# MATLAB code of isolated rat lung model

# Abstract

A wealth of information exists regarding the bioenergetic processes in isolated perfused rat lungs under physiological and pathophysiological conditions. However, the interdependence of those processes makes it difficult to quantify the impact of a change in a single or multiple process(es) on overall lung tissue bioenergetics. Integrated computational modeling provides a mechanistic and quantitative framework for the bioenergetic data at different levels of biological organization. Thus, the objective of this study was to develop and validate an integrated computational model of isolated rat lung tissue bioenergetics using existing experimental data.

The model expands our developed integrated computational model of the bioenergetics of mitochondria isolated from rat lungs by accounting for glucose uptake and phosphorylation, glycolysis, and the pentose phosphate pathway.

# Model Parameterization

For mitochondrial region of the model, values of kinetic parameters were fixed at those estimated in our recent model of the bioenergetics of mitochondria isolated from rat lungs. For cytosolic region of the model, intrinsic parameters such as binding constants were determined based on previously published enzyme kinetics data, whereas extrinsic parameters such as maximal reaction and transport velocities were estimated by fitting the model solution to published data from isolated rat lungs.

Units for the variables in the code:

|  |  |
| --- | --- |
| Volumes | L |
| Concentrations | M |
| Time | minutes |
| Vmax/Tmax | Mol/min/lung |
| Km | M |

Model reactions and transport processes

***Reactions in the isolated perfused rat lung model***

|  |  |  |
| --- | --- | --- |
| Reaction number | Enzyme | Reference reactions |
| 1 | HK | GLCc+ATPc ⇌ G6Pc+ADPc+Hc |
| 2 | PGI | G6Pc ⇌ F6Pc |
| 3 | PFK | F6Pc+ATPc ⇌ F16BP+ADPc+H+ |
| 4 | ALD | F16BPc ⇌ 2GAPc |
| 5 | GAPDH | GAPc+Pic+NADc ⇌ BPG+NADHc+Hc |
| 6 | PGK | BPGc + ADPc ⇌ PEPc+ATPc |
| 7 | PK | PEPc+ADPc+Hc ⇌ PYRc+ATPc |
| 8 | LDH | PYRc + NADHc + Hc ⇌ LACc + NADc+ |
| 9 | G6PDH | G6Pc + NADPc ⇌ PG6c + NADPHc + Hc |
| 10 | 6PGD | PG6c + NADPc ⇌ R5Pc + NADPHc + Hc + CO2 |
| 11 | GR | GSSGc + Hc + NADPH ⇌ 2GSHc + NADPc+ |
| 12 | GPx | 2GSHc + H2O2c ⇌ GSSGc + 2H2O |
| 13 | ATPase | ATPc ⇌ ADPc + Pic+ Hc |
| 14 | AK | ATPc+ AMPc ⇌ 2ADPc |
| 15 | AA | PYRc ⇌ ALAc |
| 16 | PDH | PYRm+CoAm+NADm ⇌ ACoAm+CO2+NADHm+Hm |
| 17 | CITS | ACoAm+OXAm ⇌ CITm+CoAm+ 2Hm |
| 18 | ICDH | CITm+NADm ⇌ AKGm+NADHm+CO2 |
| 19 | AKGDH | AKGm+CoAm+NADm ⇌ SCoAm+NADHm+CO2 |
| 20 | SCAS | SCoAm+GDPm+Pim ⇌ SUCm+GTPm+CoAm+Hm |
| 21 | NDK | GTPm+ADPm ⇌ GDPm+ATPm |
| 22 | SDH | SUCm+FADm ⇌ FUMm+FADH2m |
| 23 | FUM | FUMm = MALm |
| 24 | MDH | MALm+NADm ⇌ OXAm+NADHm+ Hm |
| 25 | GOT | ASPm+aKGm ⇌ GLUm+OXAm |
| 26 | CI | NADHm+UQm+Hm ⇌ NADm+UQH2m+ 4∆H |
| 27 | CII | FADH2+UQm ⇌ FADm+UQH2m |
| 28 | CIII | UQH2,m+2CytCo+2Hm ⇌ UQm+2CytCr+ 4∆H |
| 29 | CIV | 2CytCr+0.5O2+2Hm ⇌ 2CytCo+H2O+2∆H |
| 30 | CV | ADPm+Pim+Hm+3∆H ⇌ ATPm |

***: Transports in the isolated perfused rat lung model***

|  |  |  |
| --- | --- | --- |
| Transport number | Enzyme | Reference reactions |
| 1 | GLUT | GLCb ⇌ GLCc |
| 2 | PYRT | PYRb + Hb ⇌ PYRc + Hc |
| 3 | LACT | LACb + Hb ⇌ LACc + Hc |
| 4 | PIT | Pib ⇌ Pic |
| 5 | DCC (SUC) | SUCm +Pic ⇌ SUCc+Pim |
| 6 | DCC (MAL) | MALm+Pic ⇌ MALc+Pim |
| 7 | TCC | MALc+ CITm ⇌ MALm+ CITc |
| 8 | PYRH | PYRc + Hc ⇌ PYRm + Hm |
| 9 | PIC | Pic + Hc ⇌ Pim + Hm |
| 10 | ANT | ADPc + ATPm ⇌ ADPm + ATPc |
| 11 | GLUH | GLUc+ Hc ⇌ GLUm+ Hm |
| 12 | MAS | NADHc + NADm ⇌ NADHm + NADc |
| 13 | LEAK | Hi ⇌ Hm |

# Model Structure

# 

This model is build and parameterized based on experimental data of isolated perfused rat lung.

