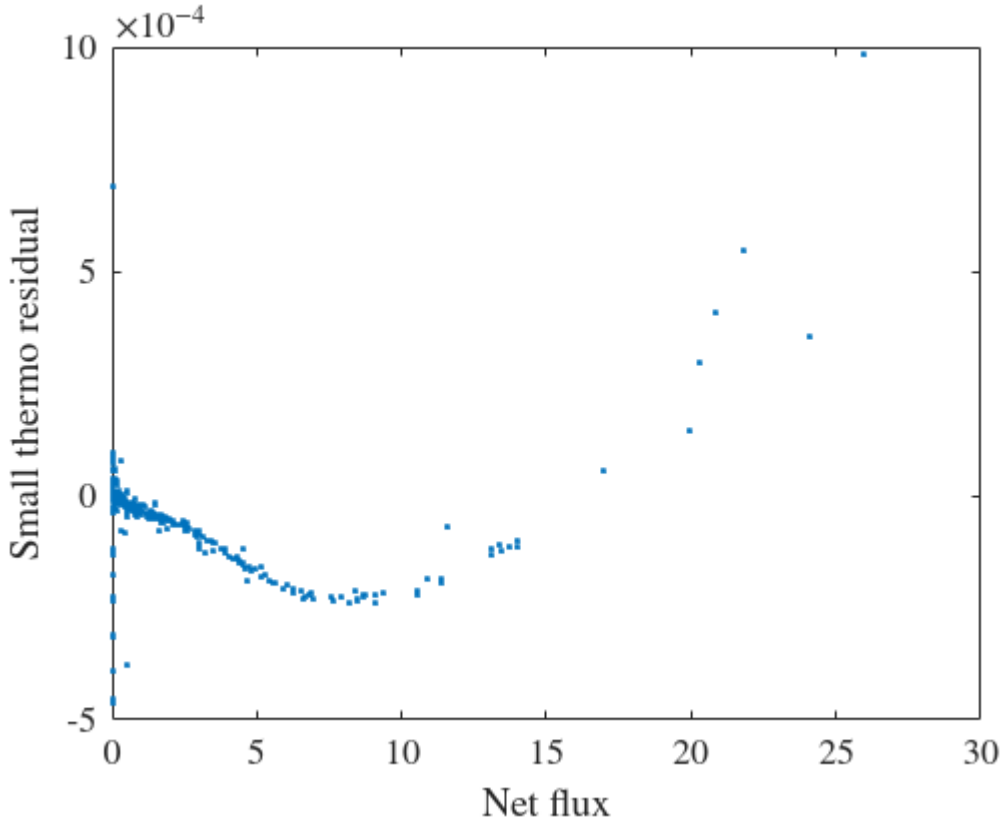
f g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*z_vi when




```
if any(~rBool)
    figure
    plot(res(~rBool),vi(~rBool),'.')
    xlabel('Net flux')
    ylabel('Small thermo residual')
end
```




```
if any(rBool)
    figure
    plot(vi(~rBool & fwdBool),res(~rBool & fwdBool),'.')
    xlabel('Net flux')
    ylabel('Small thermo residual')
end
```




```
if isequal(modelToUse,'single') && isfield(solution,'x')
    fprintf('%8.2g %s\n',norm(vf - exp(-(cf + cr - u0(1) - u0(2))/2)*x(1)),
'|| vf - exp(-(cr + cf - u0 - u0)/2)*x1 ||')
end
```

Quadratically constrained entropic flux balance analysis - all external reactions

Generate a random external flux vector that is a perturbation of the previously obtained external flux vector and then quadratically penalise any deviation from it.

```
model.h = (solution.v).*(rand(length(solution.v),1)+0.5)*2;
```

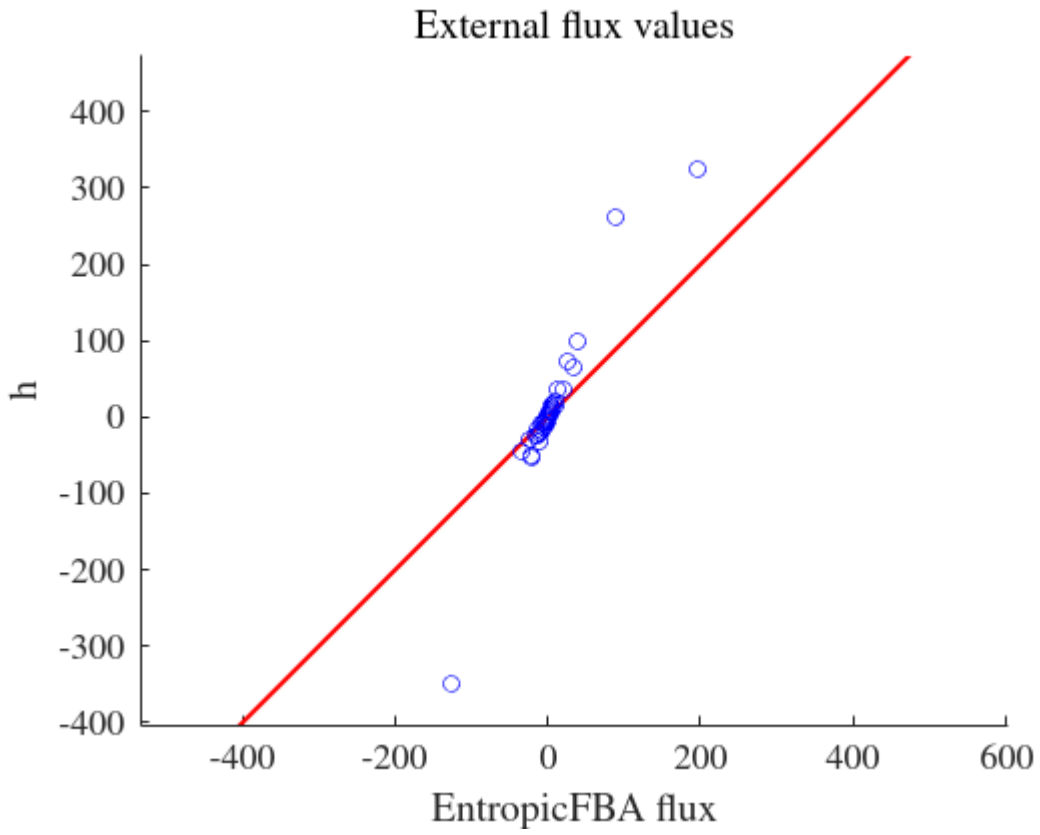
Do not optimise toward any internal net flux

```
model.h(model.SConsistentRxnBool)=NaN;
```

Compare the original external flux vector, with the external flux vector to peanlise deviation from

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(~model.SConsistentRxnBool),model.h(~model.SConsistentRxnBool)
,'o','Color','b')
```

```
xlabel('EntropicFBA flux')
ylabel('h')
title('External flux values')
axis equal
```



Set the penaltiy

```
HH = ones(length(solution.v),1);
HH(model.SConsistentRxnBool)=0;
model.H = spdiags(HH,0,length(solution.v),length(solution.v));
```

Run the optimisation

```
[solutionQEFBA,modelOut] = entropicFluxBalanceAnalysis(model,param);
```

```
Using directional internal net flux bounds only.
Using existing external net flux bounds without modification.

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Problem
  Name                   :
  Objective sense        : minimize
```

```
  Type                  : LO (linear optimization problem)
  Constraints           : 3170
  Affine conic cons.    : 0
  Disjunctive cons.     : 0
  Cones                 : 0
  Scalar variables      : 3830
  Matrix variables      : 0
  Integer variables     : 0

Optimizer started.
Presolve started.
Eliminator started.
Freed constraints in eliminator : 1219
Eliminator terminated.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 141
Eliminator terminated.
Eliminator - tries                  : 2                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 9                 dual deps.             : 0
Presolve terminated. Time: 0.02
GP based matrix reordering started.
GP based matrix reordering terminated.
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 514
Optimizer  - Cones                  : 0
Optimizer  - Scalar variables       : 1704              conic                  : 0
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.01
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 4991              after factor           : 1.23e+04
Factor     - dense dim.             : 5                 flops                  : 5.75e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   8.1e+03  1.2e+03  2.6e+04  0.00e+00   2.566112318e+04   -8.236241217e+01  1.3e+02  0.04
1   4.0e+03  6.3e-01  1.3e+04  8.50e-01   9.850126937e+03   2.790977534e+03   6.2e+01  0.05
2   1.8e+03  2.8e-01  5.6e+03  1.00e+00   5.514031979e+03   2.486949549e+03   2.8e+01  0.05
3   3.7e+02  5.8e-02  1.2e+03  1.04e+00   1.582358312e+03   9.674172343e+02   5.8e+00  0.06
4   1.4e+02  2.2e-02  4.5e+02  1.02e+00   7.750755310e+02   5.407839174e+02   2.2e+00  0.06
5   2.4e+01  3.8e-03  7.7e+01  1.01e+00   3.840553962e+02   3.438656965e+02   3.8e-01  0.06
6   7.1e+00  1.1e-03  2.3e+01  1.01e+00   3.179179905e+02   3.061918973e+02   1.1e-01  0.06
7   2.5e+00  3.9e-04  7.8e+00  1.01e+00   2.995918221e+02   2.955633008e+02   3.8e-02  0.07
8   2.1e-01  3.3e-05  6.7e-01  1.00e+00   2.907815335e+02   2.904374570e+02   3.3e-03  0.07
9   3.1e-02  4.8e-06  9.8e-02  1.00e+00   2.900770246e+02   2.900267589e+02   4.8e-04  0.07
10  9.2e-03  1.4e-06  2.9e-02  9.99e-01   2.899745013e+02   2.899594753e+02   1.4e-04  0.07
11  1.3e-03  2.1e-07  4.3e-03  1.00e+00   2.899369219e+02   2.899347208e+02   2.1e-05  0.08
12  2.3e-05  3.7e-09  7.4e-05  1.00e+00   2.899307232e+02   2.899306850e+02   3.6e-07  0.08
13  5.3e-08  8.3e-12  1.7e-07  1.00e+00   2.899306170e+02   2.899306169e+02   8.2e-10  0.08
14  1.1e-09  2.2e-15  2.5e-10  1.00e+00   2.899306168e+02   2.899306168e+02   8.4e-14  0.08
Basis identification started.
Primal basis identification phase started.
Primal basis identification phase terminated. Time: 0.00
Dual basis identification phase started.
Dual basis identification phase terminated. Time: 0.00
Basis identification terminated. Time: 0.01
Optimizer terminated. Time: 0.11


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
```

```
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061677e+02    nrm: 3e+02    Viol.  con: 7e-10    var: 3e-11
  Dual.    obj: 2.8993061677e+02    nrm: 5e+00    Viol.  con: 0e+00    var: 1e-15

Basic solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061677e+02    nrm: 3e+02    Viol.  con: 1e-12    var: 6e-14
  Dual.    obj: 2.8993061677e+02    nrm: 7e+00    Viol.  con: 1e-14    var: 1e-10
Optimizer summary
  Optimizer                 -                        time: 0.11
    Interior-point          - iterations : 14        time: 0.10
      Basis identification  -                        time: 0.01
        Primal              - iterations : 37        time: 0.00
        Dual                - iterations : 95        time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00

solveCobraEP: LP part of EPproblem is feasible according to solveCobraLP with mosek.

