# Supplementary Information Overview

The supplementary information is separated into two parts. Supplementary Tables and the Supplementary Note provide additional information and are meant to further understanding of the results presented in the manuscript. Supplementary Data provides all information required to reproduce the simulations performed.

| | **Compartment abbreviations** |
|---|---|
| (b) | bile (canalicular lumen) |
| (c) | cytosol |
| (l) | lysosomal lumen |
| (m) | mitochondrial matrix |
| (n) | nucleus |
| (p) | peroxisomal lumen |
| (r) | endoplasmic reticulum and Golgi apparatus |
| (s) | sinusoidal space |

# I Tables

## Supplementary Table 1: Pseudo Metabolites

Pseudo metabolites account for cofactor-utilizing reactions that are not part of the network.

| | |
|---|---|
| **Identifier** | Unique compound identifier |
| **Name** | Compound name |
| **Compartments** | Localization of the compound (for abbreviations see above) |
| **Explanation** | Definition of pseudo metabolites |

## Supplementary Table 2: Exchange function annotation

| | |
|---|---|
| **HC-ID** | Unique compound identifier with compartment abbreviation |
| **Names** | Compound name with compartment abbreviation |
| **Biological Process** | Annotation of a biochemical or physiological function to the compartmentalized compound |

# Supplementary Table 3: Exchange Set Definition

Definition of the different sets of metabolites that can be taken up or released by the network.
These sets were used for functional testing of the network.

| | |
|---|---|
| **ID** | Unique compound identifier |
| **Name** | Compound name |
| **Compartment** | Localization of the exchange set element (abbreviations see above) |
| **Direction** | Direction in which exchange across the system boundary may occur for the corresponding exchange set element. |

## Supplementary Table 3.1: MIMES

minimal import, minimal export set. Using this exchange set, all important internal metabolites can be synthesized and degraded.

## Supplementary Table 3.2: MIPES

minimal import, physiological export set. This set is based on MIMES with the addition that export processes are included.

## Supplementary Table 3.3: PIPES

physiological import, physiological export set. This set is based on MIPES with the addition that more import processes are included, mainly non-essential amino acids and fatty acids.

## Supplementary Table 3.4: MES

minimal exchange set. Set designed to test the producibility of metabolites.

## Supplementary Table 3.5: DES

digestion exchange set. Set designed to test the degradation of metabolites.

## Supplementary Table 3.6: HES

hypoxia exchange set. Set designed to test hypoxic conditions.

## Supplementary Table 3.7: WES

waste exchange set. Set is designed to test the degradation of complex metabolite into non-further degradable end products.

## Supplementary Table 4: Biochemical objectives – Network comparison

Comparison of HepatoNet, Recon1 and the liver-specific network computationally predicted by Shlomi et al (Shlomi et al., 2008) satisfying 123 selected physiological metabolic functions.

| | |
|---|---|
| **Simulation ID** | Unique name for the simulation |
| **HepatoNet** | Indicating with “success” or “fail” simulation results |
| **Recon1** | Indicating with “success” or “fail” simulation results |
| **Shlomi/Liver** | Indicating with “success” or “fail” simulation results for all reactions of Recon1 predicted to be active in liver according to Shlomi et al., 2008 (all reactions in Recon1 with negative confidence were omitted). |

## Supplementary Table 5: Essentiality of enzymes for tested biochemical objectives

*In-silico* “enzyme knock-outs”. List of enzymatic reactions in descending order according to the frequency of their occurrence.

| | |
|---|---|
| **Enzyme Name** | Preferred Enzyme name |
| **Rank** | A high number indicates that many objectives fail upon knockout. |
| **Disease** | A genetic disease or case report of enzymopathies |
| **Reference** | A publication according to the given disease |

## Supplementary Table 6: Gene expression discrepancy

Reactions included in HepatoNet conflicting with mRNA expression data. The detection call for the mRNA is “absent” for all analyzed mRNA expression datasets.

| | |
|---|---|
| **ID** | Crossreference to KEGG |
| **Classification** | Crossreference to Enzyme classification identifier |
| **Name** | Preferred Enzyme name |
| **Evidence** | Crossreference to Pubmed identifier |
| **Experiments** | Numbers given in the column refer to the amount of Gene expression omnibus (GEO) series found for a specific Ensembl gene ID. |
| **Samples** | Numbers given in the column refer to the amount of Gene expression omnibus (GEO) samples found for a specific Ensembl gene ID in a certain experiment. |
| **Oligos** | Numbers given in the column refer to the amount of Affymetrix ProbeSet identifiers found for a specific Ensembl gene ID in a certain experiment. |

## Supplementary Note 1: Pooled Metabolites

Detailed characterization of pooled compounds.

# II Data

## Supplementary Data 1.1: Compounds

*Supplementary_Data_1.1.tsv*

| | |
|---|---|
| **HC-ID** | Compound identifier |
| **Name** | Compound name |
| **Sum formula** | Sum formula of the compound |
| **Compartments** | Model compartments in which the compound occurs |
| **KEGG-ID** | Cross-reference to KEGG |
| **ChEBI-ID** | Cross-reference to ChEBI |
| **CAS-Registry** | Cross-reference to CAS |
| **Recon1** | Cross-reference to Recon1 |
| **PubChem-ID** | Cross-reference to PubChem Substance |

## Supplementary Data 1.2: Reactions

*Supplementary_Data_1.2.tsv*

| | |
|---|---|
| **R-ID** | Reaction identifier |
| **Equation HC-ID** | Reaction equation with compound identifiers |
| **Equation Name** | Reaction equation with compound names |
| **Reaction Category** | EC-Numbers and Transport classification database (TCDB) categories are used to characterize the type of enzymatic and transport activity, respectively. If these are unknown, generic categories are used. Virtual reaction/ potential definition: Reactions using abstract compounds which are used to connect physical model entities to biochemical processes outside the scope of the model. Example: r1319 contains the compound ATP-energy which is used to describe any effects of ATP-sinks or -sources unaccounted for, *e. g.* polynucleotide synthesis. |
| **DG** | Reaction Gibbs free energies obtained from a prediction method (Jankowski, 2008) |
| **KEGG-ID** | Cross-reference to KEGG |
| **Recon1** | Cross-reference to the Recon1 model |
| **References** | References on which the inclusion of the reaction into HepatoNet is based |

## Supplementary Data 2: SBML-model

*Supplementary_Data_2.xml*

Model HepatoNet1 in SBML

# Supplementary Data 3: Definition and Overview for Simulations

## Supplementary Data 3.1: Physiological objectives

*Supplementary_Data_3.1.tsv*

## Supplementary Data 3.2: Test objectives for network validation

*Supplementary_Data_3.2.tsv*

Simulations are defined by enumerating exchangeable and exchanged substances.

| | |
|---|---|
| **Simulation ID** | Unique name for the simulation |
| **Objective** | Metabolic objective for the simulations. Compounds implicated in metabolic objectives necessarily carry a non-zero outward (unsigned) or inward (-) flux, respectively, across the system boundary. |
| **Constraints** | Per default, compounds must not be exchanged across the system boundary. Constraints define the simulation specific exceptions. '+' indicates allowed release and '-' allowed uptake across the system boundary (no sign - arbitrary exchange). Per default, metabolites localized to the sinusoidal compartment are exchanged across the system boundary. In all other cases, localization of the exchanged metabolite is indicated. |
| **Evaluator** | Indicates compounds which in the simulation result must be associated with a non-zero flux across the system boundary for the simulation to be successful. ‘fail’ indicates that the simulation is expected to fail, *i. e*. that no solution can be obtained. |
| **Solution imports** | Actual inward (negative) fluxes across the system boundary in the determined simulation solution |
| **Solution exports** | Actual outward (positive) fluxes across the system boundary in the determined simulation solution |
| **Reactions in flux mode** | Numbers are given for each compartment and for transport reactions. |

# Supplementary Data 4:

*Supplementary_Data_4.zip*

Simulation results for metabolic objectives for HepatoNet. Each file corresponds to one objective. The files define the conditions of the simulation and contain the predicted flux distribution.

## Supplementary Data 5: Gene expression

*Supplementary_Data_5.tsv*

| | |
|---|---|
| **Reaction** | reaction-ID |
| **ENSG** | Ensembl Gene ID |
| **GSE** | Gene expression omnibus series |
| **GSM** | Gene expression omnibus sample |
| **Probeset ID** | Affymetrix ProbeSet identifiers |
| **EntrezGene Symbol** | Entrez Gene database identifier |
| **Value** | Gene expression value |
| **Analysis** | Detection call (A)absent, (P)present, (M)marginal |

## Supplementary Data 6.1: Flux minimization weights

*Supplementary_Data_6.1.tsv*

| | |
|---|---|
| **R-ID** | Unique identifier of the reaction |
| **Flux Weight** | Weight of the corresponding reaction for the scoring function in flux balance analysis |
| **Justification** | Explanation for the chosen weight |

## Supplementary Data 6.2: TR Concentration Ranges

*Supplementary_Data_6.2.tsv*

**Section I:** Concentration ranges used in the thermodynamic realizability analysis.

| | |
|---|---|
| **Class** | Unique class name |
| **Lower Bound** | Minimum concentration in mM or uM for compounds |
| **Upper Bound** | Maximum concentration n mM or uM for compounds |

**Section II:** Concentration Class Assignment

Compartment specific assignment of concentration range classes to compounds.

| | |
|---|---|
| **HC-ID** | Compound identifier |
| **Name** | Compound name |
| **Compartment** | Subcellular Localization |
| **Class** | Range class to which the compound is assigned |

Supplementary Table 1 : Pseudo Metabolites

| Identifier | Name | Compartments | Explanation |
|---|---|---|---|
| HC02111 | ATP-energy | c,m | exchange of ATP against ADP and Pi, allows for the utilization/storage of the high energy phosphate bond |
| HC02112 | NADH-redox-potential | r,c,m,p | exchange of NADH against NAD, allows for the utilization/storage of electrons |
| HC02113 | NADPH-redox-potential | r,c,m,p | exchange of NADPH against NADP, allows for the utilization/storage of electrons |
| HC02114 | FADH-redox-potential | c | exchange of FADH2 against FAD, allows for the utilization/storage of electrons |
| HC02115 | Proton-gradient | c,m | exchange of a proton across a membrane, allows for the usage or creation of a transmembrane proton gradient |
| HC02116 | activated-sulphur | c | exchange of PAPS against PAP, allows for the usage/storage of a an activated sulphur |
| HC02119 | Adenosylmethioninamine-potential | c | exchange of SAM against SAH, allows for the utilization/storage of an activated methyl group |

Supplementary Table 2 : Exchange Function Annotation

| Identifier | Name | Biological Process |
|---|---|---|
| HC00001_s | Albumin(s) | transport |
| HC00001_s | Albumin(s) | blood constituent |
| HC00002_s | Antichymotrypsin(s) | acute-phase response |
| HC00002_s | Antichymotrypsin(s) | blood constituent |
| HC00003_s | Antitrypsin(s) | acute-phase response |
| HC00003_s | Antitrypsin(s) | blood constituent |
| HC00004_s | ApoA1(s) | blood constituent |
| HC00006_r | ApoC1(r) | lipoprotein metabolic process |
| HC00007_r | ApoC2(r) | lipoprotein metabolic process |
| HC00008_r | ApoC3(r) | lipoprotein metabolic process |
| HC00012_s | ATP(s) | blood constituent |
| HC00014_c | NADH(c) | cofactor biosynthetic process |
| HC00015_c | NADPH(c) | cofactor biosynthetic process |
| HC00017_s | O2(s) | blood constituent |
| HC00017_s | O2(s) | blood constituent |
| HC00018_s | ADP(s) | blood constituent |
| HC00019_s | Pi(s) | blood constituent |
| HC00019_s | Pi(s) | blood constituent |
| HC00020_c | CoA(c) | coenzyme biosynthetic process |
| HC00020_c | CoA(c) | coenzyme A biosynthetic process |
| HC00021_b | CO2(b) | bile formation |
| HC00021_s | CO2(s) | blood constituent |
| HC00021_s | CO2(s) | oxidative phosporylation |
| HC00023_c | PPi(c) | translation |
| HC00023_s | PPi(s) | blood constituent |
| HC00024_s | NH3(s) | detoxification |
| HC00024_s | NH3(s) | blood constituent |
| HC00024_s | NH3(s) | blood constituent |
| HC00025_s | UDP(s) | blood constituent |
| HC00026_c | FAD(c) | cofactor biosynthetic process |
| HC00026_s | FAD(s) | blood constituent |
| HC00028_c | Pyridoxal-P(c) | cofactor biosynthetic process |
| HC00028_s | Pyridoxal-P(s) | blood constituent |
| HC00030_s | AMP(s) | blood constituent |
| HC00032_s | Pyruvate(s) | blood constituent |
| HC00034_c | Glutamate(c) | translation |
| HC00034_s | Glutamate(s) | blood constituent |
| HC00034_s | Glutamate(s) | blood constituent |
| HC00035_s | AKG(s) | blood constituent |
| HC00036_s | H2O2(s) | blood constituent |
| HC00036_s | H2O2(s) | reactive oxygen species metabolic process |
| HC00038_c | UDP-glucose(c) | glycoprotein biosynthetic process |
| HC00038_c | UDP-glucose(c) | proteoglycan biosynthetic process |
| HC00038_s | UDP-glucose(s) | blood constituent |
| HC00040_s | Glucose(s) | blood constituent |
| HC00040_s | Glucose(s) | blood constituent |
| HC00042_s | Acetate(s) | blood constituent |
| HC00043_s | GDP(s) | blood constituent |
| HC00045_c | Glycine(c) | translation |
| HC00045_s | Glycine(s) | blood constituent |
| HC00045_s | Glycine(s) | blood constituent |
| HC00048_c | Alanine(c) | translation |
| HC00048_s | Alanine(s) | blood constituent |
| HC00048_s | Alanine(s) | blood constituent |
| HC00049_s | Succinate(s) | blood constituent |
| HC00050_c | UDP-N-acetylglucosamine(c) | glycoprotein biosynthetic process |
| HC00050_c | UDP-N-acetylglucosamine(c) | proteoglycan biosynthetic process |
| HC00051_s | GTP(s) | blood constituent |
| HC00053_c | Lysine(c) | translation |
| HC00053_s | Lysine(s) | blood constituent |
| HC00053_s | Lysine(s) | blood constituent |
| HC00053_s | Lysine(s) | blood constituent |
| HC00055_c | Aspartate(c) | translation |
| HC00055_s | Aspartate(s) | blood constituent |
| HC00055_s | Aspartate(s) | blood constituent |
| HC00056_s | GSH(s) | blood constituent |
| HC00057_c | UDP-galactose(c) | proteoglycan biosynthetic process |
| HC00057_c | UDP-galactose(c) | glycoprotein biosynthetic process |
| HC00058_c | PAPS(c) | proteoglycan biosynthetic process |
| HC00058_c | PAPS(c) | bile acid metabolic process |

