Abbreviations: GLCT: Glucose transporter; HK: Hexokinase; PGI: Phosphoglucone isomerase; PFK: Phosphofructokinase; FBA: Fructose-1,6-bisphosphate aldolase; TPI: Triose phosphate isomerase; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; PGK: Phosphoglycerate kinase; G6PDH: Glucose-6-phosphate dehydrogenase; GLUTEX: Glutamate exchanger; GLUD: glutamate dehydrogenase; GCL: Glutamate-cysteine ligase; GS: Glutathione synthetase; GLYex: Glycine exchanger; PGCDH: Phosphoglycerate dehydrogenase; PSP: Phosphoserine phosphatase; PST: Phosphoserine transaminase; GHMT: Glycine hydroxymethyltransferase; XCT: Cystine-glutamate antiporter; CR: Cystine reductase; GTHP: Glutathione peroxidase; GTHO: Glutathione oxidoreductase; NOX: NADPH oxidase; SOD: Superoxide dismutase; ROS: Reactive oxygen species.

Nomenclature: All the enzymes names have been abbreviated in the block and italicized. For e.g. PGK refers to the enzyme phosphoglycerate kinase. All the metabolites have been abbreviated in small and italicized. For e.g. gly refers to the metabolite glycine. Only two compartments have been used in the model: extracellular matrix (e) and cytosol (c). To represent the compartment in which the metabolite belongs, the compartment abbreviation is used as a subscript. For e.g. glc_e refers to the metabolite glucose in the extracellular matrix.

1. Rate Equations in Cleland Nomenclature

Kinetic equations for all the metabolic reactions were written following the Cleland nomenclature for mono-substrate, bi-substrate, and ter-substrate reactions. Kinetic rate equations for the enzymes have been previously derived mechanistically and reported in various literature. Initial kinetics with first-order reaction rates of the enzymatic reactions have been considered for writing the equations. Since initial rates are usually measured in the presence of substrates only, there are no product terms present in the equations. Values for all the parameters have been listed in Table S1 and initial values of all the variables have been provided in section 4 of the supporting information.

Central Carbon Metabolism

Glycolysis: Kinetic rate equations for the enzymes belonging to the first half of glycolysis, from where it branches to the glycine-serine pathway have been considered in the model. The kinetics is mostly represented by uni-uni and bi-bi mechanisms. The equation forms for most of the reactions are similar except for GAPDH and PGK. Competitive inhibition of GAPDH by h2O2 has been considered. The rate kinetics of PGK follows a partial rapid equilibrium random bi-bi steady-state kinetics [1] where the binding of 1,3bpg with the enzyme is transient and has not been considered in the denominator.
Eq.1: 
\[ v_{_{GLCT}} = \frac{V_{m_{_{GLCT}}} \cdot \text{glc}_e}{k_{_{GLCT}}^e + \text{glc}_e} \] [Uni Uni Michaelis Menten]

Eq.2: 
\[ v_{_{HK}} = \frac{V_{m_{_{HK}}} \cdot (\text{atp} \cdot \text{glc}_e)}{(k_{i(atp)}^{HK}) k_{_{glc}}^e + k_{_{atp}}^{HK} \cdot \text{atp} + k_{_{atp}}^{HK} \cdot \text{glc}_e + \text{atp} \cdot \text{glc}_e)} \] [Rapid Equilibrium Random Bi – Bi mechanism]

Eq.3: 
\[ v_{_{PGI}} = \frac{V_{m_{_{PGI}}} \cdot 6p}{k_{g6p}^e + 6p} \] [Steady state uni – uni mechanism; Briggs Haldane form of Michealis Menten kinetics]

Eq.4: 
\[ v_{_{PFK}} = \frac{V_{m_{_{PFK}}} \cdot (\text{atp} \cdot 6p)}{(k_{i(atp)}^{PFK}) k_{f6p}^{PFK} + k_{f6p}^{PFK} \cdot \text{atp} + k_{f6p}^{PFK} \cdot 6p + \text{atp} \cdot 6p)} \] [Rapid Equilibrium Random Bisubstrate]