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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : CONIC (conic optimization problem)
  Constraints            : 3170
  Affine conic cons.     : 3625 (10875 rows)
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 7457
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 177
Eliminator terminated.
Eliminator started.
Freed constraints in eliminator : 0
Eliminator terminated.
Eliminator - tries                  : 2                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 25                dual deps.             : 0
Presolve terminated. Time: 0.04
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 2001
```
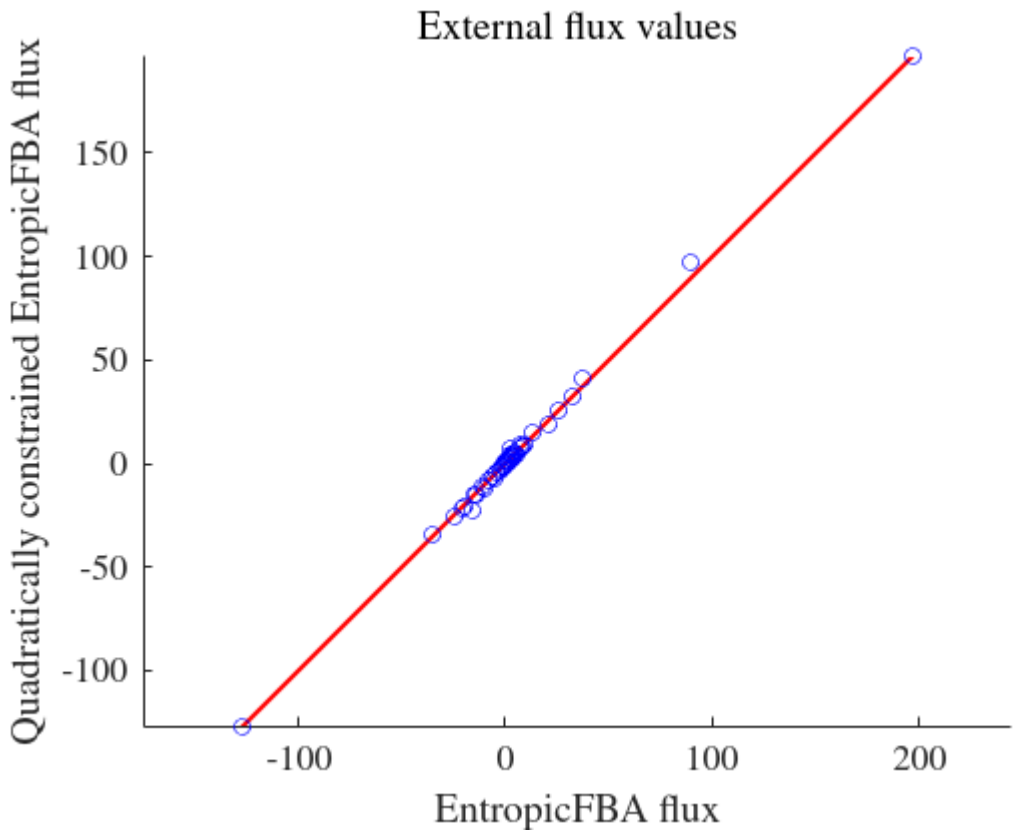

```
Optimizer  - Cones                  : 3625
Optimizer  - Scalar variables       : 11715             conic                  : 10875
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.02
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 1.21e+04          after factor           : 2.08e+04
Factor     - dense dim.             : 0                 flops                  : 7.99e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   3.5e+02  1.2e+00  1.1e+04  0.00e+00   6.142759534e+03   -4.414972768e+03  1.0e+00  0.07
1   2.1e+02  7.1e-01  8.1e+03  -9.69e-01  1.293676978e+04   2.486468134e+03   6.1e-01  0.10
2   8.4e+01  2.8e-01  4.9e+03  -9.48e-01  3.821773325e+04   2.819119065e+04   2.4e-01  0.11
3   3.5e+01  1.2e-01  2.8e+03  -8.52e-01  7.716914143e+04   6.825818530e+04   9.9e-02  0.12
4   2.4e+01  8.1e-02  2.0e+03  -5.23e-01  7.314062084e+04   6.533922498e+04   6.9e-02  0.12
5   1.8e+01  6.0e-02  1.4e+03  -2.41e-01  6.246633604e+04   5.578403824e+04   5.1e-02  0.13
6   1.4e+01  4.6e-02  1.0e+03  -8.27e-03  5.393114255e+04   4.825307503e+04   3.9e-02  0.14
7   5.7e+00  1.9e-02  3.4e+02  1.81e-01   3.383569036e+04   3.081079831e+04   1.6e-02  0.15
8   2.3e+00  7.8e-03  9.6e+01  6.23e-01   2.508943839e+04   2.371772103e+04   6.7e-03  0.16
9   1.3e+00  4.5e-03  4.4e+01  8.51e-01   2.236402705e+04   2.154830688e+04   3.9e-03  0.17
10  4.7e-01  1.6e-03  9.5e+00  9.18e-01   1.966955885e+04   1.937963274e+04   1.3e-03  0.18
11  1.5e-01  4.9e-04  1.7e+00  9.76e-01   1.861852162e+04   1.852707961e+04   4.2e-04  0.19
12  2.4e-02  8.0e-05  1.2e-01  9.94e-01   1.822719660e+04   1.821223790e+04   6.8e-05  0.20
13  5.6e-03  1.9e-05  1.3e-02  1.00e+00   1.817800220e+04   1.817447205e+04   1.6e-05  0.21
14  3.8e-03  1.3e-05  7.2e-03  9.92e-01   1.817193446e+04   1.816961635e+04   1.1e-05  0.22
15  4.5e-04  1.5e-06  3.0e-04  1.00e+00   1.816384080e+04   1.816356651e+04   1.3e-06  0.23
16  6.8e-05  2.3e-07  1.7e-05  1.00e+00   1.816291739e+04   1.816287632e+04   2.0e-07  0.25
17  3.9e-05  1.3e-07  7.5e-06  1.00e+00   1.816284866e+04   1.816282527e+04   1.1e-07  0.26
18  3.8e-05  1.3e-07  7.4e-06  1.00e+00   1.816284837e+04   1.816282506e+04   1.1e-07  0.27
19  9.6e-06  3.2e-08  9.7e-07  1.00e+00   1.816277947e+04   1.816277366e+04   2.8e-08  0.29
20  9.6e-06  3.2e-08  9.7e-07  1.00e+00   1.816277946e+04   1.816277366e+04   2.8e-08  0.30
21  9.5e-06  3.2e-08  9.7e-07  1.00e+00   1.816277943e+04   1.816277364e+04   2.8e-08  0.31
22  9.5e-06  3.2e-08  9.7e-07  1.00e+00   1.816277943e+04   1.816277363e+04   2.8e-08  0.32
23  9.5e-06  5.8e-08  9.6e-07  1.00e+00   1.816277929e+04   1.816277353e+04   2.8e-08  0.33
24  9.3e-06  1.5e-07  9.3e-07  1.00e+00   1.816277877e+04   1.816277312e+04   2.8e-08  0.34
25  9.3e-06  1.6e-07  9.3e-07  1.00e+00   1.816277874e+04   1.816277310e+04   2.8e-08  0.35
26  9.3e-06  1.7e-07  9.3e-07  1.00e+00   1.816277864e+04   1.816277302e+04   2.7e-08  0.36
27  9.3e-06  1.7e-07  9.3e-07  1.00e+00   1.816277864e+04   1.816277302e+04   2.7e-08  0.37
28  9.3e-06  1.8e-07  9.2e-07  1.00e+00   1.816277861e+04   1.816277300e+04   2.7e-08  0.38
29  9.2e-06  1.8e-07  9.2e-07  1.00e+00   1.816277857e+04   1.816277296e+04   2.7e-08  0.39
30  9.2e-06  1.8e-07  9.2e-07  1.00e+00   1.816277857e+04   1.816277296e+04   2.7e-08  0.39
31  9.2e-06  1.8e-07  9.2e-07  1.00e+00   1.816277856e+04   1.816277296e+04   2.7e-08  0.41
32  9.2e-06  1.9e-07  9.2e-07  1.00e+00   1.816277852e+04   1.816277293e+04   2.7e-08  0.42
33  2.3e-06  4.1e-08  1.1e-07  1.00e+00   1.816275925e+04   1.816275788e+04   6.7e-09  0.44
34  2.3e-06  4.4e-08  1.1e-07  1.00e+00   1.816275925e+04   1.816275788e+04   6.7e-09  0.45
35  2.3e-06  1.2e-07  1.1e-07  1.00e+00   1.816275923e+04   1.816275786e+04   6.7e-09  0.46
36  2.3e-06  1.2e-07  1.1e-07  1.00e+00   1.816275923e+04   1.816275786e+04   6.7e-09  0.47
37  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275923e+04   1.816275786e+04   6.7e-09  0.48
38  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275923e+04   1.816275786e+04   6.7e-09  0.49
39  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275923e+04   1.816275786e+04   6.7e-09  0.50
40  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.53
41  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.53
42  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.54
43  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.56
44  2.3e-06  1.3e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.56
45  2.3e-06  1.4e-07  1.1e-07  1.00e+00   1.816275922e+04   1.816275785e+04   6.7e-09  0.57
46  2.2e-06  1.4e-07  1.1e-07  1.00e+00   1.816275901e+04   1.816275769e+04   6.5e-09  0.59
47  2.2e-06  1.4e-07  1.1e-07  1.00e+00   1.816275901e+04   1.816275769e+04   6.5e-09  0.60
48  2.2e-06  1.6e-07  1.1e-07  1.00e+00   1.816275901e+04   1.816275768e+04   6.5e-09  0.61
49  2.2e-06  1.6e-07  1.1e-07  1.00e+00   1.816275901e+04   1.816275768e+04   6.5e-09  0.62
50  2.2e-06  1.6e-07  1.1e-07  1.00e+00   1.816275901e+04   1.816275768e+04   6.5e-09  0.63
51  2.2e-06  1.8e-07  1.1e-07  1.00e+00   1.816275900e+04   1.816275768e+04   6.5e-09  0.65
52  2.2e-06  1.5e-07  1.1e-07  1.00e+00   1.816275899e+04   1.816275767e+04   6.5e-09  0.67
53  2.2e-06  1.5e-07  1.1e-07  1.00e+00   1.816275899e+04   1.816275767e+04   6.5e-09  0.68
54  2.2e-06  1.5e-07  1.1e-07  1.00e+00   1.816275899e+04   1.816275767e+04   6.5e-09  0.70
Optimizer terminated. Time: 0.73
```