| Identifier | Name | Biological Process |
|---|---|---|
| HC00058_c | PAPS(c) | glycoprotein biosynthetic process |
| HC00060_s | CMP(s) | blood constituent |
| HC00061_s | Formate(s) | detoxifizierung |
| HC00062_b | Sulfate(b) | bile formation |
| HC00062_s | Sulfate(s) | blood constituent |
| HC00062_s | Sulfate(s) | blood constituent |
| HC00065_c | Arginine(c) | translation |
| HC00065_s | Arginine(s) | blood constituent |
| HC00065_s | Arginine(s) | blood constituent |
| HC00066_s | CTP(s) | blood constituent |
| HC00067_c | Glutamine(c) | translation |
| HC00067_s | Glutamine(s) | blood constituent |
| HC00067_s | Glutamine(s) | blood constituent |
| HC00068_c | Serine(c) | translation |
| HC00068_s | Serine(s) | blood constituent |
| HC00068_s | Serine(s) | blood constituent |
| HC00070_s | Formaldehyde(s) | blood constituent |
| HC00074_s | Ascorbate(s) | blood constituent |
| HC00075_c | Methionine(c) | translation |
| HC00075_s | Methionine(s) | blood constituent |
| HC00075_s | Methionine(s) | blood constituent |
| HC00075_s | Methionine(s) | blood constituent |
| HC00077_s | UTP(s) | blood constituent |
| HC00079_s | Ornithine(s) | blood constituent |
| HC00080_c | Tryptophan(c) | translation |
| HC00080_s | Tryptophan(s) | blood constituent |
| HC00080_s | Tryptophan(s) | blood constituent |
| HC00080_s | Tryptophan(s) | blood constituent |
| HC00081_c | Phenylalanine(c) | translation |
| HC00081_s | Phenylalanine(s) | blood constituent |
| HC00081_s | Phenylalanine(s) | blood constituent |
| HC00081_s | Phenylalanine(s) | blood constituent |
| HC00083_s | H+(PG)(s) | blood constituent |
| HC00084_s | ITP(s) | blood constituent |
| HC00085_c | Tyrosine(c) | translation |
| HC00085_s | Tyrosine(s) | blood constituent |
| HC00085_s | Tyrosine(s) | blood constituent |
| HC00087_s | Acetaldehyde(s) | blood constituent |
| HC00089_s | Urea(s) | detoxification |
| HC00089_s | Urea(s) | blood constituent |
| HC00089_s | Urea(s) | blood constituent |
| HC00091_s | Sucrose(s) | blood constituent |
| HC00091_s | Sucrose(s) | blood constituent |
| HC00097_s | Fructose(s) | blood constituent |
| HC00098_c | GDP-mannose(c) | glycoprotein biosynthetic process |
| HC00098_c | GDP-mannose(c) | proteoglycan biosynthetic process |
| HC00099_c | Cysteine(c) | translation |
| HC00099_s | Cysteine(s) | blood constituent |
| HC00099_s | Cysteine(s) | blood constituent |
| HC00100_s | beta-Alanine(s) | catabolism |
| HC00100_s | beta-Alanine(s) | blood constituent |
| HC00102_c | THF(c) | cofactor biosynthetic process |
| HC00102_m | THF(m) | cofactor biosynthetic process |
| HC00103_s | Glucose-1P(s) | blood constituent |
| HC00104_s | IDP(s) | blood constituent |
| HC00105_s | UMP(s) | blood constituent |
| HC00106_s | Uracil(s) | blood constituent |
| HC00106_s | Uracil(s) | export of pyrimidine |
| HC00109_s | DHAP(s) | blood constituent |
| HC00110_s | CDP(s) | blood constituent |
| HC00112_c | Choline(c) | blood constituent |
| HC00112_s | Choline(s) | blood constituent |
| HC00114_s | Glycerol(s) | blood constituent |
| HC00117_s | PRPP(s) | blood constituent |
| HC00119_s | Ribose(s) | blood constituent |
| HC00121_c | Leucine(c) | translation |
| HC00121_s | Leucine(s) | blood constituent |
| HC00121_s | Leucine(s) | blood constituent |
| HC00121_s | Leucine(s) | blood constituent |
| HC00122_s | Galactose(s) | blood constituent |

| Identifier | Name | Biological Process |
|---|---|---|
| HC00125_s | GSSG(s) | blood constituent |
| HC00126_c | CMP-N-acetylneuraminate(c) | proteoglycan biosynthetic process |
| HC00126_c | CMP-N-acetylneuraminate(c) | glycoprotein biosynthetic process |
| HC00128_s | IMP(s) | blood constituent |
| HC00130_s | Methanol(s) | blood constituent |
| HC00132_s | Putrescine(s) | blood constituent |
| HC00133_c | Histidine(c) | translation |
| HC00133_s | Histidine(s) | blood constituent |
| HC00133_s | Histidine(s) | blood constituent |
| HC00133_s | Histidine(s) | blood constituent |
| HC00135_s | Inositol(s) | blood constituent |
| HC00141_s | GMP(s) | blood constituent |
| HC00144_s | Adenine(s) | blood constituent |
| HC00144_s | Adenine(s) | export of purine |
| HC00145_c | Proline(c) | translation |
| HC00145_s | Proline(s) | blood constituent |
| HC00145_s | Proline(s) | blood constituent |
| HC00148_c | Asparagine(c) | translation |
| HC00148_s | Asparagine(s) | blood constituent |
| HC00148_s | Asparagine(s) | blood constituent |
| HC00149_s | Nicotinamide(s) | blood constituent |
| HC00149_s | Nicotinamide(s) | blood constituent |
| HC00153_s | Citrate(s) | blood constituent |
| HC00154_s | Mannose(s) | blood constituent |
| HC00158_s | Propanoate(s) | blood constituent |
| HC00159_s | Acetoacetate(s) | keton body synthesis |
| HC00159_s | Acetoacetate(s) | blood constituent |
| HC00162_c | UDP-glucuronate(c) | proteoglycan biosynthetic process |
| HC00162_c | UDP-glucuronate(c) | bile acid metabolic process |
| HC00162_c | UDP-glucuronate(c) | bilirubin conjugation |
| HC00162_c | UDP-glucuronate(c) | glycoprotein biosynthetic process |
| HC00162_c | UDP-glucuronate(c) | biotransformation |
| HC00165_c | 5-Methylthioadenosine(c) | polyamine metabolic process |
| HC00165_c | 5-Methylthioadenosine(c) | polyamine metabolic process |
| HC00170_s | Thymine(s) | blood constituent |
| HC00170_s | Thymine(s) | export of pyrimidine |
| HC00174_c | Valine(c) | translation |
| HC00174_s | Valine(s) | blood constituent |
| HC00174_s | Valine(s) | blood constituent |
| HC00174_s | Valine(s) | blood constituent |
| HC00175_s | Glycerone(s) | blood constituent |
| HC00177_s | L-Lactate(s) | blood constituent |
| HC00178_b | Cholesterol(b) | bile formation |
| HC00178_b | Cholesterol(b) | bile formation |
| HC00178_s | Cholesterol(s) | blood constituent |
| HC00178_r | Cholesterol(r) | membrane lipid metabolic process |
| HC00179_c | Threonine(c) | translation |
| HC00179_s | Threonine(s) | blood constituent |
| HC00179_s | Threonine(s) | blood constituent |
| HC00179_s | Threonine(s) | blood constituent |
| HC00180_c | Ethanolamine(c) | blood constituent |
| HC00181_c | UDP-xylose(c) | proteoglycan biosynthetic process |
| HC00190_c | UDP-N-acetyl-D-galactosamine(c) | glycoprotein biosynthetic process |
| HC00190_c | UDP-N-acetyl-D-galactosamine(c) | proteoglycan biosynthetic process |
| HC00193_s | Acetone(s) | keton body synthesis |
| HC00193_s | Acetone(s) | blood constituent |
| HC00194_s | Maltose(s) | blood constituent |
| HC00196_s | Adenosine(s) | blood constituent |
| HC00197_s | Sarcosine(s) | blood constituent |
| HC00198_s | Thymidine(s) | blood constituent |
| HC00202_s | Arachidonate(s) | blood constituent |
| HC00202_s | Arachidonate(s) | blood constituent |
| HC00216_s | K+(s) | blood constituent |
| HC00219_s | Guanine(s) | blood constituent |
| HC00219_s | Guanine(s) | export of purine |
| HC00220_s | Lactose(s) | blood constituent |
| HC00220_s | Lactose(s) | blood constituent |
| HC00222_s | Taurine(s) | blood constituent |
| HC00223_s | Butyrate(s) | blood constituent |
| HC00226_s | Palmitate(s) | blood constituent |

| Identifier | Name | Biological Process |
|---|---|---|
| HC00227_s | Pyridoxal(s) | blood constituent |
| HC00229_s | Isomaltose(s) | blood constituent |
| HC00230_s | Nicotinate(s) | blood constituent |
| HC00232_s | Riboflavin(s) | blood constituent |
| HC00238_s | Hypoxanthine(s) | blood constituent |
| HC00238_s | Hypoxanthine(s) | export of purine |
| HC00239_s | Homoserine(s) | blood constituent |
| HC00242_c | Dihydrobiopterin(c) | coenzyme biosynthetic process |
| HC00244_c | N-Acetylneuraminate(c) | lipoprotein biosynthetic process |
| HC00250_s | H2S(s) | blood constituent |
| HC00252_s | dGTP(s) | blood constituent |
| HC00253_b | HCO3-(b) | bile formation |
| HC00255_s | Inosine(s) | blood constituent |
| HC00256_s | Orotate(s) | blood constituent |
| HC00259_s | Uridine(s) | blood constituent |
| HC00260_s | Creatine(s) | blood constituent |
| HC00268_s | Pyridoxine(s) | blood constituent |
| HC00269_s | Spermidine(s) | polyamine biosynthetic process |
| HC00269_s | Spermidine(s) | polyamine metabolic process |
| HC00275_c | GDP-L-fucose(c) | glycoprotein biosynthetic process |
| HC00275_c | GDP-L-fucose(c) | proteoglycan biosynthetic process |
| HC00277_s | Citrulline(s) | blood constituent |
| HC00279_c | Glucosamine(c) | GPI anchor biosynthetic process |
| HC00279_s | Glucosamine(s) | blood constituent |
| HC00280_s | Deoxyguanosine(s) | blood constituent |
| HC00289_c | Thioredoxin(c) | cofactor biosynthetic process |
| HC00306_s | dGMP(s) | blood constituent |
| HC00307_s | dTDP(s) | blood constituent |
| HC00308_s | dTMP(s) | blood constituent |
| HC00310_s | Urate(s) | blood constituent |
| HC00310_s | Urate(s) | urate formation |
| HC00316_s | Thiamin(s) | blood constituent |
| HC00322_s | Guanosine(s) | blood constituent |
| HC00323_s | Histamine(s) | blood constituent |
| HC00323_s | Histamine(s) | hormone and neurotransmitter synthesis |
| HC00329_m | Ubiquinone(m) | blood constituent |
| HC00334_c | Isoleucine(c) | translation |
| HC00334_s | Isoleucine(s) | blood constituent |
| HC00334_s | Isoleucine(s) | blood constituent |
| HC00334_s | Isoleucine(s) | blood constituent |
| HC00368_s | dTTP(s) | blood constituent |
| HC00377_s | Ethanol(s) | blood constituent |
| HC00377_s | Ethanol(s) | detoxifizierung |
| HC00380_s | Ribitol(s) | blood constituent |
| HC00381_s | Cytidine(s) | blood constituent |
| HC00385_s | Bilirubin(s) | blood constituent |
| HC00389_s | Cystine(s) | blood constituent |
| HC00396_s | Folate(s) | blood constituent |
| HC00396_s | Folate(s) | blood constituent |
| HC00410_s | Deoxyuridine(s) | blood constituent |
| HC00415_s | NO(s) | blood constituent |
| HC00416_s | Pyridoxamine(s) | blood constituent |
| HC00418_c | Triphosphate(c) | catabolism |
| HC00425_s | Methylglyoxal(s) | blood constituent |
| HC00426_s | Noradrenaline(s) | blood constituent |
| HC00428_s | 4-Aminobutanal(s) | blood constituent |
| HC00431_s | Deoxyadenosine(s) | blood constituent |
| HC00474_c | N-Acetyl-D-mannosamine(c) | glycoprotein biosynthetic process |
| HC00474_s | N-Acetyl-D-mannosamine(s) | blood constituent |
| HC00502_b | Cholate(b) | bile formation |
| HC00502_s | Cholate(s) | blood constituent |
| HC00505_s | O2.-(s) | blood constituent |
| HC00525_s | Spermine(s) | polyamine biosynthetic process |
| HC00533_s | Serotonin(s) | blood constituent |
| HC00568_s | Pantothenate(s) | blood constituent |
| HC00568_s | Pantothenate(s) | blood constituent |
| HC00570_s | PNP(s) | blood constituent |
| HC00574_s | Deoxycytidine(s) | blood constituent |
| HC00658_s | Trehalose(s) | blood constituent |
| HC00661_s | (R)-3-Hydroxybutanoate(s) | keton body synthesis |