Eq.5: 
\[ v_{_{FBA}} = \frac{V_{m_{_{FBA}}} \cdot f16bp}{k_{f16bp}^{FBA} + f16bp} \] [Ordered Uni Bi steady state]

Eq.6: 
\[ v_{_{TPI}} = \frac{V_{m_{_{TPI}}} \cdot \text{dhap}}{k_{\text{dhap}}^{TPI} + \text{dhap}} \] [Simple steady state Uni – Uni Mechanism]
Eq. 7:

\[
V_{\text{GAPDH}} = \frac{V_m^{\text{GAPDH}} \cdot \text{gap.nad}}{\left[ k_{i\text{(gap)}}^{\text{GAPDH}} \cdot k_{\text{nad}}^{\text{GAPDH}} + k_{\text{gap}}^{\text{GAPDH}} \cdot \text{nad} \cdot \frac{h_{\text{O}_2}}{K_{\text{GAPDH}}} + k_{\text{nad}}^{\text{GAPDH}} \cdot \text{gap} + \text{gap.nad} \right]} \\
\text{[Ordered bi bi Steady State kinetics; h}_2\text{O}_2 \text{ inhibition]}
\]

Eq. 8:

\[
V_{\text{PGK}} = \frac{V_m^{\text{PGK}} \cdot (1,3bpg.adp)}{\left( k_{i(1,3bpg)}^{\text{PGK}} \cdot k_{\text{adp}}^{\text{PGK}} + k_{\text{adp}}^{\text{PGK}} \cdot 1,3bpg + 1,3bpg.adp \right)} \\
\text{[Partial Rapid Equilibrium Random Bi – Bi mechanism]}
\]

**Pentose Phosphate Pathway:** The pentose phosphate pathway has been represented by considering the enzymatic reaction G6PDH. The assumption here is that the final products of the pathway, i.e., fructose and glyceraldehyde 3-phosphate re-enter the glycolytic pathway. The whole pathway has been reduced to a single equation and the parameter values for the equation have been determined by parameter estimation technique to represent the real biological situation. Competitive inhibition of the pathway by atp has been considered.

Eq. 9:

\[
V_{\text{G6PDH}} = \frac{V_m^{\text{G6PDH}} \cdot (g6p.nadp)}{\left[ (k_{i\text{(g6p)}}^{\text{G6PDH}} \cdot k_{\text{nadp}}^{\text{G6PDH}} + k_{\text{g6p}}^{\text{G6PDH}} \cdot \text{nadp}) \cdot (1 + \frac{\text{atp}}{K_{\text{G6PDH}}} \cdot \text{g6p}) + k_{\text{nadp}}^{\text{G6PDH}} \cdot g6p + g6p.nadp \right]} \\
\text{[Ordered Bi Bi Mechanism with Competitive inhibition of g6p by atp]}
\]

**Amino Acid Metabolism**

**Glutamate Metabolism:** A part of the glutamate metabolism has been considered which includes the transport of glutamate from the extracellular matrix to the cytoplasm where a part of it is utilized in the glutathione metabolism and a part is converted into akg production by the activity of glutamate dehydrogenase and the rest is utilized in other cellular processes.

Eq. 10
GLUTEX

Uptake of glutamate from extracellular matrix

\[ v_{GLUTEX} = \frac{V^m_{GLUTEX} \cdot glut_e}{(k_m^{GLUTEX} + glut_e)} \]  

[Eq. 11]

GLUTEX

(Ordered Bi Bi)

Glycine Serine Metabolism: All the enzymatic reactions involved in the production of serine from 3pg and conversion of serine to glycine have been considered. Along with it, the exchange of glycine from the extracellular matrix has also been considered.

\[ v_{GLUD} = \frac{V^m_{GLUD} \cdot (glut.nadp)}{(k_{i(glut)}^{GLUD} k_{nadp}^{GLUD} + k_{nadp}^{GLUD} \cdot glut + k_{glut}^{GLUD} \cdot nadp + glut.nadp)} \]  

[Ordered Bi Bi]

GLUD

Michaelis Menten

\[ v_{GLYex} = \frac{V^m_{GLYex} \cdot gly_e}{k_m^{GLYex} + gly_e} \]  