```
Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 1.8162758994e+04    nrm: 5e+02    Viol.  con: 4e-05    var: 1e-06    acc: 3e-08
  Dual.    obj: 1.8162757675e+04    nrm: 8e+03    Viol.  con: 9e-08    var: 3e-06    acc: 0e+00
Optimizer summary
  Optimizer                 -                        time: 0.73
    Interior-point          - iterations : 55        time: 0.72
      Basis identification  -                        time: 0.00
        Primal              - iterations : 0         time: 0.00
        Dual                - iterations : 0         time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00


 > [mosek] Dual   optimality condition in solveCobraEP satisfied.

Optimality conditions (biochemistry)
 4.4e-05 || N*(vf - vr) + B*ve - b ||_inf
     Inf || C*(vf - vr) + s_C - d ||_inf, s_C = slack variable
 8.8e-08 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + k_vf + z_vf ||_inf
 8.8e-08 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + k_vr + z_vr ||_inf
       1 || ce + B'*y_N  + z_ve ||_inf
 8.2e+03 || k_e_1 + z_e_1 ||_inf
 8.2e+03 || -g + k_e_vf + z_e_vf||_inf
 1.5e-07 || -g + k_e_vr + z_e_vr||_inf
 1.8e-06 || e_vf + vf*log(vf) ||_inf
   3e-06 || e_vr + vr*log(vr) ||_inf
 1.6e+02 || k_q_1 + z_q_1 ||_inf

Derived optimality conditions (biochemistry)
      17 || g.*log(vf) + g - k_vf ||_inf
   0.005 || g.*log(vr) + g - k_vr ||_inf
      17 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + g.*log(vf) + g + z_vf ||_inf
   0.005 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + g.*log(vr) + g + z_vr ||_inf

Thermo conditions
 2.6e+02 || g.*log(vr/vf) - 2*N'*y_N - 2*C'*y_C ||_inf
      52 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi ||_inf
      87 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi - z_vr + z_vf ||_inf
-1.5e+02 min(slack)
     Inf max(slack)
```

Compare the original external flux vector, with the quadratically constrained external flux vector. The values should be closer to the red line than above, but not exactly, because the quadratic penalty is trading off against entropy maximisation of internal reactions. Change H(j,j) to adjust this trade off.

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(~model.SConsistentRxnBool),solutionQEFBA.v(~model.SConsistent
RxnBool),'o','Color','b')
xlabel('EntropicFBA flux')
ylabel('Quadratically constrained EntropicFBA flux')
```

```
title('External flux values')
axis equal
```



Quadratically constrained entropic flux balance analysis - subset of external reactions

Generate a random given external flux vector that is a perturbation of the previously obtained external flux vector and then quadratically penalise any deviation from it.

```
model.h = (solution.v).*(rand(length(solution.v),1)+0.5)*2;
```

Do not optimise toward any internal net flux

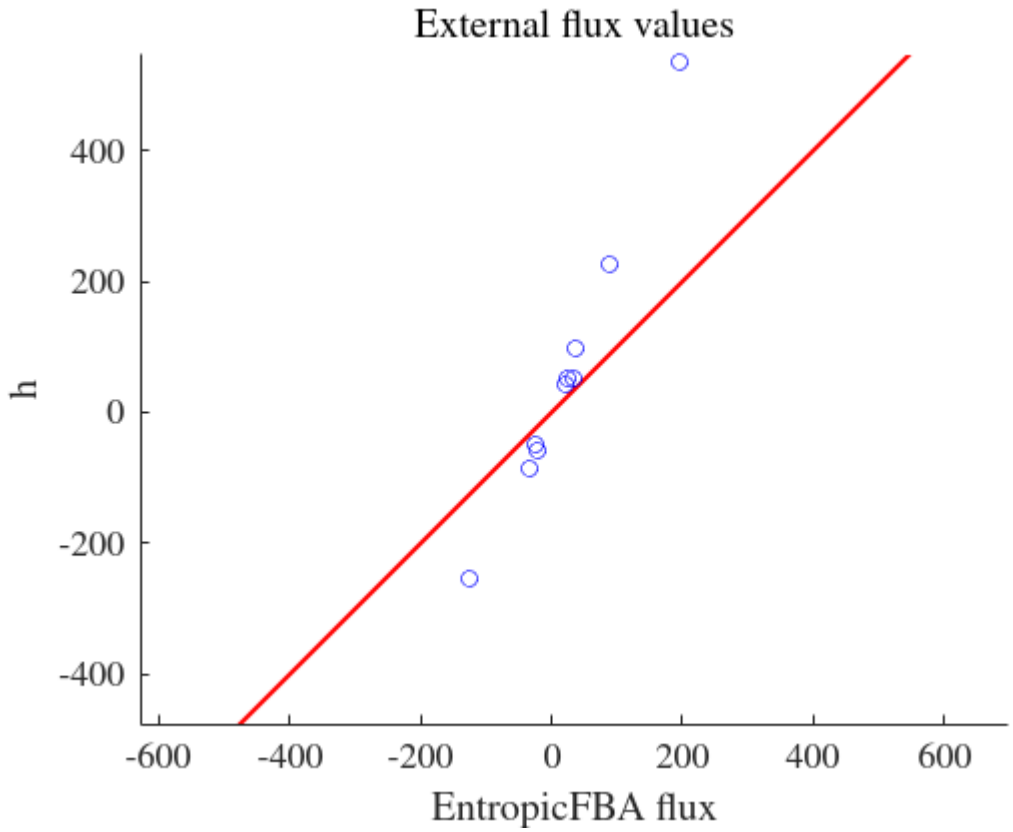
```
model.h(model.SConsistentRxnBool)=NaN;
```

Only optimise toward the top 10 magnitude given external net flux

```
[sortedh,ind]=sort(abs(model.h),'descend','MissingPlacement','last');
if length(ind)>10
    model.h(ind(11:end))=NaN;
end
```

Compare the original external flux vector, with the external flux vector to peanlise deviation from

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(isfinite(model.h)),model.h(isfinite(model.h)),'o','Color','b'
)
xlabel('EntropicFBA flux')
ylabel('h')
title('External flux values')
axis equal
```



Set the penaltiy

```
HH = ones(length(solution.v),1);
HH(model.SConsistentRxnBool)=0;
model.H = spdiags(HH,0,length(solution.v),length(solution.v));
```

Run the optimisation

```
[solutionQEFBA,modelOut] = entropicFluxBalanceAnalysis(model,param);
```

```
Using directional internal net flux bounds only.
Using existing external net flux bounds without modification.