| Identifier | Name | Biological Process |
|---|---|---|
| HC00661_s | (R)-3-Hydroxybutanoate(s) | blood constituent |
| HC00683_c | S-Adenosylmethioninamine(c) | sulfur biosynthetic process |
| HC00715_s | D-3-Amino-isobutanoate(s) | blood constituent |
| HC00763_s | Na+(s) | blood constituent |
| HC00765_s | NH4+(s) | blood constituent |
| HC00784_s | Cys-Gly(s) | blood constituent |
| HC00793_s | Stearate(s) | blood constituent |
| HC00796_s | Linoleate(s) | blood constituent |
| HC00796_s | Linoleate(s) | blood constituent |
| HC00830_s | Elaidate(s) | blood constituent |
| HC00832_c | L-Fuculose(c) | glycoprotein biosynthetic process |
| HC00833_p | Lanosterol(p) | lipid biosynthetic process |
| HC00863_b | Glycocholate(b) | bile formation |
| HC00863_s | Glycocholate(s) | blood constituent |
| HC00898_s | Leukotriene_C4(s) | blood constituent |
| HC00904_c | Protein_lysine(c) | protein modification |
| HC00945_s | Xanthurenate(s) | blood constituent |
| HC00955_s | L-3-Cyanoalanine(s) | blood constituent |
| HC00958_b | Chenodiol(b) | bile formation |
| HC00958_s | Chenodiol(s) | blood constituent |
| HC00961_s | Estrone_3-sulfate(s) | blood constituent |
| HC01104_s | 4-Nitrophenyl-P(s) | blood constituent |
| HC01175_s | Dopamine(s) | blood constituent |
| HC01314_s | Dehydroepiandrosterone_sulfate(s) | blood constituent |
| HC01361_s | Dihydroneopterin(s) | blood constituent |
| HC01367_s | 6-[(1S,2R)-1,2-Dihydroxy-3-triphosphooxypropyl]-7,8-dihydropterin(s) | blood constituent |
| HC01378_b | Taurocholate(b) | bile formation |
| HC01378_s | Taurocholate(s) | blood constituent |
| HC01440_s | 3-Keto-beta-D-galactose(s) | blood constituent |
| HC01441_s | Lactose-6P(s) | blood constituent |
| HC01444_s | Galactosylglycerol(s) | blood constituent |
| HC01446_s | 3-Ketolactose(s) | blood constituent |
| HC01471_b | Taurochenodeoxycholate(b) | bile formation |
| HC01471_s | Taurochenodeoxycholate(s) | blood constituent |
| HC01471_s | Taurochenodeoxycholate(s) | blood constituent |
| HC01472_b | Glycochenodeoxycholate(b) | bile formation |
| HC01472_s | Glycochenodeoxycholate(s) | blood constituent |
| HC01577_s | gamma-Glutamyl-beta-cyanoalanine(s) | blood constituent |
| HC01609_s | UroporphyrinogenI(s) | blood constituent |
| HC01610_s | CoproporphyrinogenI(s) | blood constituent |
| HC01616_b | Bilirubin-bisglucuronoside(b) | bile formation |
| HC01616_s | Bilirubin-bisglucuronoside(s) | blood constituent |
| HC01664_s | LTD4(s) | blood constituent |
| HC01669_s | 2-Hydroxybutyrate(s) | blood constituent |
| HC01700_s | gamma-Glutamyl-3-aminopropiononitrile(s) | blood constituent |
| HC01787_s | Lepidimoide(s) | blood constituent |
| HC01788_s | Lignocerate(s) | blood constituent |
| HC01797_c | Activated_methyl_group(c) | cofactor biosynthetic process |
| HC01797_c | Activated_methyl_group(c) | coenzyme biosynthetic process |
| HC01846_s | Fe2+(s) | blood constituent |
| HC01847_s | Fe3+(s) | blood constituent |
| HC01852_s | Fibrinogen(s) | acute-phase response |
| HC01852_s | Fibrinogen(s) | blood coagulation |
| HC01852_s | Fibrinogen(s) | blood constituent |
| HC01939_s | Haptoglobin(s) | transport |
| HC01939_s | Haptoglobin(s) | acute-phase response |
| HC01939_s | Haptoglobin(s) | blood constituent |
| HC01940_s | HDL(s) | lipoprotein metabolic process |
| HC01940_s | HDL(s) | blood constituent |
| HC01942_s | Plasminogen(s) | acute-phase response |
| HC01942_s | Plasminogen(s) | blood coagulation |
| HC01942_s | Plasminogen(s) | blood constituent |
| HC01943_s | Prothrombin(s) | acute-phase response |
| HC01943_s | Prothrombin(s) | blood coagulation |
| HC01943_s | Prothrombin(s) | blood constituent |
| HC01944_s | ApoTransferin(s) | transport |
| HC01944_s | ApoTransferin(s) | iron ion transport |
| HC01944_s | ApoTransferin(s) | blood constituent |
| HC01945_s | VLDL(s) | lipoprotein metabolic process |
| HC01945_s | VLDL(s) | very-low-density lipoprotein particle assembly |

| Identifier | Name | Biological Process |
|---|---|---|
| HC01945_s | VLDL(s) | blood constituent |
| HC01969_r | Cholesterol-ester-pool(r) | membrane lipid metabolic process |
| HC01969_r | Cholesterol-ester-pool(r) | lipoprotein metabolic process |
| HC01971_s | LDL(s) | lipoprotein metabolic process |
| HC01971_s | LDL(s) | blood constituent |
| HC01981_s | Palmitolate(s) | blood constituent |
| HC02000_s | PC-VLDL-pool(s) | blood constituent |
| HC02000_r | PC-VLDL-pool(r) | membrane lipid metabolic process |
| HC02000_r | PC-VLDL-pool(r) | lipoprotein metabolic process |
| HC02002_b | PE-VLDL-pool(b) | bile formation |
| HC02002_r | PE-VLDL-pool(r) | membrane lipid metabolic process |
| HC02002_r | PE-VLDL-pool(r) | lipoprotein metabolic process |
| HC02006_b | PS-VLDL-pool(b) | bile formation |
| HC02006_r | PS-VLDL-pool(r) | membrane lipid metabolic process |
| HC02006_r | PS-VLDL-pool(r) | lipoprotein metabolic process |
| HC02007_b | SM-pool(b) | bile formation |
| HC02007_r | SM-pool(r) | membrane lipid metabolic process |
| HC02008_c | Glucosylceramide-pool(c) | lipid biosynthetic process |
| HC02008_s | Glucosylceramide-pool(s) | blood constituent |
| HC02008_r | Glucosylceramide-pool(r) | lipid biosynthetic process |
| HC02009_r | PI-pool(r) | membrane lipid metabolic process |
| HC02016_r | 2-Lysolecithin-pool(r) | lipid biosynthetic process |
| HC02062_r | Triacylglycerol-VLDL-pool(r) | lipoprotein metabolic process |
| HC02080_b | Bile-PC-pool(b) | bile formation |
| HC02087_m | CL-pool(m) | membrane lipid metabolic process |
| HC02111_c | ATP-energy(c) | cofactor biosynthetic process |
| HC02112_c | NADH-redox-potential(c) | cofactor biosynthetic process |
| HC02113_c | NADPH-redox-potential(c) | cofactor biosynthetic process |
| HC02115_c | Proton-gradient(c) | cofactor biosynthetic process |
| HC02115_m | Proton-gradient(m) | cofactor biosynthetic process |
| HC02116_c | activated-sulphur(c) | cofactor biosynthetic process |
| HC02118_s | Chitin-component(s) | blood constituent |
| HC02119_c | Adenosylmethioninamine-potential(c) | polyamine metabolic process |
| HC02120_c | Methylthioribose-1P(c) | sulfur biosynthetic process |
| HC02134_c | Glycogenin-G4G7(c) | glycogen biosynthetic process |
| HC02134_c | Glycogenin-G4G7(c) | glycogenolysis |
| HC02154_c | GM4-pool(c) | very-low-density lipoprotein particle assembly |
| HC02154_s | GM4-pool(s) | very-low-density lipoprotein particle assembly |
| HC02160_s | GM2-pool(s) | very-low-density lipoprotein particle assembly |
| HC02161_s | GM1-pool(s) | very-low-density lipoprotein particle assembly |
| HC02162_s | LacCer-pool(s) | lipid biosynthetic process |
| HC02162_r | LacCer-pool(r) | lipid biosynthetic process |

Supplementary Table 3.1 : Exchange Set Definition - MIMES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00017 | O2 | s | import |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | import |
| HC00040 | Glucose | s | import |
| HC00053 | Lysine | s | import |
| HC00062 | Sulfate | s | both |
| HC00075 | Methionine | s | import |
| HC00080 | Tryptophan | s | import |
| HC00081 | Phenylalanine | s | import |
| HC00089 | Urea | s | export |
| HC00112 | Choline | c | both |
| HC00121 | Leucine | s | import |
| HC00133 | Histidine | s | import |
| HC00149 | Nicotinamide | s | import |
| HC00174 | Valine | s | import |
| HC00178 | Cholesterol | b | export |
| HC00179 | Threonine | s | import |
| HC00180 | Ethanolamine | c | both |
| HC00202 | Arachidonate | s | both |
| HC00232 | Riboflavin | s | import |
| HC00250 | H2S | s | export |
| HC00268 | Pyridoxine | s | import |
| HC00310 | Urate | s | export |
| HC00334 | Isoleucine | s | import |
| HC00396 | Folate | s | import |
| HC00568 | Pantothenate | s | import |
| HC00796 | Linoleate | s | import |
| HC01846 | Fe2+ | s | import |
| HC01981 | Palmitolate | s | import |

Supplementary Table 3.2 : Exchange Set Definition - MIPES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00017 | O2 | s | import |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | import |
| HC00034 | Glutamate | s | export |
| HC00040 | Glucose | s | import |
| HC00045 | Glycine | s | export |
| HC00048 | Alanine | s | export |
| HC00053 | Lysine | s | both |
| HC00055 | Aspartate | s | export |
| HC00062 | Sulfate | s | both |
| HC00065 | Arginine | s | export |
| HC00067 | Glutamine | s | export |
| HC00068 | Serine | s | export |
| HC00075 | Methionine | s | both |
| HC00080 | Tryptophan | s | both |
| HC00081 | Phenylalanine | s | both |
| HC00085 | Tyrosine | s | export |
| HC00089 | Urea | s | export |
| HC00099 | Cysteine | s | export |
| HC00112 | Choline | c | both |
| HC00121 | Leucine | s | both |
| HC00133 | Histidine | s | both |
| HC00145 | Proline | s | export |
| HC00148 | Asparagine | s | export |
| HC00149 | Nicotinamide | s | import |
| HC00174 | Valine | s | both |
| HC00177 | L-Lactate | s | export |
| HC00178 | Cholesterol | b | export |
| HC00179 | Threonine | s | both |
| HC00180 | Ethanolamine | c | both |
| HC00202 | Arachidonate | s | both |
| HC00232 | Riboflavin | s | import |
| HC00250 | H2S | s | export |
| HC00268 | Pyridoxine | s | import |
| HC00310 | Urate | s | export |
| HC00334 | Isoleucine | s | both |
| HC00389 | Cystine | s | export |
| HC00396 | Folate | s | import |
| HC00568 | Pantothenate | s | import |
| HC00796 | Linoleate | s | both |
| HC01846 | Fe2+ | s | both |
| HC01981 | Palmitolate | s | both |

Supplementary Table 3.3 : Exchange Set Definition - PIPES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00017 | O2 | s | import |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | import |
| HC00034 | Glutamate | s | both |
| HC00040 | Glucose | s | both |
| HC00045 | Glycine | s | both |
| HC00048 | Alanine | s | both |
| HC00053 | Lysine | s | both |
| HC00055 | Aspartate | s | both |
| HC00062 | Sulfate | s | both |
| HC00065 | Arginine | s | both |
| HC00067 | Glutamine | s | both |
| HC00068 | Serine | s | both |
| HC00075 | Methionine | s | both |
| HC00080 | Tryptophan | s | both |
| HC00081 | Phenylalanine | s | both |
| HC00085 | Tyrosine | s | both |
| HC00089 | Urea | s | export |
| HC00099 | Cysteine | s | both |
| HC00112 | Choline | c | both |
| HC00121 | Leucine | s | both |
| HC00133 | Histidine | s | both |
| HC00145 | Proline | s | both |
| HC00148 | Asparagine | s | both |
| HC00149 | Nicotinamide | s | import |
| HC00174 | Valine | s | both |
| HC00177 | L-Lactate | s | both |
| HC00178 | Cholesterol | b | export |
| HC00179 | Threonine | s | both |
| HC00180 | Ethanolamine | c | both |
| HC00202 | Arachidonate | s | both |
| HC00226 | Palmitate | s | both |
| HC00232 | Riboflavin | s | import |
| HC00250 | H2S | s | export |
| HC00268 | Pyridoxine | s | import |
| HC00310 | Urate | s | export |
| HC00334 | Isoleucine | s | both |
| HC00389 | Cystine | s | both |
| HC00396 | Folate | s | import |
| HC00510 | Oleate | s | both |
| HC00568 | Pantothenate | s | import |
| HC00793 | Stearate | s | both |
| HC00796 | Linoleate | s | both |
| HC01846 | Fe2+ | s | both |
| HC01981 | Palmitolate | s | both |

Supplementary Table 3.4 : Exchange Set Definition - MES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00017 | O2 | s | import |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | import |
| HC00040 | Glucose | s | import |
| HC00053 | Lysine | s | import |
| HC00062 | Sulfate | s | both |
| HC00075 | Methionine | s | import |
| HC00080 | Tryptophan | s | import |
| HC00081 | Phenylalanine | s | import |
| HC00089 | Urea | s | export |
| HC00112 | Choline | c | import |
| HC00121 | Leucine | s | import |
| HC00133 | Histidine | s | import |
| HC00149 | Nicotinamide | s | import |
| HC00174 | Valine | s | import |
| HC00179 | Threonine | s | import |
| HC00180 | Ethanolamine | c | import |
| HC00202 | Arachidonate | s | import |
| HC00232 | Riboflavin | s | import |
| HC00268 | Pyridoxine | s | import |
| HC00310 | Urate | s | export |
| HC00329 | Ubiquinone | m | import |
| HC00334 | Isoleucine | s | import |
| HC00396 | Folate | s | import |
| HC00568 | Pantothenate | s | import |
| HC00796 | Linoleate | s | import |
| HC01981 | Palmitolate | s | import |

Supplementary Table 3.5 : Exchange Set Definition - DES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00017 | O2 | s | both |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | both |
| HC00024 | NH3 | s | both |
| HC00040 | Glucose | s | both |
| HC00053 | Lysine | s | both |
| HC00062 | Sulfate | s | both |
| HC00075 | Methionine | s | both |
| HC00080 | Tryptophan | s | both |
| HC00081 | Phenylalanine | s | both |
| HC00089 | Urea | s | both |
| HC00112 | Choline | c | both |
| HC00121 | Leucine | s | both |
| HC00133 | Histidine | s | both |
| HC00149 | Nicotinamide | s | both |
| HC00174 | Valine | s | both |
| HC00178 | Cholesterol | b | export |
| HC00179 | Threonine | s | both |
| HC00180 | Ethanolamine | c | both |
| HC00202 | Arachidonate | s | export |
| HC00232 | Riboflavin | s | both |
| HC00268 | Pyridoxine | s | both |
| HC00310 | Urate | s | both |
| HC00329 | Ubiquinone | m | both |
| HC00334 | Isoleucine | s | both |
| HC00396 | Folate | s | both |
| HC00510 | Oleate | c | export |
| HC00568 | Pantothenate | s | both |
| HC00796 | Linoleate | s | export |
| HC01981 | Palmitolate | s | export |
| HC02111 | ATP-energy | c | export |
| HC02111 | ATP-energy | m | export |

Supplementary Table 3.6 : Exchange Set Definition - HES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | both |
| HC00019 | Pi | s | both |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | import |
| HC00040 | Glucose | s | import |
| HC00053 | Lysine | s | import |
| HC00062 | Sulfate | s | both |
| HC00075 | Methionine | s | import |
| HC00080 | Tryptophan | s | import |
| HC00081 | Phenylalanine | s | import |
| HC00089 | Urea | s | export |
| HC00112 | Choline | c | import |
| HC00121 | Leucine | s | import |
| HC00133 | Histidine | s | import |
| HC00149 | Nicotinamide | s | import |
| HC00174 | Valine | s | import |
| HC00179 | Threonine | s | import |
| HC00180 | Ethanolamine | c | import |
| HC00202 | Arachidonate | s | import |
| HC00232 | Riboflavin | s | import |
| HC00268 | Pyridoxine | s | import |
| HC00310 | Urate | s | export |
| HC00329 | Ubiquinone | m | import |
| HC00334 | Isoleucine | s | import |
| HC00396 | Folate | s | import |
| HC00568 | Pantothenate | s | import |
| HC00796 | Linoleate | s | import |
| HC01981 | Palmitolate | s | import |

Supplementary Table 3.7 : Exchange Set Definition - WES

| ID | name | compartment | direction |
|---|---|---|---|
| HC00011 | H2O | s | export |
| HC00019 | Pi | s | export |
| HC00021 | CO2 | s | export |
| HC00024 | NH3 | s | export |
| HC00062 | Sulfate | s | export |
| HC00089 | Urea | s | export |