[Eq. 12]

GLYex

(Ordered Bi Bi)

\[ v_{PGCDH} = \frac{V^m_{PGCDH} \cdot (3pg.nad)}{(k_{i(3pg)}^{PGCDH} k_{nad}^{PGCDH} + k_{nad}^{PGCDH} \cdot 3pg + k_{3pg}^{PGCDH} \cdot nad + 3pg.nad)} \]  

[Ordered Bi Bi]

PGCDH

\[ v_{PSP} = \frac{V^m_{PSP} \cdot pser}{k_m^{PSP} + pser} \]  

[Eq. 14]

PSP

(Ordered Bi Bi)

\[ v_{GHMT} = \frac{V^m_{GHMT} \cdot (ser.thf)}{(k_{i(ser)}^{GHMT} k_{thf}^{GHMT} + k_{thf}^{GHMT} \cdot ser + k_{ser}^{GHMT} \cdot thf + ser.thf)} \]  

[Eq. 15]

GHMT
\[ v_{\text{PST}} = \frac{V_{m}^{\text{PST}} \cdot (\text{glut.3php})}{(k_{i,\text{(glut)}}^{\text{PST}} \cdot k_{3\text{php}}^{\text{PST}} + k_{3\text{php}}^{\text{PST}} \cdot \text{glut} + k_{\text{glut},3\text{php}}^{\text{PST}} + \text{glut.3php})} \quad \text{[Rapid Equilibrium]} \]

\[ \quad \frac{V_{m}^{\text{PST}} \cdot (\text{cys,glut})}{(k_{i,\text{(cys)}}^{\text{XCT}} \cdot k_{\text{glut}}^{\text{XCT}} + k_{\text{glut}}^{\text{XCT}} \cdot \text{cys} + k_{\text{cys}}^{\text{XCT}} \cdot \text{glut} + \text{cys,glut})} \quad \text{[Random Bi Bi]} \]

\[ v_{\text{XCT}} = \frac{V_{m}^{\text{XCT}} \cdot (\text{cys,glut})}{(k_{i,\text{(cys)}}^{\text{XCT}} \cdot k_{\text{glut}}^{\text{XCT}} + k_{\text{glut}}^{\text{XCT}} \cdot \text{cys} + k_{\text{cys}}^{\text{XCT}} \cdot \text{glut} + \text{cys,glut})} \]

\[ v_{\text{CR}} = \frac{V_{m}^{\text{CR}} \cdot (\text{cys,nadph})}{(k_{i,\text{(cys)}}^{\text{CR}} \cdot k_{\text{nadph}}^{\text{CR}} + k_{\text{nadph}}^{\text{CR}} \cdot \text{cys} + k_{\text{cys}}^{\text{CR}} \cdot \text{nadph} + \text{cys,nadph})} \quad \text{[Ordered Bi Bi]} \]

**Cysteine metabolism:** This considers the transport of cystine from the extracellular matrix via the glutamate-cystine antiporter (xCT) and the conversion of cystine into cysteine, which is used as a component for building the tripeptide complex of glutathione.

**Eq.17:**

**Eq.18:**

**Thiol Metabolism**

**Glutathione Metabolism:** This pathway includes the involvement of two important enzymes, glutamyl-cysteine ligase and glutathione synthase. The former catalyzes the formation of glutamyl-cysteine which is converted into the tripeptide complex of glutathione in the later reaction. Both the reactions involve the utilization of ATP for the conversion and hence represented by three metabolites ordered ter-bi equation form.

**Eq.19:**
\[ v_{\text{GCL}} = \frac{V_{\text{m}}^{GCL} \cdot (\text{atp.glut.cysL})}{(k_{i(\text{atp})}^{GCL} + k_{i(\text{glut})}^{GCL} + k_{i(\text{cysL})}^{GCL} + k_{i(atp)}^{GCL} + k_{i(glut)}^{GCL} + k_{i(cysL)}^{GCL})} \]  