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```

```
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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : LO (linear optimization problem)
  Constraints            : 2975
  Affine conic cons.     : 0
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 3635
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Eliminator started.
Freed constraints in eliminator : 1219
Eliminator terminated.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 141
Eliminator terminated.
Eliminator - tries                  : 2                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 9                 dual deps.             : 0
Presolve terminated. Time: 0.02
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 512
Optimizer  - Cones                  : 0
Optimizer  - Scalar variables       : 1700              conic                  : 0
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.01
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 5040              after factor           : 1.19e+04
Factor     - dense dim.             : 1                 flops                  : 5.13e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   8.0e+03  1.2e+03  2.7e+04  0.00e+00   2.536209125e+04   -1.137375866e+03  1.3e+02  0.04
1   4.3e+03  7.2e-01  1.4e+04  1.01e+00   1.109112427e+04   2.131423372e+03   6.8e+01  0.05
2   1.6e+03  2.7e-01  5.2e+03  1.30e+00   5.333642613e+03   2.475579900e+03   2.5e+01  0.05
3   3.7e+02  6.2e-02  1.2e+03  1.11e+00   1.677123434e+03   1.043181022e+03   5.9e+00  0.05
4   4.5e+01  7.6e-03  1.5e+02  1.04e+00   4.494526587e+02   3.734394760e+02   7.1e-01  0.05
5   2.3e+01  3.8e-03  7.5e+01  1.01e+00   3.721136544e+02   3.336327497e+02   3.6e-01  0.06
6   4.2e+00  7.1e-04  1.4e+01  1.01e+00   3.060528620e+02   2.990462288e+02   6.7e-02  0.06
7   1.3e+00  2.3e-04  4.4e+00  1.00e+00   2.951088773e+02   2.928706595e+02   2.1e-02  0.06
8   5.7e-01  9.6e-05  1.9e+00  1.00e+00   2.921571806e+02   2.912048430e+02   9.1e-03  0.06
9   9.0e-02  1.5e-05  3.0e-01  1.00e+00   2.902963878e+02   2.901452889e+02   1.4e-03  0.07
10  2.0e-02  3.4e-06  6.6e-02  9.99e-01   2.900126991e+02   2.899790785e+02   3.2e-04  0.07
11  6.9e-03  1.2e-06  2.3e-02  1.00e+00   2.899593316e+02   2.899477152e+02   1.1e-04  0.07
12  3.9e-04  6.5e-08  1.3e-03  1.00e+00   2.899323089e+02   2.899316648e+02   6.1e-06  0.07
13  1.5e-05  2.5e-09  4.9e-05  1.00e+00   2.899306835e+02   2.899306588e+02   2.4e-07  0.08
14  3.4e-07  3.7e-10  3.5e-07  1.00e+00   2.899306169e+02   2.899306167e+02   4.6e-10  0.08
Basis identification started.
Primal basis identification phase started.
Primal basis identification phase terminated. Time: 0.00
Dual basis identification phase started.
Dual basis identification phase terminated. Time: 0.00
Basis identification terminated. Time: 0.01
```

```
Optimizer terminated. Time: 0.10


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061688e+02    nrm: 5e+02    Viol.  con: 1e-06    var: 1e-07
  Dual.    obj: 2.8993061665e+02    nrm: 5e+00    Viol.  con: 0e+00    var: 2e-10

Basic solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8993061677e+02    nrm: 5e+02    Viol.  con: 8e-13    var: 3e-14
  Dual.    obj: 2.8993061672e+02    nrm: 6e+00    Viol.  con: 6e-11    var: 4e-07
Optimizer summary
  Optimizer                 -                        time: 0.10
    Interior-point          - iterations : 14        time: 0.09
      Basis identification  -                        time: 0.01
        Primal              - iterations : 37        time: 0.00
        Dual                - iterations : 95        time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00

solveCobraEP: LP part of EPproblem is feasible according to solveCobraLP with mosek.

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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : CONIC (conic optimization problem)
  Constraints            : 2975
  Affine conic cons.     : 3430 (10290 rows)
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 7067
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 7
Eliminator terminated.
Eliminator - tries                  : 1                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 25                dual deps.             : 0
Presolve terminated. Time: 0.03
Optimizer  - threads                : 18
```

```
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 1960
Optimizer  - Cones                  : 3430
Optimizer  - Scalar variables       : 11284             conic                  : 10290
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.02
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 1.19e+04          after factor           : 2.06e+04
Factor     - dense dim.             : 0                 flops                  : 7.95e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   1.0e+04  1.2e+00  1.0e+04  0.00e+00   5.947759534e+03   -4.414972768e+03  1.0e+00  0.06
1   8.1e+03  9.5e-01  9.3e+03  -9.99e-01  8.037729882e+03   -2.321978061e+03  8.1e-01  0.08
2   7.3e+03  8.6e-01  8.8e+03  -9.96e-01  9.251313347e+03   -1.094838395e+03  7.3e-01  0.09
3   5.4e+03  6.3e-01  7.5e+03  -9.85e-01  1.411292582e+04   3.857496674e+03   5.4e-01  0.10
4   1.8e+03  2.1e-01  4.1e+03  -9.66e-01  5.104523733e+04   4.123658305e+04   1.8e-01  0.11
5   7.7e+02  9.1e-02  2.5e+03  -8.61e-01  9.839593865e+04   8.950761846e+04   7.7e-02  0.12
6   4.2e+02  4.9e-02  1.5e+03  -6.00e-01  1.025664394e+05   9.529333740e+04   4.2e-02  0.13
7   3.0e+02  3.5e-02  1.0e+03  -1.72e-01  8.505723708e+04   7.901253075e+04   3.0e-02  0.14
8   2.1e+02  2.5e-02  6.5e+02  8.13e-02   6.954940345e+04   6.468064026e+04   2.1e-02  0.14
9   1.2e+02  1.5e-02  3.3e+02  2.99e-01   5.111476715e+04   4.781160692e+04   1.2e-02  0.15
10  9.8e+01  1.2e-02  2.4e+02  5.63e-01   4.528535708e+04   4.256295185e+04   9.8e-03  0.16
11  3.6e+01  4.3e-03  5.9e+01  6.52e-01   2.920508427e+04   2.807972182e+04   3.6e-03  0.17
12  9.4e+00  1.1e-03  8.3e+00  8.79e-01   2.082004927e+04   2.051703883e+04   9.4e-04  0.18
13  4.4e+00  5.2e-04  2.8e+00  9.76e-01   1.924949650e+04   1.910574210e+04   4.4e-04  0.19
14  1.0e+00  1.2e-04  3.2e-01  9.90e-01   1.814985735e+04   1.811605395e+04   1.0e-04  0.20
15  2.1e-01  2.5e-05  3.0e-02  9.99e-01   1.792314815e+04   1.791624423e+04   2.1e-05  0.21
16  5.3e-02  6.2e-06  3.8e-03  1.00e+00   1.787841040e+04   1.787669859e+04   5.3e-06  0.22
17  7.0e-03  8.3e-07  1.9e-04  1.00e+00   1.786577541e+04   1.786554655e+04   7.0e-07  0.23
18  6.9e-03  8.1e-07  1.8e-04  1.00e+00   1.786575033e+04   1.786552448e+04   6.9e-07  0.24
19  6.0e-03  7.0e-07  1.5e-04  1.00e+00   1.786548486e+04   1.786529081e+04   6.0e-07  0.25
20  5.9e-03  6.9e-07  1.4e-04  1.00e+00   1.786545512e+04   1.786526463e+04   5.9e-07  0.26
21  5.8e-03  6.8e-07  1.4e-04  1.00e+00   1.786544992e+04   1.786526005e+04   5.8e-07  0.27
22  3.3e-03  3.9e-07  6.0e-05  1.00e+00   1.786475410e+04   1.786464697e+04   3.3e-07  0.28
23  3.2e-03  3.8e-07  5.8e-05  1.00e+00   1.786473323e+04   1.786462859e+04   3.2e-07  0.29
24  3.2e-03  3.8e-07  5.7e-05  1.00e+00   1.786472788e+04   1.786462387e+04   3.2e-07  0.30
25  3.2e-03  3.8e-07  5.7e-05  1.00e+00   1.786472784e+04   1.786462384e+04   3.2e-07  0.31
26  3.2e-03  3.8e-07  5.7e-05  1.00e+00   1.786472783e+04   1.786462383e+04   3.2e-07  0.32
27  2.9e-03  3.4e-07  4.9e-05  1.00e+00   1.786464169e+04   1.786454793e+04   2.9e-07  0.33
28  2.9e-03  3.4e-07  4.9e-05  1.00e+00   1.786463783e+04   1.786454452e+04   2.9e-07  0.34
29  2.9e-03  3.4e-07  4.9e-05  1.00e+00   1.786463779e+04   1.786454449e+04   2.9e-07  0.35
30  2.8e-03  3.3e-07  4.8e-05  1.00e+00   1.786462591e+04   1.786453402e+04   2.8e-07  0.36
31  2.8e-03  3.3e-07  4.8e-05  1.00e+00   1.786462415e+04   1.786453247e+04   2.8e-07  0.36
32  2.8e-03  3.3e-07  4.7e-05  1.00e+00   1.786462172e+04   1.786453033e+04   2.8e-07  0.37
33  2.8e-03  3.3e-07  4.7e-05  1.00e+00   1.786462156e+04   1.786453019e+04   2.8e-07  0.39
34  2.8e-03  3.3e-07  4.7e-05  1.00e+00   1.786462155e+04   1.786453017e+04   2.8e-07  0.40
35  2.8e-03  3.3e-07  4.7e-05  1.00e+00   1.786462154e+04   1.786453017e+04   2.8e-07  0.41
36  6.9e-04  8.1e-08  6.0e-06  1.00e+00   1.786404195e+04   1.786401940e+04   6.9e-08  0.43
37  6.9e-04  8.1e-08  6.0e-06  1.00e+00   1.786404189e+04   1.786401935e+04   6.9e-08  0.44
38  6.9e-04  8.1e-08  6.0e-06  1.00e+00   1.786404189e+04   1.786401935e+04   6.9e-08  0.45
39  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404177e+04   1.786401925e+04   6.9e-08  0.46
40  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404174e+04   1.786401922e+04   6.9e-08  0.47
41  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404168e+04   1.786401916e+04   6.9e-08  0.47
42  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404146e+04   1.786401897e+04   6.9e-08  0.48
43  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404146e+04   1.786401897e+04   6.9e-08  0.49
44  6.9e-04  8.1e-08  5.9e-06  1.00e+00   1.786404144e+04   1.786401895e+04   6.9e-08  0.50
45  6.3e-04  7.4e-08  5.1e-06  1.00e+00   1.786402303e+04   1.786400265e+04   6.3e-08  0.52
46  6.3e-04  7.4e-08  5.1e-06  1.00e+00   1.786402298e+04   1.786400261e+04   6.3e-08  0.53
47  6.3e-04  7.3e-08  5.1e-06  1.00e+00   1.786402288e+04   1.786400252e+04   6.3e-08  0.54
48  6.3e-04  7.3e-08  5.1e-06  1.00e+00   1.786402288e+04   1.786400251e+04   6.3e-08  0.54
49  6.1e-04  7.1e-08  4.9e-06  1.00e+00   1.786401709e+04   1.786399739e+04   6.1e-08  0.56