## Supplementary Table 4 : Biochemical objectives - Network comparison

| No. | Simulation ID | HepatoNet | Recon1 | Shlomi/liver<br>Recon1 without negative confidence |
|---|---|---|---|---|
| | **rephosphorylation of purines and pyrimidines** | | | |
| 1 | Aerobic rephosphorylation of ATP from glucose | success | success(*) | success(*) |
| 2 | Aerobic rephosphorylation of ATP from a fatty acid | success | success(*) | success(*) |
| 3 | Aerobic rephosphorylation of GTP | success | success(*) | success(*) |
| 4 | Aerobic rephosphorylation of CTP | success | success(*) | success(*) |
| 5 | Aerobic rephosphorylation of UTP | success | success(*) | success(*) |
| 6 | Anaerobic rephosphorylation of ATP | success | success(*) | success(*) |
| 7 | Anaerobic rephosphorylation of GTP | success | success(*) | success(*) |
| 8 | Anaerobic rephosphorylation of CTP | success | success(*) | success(*) |
| 9 | Anaerobic rephosphorylation of UTP | success | success(*) | success(*) |
| | **de-novo synthesis of purines and pyrimidines** | | | |
| 10 | ATP | success | success | fail |
| 11 | CTP | success | success | success |
| 12 | GTP | success | success | fail |
| 13 | UTP | success | success | success |
| 14 | dATP | success | success | fail |
| 15 | dCTP | success | success | fail |
| 16 | dGTP | success | success | fail |
| 17 | dTTP | success | success | fail |
| | **salvage of purines and pyrimidines** | | | |
| 18 | ATP salvage from Adenosine | success | success | success |
| 19 | ATP salvage from Hypoxanthine | success | success | fail |
| 20 | dTTP salvage from Thymine | success | success | fail |
| | **regeneration of NAD(P)H redox potential** | | | |
| 21 | Aerobic reduction of NAD+ | success | success | fail |
| 22 | Aerobic reduction of NADP+ | success | success | fail |
| | **gluconeogenese** | | | |
| 23 | Gluconeogenese from Lactate | success | success | success |
| 24 | Gluconeogenese from Glycerol | success | success | success |
| 25 | Gluconeogenese from Alanine | success | success | success |
| 26 | Gluconeogenese from Lactate and optionally fatty acid | success | success | success |
| 27 | Gluconeogenese from Glycerol and optionally fatty acid | success | success | success |
| 28 | Gluconeogenese from Alanine and optionally fatty acid | success | success | success |
| | **glycogenesis** | | | |
| 29 | Storage of glucose in Glycogen | success | success | success |
| | **glycogenolysis** | | | |
| 30 | Release of glucose from Glycogen | success | success | success |

Supplementary Table 4 : Biochemical objectives - Network comparison

| No. | Simulation ID | HepatoNet | Recon1 | Shlomi/liver Recon1 without negative confidence |
|---|---|---|---|---|
| | **sugar degradation** | | | |
| 31 | Fructose degradation | success | success | success |
| 32 | Galactose degradation | success | success | success |
| | **formation of nucleotide-activated sugars** | | | |
| 33 | UDP-glucose | success | success | success |
| 34 | UDP-galactose | success | success | success |
| 35 | UDP-glucuronate | success | success | success |
| 36 | GDP-L-fucose | success | success | fail |
| 37 | GDP-mannose | success | success | fail |
| 38 | UDP-N-acetyl-D-galactosamine | success | success | fail |
| 39 | CMP-N-acetylneuraminate | success | success | fail |
| | **formation of aminosugars** | | | |
| 40 | N-Acetylglucosamine | success | success | fail |
| | **formation of sugars** | | | |
| 41 | Glucuronate | success | success | success |
| | **formation of non-essential amino acids** | | | |
| 42 | Alanine | success | success | success |
| 43 | Arginine | success | success | success |
| 44 | Asparagine | success | success | fail |
| 45 | Aspartate | success | success | success |
| 46 | Cysteine | success | fail | fail |
| 47 | Cystine | success | fail | fail |
| 48 | Glutamate | success | success | success |
| 49 | Glycine | success | success | success |
| 50 | Glutamine | success | success | success |
| 51 | Proline | success | success | success |
| 52 | Serine | success | success | success |
| 53 | Tyrosine | success | success | fail |
| | **complete degradation of amino acids** | | | |
| 54 | Alanine degradation | success | success | success |
| 55 | Arginine degradation | success | success | success |
| 56 | Asparagine degradation | success | success | success |
| 57 | Aspartate degradation | success | success | success |
| 58 | Cysteine degradation | success | success | fail |
| 59 | Glutamate degradation | success | success | success |
| 60 | Glycine degradation | success | success | success |
| 61 | Histidine degradation | success | success | success |

| No. | Simulation ID | HepatoNet | Recon1 | Shlomi/liver Recon1 without negative confidence |
|---|---|---|---|---|
| | **complete degradation of amino acids (cont.)** | | | |
| 62 | Isoleucine degradation | success | success | success |
| 63 | Glutamine degradation | success | success | success |
| 64 | Leucine degradation | success | success | success |
| 65 | Lysine degradation | success | success | success |
| 66 | Methionine degradation | success | fail | fail |
| 67 | Phenylalanine degradation | success | success | fail |
| 68 | Proline degradation | success | success | success |
| 69 | Serine degradation | success | success | success |
| 70 | Threonine degradation | success | fail | fail |
| 71 | Tryptophan degradation | success | success | success |
| 72 | Tyrosine degradation | success | success | fail |
| 73 | Valine degradation | success | success | success |
| 74 | Homocysteine degradation | success | fail | fail |
| 75 | beta-Alanine degradation | success | success | success |
| 76 | Ornithine degradation | success | not defined | not defined |
| | **plasmaprotein biosynthesis** | | | |
| 77 | Albumin | success | not defined | not defined |
| | **ureogenesis** | | | |
| 78 | Urea from alanine | success | success | success |
| 79 | Urea from glutamine | success | success | success |
| | **creatine biosynthesis** | | | |
| 80 | Creatine | success | success | success |
| | **heme biosynthesis** | | | |
| 81 | Heme | success | success | fail |
| | **phospholipid biosynthesis** | | | |
| 82 | PC | success | success | success |
| 83 | PE | success | success | success |
| 84 | PS | success | success | success |
| 85 | PI | success | success | success |
| 86 | Cardiolipin | success | success | success |
| | **sphingolipid biosynthesis** | | | |
| 87 | SM | success | success | success |
| 88 | Ceramide | success | success | success |
| 89 | Lactosylceramide | success | fail | fail |

## Supplementary Table 4 : Biochemical objectives - Network comparison

|  |  |  |  | **Shlomi/liver** |
|---|---|---|---|---|
| **No.** | **Simulation ID** | **HepatoNet** | **Recon1** | **Recon1 without negative confidence** |
|  | **biosynthesis of cofactors** |  |  |  |
| 90 | CoA | success | success | success |
| 91 | NAD | success | success | fail |
| 92 | NADP | success | success | fail |
| 93 | FAD | success | success | fail |
| 94 | Thioredoxin | success | fail | fail |
| 95 | THF | success | success | success |
| 96 | Pyridoxal-P | success | success | success |
|  | **fatty acid biosynthesis** |  |  |  |
| 97 | Palmitate | success | success | fail |
| 98 | Oleate | success | fail | fail |
| 99 | Stearate | success | fail | fail |
|  | **fatty acid degradation** |  |  |  |
| 100 | Complete oxidation of oleate | success | fail | fail |
|  | **fatty acid transformation** |  |  |  |
| 101 | Arachidonate from Linoleate | success | success | fail |
|  | **triglyceride biosynthesis** |  |  |  |
| 102 | Triacylglycerol | success | success | success |
|  | **cholesterol biosynthesis** |  |  |  |
| 103 | Cholesterol | success | fail | fail |
|  | **farnesylpyrophosphate biosynthesis** |  |  |  |
| 104 | Farnesyl-PP | success | success | fail |
|  | **ketogenesis** |  |  |  |
| 105 | Acetoacetate | success | success | success |
| 106 | (R)-3-Hydroxybutanoate | success | success | success |
|  | **VLDL formation** |  |  |  |
| 107 | VLDL | success | not defined | not defined |
|  | **LDL catabolism** |  |  |  |
| 108 | LDL degradation | success | not defined | not defined |
|  | **Bile formation** |  |  |  |
| 109 | Glycocholate bile | success | success | fail |
| 110 | Glycochenodeoxycholate bile | success | success | fail |
| 111 | Taurocholate bile | success | success | fail |
| 112 | Taurochenodeoxycholate bile | success | success | fail |
| 113 | PC bile | success | success | success |
| 114 | PS bile | success | fail | fail |
| 115 | PE bile | success | fail | fail |
| 116 | SM bile | success | success | success |

Supplementary Table 4 : Biochemical objectives - Network comparison

| No. | Simulation ID | HepatoNet | Recon1 | Shlomi/liver<br>Recon1 without negative confidence |
|---|---|---|---|---|
| | **biosynthesis of cofactors** | | | |
| 117 | PAPS | success | success | fail |
| 118 | SAM | success | success | fail |
| | **formation of glutathione** | | | |
| 119 | GSH | success | fail | fail |
| | **detoxification of reactive oxygen species** | | | |
| 120 | O radical | success | success | success |
| | **bilirubin catabolism** | | | |
| 121 | Bilirubin conjugation | success | success | success |
| | **detoxification of xenobiotics** | | | |
| 122 | NH3 degradation | success | success | fail |
| 123 | Ethanol degradation | success | success | success |

(*) A balanced flux solution has been found but might be thermodynamically infeasible.

## Supplementary Table 5 : Essentiality of Enzymes for tested Objectives

| Enzyme Name | Rank | Disease | Reference |
|---|---|---|---|
| ATP:AMP phosphotransferase | 80 | adenylate kinase deficiency | PMID15315793 |
| ubiquinol:ferricytochrome-c oxidoreductase | 75 | Ubiquinol cytochrome c reductase (complex III) deficiency | PMID10453733 |
| ferrocytochrome-c:oxygen oxidoreductase | 75 | cytochrome c oxidase (COX) deficiency | PMID16326995 |
| 2-(Nomega-L-arginino)succinate arginine-lyase (fumarate-forming) | 29 | argininosuccinic aciduria | PMID20298553 |
| L-citrulline:L-aspartate ligase (AMP-forming) | 29 | argininosuccinate synthetase deficiency | PMID2358466 |
| carbon-dioxide:ammonia ligase (ADP-forming, carbamate-phosphorylating) | 29 | Carbamyl phosphate synthetase I deficiency | PMID3270854 |
| carbamoyl-phosphate:L-ornithine carbamoyltransferase | 29 | Ornithine transcarbamylase (OTC) deficiency | PMID9686344 |
| L-glutamate:ammonia ligase (ADP-forming) | 23 | glutamine synthetase deficiency | PMID16763901 |
| ATP:D-ribose-5-phosphate diphosphotransferase | 22 | | |
| 5,10-methylenetetrahydrofolate:NADP+ oxidoreductase | 21 | 5,10-Methylenetetrahydrofolate reductase deficiency | PMID3939530 |
| 5,10-methylenetetrahydrofolate:glycine hydroxymethyltransferase | 18 | serine hydroxymethyltransferase (SHMT) deficiency | PMID8533763 |
| succinate:ubiquinone oxidoreductase | 18 | Succinate dehydrogenase deficiency | PMID16143825 |
| D-glyceraldehyde-3-phosphate:NAD+ oxidoreductase (phosphorylating) | 14 | | |
| ATP:3-phospho-D-glycerate 1-phosphotransferase | 14 | Phosphoglycerate Kinase Deficiency | PMID11596414 |
| 10-formyltetrahydrofolate:5'-phosphoribosylglycinamide N-formyltransferase | 12 | | |
| 10-formyltetrahydrofolate:5'-phosphoribosyl-5-amino-4-imidazole-carb oxamide N-formyltransferase | 12 | AICA-Ribosiduria | PMID15114530 |
| 5-phospho-D-ribosylamine:glycine ligase (ADP-forming) | 12 | | |
| 5-phospho-beta-D-ribosylamine:diphosphate phospho-alpha-D-ribosyltransferase (glutamate-amidating) | 12 | | |
| 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate:L-aspartate ligase (ADP-forming) | 12 | | |
| 5-amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxylate carboxy-lyase | 12 | | |
| 2-(formamido)-N1-(5-phosphoribosyl)acetamidine cyclo-ligase (ADP-forming) | 12 | | |
| N6-(1,2-dicarboxyethyl)AMP AMP-lyase (fumarate-forming) | 12 | Adenylosuccinase deficiency | PMID3234432 |
| N2-formyl-N1-(5-phospho-D-ribosyl)glycinamide:L-glutamine amido-ligase (ADP-forming) | 12 | | |
| IMP 1,2-hydrolase (decyclizing) | 12 | AICA-Ribosiduria | PMID15114530 |
| 2-phospho-D-glycerate hydro-lyase (phosphoenolpyruvate-forming) | 10 | | |
| 2-oxobutanoate:ferredoxin 2-oxidoreductase (CoA-propanoylating) | 10 | | |
| D-phosphoglycerate 2,3-phosphomutase | 10 | Phosphoglycerate mutase deficiency | PMID19322572 |
| D-glyceraldehyde-3-phosphate aldose-ketose-isomerase | 10 | Triose phosphate isomerase deficiency | PMID3729826 |
| D-glucose-6-phosphate aldose-ketose-isomerase | 10 | glucose-phosphate-isomerase | PMID19786097 |
| ATP:nucleoside-phosphate phosphotransferase | 10 | | |
| (S)-dihydroorotate amidohydrolase | 9 | | |
| orotidine-5'-phosphate:diphosphate phospho-alpha-D-ribosyl-transferase | 9 | | |
| orotidine-5'-phosphate carboxy-lyase (UMP-forming) | 9 | | |
| L-serine hydro-lyase (adding homocysteine; L-cystathionine-forming) | 9 | | |
| IMP:L-aspartate ligase (GDP-forming) | 9 | adenylosuccinate synthetase deficiency | PMID6957854 |
| hydrogen-carbonate:L-glutamine amido-ligase (ADP-forming, carbamate-phosphorylating) | 9 | | |
| carbamoyl-phosphate:L-aspartate carbamoyltransferase | 9 | | |
| acetyl-CoA:oxaloacetate C-acetyltransferase [thioester-hydrolysing, (pro-S)-carboxymethyl forming] | 9 | | |
| 5-methyltetrahydrofolate:L-homocysteine S-methyltransferase | 8 | Methionine synthase deficiency | PMID15931548 |
| 5,10-methenyltetrahydrofolate 5-hydrolase (decyclizing) | 7 | | |
| isopentenyl-diphosphate Delta3-Delta2-isomerase | 7 | | |
| geranyl-diphosphate:isopentenyl-diphosphate geranyltranstransferase | 7 | | |
| dimethylallyl-diphosphate:isopentenyl-diphosphate dimethylallyltranstransferase | 7 | | |
| ATP:(R)-mevalonate 5-phosphotransferase | 7 | | |
| ATP:(R)-5-phosphomevalonate phosphotransferase | 7 | | |
| ATP:(R)-5-diphosphomevalonate carboxy-lyase (adding ATP; isopentenyl-diphosphate-forming) | 7 | | |
| 4,4-dimethyl-5alpha-cholesta-8,24-dien-3beta-ol:NADP+ Delta14-oxidoreductase | 6 | | |
| 4,4-dimethyl-5alpha-cholest-7-en-3beta-ol,NAD(P)H:oxygen oxidoreductase (hydroxylating) | 6 | | |
| 3beta-hydroxy-steroid:NADP+ 3-oxidoreductase | 6 | | |
| 3beta-hydroxy-4beta-methyl-5alpha-cholest-7-ene-4alpha-carboxylate:N AD(P)+ 3-oxidoreductase (decarboxylating) | 6 | | |