[Ordered Ter Bi]

\[ v_{\text{GS}} = \frac{V_{\text{m}}^{GS} \cdot (\text{atp.gly.glucys})}{(k_{i(\text{atp})}^{GS} + k_{i(\text{gly})}^{GS} + k_{i(\text{glucys})}^{GS} + k_{i(atp)}^{GS} + k_{i(gly)}^{GS} + k_{i(glucys)}^{GS})} \]

\[ v_{\text{GSH-GSSG cycle:}} \] This is represented by two enzymes, glutathione peroxidase which catalyzes the conversion of gsh into gssg while neutralizing \( \text{h}_2\text{o}_2 \) to \( \text{h}_2\text{O} \) and glutathione oxidoreductase which replenishes gsh back into the system by converting gssg to gsh with the involvement of nadph. The equations for the reactions have been represented using an ordered bi-bi mechanism.

\[ v_{\text{GTHP}} = \frac{V_{\text{m}}^{GTHP} \cdot \text{h}_2\text{o}_2.gsh}{(k_{i(\text{h}_2\text{o}_2})^{GTHP} + k_{i(gsh)}^{GTHP} \cdot \text{h}_2\text{o}_2 + k_{i(gsh)}^{GTHP} \cdot \text{gsh} + \text{h}_2\text{o}_2 \cdot \text{gsh})} \]  

[Ordered Bi Uni]

\[ v_{\text{GTHO}} = \frac{V_{\text{m}}^{GTHO} \cdot (\text{gssg.nadph})}{(k_{i(\text{gssg})}^{GTHO} + k_{i(\text{nadph})}^{GTHO} \cdot \text{gssg} + k_{i(\text{nadph})}^{GTHO} \cdot \text{nadph} + \text{gssg.nadph})} \]  

[Ordered Bi Bi]

\[ \text{h}_2\text{o}_2 \] production and metabolism

\[ \text{h}_2\text{o}_2 \] production machinery: This is represented by two enzymatic reactions: NADPH oxidase (NOX) which converts oxygen into oxygen free radicals and superoxide dismutase (SOD) which converts the free radicals into \( \text{h}_2\text{o}_2 \). The former equation has been represented by ordered bi-bi mechanism and the later by a uni-uni mechanism.
\[ V_{NOX} = \frac{V_m^{NOX} \cdot (nadph \cdot O_2)}{(k_{i(nadph)}^{NOX} k_{O_2}^{NOX} + k_{nadph}^{NOX} \cdot nadph + k_{nadph}^{NOX} O_2 + nadph \cdot O_2)} \] [Ordered Bi Bi]

Eq.24:

\[ v_{SOD} = \frac{V_m^{SOD} \cdot (oxrad)}{(k_{oxrad}^{SOD} + oxrad)} \] [Ordered Uni Bi]

Oxygen Uptake: The uptake of oxygen has been represented using a simple Michaelis-Menten equation form. Here \( V_{\text{max}} \) represents the maximum rate of uptake of oxygen by the cell and \( k_m \) represents affinity of the cell for external oxygen. The lower the value of \( k_m \), the higher is the affinity for external oxygen.

Eq.25:

\[ v_{O_2} = \frac{V_m^{O_2} O_{2(\text{ex})}}{k_m^{O_2} + O_{2(\text{ex})}} \]

2. Differential Equations:

All the differential equations with metabolites as the variables have been formulated by considering the involvement of the metabolites in different enzymatic reactions. A few natural productions and decay rates have been considered to take into account the formation of metabolites from other sources and their utilization in other cellular processes respectively. Values to all the parameters considered in the differential equations have been tabulated in Table S1.