50  6.1e-04  7.1e-08  4.9e-06  1.00e+00   1.786401706e+04   1.786399736e+04   6.1e-08  0.57
51  6.1e-04  7.1e-08  4.9e-06  1.00e+00   1.786401704e+04   1.786399735e+04   6.1e-08  0.58
52  6.1e-04  7.1e-08  4.9e-06  1.00e+00   1.786401697e+04   1.786399728e+04   6.1e-08  0.59
53  6.0e-04  7.1e-08  4.8e-06  1.00e+00   1.786401648e+04   1.786399685e+04   6.0e-08  0.60
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54	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401642e+04	1.786399680e+04	6.0e-08	0.61
55	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401641e+04	1.786399678e+04	6.0e-08	0.62
56	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401635e+04	1.786399673e+04	6.0e-08	0.63
57	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401627e+04	1.786399667e+04	6.0e-08	0.64
58	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401624e+04	1.786399664e+04	6.0e-08	0.65
59	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401613e+04	1.786399654e+04	6.0e-08	0.66
60	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401596e+04	1.786399639e+04	6.0e-08	0.67
61	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401596e+04	1.786399639e+04	6.0e-08	0.67
62	6.0e-04	7.1e-08	4.8e-06	1.00e+00	1.786401591e+04	1.786399635e+04	6.0e-08	0.68
63	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401513e+04	1.786399565e+04	6.0e-08	0.70
64	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401502e+04	1.786399556e+04	6.0e-08	0.71
65	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401502e+04	1.786399556e+04	6.0e-08	0.72
66	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401498e+04	1.786399552e+04	6.0e-08	0.73
67	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401498e+04	1.786399552e+04	6.0e-08	0.73
68	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401495e+04	1.786399550e+04	6.0e-08	0.74
69	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401495e+04	1.786399549e+04	6.0e-08	0.75
70	6.0e-04	7.0e-08	4.8e-06	1.00e+00	1.786401473e+04	1.786399530e+04	6.0e-08	0.77
71	5.9e-04	7.0e-08	4.7e-06	1.00e+00	1.786401388e+04	1.786399455e+04	5.9e-08	0.79
72	5.9e-04	6.9e-08	4.7e-06	1.00e+00	1.786401317e+04	1.786399392e+04	5.9e-08	0.81
73	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401117e+04	1.786399215e+04	5.9e-08	0.83
74	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401117e+04	1.786399215e+04	5.9e-08	0.84
75	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401115e+04	1.786399214e+04	5.9e-08	0.85
76	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401114e+04	1.786399212e+04	5.9e-08	0.86
77	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401114e+04	1.786399212e+04	5.9e-08	0.87
78	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401111e+04	1.786399210e+04	5.9e-08	0.88
79	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401109e+04	1.786399207e+04	5.9e-08	0.89
80	5.9e-04	6.9e-08	4.6e-06	1.00e+00	1.786401107e+04	1.786399206e+04	5.9e-08	0.89
81	5.8e-04	6.8e-08	4.6e-06	1.00e+00	1.786401041e+04	1.786399148e+04	5.8e-08	0.91
82	5.8e-04	6.8e-08	4.6e-06	1.00e+00	1.786401039e+04	1.786399146e+04	5.8e-08	0.93
83	5.8e-04	6.8e-08	4.6e-06	1.00e+00	1.786401037e+04	1.786399144e+04	5.8e-08	0.95
84	5.8e-04	6.8e-08	4.6e-06	1.00e+00	1.786401037e+04	1.786399144e+04	5.8e-08	0.96
85	5.8e-04	6.8e-08	4.6e-06	1.00e+00	1.786401036e+04	1.786399143e+04	5.8e-08	0.96
86	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400875e+04	1.786399001e+04	5.8e-08	0.98
87	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400874e+04	1.786399000e+04	5.8e-08	0.99
88	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400874e+04	1.786398999e+04	5.8e-08	1.00
89	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400874e+04	1.786398999e+04	5.8e-08	1.01
90	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400869e+04	1.786398996e+04	5.8e-08	1.03
91	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400869e+04	1.786398995e+04	5.8e-08	1.04
92	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400855e+04	1.786398983e+04	5.8e-08	1.06
93	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400854e+04	1.786398982e+04	5.8e-08	1.07
94	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400853e+04	1.786398981e+04	5.8e-08	1.08
95	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400852e+04	1.786398980e+04	5.8e-08	1.09
96	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400851e+04	1.786398980e+04	5.8e-08	1.10
97	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400849e+04	1.786398978e+04	5.8e-08	1.11
98	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400849e+04	1.786398978e+04	5.8e-08	1.14
99	5.8e-04	6.8e-08	4.5e-06	1.00e+00	1.786400849e+04	1.786398978e+04	5.8e-08	1.15
100	5.8e-04	6.7e-08	4.5e-06	1.00e+00	1.786400830e+04	1.786398960e+04	5.8e-08	1.15
101	5.8e-04	6.7e-08	4.5e-06	1.00e+00	1.786400824e+04	1.786398955e+04	5.8e-08	1.16
102	5.7e-04	6.7e-08	4.5e-06	1.00e+00	1.786400790e+04	1.786398925e+04	5.7e-08	1.17
103	5.7e-04	6.7e-08	4.5e-06	1.00e+00	1.786400770e+04	1.786398908e+04	5.7e-08	1.18
104	5.7e-04	6.7e-08	4.5e-06	1.00e+00	1.786400759e+04	1.786398898e+04	5.7e-08	1.19
105	5.7e-04	6.7e-08	4.5e-06	1.00e+00	1.786400759e+04	1.786398897e+04	5.7e-08	1.20
106	5.2e-04	6.1e-08	3.8e-06	1.00e+00	1.786399159e+04	1.786397481e+04	5.2e-08	1.23
107	5.2e-04	6.1e-08	3.8e-06	1.00e+00	1.786399156e+04	1.786397479e+04	5.2e-08	1.24
108	5.2e-04	6.1e-08	3.8e-06	1.00e+00	1.786399154e+04	1.786397477e+04	5.2e-08	1.24
109	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399031e+04	1.786397367e+04	5.1e-08	1.26
110	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399014e+04	1.786397353e+04	5.1e-08	1.28
111	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399012e+04	1.786397351e+04	5.1e-08	1.30
112	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399005e+04	1.786397344e+04	5.1e-08	1.31
113	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399004e+04	1.786397344e+04	5.1e-08	1.32
114	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399003e+04	1.786397343e+04	5.1e-08	1.33
115	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399003e+04	1.786397343e+04	5.1e-08	1.34
116	5.1e-04	6.0e-08	3.8e-06	1.00e+00	1.786399000e+04	1.786397340e+04	5.1e-08	1.36
117	3.0e-04	3.6e-08	1.7e-06	1.00e+00	1.786393151e+04	1.786392160e+04	3.0e-08	1.37

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118 3.0e-04  3.5e-08  1.7e-06  1.00e+00   1.786393094e+04   1.786392111e+04   3.0e-08  1.39
119 3.0e-04  3.5e-08  1.7e-06  1.00e+00   1.786393094e+04   1.786392110e+04   3.0e-08  1.40
120 3.0e-04  3.5e-08  1.7e-06  1.00e+00   1.786393091e+04   1.786392108e+04   3.0e-08  1.41
121 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392763e+04   1.786391817e+04   2.9e-08  1.43
122 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392762e+04   1.786391816e+04   2.9e-08  1.45
123 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392762e+04   1.786391817e+04   2.9e-08  1.46
124 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392762e+04   1.786391817e+04   2.9e-08  1.46
125 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392753e+04   1.786391808e+04   2.9e-08  1.48
126 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392752e+04   1.786391807e+04   2.9e-08  1.50
127 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392752e+04   1.786391807e+04   2.9e-08  1.51
128 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392748e+04   1.786391804e+04   2.9e-08  1.53
129 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392748e+04   1.786391804e+04   2.9e-08  1.54
130 2.9e-04  3.4e-08  1.6e-06  1.00e+00   1.786392748e+04   1.786391804e+04   2.9e-08  1.55
Optimizer terminated. Time: 1.59


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 1.7863927476e+04    nrm: 5e+02    Viol.  con: 5e-04    var: 1e-05    acc: 1e-07
  Dual.    obj: 1.7863918037e+04    nrm: 8e+03    Viol.  con: 6e-07    var: 1e-06    acc: 0e+00
Optimizer summary
  Optimizer                 -                        time: 1.59
    Interior-point          - iterations : 131       time: 1.57
      Basis identification  -                        time: 0.00
        Primal              - iterations : 0         time: 0.00
        Dual                - iterations : 0         time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00


 > [mosek] Dual   optimality condition in solveCobraEP satisfied.

Optimality conditions (biochemistry)
 0.00049 || N*(vf - vr) + B*ve - b ||_inf
     Inf || C*(vf - vr) + s_C - d ||_inf, s_C = slack variable
 6.4e-07 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + k_vf + z_vf ||_inf
 6.4e-07 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + k_vr + z_vr ||_inf
       1 || ce + B'*y_N  + z_ve ||_inf
 8.2e+03 || k_e_1 + z_e_1 ||_inf
 8.2e+03 || -g + k_e_vf + z_e_vf||_inf
 1.1e-06 || -g + k_e_vr + z_e_vr||_inf
 1.5e-05 || e_vf + vf*log(vf) ||_inf
 1.5e-05 || e_vr + vr*log(vr) ||_inf
     1.7 || k_q_1 + z_q_1 ||_inf

Derived optimality conditions (biochemistry)
      21 || g.*log(vf) + g - k_vf ||_inf
   0.022 || g.*log(vr) + g - k_vr ||_inf
      21 || cf + ci + N'*y_N + C'*y_C + y_vi + Qv*vf + g.*log(vf) + g + z_vf ||_inf
   0.022 || cr - ci - N'*y_N - C'*y_C - y_vi + Qv*vf + g.*log(vr) + g + z_vr ||_inf

Thermo conditions
 2.7e+02 || g.*log(vr/vf) - 2*N'*y_N - 2*C'*y_C ||_inf
      56 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi ||_inf
      91 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*C'*y_C - 2*y_vi - z_vr + z_vf ||_inf
-1.5e+02 min(slack)
     Inf max(slack)
```
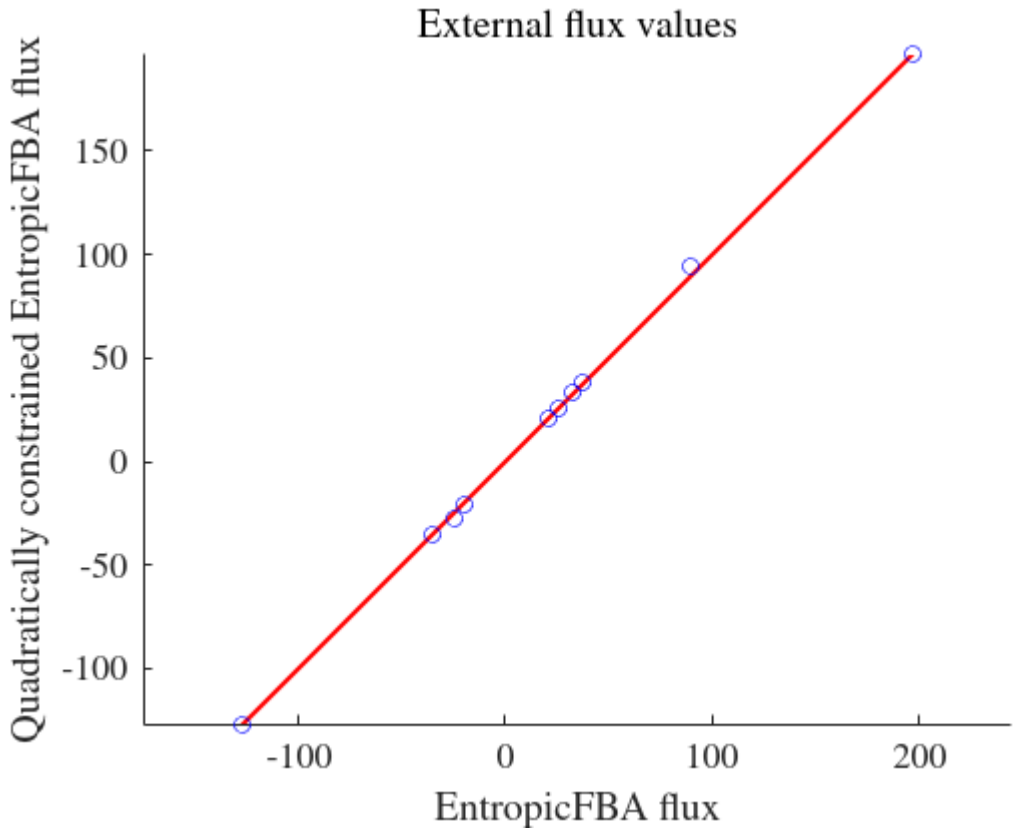