## Supplementary Table 5 : Essentiality of Enzymes for tested Objectives

| Enzyme Name | Rank | Disease | Reference |
|---|---|---|---|
| UTP:alpha-D-glucose-1-phosphate uridylyltransferase | 6 | | |
| sterol,NADPH:oxygen oxidoreductase (14-methyl cleaving) | 6 | | |
| squalene,hydrogen-donor:oxygen oxidoreductase (2,3-epoxidizing) | 6 | | |
| (S)-lactate:NAD+ oxidoreductase | 6 | | |
| (S)-2,3-epoxysqualene mutase (cyclizing, lanosterol-forming) | 6 | | |
| palmitoyl-CoA:L-serine C-palmitoyltransferase (decarboxylating) | 6 | serine palmitoyltransferase | PMID19648608 |
| farnesyl-diphosphate:farnesyl-diphosphate farnesyltransferase | 6 | | |
| D-erythro-dihydrosphingosine:NADP+ 3-oxidoreductase | 6 | | |
| alpha-D-glucose 1,6-phosphomutase | 6 | phosphoglucomutase 1 deficiency | PMID19625727 |
| CTP:ethanolamine-phosphate cytidylyltransferase | 5 | | |
| CTP:choline-phosphate cytidylyltransferase | 5 | | |
| ATP:ethanolamine O-phosphotransferase | 5 | | |
| ATP:choline phosphotransferase | 5 | | |
| acyl-CoA:sphingosine N-acyltransferase | 5 | | |
| 3-phospho-D-glycerate:NAD+ 2-oxidoreductase | 4 | 3-phosphoglycerate dehydrogenase deficiency | PMID20196394 |
| O-phosphoserine phosphohydrolase | 4 | 3-phosphoserine phosphatase deficiency | PMID14673469 |
| O-phospho-L-serine:2-oxoglutarate aminotransferase | 4 | Phosphoserine aminotransferase deficiency | PMID17436247 |
| long-chain-(S)-3-hydroxyacyl-CoA:NAD+ oxidoreductase | 4 | | |
| L-cystathionine cysteine-lyase (deaminating; 2-oxobutanoate-forming) | 4 | | |
| IMP:NAD+ oxidoreductase | 4 | | |
| cholesterol,NADPH:oxygen oxidoreductase (7alpha-hydroxylating) | 4 | 7alpha-hydroxylase deficiency | PMID12093894 |
| cholest-5-ene-3beta,7alpha-diol:NAD+ 3-oxidoreductase | 4 | | |
| acyl-CoA:oxygen 2-oxidoreductase | 4 | | |
| acyl-CoA:acetyl-CoA C-acyltransferase | 4 | thiolase deficiency | PMID19291920 |
| 1D-myo-inositol-3-phosphate lyase (isomerizing) | 3 | | |
| UTP:N-acetyl-alpha-D-glucosamine-1-phosphate uridylyltransferase | 3 | | |
| UDP-glucose 4-epimerase | 3 | Epimerase-deficiency galactosemia | PMID16385452 |
| sn-glycerol 3-phosphate:quinone oxidoreductase | 3 | | |
| (S)-1-pyrroline-5-carboxylate:NAD+ oxidoreductase | 3 | | |
| N-acetyl-alpha-D-glucosamine 1,6-phosphomutase | 3 | | |
| myo-inositol-phosphate phosphohydrolase | 3 | | |
| L-ornithine:2-oxo-acid aminotransferase | 3 | ornithine delta-aminotransferase deficiency | PMID19345633 |
| CDP-diacylglycerol:myo-inositol 3-phosphatidyltransferase | 3 | | |
| CDP-choline:N-acylsphingosine cholinephosphotransferase | 3 | Sphingomyelin synthase 2 deficiency | PMID18566297 |
| ATP:glycerol 3-phosphotransferase | 3 | glycerol kinase deficiency | PMID17489818 |
| acid:CoA ligase (AMP-forming) | 3 | | |
| 10-formyltetrahydrofolate:NADP+ oxidoreductase | 2 | | |
| 5beta-cholestane-3alpha,7alpha,12alpha-triol,NADPH:oxygen oxidoreductase (26-hydroxylating) | 2 | | |
| 5beta-cholestan-3-one:NADP+ 4,5-oxidoreductase | 2 | | |
| 4-maleylacetoacetate cis-trans-isomerase | 2 | | |
| 4-hydroxyphenylpyruvate:oxygen oxidoreductase (hydroxylating, decarboxylating) | 2 | hypertyrosinaemia | PMID6133038 |
| 4-fumarylacetoacetate fumarylhydrolase | 2 | fumarylacetoacetate hydrolase deficiency | PMID8821854 |
| 4-aminobutanoate:2-oxoglutarate aminotransferase | 2 | GABA-transaminase deficiency | PMID10407778 |
| 3-oxo-5beta-steroid:acceptor Delta4-oxidoreductase | 2 | Delta 4-3-oxosteroid 5 beta-reductase deficiency | PMID7965448 |
| 2-methyl-3-oxopropanoate:NAD+ 3-oxidoreductase (CoA-propanoylating) | 2 | | |
| UDP-N-acetyl-D-glucosamine 2-epimerase | 2 | | |
| UDP-glucose:NAD+ 6-oxidoreductase | 2 | UDP-glucose dehydrogenase | PMID17927902 |
| triacylglycerol acylhydrolase | 2 | Lipoprotein Lipase Deficiency | PMID20301485 |
| (S)-3-hydroxyacyl-CoA:NAD+ oxidoreductase | 2 | 3-Hydroxyacyl-coenzyme A dehydrogenase deficiency | PMID19417036 |
| (S)-3-hydroxy-3-methylglutaryl-CoA acetoacetate-lyase (acetyl-CoA-forming) | 2 | HMG-CoA lyase deficiency | PMID17692550 |

Supplementary Table 5 : Essentiality of Enzymes for tested Objectives

| Enzyme Name | Rank | Disease | Reference |
|---|---|---|---|
| L-tyrosine:2-oxoglutarate aminotransferase | 2 | | |
| L-phenylalanine,tetrahydrobiopterin:oxygen oxidoreductase (4-hydroxylating) | 2 | PKU | PMID19786003 |
| hypotaurine:NAD+ oxidoreductase | 2 | | |
| hydrogen-peroxide:hydrogen-peroxide oxidoreductase | 2 | catalase deficiency | PMID1551654 |
| homogentisate:oxygen 1,2-oxidoreductase (decyclizing) | 2 | alkaptonuria | PMID19862842 |
| GTP:alpha-D-mannose-1-phosphate guanylyltransferase | 2 | | |
| glutaryl-CoA:acceptor 2,3-oxidoreductase (decarboxylating) | 2 | glutaryl-coenzyme A dehydrogenase deficiency | PMID20032085 |
| D-mannose-6-phosphate aldose-ketose-isomerase | 2 | phosphomannose isomerase deficiency | PMID10963387 |
| deamido-NAD+:L-glutamine amido-ligase (AMP-forming) | 2 | | |
| ATP:nucleoside-diphosphate phosphotransferase | 2 | | |
| ATP:nicotinamide-nucleotide adenylyltransferase | 2 | | |
| ATP:L-methionine S-adenosyltransferase | 2 | Methionine adenosyltransferase deficiency | PMID16435220 |
| ATP:dTMP phosphotransferase | 2 | | |
| ATP diphosphohydrolase (phosphate-forming) | 2 | | |
| alpha-D-mannose 1,6-phosphomutase | 2 | | |
| aldehyde:NAD+ oxidoreductase | 2 | | |
| acetyl-CoA:acetoacetyl-CoA C-acetyltransferase (thioester-hydrolysing, carboxymethyl-forming) | 2 | HMG-CoA synthase deficiency | PMID11479731 |
| (25R)-5beta-cholestane-3alpha,7alpha,12alpha,26-tetraol:NAD+ 26-oxidoreductase | 2 | | |
| (25R)-3alpha,7alpha,12alpha-trihydroxy-5beta-cholestan-26-al:NAD+ 26-oxidoreductase | 2 | | |
| (24R,25R)-3alpha,7alpha,12alpha,24-tetrahydroxy-5beta-cholestanoyl-C oA hydro-lyase | 2 | | |
| 5,10-methylenetetrahydrofolate:dUMP C-methyltransferase | 1 | | |
| 5,6-dihydropyrimidine amidohydrolase | 1 | dihydropyrimidinase deficiency | PMID17383919 |
| 6-phospho-D-glucono-1,5-lactone lactonohydrolase | 1 | 6-Phosphogluconolactonase deficiency | PMID3858849 |
| 6-phospho-D-gluconate:NADP+ 2-oxidoreductase (decarboxylating) | 1 | | |
| 5-formimidoyltetrahydrofolate:L-glutamate N-formimidoyltransferase | 1 | glutamate formiminotransferase deficiency | PMID12815595 |
| 5-formimidoyltetrahydrofolate ammonia-lyase (cyclizing; 5,10-methenyltetrahydrofolate-forming) | 1 | | |
| 5-aminolevulinate hydro-lyase (adding 5-aminolevulinate and cyclizing; porphobilinogen-forming) | 1 | porphyria | PMID15303011 |
| 3-sn-phosphatidate phosphohydrolase | 1 | | |
| 3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming) | 1 | 3-Methylcrotonyl-CoA carboxylase deficiency | PMID19339287 |
| 3-methylbutanoyl-CoA:acceptor oxidoreductase | 1 | isovaleric acidemia | PMID3326738 |
| 3-hydroxyanthranilate:oxygen 3,4-oxidoreductase (decyclizing) | 1 | | |
| 3-hydroxy-2-methylpropanoyl-CoA hydrolase | 1 | beta-hydroxyisobutyryl coenzyme A deacylase deficiency | PMID7122152 |
| 3-hydroxy-2-methylpropanoate:NAD+ oxidoreductase | 1 | | |
| 3-(5-oxo-4,5-dihydro-3H-imidazol-4-yl)propanoate hydro-lyase (urocanate-forming) | 1 | urocanase deficiency | PMID6107814 |
| 3-(5-oxo-4,5-dihydro-3H-imidazol-4-yl)propanoate amidohydrolase | 1 | | |
| 2-methylbutanoyl-CoA:acceptor oxidoreductase | 1 | isobutyrylglycinuria | PMID15505379 |
| 2-aminomuconate-6-semialdehyde:NAD+ 6-oxidoreductase | 1 | | |
| 2-amino-3-(3-oxoprop-1-en-1-yl)but-2-enedioate carboxy-lyase | 1 | | |
| uroporphyrinogen-III carboxy-lyase (coproporphyrinogen-III-forming) | 1 | porphyria | PMID2243121 |
| UDP-N-acetyl-D-glucosamine 4-epimerase | 1 | | |
| UDP-glucuronate beta-D-glucuronosyltransferase (acceptor-unspecific) | 1 | Gilbert-Meulengracht syndrom | PMID976795 |
| UDP-glucose:N-acylsphingosine D-glucosyltransferase | 1 | | |
| UDP-glucose:glycogen 4-alpha-D-glucosyltransferase | 1 | glycogen storage disease type 0 | PMID20051115 |
| UDP-glucose:alpha-D-galactose-1-phosphate uridylyltransferase | 1 | | |
| thymidine:phosphate deoxy-alpha-D-ribosyltransferase | 1 | | |
| thioredoxin:NADP+ oxidoreductase | 1 | | |
| superoxide:superoxide oxidoreductase | 1 | amyotrophic lateral sclerosis | PMID19703565 |
| S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase | 1 | Guanidinoacetate methyltransferase (GAMT) deficiency | PMID19388150 |
| S-adenosyl-L-methionine carboxy-lyase | 1 | | |
| S-adenosyl-L-homocysteine hydrolase | 1 | S-adenosylhomocysteine hydrolase (AHCY) deficiency | PMID19177456 |

Supplementary Table 5 : Essentiality of Enzymes for tested Objectives

| Enzyme Name | Rank | Disease | Reference |
|---|---|---|---|
| (S)-3-hydroxy-3-methylglutaryl-CoA hydro-lyase (trans-3-methylglutaconyl-CoA-forming) | 1 | 3-Methylglutaconyl-CoA hydratase deficiency | PMID10896289 |
| (R)-3-hydroxybutanoate:NAD+ oxidoreductase | 1 | | |
| protoporphyrinogen-IX:oxygen oxidoreductase | 1 | porphyria | PMID10874330 |
| protoheme ferro-lyase (protoporphyrin-forming) | 1 | protoporphyria | PMID18160121 |
| [protein]-S8-aminomethyldihydrolipoyllysine:tetrahydrofolate aminomethyltransferase | 1 | | |
| porphobilinogen:(4-[2-carboxyethyl]-3-[carboxymethyl]pyrrol-2-yl)met hyltransferase (hydrolysing) | 1 | porphyria | PMID10782018 |
| phosphoenolpyruvate:N-acyl-D-mannosamine-6-phosphate 1-(2-carboxy-2-oxoethyl)transferase | 1 | | |
| phosphatidylglycerophosphate phosphohydrolase | 1 | | |
| phosphatidylcholine phosphatidohydrolase | 1 | | |
| N-carbamoyl-beta-alanine amidohydrolase | 1 | beta-ureidopropionase deficiency | PMID17065070 |
| N-acylneuraminate-9-phosphate phosphohydrolase | 1 | | |
| N-acyl-D-glucosamine 2-epimerase | 1 | | |
| N6-(L-1,3-dicarboxypropyl)-L-lysine:NADP+ oxidoreductase (L-lysine-forming) | 1 | | |
| myo-inositol:oxygen oxidoreductase | 1 | | |
| L-tryptophan:oxygen 2,3-oxidoreductase (decyclizing) | 1 | | |
| L-threonine ammonia-lyase (2-oxobutanoate-forming) | 1 | | |
| L-kynurenine,NADPH:oxygen oxidoreductase (3-hydroxylating) | 1 | | |
| L-kynurenine hydrolase | 1 | Xanthurenic aciduria | PMID17334708 |
| L-histidine ammonia-lyase (urocanate-forming) | 1 | Histidinemia | PMID13863215 |
| L-glutamine(L-asparagine) amidohydrolase | 1 | | |
| L-aspartate:L-glutamine amido-ligase (AMP-forming) | 1 | | |
| L-arginine:glycine amidinotransferase | 1 | creatine deficiency syndrome | PMID20159424 |
| L-2-aminoadipate-6-semialdehyde:NAD(P)+ 6-oxidoreductase | 1 | | |
| L-2-aminoadipate:2-oxoglutarate aminotransferase | 1 | | |
| IMP:diphosphate phospho-D-ribosyltransferase | 1 | Lesh-Nyhan syndrome | PMID18779430 |
| hydroxymethylbilane hydro-lyase (cyclizing; uroporphyrinogen-III-forming) | 1 | porphyria | PMID1519940 |
| glycogen phosphorylase-limit dextrin 6-alpha-glucohydrolase | 1 | glycogen storage disease type III Cori's/Forbes disease | PMID |
| glycerol-ester acylhydrolase | 1 | | |
| GDP-mannose 4,6-hydro-lyase (GDP-4-dehydro-6-deoxy-D-mannose-forming) | 1 | leukocyte adhesion deficiency type II syndrome | PMID9662431 |
| GDP-L-fucose:NADP+ 4-oxidoreductase (3,5-epimerizing) | 1 | | |
| dodecenoyl-CoA (3Z)-(2E)-isomerase | 1 | | |
| diphosphate phosphohydrolase | 1 | | |
| diacylglycerol acylhydrolase | 1 | | |
| D-glucose-6-phosphate:NADP+ 1-oxidoreductase | 1 | G6PD deficiency | PMID19654083 |
| CTP:phosphatidate cytidylyltransferase | 1 | | |
| CTP:N-acylneuraminate cytidylyltransferase | 1 | | |
| coproporphyrinogen:oxygen oxidoreductase (decarboxylating) | 1 | coproporphyria | PMID9843038 |
| CDP-diacylglycerol:sn-glycerol-3-phosphate 3-phosphatidyltransferase | 1 | | |
| CDP-choline:1,2-diacyl-sn-glycerol cholinephosphotransferase | 1 | | |
| butanoyl-CoA:acceptor 2,3-oxidoreductase | 1 | | |
| ATP:riboflavin 5'-phosphotransferase | 1 | | |
| ATP:NAD+ 2'-phosphotransferase | 1 | | |
| ATP:N-acyl-D-mannosamine 6-phosphotransferase | 1 | inclusion-body myopathy | PMID12811782 |
| ATP:FMN adenylyltransferase | 1 | | |
| ATP:D-galactose 1-phosphotransferase | 1 | galactokinase deficiency | PMID15024738 |
| ATP:CMP phosphotransferase | 1 | | |
| ATP:adenylyl-sulfate 3'-phosphotransferase | 1 | | |
| aryl-formylamine amidohydrolase | 1 | | |
| alcohol:NAD+ oxidoreductase | 1 | | |
| acyl-CoA:sn-glycerol-3-phosphate 1-O-acyltransferase | 1 | | |