1. \[ \frac{d[glc_e]}{dt} = l_r - v_{GLCT} - d_g [glc_e] \]
2. \[ \frac{d[glc_c]}{dt} = v_{GLCT} - v_{HK} \]
3. \[ \frac{d(g6p)}{dt} = v_{HK} - v_{PGL} - v_{G6PDH} \]
\[
\begin{align*}
4. & \quad \frac{d(f6p)}{dt} = v_{PGl} + v_{G6PDH} - v_{PFK} \\
5. & \quad \frac{d(f16bp)}{dt} = v_{PFK} - v_{FBA} \\
6. & \quad \frac{d(gap)}{dt} = v_{FBA} + v_{G6PDH} + v_{TPI} - v_{GAPDH} \\
7. & \quad \frac{d(dhap)}{dt} = v_{FBA} - v_{TPI} \\
8. & \quad \frac{d(1,3bp)}{dt} = v_{GAPDH} - v_{PGK} \\
9. & \quad \frac{d(3pg)}{dt} = v_{PGK} - v_{PGCDH} - d_{3pg}[3pg] \\
10. & \quad \frac{d(atp)}{dt} = l_{atp} + v_{PGK} - v_{HK} - v_{PFK} - v_{GCL} - v_{GS} - d_{atp}[atp] \\
11. & \quad \frac{d(adp)}{dt} = l_{adp} + v_{HK} + v_{PFK} + v_{GCL} + v_{GS} - v_{PGK} - d_{adp}[adp] \\
12. & \quad \frac{d(nadph)}{dt} = l_{nadph} + v_{G6PDH} + v_{GLUD} - v_{GTO} - v_{NOX} - v_{CR} - d_{nadph}[nadph] \\
13. & \quad \frac{d(nadp)}{dt} = l_{nadp} + v_{GTO} + v_{NOX} + v_{CR} - v_{GLUD} - v_{GAPDH} - d_{nadp}[nadp] \\
14. & \quad \frac{d(nadh)}{dt} = l_{nadh} + v_{GAPDH} + v_{PGCDH} - d_{nadh}[nadh] \\
15. & \quad \frac{d(nad)}{dt} = l_{nad} - v_{GAPDH} - v_{PGCDH} - d_{nad}[nad] \\
16. & \quad \frac{d(3php)}{dt} = v_{PGCDH} - v_{PST} \\
17. & \quad \frac{d(glut)}{dt} = v_{GLUTEX} - v_{GCL} - v_{PST} - v_{XCT} - v_{GLUD} \\
18. & \quad \frac{d(akg)}{dt} = v_{PST} + v_{GLUD} - d_{akg}[akg] \\
19. & \quad \frac{d(pser)}{dt} = v_{PST} - v_{PSP}
\end{align*}
\]
\[
\begin{align*}
20. \quad \frac{d(\text{ser})}{dt} &= v_{PSP} - v_{GHMT} \\
21. \quad \frac{d(\text{thf})}{dt} &= l_{thf} - v_{GHMT} - d_{thf}[\text{thf}] \\
22. \quad \frac{d(\text{mlthf})}{dt} &= l_{mlthf} + v_{GHMT} - d_{mlthf}[\text{mlthf}] \\
23. \quad \frac{d(\text{gly})}{dt} &= v_{GLY\text{ex}} + v_{GHMT} - v_{GS} - d_{\text{gly}}[\text{gly}] \\
24. \quad \frac{d(\text{cysL})}{dt} &= v_{CR} - v_{GCL} \\
25. \quad \frac{d(\text{glucys})}{dt} &= v_{GCL} - v_{GS} - d_{\text{glucyc}}[\text{glucys}] \\
26. \quad \frac{d(\text{gsh})}{dt} &= v_{GS} + v_{GTHO} - v_{GTHP} - d_{\text{gsh}}[\text{gsh}] \\
27. \quad \frac{d(\text{cys})}{dt} &= v_{XCT} - v_{CR} \\
28. \quad \frac{d(\text{h}_2\text{o}_2)}{dt} &= v_{SOD} - v_{GTHP} - d_{\text{h}_2\text{o}_2}[\text{h}_2\text{o}_2] \\
29. \quad \frac{d(\text{gssg})}{dt} &= v_{GTHP} - v_{GTHO} - d_{\text{gssg}}[\text{gssg}] \\
30. \quad \frac{d(\text{glut})}{dt} &= l_{gl} + v_{XCT} - v_{GLUTEX} - d_{gl}[\text{glut}] \\
31. \quad \frac{d(\text{cys}_{\text{e}})}{dt} &= l_{cy} - v_{XCT} - d_{cy}[\text{cys}_{\text{e}}] \\
32. \quad \frac{d(O_{2}(\text{ex}))}{dt} &= L_{\text{oxy}} - v_{O_2} - d_{\text{oxy}}[O_2(\text{ex})] \\
33. \quad \frac{d(O_2)}{dt} &= v_{O_2} + v_{SOD} - v_{NOX} - d_{in}[O_2] \\
34. \quad \frac{d(\text{oxrad})}{dt} &= v_{NOX} - v_{SOD}
\end{align*}
\]
3. **Positivity and Boundedness**

**Positivity:**

**Proposition 1:** All the solutions of Eq. 1-35 (Section 2) which initiate in $R^35_+$ lie in a positive solution space.