Compare the original external flux vector, with the quadratically constrained external flux vector. The values should be closer to the red line than above, but not exactly, because the quadratic penalty is trading off against entropy maximisation of internal reactions. Change H(j,j) to adjust this trade off.

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(isfinite(model.h)),solutionQEFBA.v(isfinite(model.h)),'o','Co
lor','b')
xlabel('EntropicFBA flux')
ylabel('Quadratically constrained EntropicFBA flux')
title('External flux values')
axis equal
```



Quadratically constrained entropic flux balance analysis - subset of external reactions and no coupling constraints

```
model = rmfield(model,{'C','d'});
```

Generate a random given external flux vector that is a perturbation of the previously obtained external flux vector and then quadratically penalise any deviation from it.

```
model.h = (solution.v).*(rand(length(solution.v),1)+0.5)*2;
```

Do not optimise toward any internal net flux

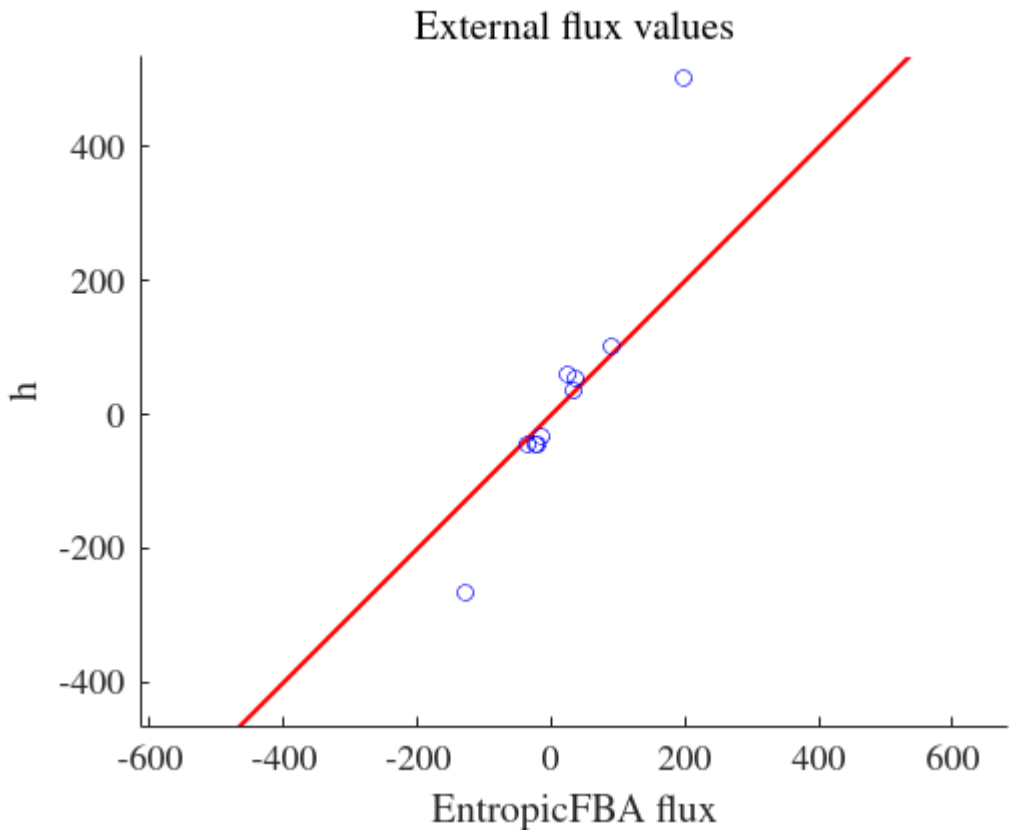
```
model.h(model.SConsistentRxnBool)=NaN;
```

Only optimise toward the top 10 magnitude given external net flux

```
[sortedh,ind]=sort(abs(model.h),'descend','MissingPlacement','last');
if length(ind)>10
    model.h(ind(11:end))=NaN;
end
```

Compare the original external flux vector, with the external flux vector to peanlise deviation from

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(isfinite(model.h)),model.h(isfinite(model.h)),'o','Color','b'
)
xlabel('EntropicFBA flux')
ylabel('h')
title('External flux values')
axis equal
```



Set the penaltiy

```
HH = ones(length(solution.v),1);
```

```
HH(model.SConsistentRxnBool)=0;
model.H = spdiags(HH,0,length(solution.v),length(solution.v));
```

