Computational modeling to determine key regulators of hypoxia effects on lactate production in the glycolysis pathway

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MATLAB program

```
%This program investigates the influence of hypoxia on the production
%of glycolysis metabolites, especially lactate (y(11)). The program
%output is the enzymes and or metabolites concentration vs time, you can
%modify the program to have different levels of hypoxia (h=0:0.1:1). Hence,
%metabolites concentration can be reported vs Hif-1 or oxygen levels during
%different time intervals of hypoxia exposure. The detailed description of
%the model has been explained in the paper.



clc
close all
clear

Vmglut3=8000;              %micM/min
kmglut3=5000;              %micM
kmglut1=3000;              %micM
kcatglut1=69960;           %min-1
E0glut=0.014;              %micM
kgluth=0.0001;             %min-1
kmglut2=25000;             %micM
kcatglut2=445500;          %min-1
kdglut=0.00016;            %min-1
kmhk=40.7;                 %micM
khkh=0.003;                %min-1
kdhk=0.002;                %min-1
kcathk=12000;              %min-1
E0hk=0.47;                 %micM
kpgih=0.037;               %min-1
kmpgi1=480;                %micM
kmpgi2=272;                %micM
kcatpgi1=125400;           %min-1
kcatpgi2=119586.8;         %min-1
kdpgi=0.00048;             %min-1
E0pgi=33.2;                %micM
kmpfk=2000;                %micM
kcatpfk=61200;             %min-1
E0pfk=42.5;                %micM
kdpfk=0.00085;             %min-1
kpfkh=0.026;               %min-1
vmaldo1=1028106;           %micM/min
kmaldo1=3;                 %micM
vmaldo2=832276.3;          %micM/min
kmaldo2=1000;              %micM
kmaldo22=2000;             %micM, for metabolite 2 in reverse direction
kmgapdh1=82;               %micM
kmgapdh2=130;              %micM
kgapdhh=0.83;              %min-1
kdgapdh=0.00016;           %min-1
E0gapdh=1195;              %micM
kcatgapdh1=17400;          %min-1
kcatgapdh2=19.81;          %min-1
kcatpgk=29210;             %min-1
```

```
kmpgk=16.7;              %micM
E0pgk=64.4;              %micM
kdpgk=0.0013;            %min-1
kpgkh=0.3;               %min-1
kmpgm1=200;              %micM
kmpgm2=190;              %micM
kcatpgm1=60000;          %min-1
kcatpgm2=27272.7;        %min-1
E0pgm=173;               %micM
kdpgm=0.0197;            %min-1
kpgmh=0.36;              %min-1
kmeno1=16.2;             %micM
kmeno2=238;              %micM
kenoh=0.23;              %min-1
kcateno1=11160;          %min-1
kcateno2=2610.96;        %min-1
E0eno=135;               %micM
kdeno=0.00048;           %min-1
vmpk=2819725.8;          %micM/min
kmpk=1500;               %micM
kmpdk=20;                %micM
kpdkh=0.000017;          %min-1
kdpdk=0.00048;           %min-1
kcatpdk=33;              %min-1
E0pdk=0.01;              %micM
kmpdh=10;                %micM
E0pdh=27.2;              %micM
kmldh1=200;              %micM
kmldh2=11000;            %micM
kcattpi1=350000;         %micM
kcattpi2=7700092.4;      %micM
kmtpi1=870;              %micM
kmtpi2=460;              %micM
E0tpi=96.6;              %micM
ktpih=0.3;               %min-1
kdtpi=0.069;             %min-1
kldhh=0.003;             %min-1
kcatldh1=122000;         %min-1
kcatldh2=4900;           %min-1
E0ldh=1.2;               %micM
kdldh=0.0013;            %min-1
kcatpdh=105800;          %micM
kmg6pdh=77;              %micM
kmpgcm2=45;              %micM
kmpgcm1=670;             %micM
E0pgcm=28.2;             %micM
kpgcmh=0.065;            %min-1
kdpgcm=0.00016;          %min-1
kcatpgcm1=73700;         %min-1
kcatpgcm2=127220.9;      %min-1
glucose1ph=25;           %micM
Eg=10000;                %micM
vmg6pdh=120120;          %micM/min
E0g6pdh=4.4;             %micM
kAcCoA=10000;            %min-1
E0pdp=0.02;              %micM