**Proof:** The system of equations described in Supplementary Section 2 (Eq. 1-35) can be analyzed with the initial conditions (Supplementary Section 5) defined in the thirty-five-dimensional variable space

$$R^35_+ = \{ (\text{glc}_e, \text{glc}_e, \text{g}6\text{p}, f 6\text{p}, f 16\text{bp}, \text{gap}, \text{dhap}, 1,3\text{bp}, 3 \text{pg}, \text{atp}, \text{adp}, \text{nadph}, \text{nadp}, \text{nadh}, \text{nad}, 3\text{php}, \text{glut}, \text{akg}, \text{psr}, \text{ser}, \text{thf}, \text{mlthf}, \text{gly}, \text{cysL}, \text{glucys}, \text{gsh}, \text{cys}, \text{h}_2\text{o}_2, \text{gssg}, \text{glut}_e, \text{cys}_e, \text{O}_2(\text{ex}), \text{oxrad}, \text{gly}_e) \in R^{35} | (\text{glc}_e, \text{glc}_e, \text{g}6\text{p}, f 6\text{p}, f 16\text{bp}, \text{gap}, \text{dhap}, 1,3\text{bp}, 3 \text{pg}, \text{atp}, \text{adp}, \text{nadph}, \text{nadp}, \text{nadh}, \text{nad}, 3\text{php}, \text{glut}, \text{akg}, \text{psr}, \text{ser}, \text{thf}, \text{mlthf}, \text{gly}, \text{cysL}, \text{glucys}, \text{gsh}, \text{cys}, \text{h}_2\text{o}_2, \text{gssg}, \text{glut}_e, \text{cys}_e, \text{O}_2(\text{ex}), \text{oxrad}, \text{gly}_e) \geq 0 \}$$

It can be proven, that all solutions of the system in $R^35_+$ remain in $R^35_+$. Hence, $R^35_+$ is positively invariant, and it is sufficient to consider solutions only in $R^35_+$. In this region, the usual existence, uniqueness and continuation results hold for the system. From our numerical simulations, we have observed the existence of positive solutions for the parameter values presented in Table S1. The steady-state attained by all the variables of the model is a part of this positive solution space. We observe that the right-hand side of Eq. 1-35 (Section 2) are smooth functions of the variables $(\text{glc}_e, \text{glc}_e, \text{g}6\text{p}, f 6\text{p}, f 16\text{bp}, \text{gap}, \text{dhap}, 1,3\text{bp}, 3 \text{pg}, \text{atp}, \text{adp}, \text{nadph}, \text{nadp}, \text{nadh}, \text{nad}, 3\text{php}, \text{glut}, \text{akg}, \text{psr}, \text{ser}, \text{thf}, \text{mlthf}, \text{gly}, \text{cysL}, \text{glucys}, \text{gsh}, \text{cys}, \text{h}_2\text{o}_2, \text{gssg}, \text{glut}_e, \text{cys}_e, \text{O}_2(\text{ex}), \text{oxrad}, \text{gly}_e)$

Since all the parameters are non-negative, local existence and uniqueness properties hold in $R^35_+$, and if the following necessary conditions are satisfied,

1. $l_g > d_g[\text{glc}_e]$
2. $l_{\text{atp}} > d_{\text{atp}}[\text{atp}]$
3. $l_{\text{adp}} > d_{\text{adp}}[\text{adp}]$
4. $l_{\text{nadph}} > d_{\text{nadph}}[\text{nadph}]$
5. $l_{\text{nadp}} > d_{\text{nadp}}[\text{nadp}]$
6. $l_{\text{nadh}} > d_{\text{nadh}}[\text{nadh}]$
Boundedness:

Theorem: All the solutions of Eq. 1-35 (Section 2) which initiate in $\mathbb{R}^+_{35}$ are uniformly bounded.