Run the optimisation

```
[solutionQEFBA,modelOut] = entropicFluxBalanceAnalysis(model,param);
```

```
Using directional internal net flux bounds only.
Using existing external net flux bounds without modification.

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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : LO (linear optimization problem)
  Constraints            : 2964
  Affine conic cons.     : 0
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 3635
  Matrix variables       : 0
  Integer variables      : 0

Optimizer started.
Presolve started.
Eliminator started.
Freed constraints in eliminator : 1218
Eliminator terminated.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 141
Eliminator terminated.
Eliminator - tries                  : 2                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 9                 dual deps.             : 0
Presolve terminated. Time: 0.02
GP based matrix reordering started.
GP based matrix reordering terminated.
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 502
Optimizer  - Cones                  : 0
Optimizer  - Scalar variables       : 1690              conic                  : 0
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.01
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 4935              after factor           : 1.17e+04
Factor     - dense dim.             : 2                 flops                  : 5.02e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   8.0e+03  1.2e+03  2.6e+04  0.00e+00   2.503116488e+04   -1.234172434e+03  1.3e+02  0.04
1   3.9e+03  6.4e-01  1.3e+04  9.99e-01   1.002253781e+04   2.316670551e+03   6.2e+01  0.05
2   1.7e+03  2.8e-01  5.6e+03  1.18e+00   5.545217022e+03   2.452230824e+03   2.7e+01  0.05
```

```
3   3.6e+02  5.9e-02  1.2e+03  1.09e+00   1.613658539e+03   9.982955221e+02   5.6e+00  0.06
4   1.5e+02  2.5e-02  4.9e+02  1.03e+00   8.264611299e+02   5.722855572e+02   2.4e+00  0.06
5   2.8e+01  4.5e-03  9.1e+01  1.01e+00   3.934480893e+02   3.467403504e+02   4.4e-01  0.06
6   5.5e+00  9.0e-04  1.8e+01  1.02e+00   3.052316807e+02   2.960376884e+02   8.6e-02  0.06
7   4.2e-01  6.9e-05  1.4e+00  1.01e+00   2.838759387e+02   2.831788041e+02   6.6e-03  0.07
8   2.4e-02  4.0e-06  7.9e-02  1.01e+00   2.820862755e+02   2.820463229e+02   3.8e-04  0.07
9   1.2e-03  1.9e-07  3.9e-03  1.01e+00   2.819644523e+02   2.819625049e+02   1.9e-05  0.07
10  2.7e-05  4.4e-09  8.8e-05  1.00e+00   2.819572914e+02   2.819572471e+02   4.2e-07  0.07
11  2.4e-06  1.9e-08  1.1e-08  1.01e+00   2.819571856e+02   2.819571856e+02   1.2e-08  0.08
12  2.4e-06  1.9e-08  1.1e-08  1.00e+00   2.819571856e+02   2.819571856e+02   1.2e-08  0.08
Basis identification started.
Primal basis identification phase started.
Primal basis identification phase terminated. Time: 0.00
Dual basis identification phase started.
Dual basis identification phase terminated. Time: 0.00
Basis identification terminated. Time: 0.01
Optimizer terminated. Time: 0.10


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8195718558e+02    nrm: 5e+02    Viol.  con: 7e-06    var: 3e-07
  Dual.    obj: 2.8195717596e+02    nrm: 5e+00    Viol.  con: 0e+00    var: 9e-09

Basic solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 2.8195718114e+02    nrm: 5e+02    Viol.  con: 8e-13    var: 1e-14
  Dual.    obj: 2.8195718114e+02    nrm: 8e+00    Viol.  con: 0e+00    var: 8e-16
Optimizer summary
  Optimizer                 -                        time: 0.10
    Interior-point          - iterations : 12        time: 0.09
      Basis identification  -                        time: 0.01
        Primal              - iterations : 47        time: 0.00
        Dual                - iterations : 103       time: 0.00
        Clean primal        - iterations : 0         time: 0.00
        Clean dual          - iterations : 0         time: 0.00
    Simplex                 -                        time: 0.00
      Primal simplex        - iterations : 0         time: 0.00
      Dual simplex          - iterations : 0         time: 0.00
    Mixed integer           - relaxations: 0         time: 0.00

solveCobraEP: LP part of EPproblem is feasible according to solveCobraLP with mosek.

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Platform: Linux/64-X86

Problem
  Name                   :
  Objective sense        : minimize
  Type                   : CONIC (conic optimization problem)
  Constraints            : 2964
  Affine conic cons.     : 3430 (10290 rows)
  Disjunctive cons.      : 0
  Cones                  : 0
  Scalar variables       : 7067
  Matrix variables       : 0
```
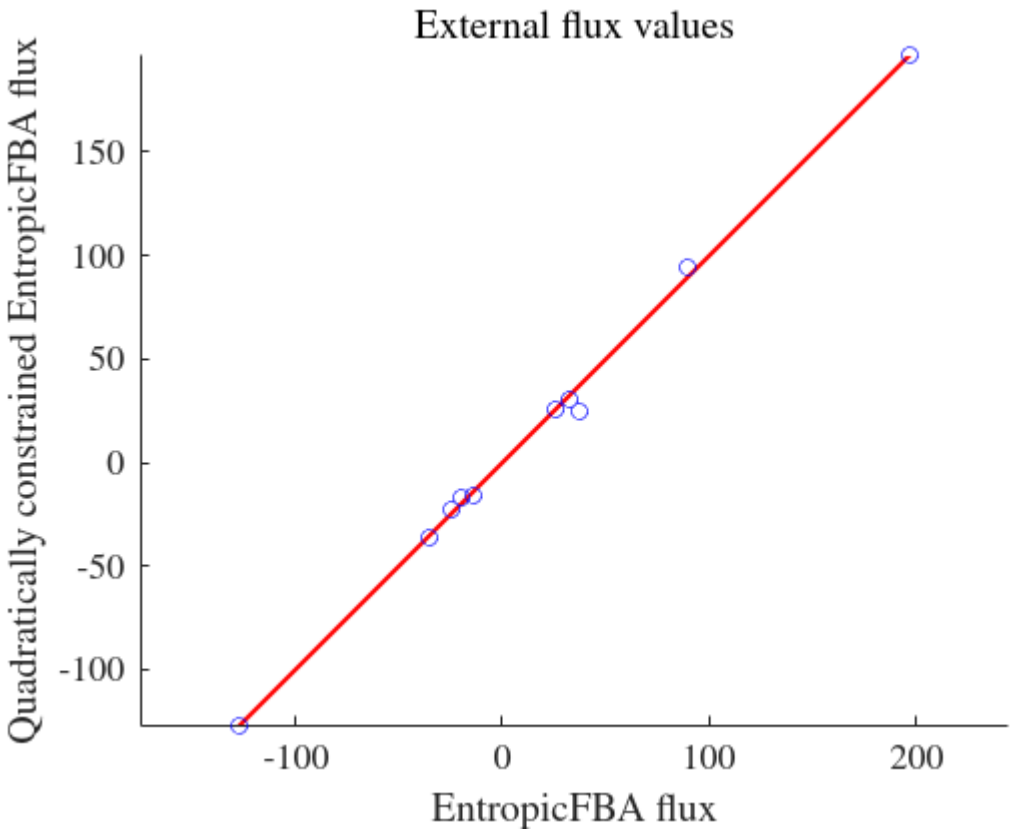

```
  Integer variables      : 0

Optimizer started.
Presolve started.
Linear dependency checker started.
Linear dependency checker terminated.
Eliminator started.
Freed constraints in eliminator : 8
Eliminator terminated.
Eliminator - tries                  : 1                 time                   : 0.00
Lin. dep.  - tries                  : 1                 time                   : 0.00
Lin. dep.  - primal attempts        : 1                 successes              : 1
Lin. dep.  - dual attempts          : 0                 successes              : 0
Lin. dep.  - primal deps.           : 25                dual deps.             : 0
Presolve terminated. Time: 0.03
Optimizer  - threads                : 18
Optimizer  - solved problem         : the primal
Optimizer  - Constraints            : 1949
Optimizer  - Cones                  : 3430
Optimizer  - Scalar variables       : 11273             conic                  : 10290
Optimizer  - Semi-definite variables: 0                 scalarized             : 0
Factor     - setup time             : 0.02
Factor     - dense det. time        : 0.00              GP order time          : 0.00
Factor     - nonzeros before factor : 1.17e+04          after factor           : 2.01e+04
Factor     - dense dim.             : 0                 flops                  : 7.52e+05
ITE PFEAS    DFEAS    GFEAS    PRSTATUS   POBJ              DOBJ              MU       TIME
0   1.0e+04  1.2e+00  1.0e+04  0.00e+00   5.947759534e+03   -4.414972768e+03  1.0e+00  0.06
1   7.9e+03  9.3e-01  9.2e+03  -9.99e-01  8.232311490e+03   -2.127371810e+03  7.9e-01  0.09
2   7.2e+03  8.4e-01  8.8e+03  -9.96e-01  9.502069016e+03   -8.439738464e+02  7.2e-01  0.10
3   5.3e+03  6.2e-01  7.5e+03  -9.85e-01  1.447239244e+04   4.217526204e+03   5.3e-01  0.15
4   1.7e+03  2.0e-01  4.1e+03  -9.66e-01  5.230892004e+04   4.250374657e+04   1.7e-01  0.33
5   7.0e+02  8.2e-02  2.4e+03  -8.61e-01  1.067632391e+05   9.800078150e+04   7.0e-02  0.34
6   4.0e+02  4.7e-02  1.4e+03  -5.59e-01  1.049141326e+05   9.770526243e+04   4.0e-02  0.35
7   2.8e+02  3.3e-02  9.6e+02  -1.56e-01  8.608338702e+04   8.013144341e+04   2.8e-02  0.36
8   1.7e+02  2.0e-02  5.3e+02  1.01e-01   6.412938836e+04   5.978465784e+04   1.7e-02  0.37
9   1.2e+02  1.4e-02  3.2e+02  3.93e-01   5.168438193e+04   4.842911750e+04   1.2e-02  0.38
10  6.6e+01  7.7e-03  1.4e+02  5.72e-01   3.786764539e+04   3.590026862e+04   6.6e-03  0.39
11  4.6e+01  5.4e-03  8.3e+01  7.65e-01   3.225068439e+04   3.083571157e+04   4.6e-03  0.40
12  1.2e+01  1.4e-03  1.2e+01  8.40e-01   2.140669702e+04   2.101253429e+04   1.2e-03  0.41
13  3.7e+00  4.3e-04  2.1e+00  9.68e-01   1.845839483e+04   1.833657509e+04   3.7e-04  0.42
14  1.0e+00  1.2e-04  3.1e-01  9.93e-01   1.755884221e+04   1.752535817e+04   1.0e-04  0.43
15  2.7e-01  3.1e-05  4.4e-02  9.99e-01   1.733318360e+04   1.732430925e+04   2.7e-05  0.44
16  6.6e-02  7.7e-06  5.4e-03  1.00e+00   1.727034946e+04   1.726816170e+04   6.6e-06  0.45
17  1.4e-02  1.6e-06  5.2e-04  1.00e+00   1.725455691e+04   1.725410508e+04   1.4e-06  0.46
18  8.8e-03  1.0e-06  2.7e-04  1.00e+00   1.725310464e+04   1.725281349e+04   8.8e-07  0.46
19  5.6e-03  6.6e-07  1.4e-04  1.00e+00   1.725214547e+04   1.725196026e+04   5.6e-07  0.48
20  5.0e-03  5.8e-07  1.1e-04  1.00e+00   1.725196013e+04   1.725179540e+04   5.0e-07  0.49
21  4.9e-03  5.8e-07  1.1e-04  1.00e+00   1.725194216e+04   1.725177942e+04   4.9e-07  0.50
22  4.8e-03  5.7e-07  1.1e-04  1.00e+00   1.725192055e+04   1.725176019e+04   4.8e-07  0.51
23  4.7e-03  5.5e-07  1.1e-04  1.00e+00   1.725188600e+04   1.725172946e+04   4.7e-07  0.52
24  4.7e-03  5.5e-07  1.1e-04  1.00e+00   1.725188038e+04   1.725172446e+04   4.7e-07  0.53
25  4.5e-03  5.3e-07  9.8e-05  1.00e+00   1.725181785e+04   1.725166884e+04   4.5e-07  0.54
26  4.5e-03  5.3e-07  9.8e-05  1.00e+00   1.725181614e+04   1.725166732e+04   4.5e-07  0.55
27  4.5e-03  5.3e-07  9.8e-05  1.00e+00   1.725181610e+04   1.725166728e+04   4.5e-07  0.56