kcatpdp=300;             %min-1
```

```
kmpdp=7.6;              %micM
h=0;                    %micM,0:0.1:1

%d[C]/dt=vp-vd
f=@(t,y)[kcatglut1*y(14)*Eg/(kmglut1+Eg)-kcatglut2*y(14)*y(1)/(kmglut2+y(1))-
kcathk*y(15)*y(1)/(kmhk+y(1))+Vmglut3*Eg/(kmglut3+Eg);...
%dy(1)/dt
kcathk*y(15)*y(1)/(kmhk+y(1))-
kcatpgi1*y(16)*y(2)/(kmpgi1+y(2))+kcatpgi2*y(16)*y(3)/(kmpgi2+y(3))-
vmg6pdh*y(2)/(kmg6pdh+y(2))-
kcatpgcm1*y(26)*y(2)/(kmpgcm1+y(2))+kcatpgcm2*y(26)*glucose1ph/(kmpgcm2+gluco
se1ph);...                    %dy(2)/dt
kcatpgi1*y(16)*y(2)/(kmpgi1+y(2))-kcatpgi2*y(16)*y(3)/(kmpgi2+y(3))-
kcatpfk*y(17)*y(3)/(kmpfk+y(3));...
%dy(3)/dt
kcatpfk*y(17)*y(3)/(kmpfk+y(3))-
vmaldo1*y(4)/(kmaldo1+y(4))+vmaldo2*y(5)/(kmaldo2+y(5))+
vmaldo2*y(12)/(kmaldo22+y(12));...
%dy(4)/dt
vmaldo1*y(4)/(kmaldo1+y(4))-
vmaldo2*y(5)/(kmaldo2+y(5))+kcattpi1*y(18)*y(12)/(kmtpi1+y(12))-
kcattpi2*y(18)*y(5)/(kmtpi2+y(5))+kcatgapdh2*y(19)*y(13)/(kmgapdh2+y(13))-
kcatgapdh1*y(19)*y(5)/(kmgapdh1+y(5));...                            %dy(5)/dt
kcatpgk*y(20)*y(13)/(kmpgk+y(13))-
kcatpgm1*y(21)*y(6)/(kmpgm1+y(6))+kcatpgm2*y(21)*y(7)/(kmpgm2+y(7));...
%dy(6)/dt
kcatpgm1*y(21)*y(6)/(kmpgm1+y(6))-kcatpgm2*y(21)*y(7)/(kmpgm2+y(7))-
kcateno1*y(22)*y(7)/(kmeno1+y(7))+kcateno2*y(22)*y(8)/(kmeno2+y(8));...
%dy(7)/dt
kcateno1*y(22)*y(7)/(kmeno1+y(7))-vmpk*y(8)/(kmpk+y(8))-
kcateno2*y(22)*y(8)/(kmeno2+y(8));...
%dy(8)/dt
kcatpdh*y(24)*y(10)/(kmpdh+y(10))-kAcCoA*y(9);...
%dy(9)/dt
vmpk*y(8)/(kmpk+y(8))-kcatpdh*y(24)*y(10)/(kmpdh+y(10))-
kcatldh1*y(23)*y(10)/(kmldh1+y(10))+kcatldh2*y(23)*y(11)/(kmldh2+y(11));...
%dy(10)/dt
kcatldh1*y(23)*y(10)/(kmldh1+y(10))-kcatldh2*y(23)*y(11)/(kmldh2+y(11));...
%dy(11)/dt
vmaldo1*y(4)/(kmaldo1+y(4))-vmaldo2*y(12)/(kmaldo22+y(12))-
kcattpi1*y(18)*y(12)/(kmtpi1+y(12))+kcattpi2*y(18)*y(5)/(kmtpi2+y(5));...
%dy(12)/dt
kcatgapdh1*y(19)*y(5)/(kmgapdh1+y(5))-
kcatgapdh2*y(19)*y(13)/(kmgapdh2+y(13))-kcatpgk*y(20)*y(13)/(kmpgk+y(13));...
%dy(13)/dt
%d[E]/dt=kEh[h]-kd[E-E0]
(kgluth*h)-(kdglut*(y(14)-E0glut));...
%dy(14)/dt
(khkh*h)-(kdhk*(y(15)-E0hk));...
%dy(15)/dt
(kpgih*h)-(kdpgi*(y(16)-E0pgi));...
%dy(16)/dt
(kpfkh*h)-(kdpfk*(y(17)-E0pfk));...
%dy(17)/dt
(ktpih*h)-(kdtpi*(y(18)-E0tpi));...
%dy(18)/dt
```

```
(kgapdhh*h)-(kdgapdh*(y(19)-E0gapdh));...
%dy(19)/dt
(kpgkh*h)-(kdpgk*(y(20)-E0pgk));...
%dy(20)/dt
(kpgmh*h)-(kdpgm*(y(21)-E0pgm));...
%dy(21)/dt
(kenoh*h)-(kdeno*(y(22)-E0eno));...
%dy(22)/dt
(kldhh*h)-(kdldh*(y(23)-E0ldh));...
%dy(23)/dt
-kcatpdk*y(25)*(y(24))^2.3/(kmpdk+(y(24))^2.3)+kcatpdp*E0pdp*(E0pdh-
y(24))/(kmpdp+(E0pdh-y(24)));...
%dy(24)/dt
(kpdkh*h)-(kdpdk*(y(25)-E0pdk));...
%dy(25)/dt
(kpgcmh*h)-(kdpgcm*(y(26)-E0pgcm))];
%dy(26)/dt
 [t, y]=ode45(f, [0, 30], [2377 1033 362 46 21 44 5 8 1.3 56 4680 43 0.18
0.014 0.47 33.2 42.5 96.6 1195 64.4 173 135 1.2 27.2 0.01 28.2]);

 %glucose
figure(1)
plot(t,y(:,1));
%glucose 6-phosphate
figure(2)
plot(t,y(:,2));
%fructose 6-phosphate
figure(3)
plot(t,y(:,3));
%fructose 1,6-bisphosphate
figure(4)
plot(t,y(:,4));
%glyceraldehyde 3-phosphate
figure(5)
plot(t,y(:,5));
%3-phosphoglycerate
figure(6)
plot(t,y(:,6));
%2-phosphoglycerate
figure(7)
plot(t,y(:,7));
%phosphoenolpyruvate
figure(8)
plot(t,y(:,8));
%Ac-CoA
figure(9)
plot(t,y(:,9));
%pyruvate
figure(10)
plot(t,y(:,10));
%lactate
figure(11)
plot(t,y(:,11));
%dihydroxyacetone phosphate
figure(12)
plot(t,y(:,12));
%1,3-bis phosphoglycerate
```

```
figure(13)
plot(t,y(:,13));
%glut
figure(14)
plot(t,y(:,14));
%hk
figure(15)
plot(t,y(:,15));
%pgi
figure(16)
plot(t,y(:,16));
%pfk
figure(17)
plot(t,y(:,17));
%tpi
figure(18)
plot(t,y(:,18));
%gapdh
figure(19)
plot(t,y(:,19));
%pgk
figure(20)
plot(t,y(:,20));
%pgm
figure(21)
plot(t,y(:,21));
%eno
figure(22)
plot(t,y(:,22));
%ldh
figure(23)
plot(t,y(:,23));
%pdh
figure(24)
plot(t,y(:,24));
%pdk
figure(25)
plot(t,y(:,25));
%pgcm
figure(26)
plot(t,y(:,26));
```