Proof:

Let

$$W_1 = [glc,] + [3pg] + [atp] + [adp] + [nadph] + [nadp] + [nadh] + [nad] + [akg] + [thf] + [mlthf] + [gly] + [glcys] + [gsh] + [h_2o_2] + [gssg] + [glut_e] + [cys_e] + [O_2] + [gly_e]$$

Then taking time derivative and using the equation, we have

$$\frac{dW_1}{dt} \leq W_1 \left(G_{6PDH} + v_{FBA} + v_{SOD} - v_{GCL} - v_{GS} - v_{GTHP} - d_{wl} W_1\right)$$

where,

$$d_{wl} = \min\{d_{gl}, d_{3pg}, d_{atp}, d_{adp}, d_{nadph}, d_{nadp}, d_{nadh}, d_{nad}, d_{akg}, d_{thf}, d_{mlthf}, d_{gly}, d_{glcys}, d_{gsh}, d_{h_2o_2}, d_{gssg}, d_{cys}, d_{oxy}, d_{gly(e)}\}$$

and

$$l_{wl} = \max\{l_{gl}, l_{atp}, l_{adp}, l_{nadph}, l_{nadp}, l_{nadh}, l_{nad}, l_{akg}, l_{thf}, l_{mlthf}, l_{gly}, l_{cys}, l_{oxy}, l_{gly(e)}\}$$

Let

$$L_p = \sum_{m=1}^{\infty} G_{6PDH} m + \sum_{m=1}^{\infty} v_{FBA} m + \sum_{m=1}^{\infty} v_{SOD} m$$

and

$$L_n = \sum_{m=1}^{\infty} v_{GCL} m + \sum_{m=1}^{\infty} v_{GS} m + \sum_{m=1}^{\infty} v_{GTHP} m$$

where

$$v_{G6PDH} + v_{FBA} + v_{SOD} \leq L_p$$

and

$$v_{G6PDH} \leq L_p$$

and so on; and

$$v_{GCL} + v_{GS} + v_{GTHP} \leq L_n$$

and

$$v_{GCL} \leq L_n$$

and so on.
\[
\frac{dW_i}{dt} \leq l_{wl} + L_p - d_{wl} W_i
\]

\[
\frac{dW_i}{dt} + d_{wl} W_i \leq l_{wl} + L_p
\]

\[
\frac{dW_i}{dt} + d_{wl} W_i \leq \theta_1 \text{ where, } \theta_1 = l_{wl} + L_p
\]

From the theory of differential inequalities, we then obtain

\[0 < W_i([glc]_e,[3pg],[atp],[adp],[nadph],[nadp],[nadh],[nad],[akg],[thf],[mthf],[gly],[glucys],[gsh],[h_2o_2],[gssg],[glut_e],[cys_e],[O_2(ox)],[O_2],[gly_e]) < \frac{\theta_1}{d_{wl}} (1 - e^{-d_{wl}t}) + W_i([glc]_e(0),[3pg](0),[atp](0),[adp](0),[nadph](0),[nadp](0),[nadh](0),[nad](0),[akg](0),[thf](0),[mthf](0),[gly](0),[glucys](0),[gsh](0),[h_2o_2](0),[gssg](0),[glut_e](0),[cys_e](0),[O_2(ox)]](0),[O_2](0),[gly_e](0)) e^{-d_{wl}t}
\]

and for \(t \rightarrow \infty\), it follows \(0 < W_i < \frac{\theta_1}{d_{wl}}\).

Hence all solutions of \(W_i(t)\) that initiate at \(W_i(0) \in \mathbb{R}^{35}\) are confined to the region:

\[G_i = \{ (W_i)^T \in \mathbb{R}^{35} : W_i = \frac{\theta_1}{d_{wl}} + \epsilon_i \text{ for any } \epsilon_i > 0 \}\] for all \(t \geq T^*\) where \(T^*\) depends on the initial value \((W_i(0))^T\) and lie in a positive solution space provided the necessary conditions specified in Proposition 1 are satisfied.