Supplementary Table 5 : Essentiality of Enzymes for tested Objectives

| Enzyme Name | Rank | Disease | Reference |
|---|---|---|---|
| acyl-CoA:malonyl-CoA C-acyltransferase (decarboxylating, oxoacyl- and enoyl- reducing) | 1 | | |
| acyl-CoA:cholesterol O-acyltransferase | 1 | ACAT1 deficiency | PMID15499044 |
| acyl-CoA:1-acyl-sn-glycerol-3-phosphate 2-O-acyltransferase | 1 | | |
| (3S)-3-hydroxyacyl-CoA hydro-lyase | 1 | | |
| (2S,3S)-3-hydroxy-2-methylbutanoyl-CoA:NAD+ oxidoreductase | 1 | 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency | PMID16148061 |
| (1->4)-alpha-D-glucan:phosphate alpha-D-glucosyltransferase | 1 | Glycogen storage disease type VI  Andersen's disease | PMID12809646 |
| (1->4)-alpha-D-glucan:(1->4)-alpha-D-glucan 6-alpha-D-[(1->4)-alpha-D-glucano]-transferase | 1 | | |

Supplementary Table 6 : Gene expression discrepancy

| Ensembl Gene ID | ID | Classification | Name | Evidence | Experiments | Samples | Oligos |
|---|---|---|---|---|---|---|---|
| ENSG00000160211 | R02736<br>R00835 | EC:1.1.1.49 | Glucose-6-phosphate 1-dehydrogenase (G6PD) | PMID:2753047 | 2 | 2 | 1 |
| ENSG00000109193 | R02350 | EC:2.8.2.15 | Sulfotransferase, estrogen preferring | PMID:8297382 | 2 | 2 | 1 |
| ENSG00000102230 | R01890 | EC:2.7.7.15 | Choline-phosphate cytidylyltransferase B | PMID:10480912<br>PMID:9593753<br>PMID:2557076 | 4 | 8 | 5 |
| ENSG00000167508 | R01121 | EC:4.1.1.33 | Diphosphomevalonate-decarboxylase | PMID:14972328 | 4 | 6 | 2 |
| ENSG00000138621 | R03269 | EC:4.1.1.36 | Phosphopantothenoyl-cysteinedecarboxylase | PMID:11923312<br>PMID:4459135<br>PMID:6061681 | 3 | 6 | 5 |

# Pools — metabolites with variable composition

## 1 Introduction

Here, species are described which are not a single physical entry. They can be seen as pools holding a number of species with a fixed ratio. More precisely it can be seen as a metabolite with a (finite) probability distribution of several similar species — a probabilistic metabolite.

All these species describe lipids with varying fatty acid residues, e.g. PC (phosphatidyl choline). Since the length distribution of these fatty acids is considerably different between different types of lipids (e.g. in PC different from PE, phosphatidyl ethanolamine) different fatty acid distributions are distinguished.

In HepatoNet a number of chemical reactions and transporters are written as processes of pools (e.g. from CDP-diacyl glycerol to PC). The specific fatty acid distribution is carried over from one of these probabilistic metabolite to the other. It is necessary that processes which assume a certain fatty acid distribution are separated from each other (e.g. the PC synthesis pathway is separated from the PE synthesis pathway). These distinguished pathways are described below as "pool areas". Thus, some intermediates must be distinguished (e.g. 1-acyl-phosphate for the PC synthesis is distinguished from the 1-acyl-phosphate for the PE synthesis).

## 2 VLDL-pools

Although the fatty acid distributions are experimentally determined for lipoprotein particles they can also be used as a rough estimate for other metabolites with fatty acid residues, for instance different Cerebrosides in HepatoNet inherit their fatty acid composition from sphingomyelin in VLDL. This is a reasonable estimate due to the good availability of VLDL for cells — it is a reasonable assumption that the fatty acid distribution does not differ much.

The fatty acid distribution of the different precursors of VLDL are taken from Shorten et al. [SU05].

### 2.1 VLDL-TG1-pool area

Shorten et al. distinguished the different positions for triacyl glycerol (TG) in VLDL. Thus, each position in TG has its own pool area. This pool describes the first position. Even though the molecule is symmetric the first position is distinguished from the third due to the kinetics of synthesis path [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 6440 |
| 18:0 | 823 |
| 18:1 | 1220 |
| 18:2 | 741 |
| 20:4 | 24 |
| total | 9248 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC02037_c | 1-Acylglycerol-3P-VLDL-TG1-pool(c) |
| HC02049_c | Phosphatidate-VLDL-TG-pool(c) |
| HC02055_c | 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| HC02062_r | Triacylglycerol-VLDL-pool(r) |
| HC02062_c | Triacylglycerol-VLDL-pool(c) |
| HC02062_l | Triacylglycerol-VLDL-pool(l) |
| HC02065_c | Fatty-acid-VLDL-TG1-pool(c) |
| HC02071_c | 1-Acylglycerol-VLDL-TG1-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1198 | 1220 1-Acylglycerol-3P-ol(c) + 741 1-Acylglycerol-3P-lin(c) + 24 1-Acylglycerol-3P-arach(c) + 6440 1-Acylglycerol-3P-palm(c) + 823 1-Acylglycerol-3P-stea(c) ⇔ 9248 1-Acylglycerol-3P-VLDL-TG1-pool(c) |
| r1241 | 6440 Palmitate(c) + 823 Stearate(c) + 741 Linoleate(c) + 24 Arachidonate(c) + 1220 Oleate(c) ⇔ 9248 Fatty-acid-VLDL-TG1-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1211 | 1 Phosphatidate-VLDL-TG-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-TG2-pool(c) + 1 1-Acylglycerol-3P-VLDL-TG1-pool(c) |
| r1217 | 1 Phosphatidate-VLDL-TG-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-TG-pool(c) + 1 Pi(c) |
| r1223 | 1 Triacylglycerol-VLDL-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1224 | 1 Triacylglycerol-VLDL-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1225 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) → 1 1-Acylglycerol-VLDL-TG1-pool(c) + 1 Fatty-acid-VLDL-TG2-pool(c) |
| r1231 | 1 1-Acylglycerol-VLDL-TG1-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-TG1-pool(c) + 1 Glycerol(c) |
| r1264 | 1 Triacylglycerol-VLDL-pool(c) ⇔ 1 Triacylglycerol-VLDL-pool(r) |
| r1265 | 1 Triacylglycerol-VLDL-pool(l) → 1 Triacylglycerol-VLDL-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |

## 2.2 VLDL-TG2-pool area

The fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 1200 |
| 18:0 | 384 |
| 18:1 | 4260 |
| 18:2 | 2810 |
| 20:4 | 521 |
| total | 9175 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC02043_c | Acyl-CoA-VLDL-TG2-pool(c) |
| HC02049_c | Phosphatidate-VLDL-TG-pool(c) |
| HC02055_c | 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| HC02062_r | Triacylglycerol-VLDL-pool(r) |
| HC02062_c | Triacylglycerol-VLDL-pool(c) |
| HC02062_l | Triacylglycerol-VLDL-pool(l) |
| HC02064_c | Fatty-acid-VLDL-TG2-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1204 | 1200 Palmitoyl-CoA(c) + 384 Stearoyl-CoA(c) + 4260 Oleoyl-CoA(c) + 521 Arachidonyl-CoA(c) + 2810 Linoleoyl-CoA(c) ⇔ 9175 Acyl-CoA-VLDL-TG2-pool(c) |
| r1242 | 1200 Palmitate(c) + 384 Stearate(c) + 2810 Linoleate(c) + 521 Arachidonate(c) + 4260 Oleate(c) ⇔ 9175 Fatty-acid-VLDL-TG2-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1211 | 1 Phosphatidate-VLDL-TG-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-TG2-pool(c) + 1 1-Acylglycerol-3P-VLDL-TG1-pool(c) |
| r1217 | 1 Phosphatidate-VLDL-TG-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-TG-pool(c) + 1 Pi(c) |
| r1223 | 1 Triacylglycerol-VLDL-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1224 | 1 Triacylglycerol-VLDL-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1225 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) → 1 1-Acylglycerol-VLDL-TG1-pool(c) + 1 Fatty-acid-VLDL-TG2-pool(c) |
| r1264 | 1 Triacylglycerol-VLDL-pool(c) ⇔ 1 Triacylglycerol-VLDL-pool(r) |
| r1265 | 1 Triacylglycerol-VLDL-pool(l) → 1 Triacylglycerol-VLDL-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |

## 2.3 VLDL-TG3-pool area

Again, the fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 849 |
| 18:0 | 584 |
| 18:1 | 4570 |
| 18:2 | 2780 |
| 20:4 | 264 |
| total | 9047 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC02061_c | Acyl-CoA-VLDL-TG3-pool(c) |
| HC02062_r | Triacylglycerol-VLDL-pool(r) |
| HC02062_c | Triacylglycerol-VLDL-pool(c) |
| HC02062_l | Triacylglycerol-VLDL-pool(l) |
| HC02063_c | Fatty-acid-VLDL-TG3-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1205 | 849 Palmitoyl-CoA(c) + 584 Stearoyl-CoA(c) + 4570 Oleoyl-CoA(c) + 264 Arachidonyl-CoA(c) + 2780 Linoleoyl-CoA(c) ⇔ 9047 Acyl-CoA-VLDL-TG3-pool(c) |
| r1243 | 849 Palmitate(c) + 584 Stearate(c) + 2780 Linoleate(c) + 264 Arachidonate(c) + 4570 Oleate(c) ⇔ 9047 Fatty-acid-VLDL-TG3-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1223 | 1 Triacylglycerol-VLDL-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1224 | 1 Triacylglycerol-VLDL-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-TG3-pool(c) + 1 1,2-Diacylglycerol-VLDL-TG-pool(c) |
| r1264 | 1 Triacylglycerol-VLDL-pool(c) ⇔ 1 Triacylglycerol-VLDL-pool(r) |
| r1265 | 1 Triacylglycerol-VLDL-pool(l) → 1 Triacylglycerol-VLDL-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |

## 2.4 VLDL-PC-pool area

This pool is also used for 2-Lysolecithin. Its fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 3010 |
| 18:0 | 1300 |
| 18:1 | 1170 |
| 18:2 | 2350 |
| 20:4 | 726 |
| total | 8556 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01940_r | HDL(r) |
| HC01940_s | HDL(s) |
| HC01940_l | HDL(l) |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |
| HC02000_r | PC-VLDL-pool(r) |
| HC02000_c | PC-VLDL-pool(c) |
| HC02000_s | PC-VLDL-pool(s) |
| HC02000_l | PC-VLDL-pool(l) |
| HC02016_r | 2-Lysolecithin-pool(r) |
| HC02016_c | 2-Lysolecithin-pool(c) |
| HC02016_l | 2-Lysolecithin-pool(l) |
| HC02038_c | 1-Acylglycerol-3P-VLDL-PC-pool(c) |
| HC02044_c | Acyl-CoA-VLDL-PC-pool(c) |
| HC02050_c | Phosphatidate-VLDL-PC-pool(c) |
| HC02056_c | 1,2-Diacylglycerol-VLDL-PC-pool(c) |
| HC02066_r | Fatty-acid-VLDL-PC-pool(r) |
| HC02066_c | Fatty-acid-VLDL-PC-pool(c) |
| HC02066_l | Fatty-acid-VLDL-PC-pool(l) |
| HC02072_c | 1-Acylglycerol-VLDL-PC-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1199 | 1170 1-Acylglycerol-3P-ol(c) + 2350 1-Acylglycerol-3P-lin(c) + 726 1-Acylglycerol-3P-arach(c) + 3010 1-Acylglycerol-3P-palm(c) + 1300 1-Acylglycerol-3P-stea(c) ⇔ 8556 1-Acylglycerol-3P-VLDL-PC-pool(c) |
| r1206 | 3010 Palmitoyl-CoA(c) + 1300 Stearoyl-CoA(c) + 1170 Oleoyl-CoA(c) + 726 Arachidonyl-CoA(c) + 2350 Linoleoyl-CoA(c) ⇔ 8556 Acyl-CoA-VLDL-PC-pool(c) |
| r1244 | 3010 Palmitate(r) + 1300 Stearate(r) + 2350 Linoleate(r) + 726 Arachidonate(r) + 1170 Oleate(r) ⇔ 8556 Fatty-acid-VLDL-PC-pool(r) |
| r1245 | 3010 Palmitate(c) + 1300 Stearate(c) + 2350 Linoleate(c) + 726 Arachidonate(c) + 1170 Oleate(c) ⇔ 8556 Fatty-acid-VLDL-PC-pool(c) |
| r1246 | 3010 Palmitate(l) + 1300 Stearate(l) + 2350 Linoleate(l) + 726 Arachidonate(l) + 1170 Oleate(l) ⇔ 8556 Fatty-acid-VLDL-PC-pool(l) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r0003 | 1 HDL(r) ← 2 ApoA1(r) + 90 PC-VLDL-pool(r) + 30 PS-VLDL-pool(r) + 20 Cholesterol(r) + 25 PE-VLDL-pool(r) + 75 SM-pool(r) |
| r0004 | 1 HDL(l) → 2 ApoA1(l) + 90 PC-VLDL-pool(l) + 30 PS-VLDL-pool(l) + 20 Cholesterol(l) + 25 PE-VLDL-pool(l) + 75 SM-pool(l) |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1160 | 1 HDL(r) ⇔ 1 HDL(s) |
| r1161 | 1 HDL(s) ⇔ 1 HDL(l) |
| r1212 | 1 Phosphatidate-VLDL-PC-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-PC-pool(c) + 1 1-Acylglycerol-3P-VLDL-PC-pool(c) |
| r1218 | 1 Phosphatidate-VLDL-PC-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-PC-pool(c) + 1 Pi(c) |
| r1226 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-PC-pool(c) → 1 1-Acylglycerol-VLDL-PC-pool(c) + 1 Fatty-acid-VLDL-PC-pool(c) |
| r1232 | 1 1-Acylglycerol-VLDL-PC-pool(c) + 1 H2O(c) → 1 Glycerol(c) + 1 Fatty-acid-VLDL-PC-pool(c) |
| r1237 | 1 CDP-choline(c) + 1 1,2-Diacylglycerol-VLDL-PC-pool(c) → 1 PC-VLDL-pool(c) + 1 CMP(c) |
| r1266 | 1 PC-VLDL-pool(c) ⇔ 1 PC-VLDL-pool(r) |
| r1267 | 1 PC-VLDL-pool(l) → 1 PC-VLDL-pool(r) |
| r1277 | 1 PC-VLDL-pool(r) + 1 H2O(r) ⇔ 1 2-Lysolecithin-pool(r) + 1 Fatty-acid-VLDL-PC-pool(r) |
| r1278 | 1 PC-VLDL-pool(c) + 1 H2O(c) ⇔ 1 2-Lysolecithin-pool(c) + 1 Fatty-acid-VLDL-PC-pool(c) |
| r1279 | 1 PC-VLDL-pool(l) + 1 H2O(l) ⇔ 1 2-Lysolecithin-pool(l) + 1 Fatty-acid-VLDL-PC-pool(l) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1282 | 1 2-Lysolecithin-pool(c) ⇔ 1 2-Lysolecithin-pool(r) |
| r1283 | 1 2-Lysolecithin-pool(l) → 1 2-Lysolecithin-pool(r) |
| r1369 | 1 PC-VLDL-pool(c) + 1 H2O(c) → 1 Phosphatidate-VLDL-PC-pool(c) + 1 Choline(c) |
| r1524 | 1 PC-VLDL-pool(c) + 1 ATP(c) + 1 H2O(c) → 1 PC-VLDL-pool(s) + 1 ADP(c) + 1 Pi(c) |