# Code structure

Eleven main code files are included in the folder (ten for model simulations and one for model parameter estimation using genetic algorithm). Name of code file indicates simulation in reference.

For example, Fig2\_Steady\_state.m is used to run steady state simulation. Fig4\_4\_dPO2.m is for the simulation of different oxygen partial pressure.

Set\_initial\_concentration.m:

No input, output is an array of initial concentrations.

Set default initial concentrations for model state variables based on experimental protocol.

Example:

IC=Set\_Initial\_Concentrations;

Initial concentration values are stored in “IC”. User can change initial concentrations of species based on experimental protocol. For example, the syntax below change initial buffer glucose concentration to 10 mM (default buffer glucose concentration is 5.6 mM)

IC=Set\_Initial\_Concentrations;

IC(iGLCr)=10e-3;

Where “iGLCr” is the index for buffer glucose (r indicates reservoir region)

## Odeq.m:

Model ordinary differential equations (Mass balance equations).

Input: time (t), Initial concentrations (IC), Adjustable parameters (para).

Output: dC/dt

Fluxes.m:

Model reaction and transport flux expressions.

Input: Concentration of species at certain time (C\_t), Adjustable parameters (para)

Output: reaction and transport fluxes (rtfluxes).

List of adjustable parameters

In the code, adjustable parameters are stored in array “Para”, below is the list of adjustable parameters. These adjustable parameters are Vmax and Tmax of reactions and transport processes. Note not all of these parameters are estimated by genetic algorithm. For example, Para (17) to Para (31) are Vmax values in mitochondria region, and are fixed to values from the mitochondria model.

|  |  |  |  |
| --- | --- | --- | --- |
| Para(1) | Vmax,HEX | Para(32) | Tmax,GLUT |
| Para(2) | Vmax,PGI | Para(33) | Tmax,PYRT |
| Para(3) | Vmax,PFK | Para(34) | Tmax,LACT |
| Para(4) | Vmax,ALD | Para(35) | Tmax,PIT |
| Para(5) | Vmax,GAPDH | Para(36) | Tmax,DCC1 |
| Para(6) | Vmax,PHK | Para(37) | Tmax,DCC2 |
| Para(7) | Vmax,PK | Para(38) | Tmax,OME |
| Para(8) | Vmax,LDH | Para(39) | Tmax,TCC |
| Para(9) | Vmax,PPP1 | Para(40) | Tmax,PYRH |
| Para(10) | Vmax,PPP2 | Para(41) | Tmax,PIC |
| Para(11) | Vmax,GSH1 | Para(42) | Tmax,ANT |
| Para(12) | Vmax,GSH2 | Para(43) | Tmax,GLUH |
| Para(13) | Vmax,ATPase | Para(44) | Tmax,GAE |
| Para(14) | Vmax,AK | Para(45) | Tmax,Leak |
| Para(15) | Not used | Para(46) | Tmax,MAS |
| Para(16) | Not used |  |  |
| Para(17) | Vmax,PDH |  |  |
| Para(18) | Vmax,CITS |  |  |
| Para(19) | Vmax,CITD |  |  |
| Para(20) | Vmax,AKGDH |  |  |
| Para(21) | Vmax,SCAS |  |  |
| Para(22) | Vmax,NDK |  |  |
| Para(23) | Vmax,SDH |  |  |
| Para(24) | Vmax,FUM |  |  |
| Para(25) | Vmax,MDH |  |  |
| Para(26) | Vmax,GOT |  |  |
| Para(27) | Vmax,CI |  |  |
| Para(28) | Vmax,CII |  |  |
| Para(29) | Vmax,CIII |  |  |
| Para(30) | Vmax,CIV |  |  |
| Para(31) | Vmax,CV |  |  |

Objective\_functions:

File name: **Lung\_Parameter\_Estimation\_obj.m**

Input: An array of parameters to be estimated

Output: objective function (Sum of squared difference between data and model simulations)

The function is used for model parameter estimation in genetic algorithm. The output for this function is sum of squared difference between experimental data and model simulations. Experimental data in figure 2-4 are included in this objective function.

Genetic algorithm (GA) try to find the optimal parameters that minimize these objective functions.

## Calculate\_SSE.m

Used for calculation of sum of squared errors (SSE) between experimental data and model simulations.

Input: Adjustable model parameters. Output: SSE

## Program requirement: The optimization function “ga” requires “Global Optimization Toolbox” in MATLAB 2016 or after.