Table S1. Constants and initial conditions

Constants, initial conditions	**Value** (μM)	**Ref.**	**Constants, initial conditions**	**Value** (μM)	**Ref.**
[*glucose1-phosphate*]0	25	1	Km_{GLUT}	3000	2
[E_g]	10000	3	Km_{GLUT2}	25000	4
[y1]0=[*glucose*]0	2377	5	Km_{HK}	40.7	6
[y2]0=[*glucose 6-ph*]0	1033	5	Km_{PGI1}	480	7
[y3]0=[*fructose 6-ph*]0	362	5	Km_{PGI2}	272	7
[y4]0=[*fructose 1,6-bisphosphate*]0	46	5	Km_{PFK-1}	2000	8
[y5]0=[*glyceraldehyde 3-phoaphate*]0	21	5	Km_{ALDO1}	3	9
[y6]0=[*3-phosphoglycerate*]0	44	5	Km_{ALDO2}	1000	9
[y7]0=[*2-phosphoglycerate*]0	5	5	Km_{ALDO22}	2000	9
[y8]0=[*phosphoenolpyruvate*]0	8	5	Km_{GAPDH1}	82	10
[y9]0=[*Ac-CoA*]0	1.3	5	Km_{GAPDH2}	130	10
[y10]0=[*pyruvate*]0	56	5	Km_{PGK}	16.7	11
[y11]0=[*lactate*]0	4680	5	Km_{PGM1}	200	12
[y12]0=[*dihydroxyacetone phosphate*]0	43	5	Km_{PGM2}	190	12
[y13]0=[*1,3-bis phosphoglycerate*]0	0. 18	13	Km_{ENO1}	16.2	14
[y14]0=[*GLU*	0.014	2,15	Km_{ENO2}	238	14
[y15]0=[*HK*]0	0.47	5	Km_{PK}	1500	16
[y16]0=[*PGI*]0	33.2	5	Km_{PDK}	20	17
[y17]0=[*PFK-1*]0	42.5	5	Km_{PDH}	10	18
[y18]0=[*TPI*]0	96.6	5	Km_{LDH1}	200	19
[y19]0=[*GAPDH*]0	1195	5	Km_{LDH2}	11000	19
[y20]0=[*PGK*]0	64.4	5	Km_{TPI1}	870	20
[y21]0= [*PGM*]0	173	5	Km_{TPI2}	460	20
[y22]0=[*ENO*]0	135	5	Km_{G6PDH}	77	21
[y23]0= [*LDH*]0	1.2	5	Km_{PGCM1}	670	22
[y24]0=[*PDH*]0	27.2	5	Km_{PGCM2}	45	22
[y25]0=[*PDK*]0	0.01	23			
[y26]0=[*PGCM*]0	28.2	5			
H	0:0.1:1	24			