## 2.5 VLDL-PE-pool area

Again, the fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 1260 |
| 18:0 | 2010 |
| 18:1 | 628 |
| 18:2 | 1330 |
| 20:4 | 2220 |
| total | 7448 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01940_r | HDL(r) |
| HC01940_s | HDL(s) |
| HC01940_l | HDL(l) |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |
| HC02002_r | PE-VLDL-pool(r) |
| HC02002_b | PE-VLDL-pool(b) |
| HC02002_c | PE-VLDL-pool(c) |
| HC02002_l | PE-VLDL-pool(l) |
| HC02039_c | 1-Acylglycerol-3P-VLDL-PE-pool(c) |
| HC02045_c | Acyl-CoA-VLDL-PE-pool(c) |
| HC02051_c | Phosphatidate-VLDL-PE-pool(c) |
| HC02057_c | 1,2-Diacylglycerol-VLDL-PE-pool(c) |
| HC02067_c | Fatty-acid-VLDL-PE-pool(c) |
| HC02073_c | 1-Acylglycerol-VLDL-PE-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1200 | 628 1-Acylglycerol-3P-ol(c) + 1330 1-Acylglycerol-3P-lin(c) + 2220 1-Acylglycerol-3P-arach(c) + 1260 1-Acylglycerol-3P-palm(c) + 2010 1-Acylglycerol-3P-stea(c) ⇔ 7448 1-Acylglycerol-3P-VLDL-PE-pool(c) |
| r1207 | 1260 Palmitoyl-CoA(c) + 2010 Stearoyl-CoA(c) + 628 Oleoyl-CoA(c) + 2220 Arachidonyl-CoA(c) + 1330 Linoleoyl-CoA(c) ⇔ 7448 Acyl-CoA-VLDL-PE-pool(c) |
| r1247 | 1260 Palmitate(c) + 2010 Stearate(c) + 1330 Linoleate(c) + 2220 Arachidonate(c) + 628 Oleate(c) ⇔ 7448 Fatty-acid-VLDL-PE-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r0003 | 1 HDL(r) ← 2 ApoA1(r) + 90 PC-VLDL-pool(r) + 30 PS-VLDL-pool(r) + 20 Cholesterol(r) + 25 PE-VLDL-pool(r) + 75 SM-pool(r) |
| r0004 | 1 HDL(l) → 2 ApoA1(l) + 90 PC-VLDL-pool(l) + 30 PS-VLDL-pool(l) + 20 Cholesterol(l) + 25 PE-VLDL-pool(l) + 75 SM-pool(l) |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1160 | 1 HDL(r) ⇔ 1 HDL(s) |
| r1161 | 1 HDL(s) ⇔ 1 HDL(l) |
| r1191 | 1 PE-VLDL-pool(c) + 1 Serine(c) ⇔ 1 PS-VLDL-pool(c) + 1 Ethanolamine(c) |
| r1194 | 1 1,2-Diacylglycerol-VLDL-PE-pool(c) + 1 CDP-ethanolamine(c) → 1 PE-VLDL-pool(c) + 1 CMP(c) |
| r1213 | 1 Phosphatidate-VLDL-PE-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-PE-pool(c) + 1 1-Acylglycerol-3P-VLDL-PE-pool(c) |
| r1219 | 1 Phosphatidate-VLDL-PE-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-PE-pool(c) + 1 Pi(c) |
| r1227 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-PE-pool(c) → 1 1-Acylglycerol-VLDL-PE-pool(c) + 1 Fatty-acid-VLDL-PE-pool(c) |
| r1233 | 1 1-Acylglycerol-VLDL-PE-pool(c) + 1 H2O(c) → 1 Glycerol(c) + 1 Fatty-acid-VLDL-PE-pool(c) |
| r1268 | 1 PE-VLDL-pool(c) ⇔ 1 PE-VLDL-pool(r) |
| r1269 | 1 PE-VLDL-pool(l) → 1 PE-VLDL-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1371 | 1 H2O(c) + 1 PE-VLDL-pool(c) → 1 Phosphatidate-VLDL-PE-pool(c) + 1 Ethanolamine(c) |
| r1509 | 1 PE-VLDL-pool(c) + 1 ATP(c) + 1 H2O(c) → 1 PE-VLDL-pool(b) + 1 ADP(c) + 1 Pi(c) |

## 2.6 VLDL-PS-pool area

Again, the fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 345 |
| 18:0 | 4820 |
| 18:1 | 332 |
| 18:2 | 181 |
| 20:4 | 2050 |
| total | 7728 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01940_r | HDL(r) |
| HC01940_s | HDL(s) |
| HC01940_l | HDL(l) |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |
| HC02006_r | PS-VLDL-pool(r) |
| HC02006_b | PS-VLDL-pool(b) |
| HC02006_c | PS-VLDL-pool(c) |
| HC02006_l | PS-VLDL-pool(l) |
| HC02040_c | 1-Acylglycerol-3P-VLDL-PS-pool(c) |
| HC02046_c | Acyl-CoA-VLDL-PS-pool(c) |
| HC02052_c | Phosphatidate-VLDL-PS-pool(c) |
| HC02058_c | 1,2-Diacylglycerol-VLDL-PS-pool(c) |
| HC02068_c | Fatty-acid-VLDL-PS-pool(c) |
| HC02074_c | 1-Acylglycerol-VLDL-PS-pool(c) |
| HC02079_c | PE-PS-VLDL-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1201 | 332 1-Acylglycerol-3P-ol(c) + 181 1-Acylglycerol-3P-lin(c) + 2050 1-Acylglycerol-3P-arach(c) + 345 1-Acylglycerol-3P-palm(c) + 4820 1-Acylglycerol-3P-stea(c) ⇔ 7728 1-Acylglycerol-3P-VLDL-PS-pool(c) |
| r1208 | 345 Palmitoyl-CoA(c) + 4820 Stearoyl-CoA(c) + 332 Oleoyl-CoA(c) + 2050 Arachidonyl-CoA(c) + 181 Linoleoyl-CoA(c) ⇔ 7728 Acyl-CoA-VLDL-PS-pool(c) |
| r1248 | 345 Palmitate(c) + 4820 Stearate(c) + 181 Linoleate(c) + 2050 Arachidonate(c) + 332 Oleate(c) ⇔ 7728 Fatty-acid-VLDL-PS-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r0003 | 1 HDL(r) ← 2 ApoA1(r) + 90 PC-VLDL-pool(r) + 30 PS-VLDL-pool(r) + 20 Cholesterol(r) + 25 PE-VLDL-pool(r) + 75 SM-pool(r) |
| r0004 | 1 HDL(l) → 2 ApoA1(l) + 90 PC-VLDL-pool(l) + 30 PS-VLDL-pool(l) + 20 Cholesterol(l) + 25 PE-VLDL-pool(l) + 75 SM-pool(l) |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1160 | 1 HDL(r) ⇔ 1 HDL(s) |
| r1161 | 1 HDL(s) ⇔ 1 HDL(l) |
| r1191 | 1 PE-VLDL-pool(c) + 1 Serine(c) ⇔ 1 PS-VLDL-pool(c) + 1 Ethanolamine(c) |
| r1195 | 1 1,2-Diacylglycerol-VLDL-PS-pool(c) + 1 CDP-ethanolamine(c) → 1 PE-PS-VLDL-pool(c) + 1 CMP(c) |
| r1214 | 1 Phosphatidate-VLDL-PS-pool(c) + 1 CoA(c) ← 1 Acyl-CoA-VLDL-PS-pool(c) + 1 1-Acylglycerol-3P-VLDL-PS-pool(c) |
| r1220 | 1 Phosphatidate-VLDL-PS-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-PS-pool(c) + 1 Pi(c) |
| r1228 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-PS-pool(c) → 1 1-Acylglycerol-VLDL-PS-pool(c) + 1 Fatty-acid-VLDL-PS-pool(c) |
| r1234 | 1 1-Acylglycerol-VLDL-PS-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-PS-pool(c) + 1 Glycerol(c) |
| r1270 | 1 PS-VLDL-pool(b) ⇔ 1 PS-VLDL-pool(c) |
| r1271 | 1 PS-VLDL-pool(c) ⇔ 1 PS-VLDL-pool(r) |
| r1272 | 1 PS-VLDL-pool(l) → 1 PS-VLDL-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1370 | 1 PS-VLDL-pool(c) ⇔ 1 PE-PS-VLDL-pool(c) + 1 CO2(c) |

## 2.7 VLDL-PI-pool area

Again, the fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 694 |
| 18:0 | 3640 |
| 18:1 | 1360 |
| 18:2 | 694 |
| 20:4 | 2170 |
| total | 8558 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |
| HC02009_r | PI-pool(r) |
| HC02009_c | PI-pool(c) |
| HC02009_l | PI-pool(l) |
| HC02041_c | 1-Acylglycerol-3P-VLDL-PI-pool(c) |
| HC02047_c | Acyl-CoA-VLDL-PI-pool(c) |
| HC02053_c | Phosphatidate-VLDL-PI-pool(c) |
| HC02059_c | 1,2-Diacylglycerol-VLDL-PI-pool(c) |
| HC02069_c | Fatty-acid-VLDL-PI-pool(c) |
| HC02075_c | 1-Acylglycerol-VLDL-PI-pool(c) |
| HC02078_r | CDP-diacylglycerol-VLDL-PI-pool(r) |
| HC02078_c | CDP-diacylglycerol-VLDL-PI-pool(c) |
| HC02078_l | CDP-diacylglycerol-VLDL-PI-pool(l) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1202 | 1360 1-Acylglycerol-3P-ol(c) + 694 1-Acylglycerol-3P-lin(c) + 2170 1-Acylglycerol-3P-arach(c) + 694 1-Acylglycerol-3P-palm(c) + 3640 1-Acylglycerol-3P-stea(c) ⇔ 8558 1-Acylglycerol-3P-VLDL-PI-pool(c) |
| r1209 | 694 Palmitoyl-CoA(c) + 3640 Stearoyl-CoA(c) + 1360 Oleoyl-CoA(c) + 2170 Arachidonyl-CoA(c) + 694 Linoleoyl-CoA(c) ⇔ 8558 Acyl-CoA-VLDL-PI-pool(c) |
| r1249 | 694 Palmitate(c) + 3640 Stearate(c) + 694 Linoleate(c) + 2170 Arachidonate(c) + 1360 Oleate(c) ⇔ 8558 Fatty-acid-VLDL-PI-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1196 | 1 CDP-diacylglycerol-VLDL-PI-pool(r) + 1 Inositol(r) ⇔ 1 PI-pool(r) + 1 CMP(r) |
| r1197 | 1 CDP-diacylglycerol-VLDL-PI-pool(c) + 1 Inositol(c) ⇔ 1 PI-pool(c) + 1 CMP(c) |
| r1215 | 1 Phosphatidate-VLDL-PI-pool(c) + 1 CoA(c) ← 1 1-Acylglycerol-3P-VLDL-PI-pool(c) + 1 Acyl-CoA-VLDL-PI-pool(c) |
| r1221 | 1 Phosphatidate-VLDL-PI-pool(c) + 1 H2O(c) → 1 1,2-Diacylglycerol-VLDL-PI-pool(c) + 1 Pi(c) |
| r1229 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-PI-pool(c) → 1 1-Acylglycerol-VLDL-PI-pool(c) + 1 Fatty-acid-VLDL-PI-pool(c) |
| r1235 | 1 1-Acylglycerol-VLDL-PI-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-PI-pool(c) + 1 Glycerol(c) |
| r1238 | 1 Phosphatidate-VLDL-PI-pool(c) + 1 CTP(c) ⇔ 1 CDP-diacylglycerol-VLDL-PI-pool(c) + 1 PPi(c) |
| r1273 | 1 PI-pool(c) ⇔ 1 PI-pool(r) |
| r1274 | 1 PI-pool(l) → 1 PI-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1360 | 1 CDP-diacylglycerol-VLDL-PI-pool(l) → 1 CDP-diacylglycerol-VLDL-PI-pool(r) |
| r1372 | 1 PI-pool(c) + 1 H2O(c) → 1 Inositol-1P(c) + 1 1,2-Diacylglycerol-VLDL-PI-pool(c) |