28  4.4e-03  5.2e-07  9.7e-05  1.00e+00   1.725180155e+04   1.725165434e+04   4.4e-07  0.56
29  4.4e-03  5.2e-07  9.6e-05  1.00e+00   1.725179983e+04   1.725165281e+04   4.4e-07  0.57
30  4.4e-03  5.2e-07  9.6e-05  1.00e+00   1.725179981e+04   1.725165279e+04   4.4e-07  0.58
31  4.2e-03  4.9e-07  8.8e-05  1.00e+00   1.725171945e+04   1.725158131e+04   4.2e-07  0.59
32  4.1e-03  4.8e-07  8.6e-05  1.00e+00   1.725170588e+04   1.725156924e+04   4.1e-07  0.60
33  4.0e-03  4.7e-07  8.2e-05  1.00e+00   1.725166415e+04   1.725153212e+04   4.0e-07  0.61
34  3.9e-03  4.6e-07  8.1e-05  1.00e+00   1.725165276e+04   1.725152199e+04   3.9e-07  0.62
35  3.9e-03  4.6e-07  8.1e-05  1.00e+00   1.725165262e+04   1.725152186e+04   3.9e-07  0.63
36  3.9e-03  4.6e-07  8.1e-05  1.00e+00   1.725165254e+04   1.725152179e+04   3.9e-07  0.64
37  3.9e-03  4.6e-07  7.9e-05  1.00e+00   1.725163673e+04   1.725150773e+04   3.9e-07  0.65
```

```
38  3.9e-03  4.5e-07  7.9e-05  1.00e+00   1.725163234e+04   1.725150382e+04   3.9e-07  0.65
39  3.8e-03  4.5e-07  7.8e-05  1.00e+00   1.725162216e+04   1.725149476e+04   3.8e-07  0.67
40  3.8e-03  4.5e-07  7.7e-05  1.00e+00   1.725161063e+04   1.725148450e+04   3.8e-07  0.67
41  3.8e-03  4.5e-07  7.7e-05  1.00e+00   1.725160908e+04   1.725148313e+04   3.8e-07  0.68
42  3.8e-03  4.5e-07  7.7e-05  1.00e+00   1.725160845e+04   1.725148257e+04   3.8e-07  0.69
43  3.8e-03  4.5e-07  7.7e-05  1.00e+00   1.725160838e+04   1.725148251e+04   3.8e-07  0.70
44  3.0e-03  3.6e-07  5.5e-05  1.00e+00   1.725137931e+04   1.725127873e+04   3.0e-07  0.71
45  3.0e-03  3.6e-07  5.5e-05  1.00e+00   1.725137837e+04   1.725127789e+04   3.0e-07  0.72
46  3.0e-03  3.5e-07  5.4e-05  1.00e+00   1.725137662e+04   1.725127634e+04   3.0e-07  0.73
47  3.0e-03  3.5e-07  5.4e-05  1.00e+00   1.725137360e+04   1.725127365e+04   3.0e-07  0.74
48  3.0e-03  3.5e-07  5.4e-05  1.00e+00   1.725137289e+04   1.725127302e+04   3.0e-07  0.75
49  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136541e+04   1.725126636e+04   3.0e-07  0.76
50  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136508e+04   1.725126607e+04   3.0e-07  0.77
51  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136501e+04   1.725126601e+04   3.0e-07  0.78
52  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136419e+04   1.725126528e+04   3.0e-07  0.79
53  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136416e+04   1.725126525e+04   3.0e-07  0.80
54  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136391e+04   1.725126503e+04   3.0e-07  0.81
55  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136324e+04   1.725126444e+04   3.0e-07  0.81
56  3.0e-03  3.5e-07  5.3e-05  1.00e+00   1.725136313e+04   1.725126433e+04   3.0e-07  0.82
57  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068311e+04   1.725065935e+04   7.2e-08  0.84
58  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068310e+04   1.725065934e+04   7.2e-08  0.85
59  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068301e+04   1.725065926e+04   7.2e-08  0.86
60  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068289e+04   1.725065915e+04   7.2e-08  0.86
61  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068288e+04   1.725065914e+04   7.2e-08  0.87
62  7.2e-04  8.4e-08  6.4e-06  1.00e+00   1.725068253e+04   1.725065883e+04   7.1e-08  0.89
63  7.1e-04  8.4e-08  6.4e-06  1.00e+00   1.725068252e+04   1.725065882e+04   7.1e-08  0.90
64  7.1e-04  8.4e-08  6.3e-06  1.00e+00   1.725068231e+04   1.725065863e+04   7.1e-08  0.91
65  7.1e-04  8.4e-08  6.3e-06  1.00e+00   1.725068227e+04   1.725065860e+04   7.1e-08  0.92
66  7.1e-04  8.4e-08  6.3e-06  1.00e+00   1.725068226e+04   1.725065859e+04   7.1e-08  0.93
67  7.1e-04  8.4e-08  6.3e-06  1.00e+00   1.725068225e+04   1.725065858e+04   7.1e-08  0.94
68  7.1e-04  8.4e-08  6.3e-06  1.00e+00   1.725068225e+04   1.725065858e+04   7.1e-08  0.95
69  7.1e-04  8.3e-08  6.2e-06  1.00e+00   1.725067970e+04   1.725065631e+04   7.1e-08  0.97
70  7.0e-04  8.3e-08  6.2e-06  1.00e+00   1.725067928e+04   1.725065594e+04   7.0e-08  0.98
71  7.0e-04  8.3e-08  6.2e-06  1.00e+00   1.725067923e+04   1.725065589e+04   7.0e-08  0.99
72  7.0e-04  8.3e-08  6.2e-06  1.00e+00   1.725067923e+04   1.725065589e+04   7.0e-08  1.00
73  7.0e-04  8.3e-08  6.2e-06  1.00e+00   1.725067921e+04   1.725065587e+04   7.0e-08  1.01
74  6.7e-04  7.8e-08  5.7e-06  1.00e+00   1.725066747e+04   1.725064542e+04   6.6e-08  1.03
75  6.7e-04  7.8e-08  5.7e-06  1.00e+00   1.725066746e+04   1.725064542e+04   6.6e-08  1.04
76  6.4e-04  7.5e-08  5.4e-06  1.00e+00   1.725066042e+04   1.725063915e+04   6.4e-08  1.05
77  6.4e-04  7.5e-08  5.4e-06  1.00e+00   1.725066041e+04   1.725063914e+04   6.4e-08  1.06
78  6.4e-04  7.5e-08  5.4e-06  1.00e+00   1.725066041e+04   1.725063914e+04   6.4e-08  1.07
79  1.5e-04  1.8e-08  6.3e-07  1.00e+00   1.725051265e+04   1.725050760e+04   1.5e-08  1.09
80  1.5e-04  1.8e-08  6.3e-07  1.00e+00   1.725051265e+04   1.725050760e+04   1.5e-08  1.09
81  1.5e-04  1.8e-08  6.3e-07  1.00e+00   1.725051265e+04   1.725050760e+04   1.5e-08  1.11
82  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051262e+04   1.725050757e+04   1.5e-08  1.11
83  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051262e+04   1.725050757e+04   1.5e-08  1.13
84  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051262e+04   1.725050757e+04   1.5e-08  1.15
85  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051262e+04   1.725050757e+04   1.5e-08  1.17
86  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051260e+04   1.725050756e+04   1.5e-08  1.18
87  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051260e+04   1.725050756e+04   1.5e-08  1.20
88  1.5e-04  1.8e-08  6.2e-07  1.00e+00   1.725051260e+04   1.725050756e+04   1.5e-08  1.22
Optimizer terminated. Time: 1.24


Interior-point solution summary
  Problem status  : PRIMAL_AND_DUAL_FEASIBLE
  Solution status : OPTIMAL
  Primal.  obj: 1.7250512601e+04    nrm: 5e+02    Viol.  con: 2e-04    var: 7e-06    acc: 7e-08
  Dual.    obj: 1.7250507555e+04    nrm: 8e+03    Viol.  con: 3e-07    var: 6e-07    acc: 0e+00
Optimizer summary
  Optimizer                 -                        time: 1.24
    Interior-point          - iterations : 89        time: 1.23
      Basis identification  -                        time: 0.00
        Primal              - iterations : 0         time: 0.00
```

```
        Dual               - iterations : 0         time: 0.00
        Clean primal       - iterations : 0         time: 0.00
        Clean dual         - iterations : 0         time: 0.00
    Simplex                -                        time: 0.00
      Primal simplex       - iterations : 0         time: 0.00
      Dual simplex         - iterations : 0         time: 0.00
    Mixed integer          - relaxations: 0         time: 0.00


 > [mosek] Dual   optimality condition in solveCobraEP satisfied.

Optimality conditions (biochemistry)
 0.00025 || N*(vf - vr) + B*ve - b ||_inf
 3.4e-07 || cf + ci + N'*y_N + y_vi + Qv*vf + k_vf + z_vf ||_inf
 3.4e-07 || cr - ci - N'*y_N - y_vi + Qv*vf + k_vr + z_vr ||_inf
       1 || ce + B'*y_N  + z_ve ||_inf
   8e+03 || k_e_1 + z_e_1 ||_inf
   8e+03 || -g + k_e_vf + z_e_vf||_inf
 5.7e-07 || -g + k_e_vr + z_e_vr||_inf
 8.2e-06 || e_vf + vf*log(vf) ||_inf
 7.9e-06 || e_vr + vr*log(vr) ||_inf
     1.3 || k_q_1 + z_q_1 ||_inf

Derived optimality conditions (biochemistry)
      20 || g.*log(vf) + g - k_vf ||_inf
  0.0082 || g.*log(vr) + g - k_vr ||_inf
      20 || cf + ci + N'*y_N + y_vi + Qv*vf + g.*log(vf) + g + z_vf ||_inf
  0.0082 || cr - ci - N'*y_N - y_vi + Qv*vf + g.*log(vr) + g + z_vr ||_inf

Thermo conditions
 2.4e+02 || g.*log(vr/vf) - 2*N'*y_N ||_inf
      54 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*y_vi ||_inf
      88 || g.*log(vr/vf) + cr - cf - 2*ci - 2*N'*y_N - 2*y_vi - z_vr + z_vf ||_inf
-1.5e+02 min(slack)
   2e+02 max(slack)
```

Compare the original external flux vector, with the quadratically constrained external flux vector. The values should be closer to the red line than above, but not exactly, because the quadratic penalty is trading off against entropy maximisation of internal reactions. Change H(j,j) to adjust this trade off.

```
figure
hold on
fplot(@(x) x, 'LineWidth', 1.5,'Color','r')
plot(solution.v(isfinite(model.h)),solutionQEFBA.v(isfinite(model.h)),'o','Co
lor','b')
xlabel('EntropicFBA flux')
ylabel('Quadratically constrained EntropicFBA flux')
title('External flux values')
axis equal
```



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