Table S1. Constants and initial conditions (continue)

Constants, initial conditions	**Value** (min^{-1})	**Ref.**	**Constants, initial conditions**	**Value** (min^{-1})	**Ref.**
$Kcat_{GLUT\ 1}$	69960	15	Kd_{ENO}	0.00048	25
$Kcat_{GLUT\ 2}$	445500	Est	Kd_{PDK}	0.00048	26
$Kcat_{HK}$	12000	5	Kd_{TPI}	0.069	27
$Kcat_{PGI1}$	125400	5	Kd_{LDH}	0.0013	28
$Kcat_{PGI2}$	119586.8	5,22	Kd_{PGCM}	0.00016	29
$Kcat_{PFK\text{-}1}$	61200	5	K_{GLUTh}	0.0001	30
$Kcat_{GAPDH1}$	17400	5	K_{HKh}	0.003	30
$Kcat_{GAPDH2}$	19.81	5,31	K_{PGIh}	0.037	32
$Kcat_{PGK}$	29210	5	$K_{PFK\text{-}1h}$	0.026	32
$Kcat_{PGM1}$	60000	5	K_{PAPDHh}	0.83	33
$Kcat_{PGM2}$	27272.7	5,12	K_{PGKh}	0.3	34
$Kcat_{ENO1}$	11160	5	K_{PGMh}	0.36	35
$Kcat_{ENO2}$	2610.96	5,36	K_{ENOh}	0.23	37
$Kcat_{PDK}$	33	38	K_{PDHh}	0.000017	39
$kcat_{TPI1}$	350000	5	K_{TPIh}	0.3	40
$Kcat_{TPI2}$	7700092.4	5,20	K_{LDHh}	0.003	41
$Kcat_{LDH1}$	122000	19	K_{PGCMh}	0.065	42
$Kcat_{LDH2}$	4900	43	$Kd_{Ac\text{-}CoA}$	10000	Est
$Kcat_{PDH}$	105800	5	Kd_{PDK}	0.00048	26
$Kcat_{PGCM1}$	73700	5	Kd_{TPI}	0.069	27
$Kcat_{PGCM2}$	127220.9	5,22	Kd_{LDH}	0.0013	28
Kd_{GLUT}	0.00016	44	Kd_{PGCM}	0.00016	29
Kd_{HK}	0.002	28	**Constants, initial conditions**	**Value** ($\mu M.min^{-1}$)	**Ref.**
Kd_{PGI}	0.00048	26	$Vm_{GLUT'}$	8000	2
$Kd_{PFK\text{-}1}$	0.00085	26	Vm_{ALDO1}	1028106	5
Kd_{GAPDH}	0.00016	45	Vm_{ALDO2}	832276.3	5,46
Kd_{PGK}	0.0013	28	Vm_{PK}	2819725.8	5
Kd_{PGM}	0.0197	47	Vm_{G6PDH}	120120	5

K_{cat}=catalytic constant, K_m= Michaelis–Menten constant, V_m=maximum velocity, K_d=degradation constant, K_{Eh}=constant of HIF effect on enzyme production, (calculated based on experimental data reported in respective references), 1=in forward direction, 2=in reverse direction. GLUT: glucose transporter, HK: hexokinase, PGI: phosphoglucoisomerase, PFK-1: phosphofructokinase-1, ALDO: aldolase, TPI: triosephosphate isomerase, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, PGK: phosphoglycerate kinase, PGM: phosphoglycerate mutase, ENO: enolase, PK: pyruvate kinase, PDH: pyruvate dehydrogenase, PDK: pyruvate dehydrogenase kinase, PDP: pyruvate dehydrogenase phosphatase, p-PDH: phosphorylated pyruvate dehydrogenase, LDH: lactate dehydrogenase, PGCM: phosphoglucomutase, G6PDH: glucose 6-phosphate dehydrogenase, Eg: extracellular glucose, h: HIF-1, Est: estimated by the proposed model.

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