## 2.8 VLDL-SM-pool area

This pool is also used for the various derivates of cerebrosides. Again, the fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 6260 |
| 18:0 | 1490 |
| 18:1 | 656 |
| 18:2 | 270 |
| 20:4 | 147 |
| total | 8823 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01940_r | HDL(r) |
| HC01940_s | HDL(s) |
| HC01940_l | HDL(l) |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |
| HC01990_r | Ceramide-pool(r) |
| HC01990_c | Ceramide-pool(c) |
| HC02007_r | SM-pool(r) |
| HC02007_b | SM-pool(b) |
| HC02007_c | SM-pool(c) |
| HC02007_l | SM-pool(l) |
| HC02008_r | Glucosylceramide-pool(r) |
| HC02008_c | Glucosylceramide-pool(c) |
| HC02008_s | Glucosylceramide-pool(s) |
| HC02042_c | 1-Acylglycerol-3P-VLDL-SM-pool(c) |
| HC02048_c | Acyl-CoA-VLDL-SM-pool(c) |
| HC02054_c | Phosphatidate-VLDL-SM-pool(c) |
| HC02060_c | 1,2-Diacylglycerol-VLDL-SM-pool(c) |
| HC02070_c | Fatty-acid-VLDL-SM-pool(c) |
| HC02076_c | 1-Acylglycerol-VLDL-SM-pool(c) |
| HC02158_c | Dihydroceramide-pool(c) |
| HC02162_r | LacCer-pool(r) |
| HC02162_s | LacCer-pool(s) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1203 | 656 1-Acylglycerol-3P-ol(c) + 270 1-Acylglycerol-3P-lin(c) + 147 1-Acylglycerol-3P-arach(c) + 6260 1-Acylglycerol-3P-palm(c) + 1490 1-Acylglycerol-3P-stea(c) ⇔ 8823 1-Acylglycerol-3P-VLDL-SM-pool(c) |
| r1210 | 6260 Palmitoyl-CoA(c) + 1490 Stearoyl-CoA(c) + 656 Oleoyl-CoA(c) + 147 Arachidonyl-CoA(c) + 270 Linoleoyl-CoA(c) ⇔ 8823 Acyl-CoA-VLDL-SM-pool(c) |
| r1250 | 6260 Palmitate(c) + 1490 Stearate(c) + 270 Linoleate(c) + 147 Arachidonate(c) + 656 Oleate(c) ⇔ 8823 Fatty-acid-VLDL-SM-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r0003 | 1 HDL(r) ← 2 ApoA1(r) + 90 PC-VLDL-pool(r) + 30 PS-VLDL-pool(r) + 20 Cholesterol(r) + 25 PE-VLDL-pool(r) + 75 SM-pool(r) |
| r0004 | 1 HDL(l) → 2 ApoA1(l) + 90 PC-VLDL-pool(l) + 30 PS-VLDL-pool(l) + 20 Cholesterol(l) + 25 PE-VLDL-pool(l) + 75 SM-pool(l) |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1160 | 1 HDL(r) ⇔ 1 HDL(s) |
| r1161 | 1 HDL(s) ⇔ 1 HDL(l) |
| r1216 | 1 CoA(c) + 1 Phosphatidate-VLDL-SM-pool(c) ← 1 Acyl-CoA-VLDL-SM-pool(c) + 1 1-Acylglycerol-3P-VLDL-SM-pool(c) |
| r1222 | 1 H2O(c) + 1 Phosphatidate-VLDL-SM-pool(c) → 1 Pi(c) + 1 1,2-Diacylglycerol-VLDL-SM-pool(c) |
| r1230 | 1 H2O(c) + 1 1,2-Diacylglycerol-VLDL-SM-pool(c) → 1 1-Acylglycerol-VLDL-SM-pool(c) + 1 Fatty-acid-VLDL-SM-pool(c) |
| r1236 | 1 1-Acylglycerol-VLDL-SM-pool(c) + 1 H2O(c) → 1 Fatty-acid-VLDL-SM-pool(c) + 1 Glycerol(c) |
| r1239 | 1 Sphingosine(c) + 1 Acyl-CoA-VLDL-SM-pool(c) ⇔ 1 CoA(c) + 1 Ceramide-pool(c) |
| r1240 | 1 Ceramide-pool(c) ⇔ 1 Ceramide-pool(r) |
| r1275 | 1 SM-pool(c) ⇔ 1 SM-pool(r) |
| r1276 | 1 SM-pool(l) → 1 SM-pool(r) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1404 | 1 ATP(c) + 1 Ceramide-pool(c) → 1 ADP(c) + 1 Ceramide-1P-pool(c) |
| r1405 | 1 UDP-glucose(c) + 1 Ceramide-pool(c) ⇔ 1 UDP(c) + 1 Glucosylceramide-pool(c) |
| r1406 | 1 H2O(c) + 1 Glucosylceramide-pool(c) → 1 Glucose(c) + 1 Ceramide-pool(c) |
| r1407 | 1 CDP-choline(r) + 1 Ceramide-pool(r) ⇔ 1 CMP(r) + 1 SM-pool(r) |
| r1408 | 1 SM-pool(c) + 1 H2O(c) ⇔ 1 Ceramide-pool(c) + 1 Phosphocholine(c) |
| r1409 | 1 UDP-galactose(r) + 1 Glucosylceramide-pool(r) ⇔ 1 LacCer-pool(r) + 1 UDP(r) |
| r1410 | 1 LacCer-pool(s) + 1 H2O(s) ⇔ 1 Galactose(s) + 1 Glucosylceramide-pool(s) |
| r1412 | 1 Sphinganine(c) + 1 Acyl-CoA-VLDL-SM-pool(c) ⇔ 1 Dihydroceramide-pool(c) + 1 CoA(c) |
| r1413 | 1 Dihydroceramide-pool(c) + 1 H2O(c) ⇔ 1 Sphinganine(c) + 1 Fatty-acid-VLDL-SM-pool(c) |
| r1414 | 1 Dihydroceramide-pool(c) + 1 O2(c) + 1 NADPH(c) ⇔ 2 H2O(c) + 1 Ceramide-pool(c) + 1 NADP+(c) |
| r1415 | 1 Ceramide-1P-pool(c) + 1 H2O(c) → 1 Pi(c) + 1 Ceramide-pool(c) |
| r1416 | 1 Glucosylceramide-pool(c) ⇔ 1 Glucosylceramide-pool(r) |
| r1510 | 1 SM-pool(c) + 1 ATP(c) + 1 H2O(c) → 1 SM-pool(b) + 1 ADP(c) + 1 Pi(c) |

## 2.9 Cholesterol-ester-pool area

The fatty acid distribution is taken from Shorten et al. [SU05].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 1420 |
| 18:0 | 280 |
| 18:1 | 2050 |
| 18:2 | 4880 |
| 20:4 | 542 |
| total | 9172 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |
| HC01969_r | Cholesterol-ester-pool(r) |
| HC01969_l | Cholesterol-ester-pool(l) |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1192 | 2050 Cholesterol-ester-ol(r) + 4880 Cholesterol-ester-lin(r) + 1420 Cholesterol-ester-palm(r) + 280 Cholesterol-ester-stea(r) + 542 Cholesterol-ester-arach(r) ⇔ 9172 Cholesterol-ester-pool(r) |
| r1193 | 2050 Cholesterol-ester-ol(l) + 4880 Cholesterol-ester-lin(l) + 1420 Cholesterol-ester-palm(l) + 280 Cholesterol-ester-stea(l) + 542 Cholesterol-ester-arach(l) ⇔ 9172 Cholesterol-ester-pool(l) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |
| r1361 | 1 Cholesterol-ester-pool(l) → 1 Cholesterol-ester-pool(r) |

## 2.10 VLDL particle

The relations of the different lipid categories have been optained from Swift et al. [SMDL80]. The relative shares of the different phospholipids are from [Phi59] and [VV90].

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01945_r | VLDL(r) |
| HC01945_s | VLDL(s) |
| HC01945_l | VLDL(l) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1280 | 1 VLDL(r) ← 7 ApoE(r) + 10385 Triacylglycerol-VLDL-pool(r) + 2165 PC-VLDL-pool(r) + 1645 Cholesterol-ester-pool(r) + 1 PI-pool(r) + 165 2-Lysolecithin-pool(r) + 185 PE-VLDL-pool(r) + 1 ApoB100(r) + 500 Cholesterol(r) + 755 SM-pool(r) |
| r1281 | 1 VLDL(l) → 7 ApoE(l) + 10385 Triacylglycerol-VLDL-pool(l) + 2165 PC-VLDL-pool(l) + 1645 Cholesterol-ester-pool(l) + 1 PI-pool(l) + 165 2-Lysolecithin-pool(l) + 185 PE-VLDL-pool(l) + 1 ApoB100(l) + 500 Cholesterol(l) + 755 SM-pool(l) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1083 | 1 VLDL(r) ⇔ 1 VLDL(s) |
| r1084 | 1 VLDL(s) ⇔ 1 VLDL(l) |

## 2.11 HDL particle

The relations of the different lipid categories have been optained from Barrans et al. [BJB+96] and Wu et al. [WWZ+07]. The phospholipid composition is obtained from Barrans et al. [BJB+96].

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01940_r | HDL(r) |
| HC01940_s | HDL(s) |
| HC01940_l | HDL(l) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r0003 | 1 HDL(r) ← 2 ApoA1(r) + 90 PC-VLDL-pool(r) + 30 PS-VLDL-pool(r) + 20 Cholesterol(r) + 25 PE-VLDL-pool(r) + 75 SM-pool(r) |
| r0004 | 1 HDL(l) → 2 ApoA1(l) + 90 PC-VLDL-pool(l) + 30 PS-VLDL-pool(l) + 20 Cholesterol(l) + 25 PE-VLDL-pool(l) + 75 SM-pool(l) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1160 | 1 HDL(r) ⇔ 1 HDL(s) |
| r1161 | 1 HDL(s) ⇔ 1 HDL(l) |

## 2.12 LDL particle

The composition has been induced from [TSBH04, Phi59, VV90].

| Involved metabolites | |
|---|---|
| identfier | name |
| HC01971_s | LDL(s) |
| HC01971_l | LDL(l) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1158 | 1 LDL(l) → 1515 Cholesterol-ester-pool(l) + 1 ApoB100(l) + 680 Cholesterol(l) + 110 CDP-diacylglycerol-VLDL-PI-pool(l) + 425 PC-VLDL-pool(l) + 25 2-Lysolecithin-pool(l) + 160 SM-pool(l) + 30 PE-VLDL-pool(l) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1053 | 1 LDL(s) ⇔ 1 LDL(l) |

# 3 Bile-PC-pool area

Fatty acid distribution of PC in bile is measured by van Berge Henegouwen et al. [vBHWR87].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 4140 |
| 16:1 | 268 |
| 18:0 | 550 |
| 18:1 | 1209 |
| 18:2 | 3283 |
| 20:4 | 564 |
| total | 10014 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC02080_b | Bile-PC-pool(b) |
| HC02080_c | Bile-PC-pool(c) |
| HC02082_c | Acyl-CoA-Bile-PC-pool(c) |
| HC02084_c | 1-Acylglycerol-3P-Bile-PC-pool(c) |
| HC02085_c | 1,2-Diacylglycerol-Bile-PC-pool(c) |
| HC02086_c | Phosphatidate-Bile-PC-pool(c) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1284 | 268 1-Acylglycerol-3P-palmn(c) + 1209 1-Acylglycerol-3P-ol(c) + 3283 1-Acylglycerol-3P-lin(c) + 564 1-Acylglycerol-3P-arach(c) + 4140 1-Acylglycerol-3P-palm(c) + 550 1-Acylglycerol-3P-stea(c) ⇔ 10014 1-Acylglycerol-3P-Bile-PC-pool(c) |
| r1285 | 4140 Palmitoyl-CoA(c) + 268 (2E)-Hexadecenoyl-CoA(c) + 550 Stearoyl-CoA(c) + 1209 Oleoyl-CoA(c) + 564 Arachidonyl-CoA(c) + 3283 Linoleoyl-CoA(c) ⇔ 10014 Acyl-CoA-Bile-PC-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1286 | 1 Phosphatidate-Bile-PC-pool(c) + 1 CoA(c) ⇔ 1 Acyl-CoA-Bile-PC-pool(c) + 1 1-Acylglycerol-3P-Bile-PC-pool(c) |
| r1287 | 1 Phosphatidate-Bile-PC-pool(c) + 1 H2O(c) → 1 Pi(c) + 1 1,2-Diacylglycerol-Bile-PC-pool(c) |
| r1288 | 1 CDP-choline(c) + 1 1,2-Diacylglycerol-Bile-PC-pool(c) → 1 Bile-PC-pool(c) + 1 CMP(c) |
| r1511 | 1 Bile-PC-pool(c) + 1 ATP(c) + 1 H2O(c) → 1 Bile-PC-pool(b) + 1 ADP(c) + 1 Pi(c) |

# 4 CL-pool area

Cardiolipin is synthesized in human mitochondria and the respective fatty acid distributions are taken from [Hoc92].

| Constitution | |
|---|---|
| fatty acid | per mill |
| 16:0 | 43 |
| 16:1 | 47 |
| 18:0 | 19 |
| 18:1 | 138 |
| 18:2 | 738 |
| total | 985 |

| Involved metabolites | |
|---|---|
| identfier | name |
| HC02087_m | CL-pool(m) |
| HC02089_c | Acyl-CoA-CL-pool(c) |
| HC02089_m | Acyl-CoA-CL-pool(m) |
| HC02091_m | 1-Acylglycerol-3P-CL-pool(m) |
| HC02093_m | Phosphatidate-CL-pool(m) |
| HC02094_m | CDP-diacylglycerol-CL-pool(m) |
| HC02095_m | PGP-CL-pool(m) |
| HC02096_m | PG-CL-pool(m) |

| Processes defining this pool | |
|---|---|
| identfier | name |
| r1305 | 43 Palmitoyl-CoA(c) + 47 (2E)-Hexadecenoyl-CoA(c) + 19 Stearoyl-CoA(c) + 138 Oleoyl-CoA(c) + 738 Linoleoyl-CoA(c) ⇔ 985 Acyl-CoA-CL-pool(c) |

| Other involved reactions | |
|---|---|
| identfier | name |
| r1306 | 1 Acyl-CoA-CL-pool(c) ⇔ 1 Acyl-CoA-CL-pool(m) |
| r1307 | 1 Acyl-CoA-CL-pool(m) + 1 sn-Glycerol-3P(m) ⇔ 1 CoA(m) + 1 1-Acylglycerol-3P-CL-pool(m) |
| r1308 | 1 Phosphatidate-CL-pool(m) + 1 CoA(m) ⇔ 1 Acyl-CoA-CL-pool(m) + 1 1-Acylglycerol-3P-CL-pool(m) |
| r1309 | 1 Phosphatidate-CL-pool(m) + 1 CTP(m) ⇔ 1 CDP-diacylglycerol-CL-pool(m) + 1 PPi(m) |
| r1310 | 1 CDP-diacylglycerol-CL-pool(m) + 1 sn-Glycerol-3P(m) ⇔ 1 CMP(m) + 1 PGP-CL-pool(m) |
| r1311 | 1 PGP-CL-pool(m) + 1 H2O(m) ⇔ 1 PG-CL-pool(m) + 1 Pi(m) |
| r1312 | 2 PG-CL-pool(m) ⇔ 1 CL-pool(m) + 1 Pi(m) |

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