4. **Parameter values and reported range of initial values of variables:**

All the parameters have been defined and the values have been provided along with the reference to the literature from which they have been obtained. A set of parameters has been estimated using the Delayed Rejection Adaptive Metropolis (DRAM) algorithm of Markov Chain Monte Carlo (MCMC) Toolbox in MATLAB 2017a. These parameters have been referenced as “Estimated”. Another set of parameters has been referenced as “Expected”. These parameters have been estimated by varying the parameters within the biologically feasible ranges as reported in various literature to determine their expected value to calibrate the model with experimental observations.

**Table S1:** Parameter values and their units used for the model simulation and their references
| Sr. No. | Parameter       | Description                                                                 | Value       | Unit            | Reference |
|--------|-----------------|------------------------------------------------------------------------------|-------------|-----------------|-----------|
| 1      | $V_{GLCT}^{m}$  | $V_{\text{max}}$ of Glucose transporter                                      | 7.67        | mM hr$^{-1}$    | [1]       |
| 2      | $k_{GLCT \text{glic}}$ | Rate constant for association of cytosolic glucose with Glucose transporter | 2.1         | mM              | [1]       |
| 3      | $l_g$           | Rate of glucose influx from other extracellular sources in the ECM           | 5.6         | mM hr$^{-1}$    |           |
| 4      | $d_g$           | Depletion of extracellular glucose for utilization by other cell types       | 0.2         | hr$^{-1}$       | Expected* |
| 5      | $V_{HK}^{m}$    | $V_{\text{max}}$ of Hexokinase                                              | 9.59*10^2   | mM hr$^{-1}$    | [1]       |
| 6      | $k_{HK \text{i atp}}^{m}$ | Rate constant for dissociation of ATP with Hexokinase                      | 1           | mM              | [1]       |
| 7      | $k_{HK \text{glic}}^{m}$ | Rate constant for association of cytosolic glucose with Hexokinase         | 0.47        | mM              | **       |
| 8      | $k_{HK \text{atp}}^{m}$ | Rate constant for association of ATP with Hexokinase                        | 1           | mM              | [1]       |
| 9      | $V_{PGI}^{m}$   | $V_{\text{max}}$ of Phosphoglucose Isomerase                               | 2.4*10^3    | mM hr$^{-1}$    | [1]       |
| 10     | $k_{PGI \text{g6p}}^{m}$ | Rate constant for association of G6P with Phosphoglucose Isomarase         | 9.6*10^{-1} | mM              | [1]       |
| 11     | $V_{PFK}^{m}$   | $V_{\text{max}}$ of Phosphofructokinase                                     | 2.63*10^2   | mM hr$^{-1}$    | [1]       |
| 12     | $k_{PFK \text{f6p}}^{m}$ | Rate constant for association of F6P with Phosphofructokinase              | 6*10^{-2}   | mM              | [1]       |
| 13     | $k_{PFK \text{atp}}^{m}$ | Rate constant for association of ATP with Phosphofructokinase            | 6.8*10^{-2} | mM              | [1]       |
| 14     | $k_{PFK \text{i(atp)}}^{m}$ | Rate constant for dissociation of ATP from Phosphofructokinase            | 10.204      | mM              | Estimated |
| 15     | $V_{FBA}^{m}$   | $V_{\text{max}}$ of Fructose Bisphosphate Aldolase                        | 1.33*10^2   | mM hr$^{-1}$    | [1]       |
| 16     | $k_{FBA \text{f16bp}}^{m}$ | Rate constant for association of F16BP with Fructose Bisphosphate Aldolase | 5*10^{-2}   | mM              | [1]       |
| 17     | $V_{TPI}^{m}$   | $V_{\text{max}}$ of Triosephosphate Isomerase                             | 5.10*10^{-2} | mM hr$^{-1}$    | [1]       |
| 18     | $k_{TPI \text{dihap}}^{m}$ | Rate constant for association of Triosephosphate Isomerase                | 1.62*10^{-1} | mM              | [1]       |
| 19     | $V_{GAPDH}^{m}$ | $V_{\text{max}}$ of Glyceraldehyde phosphate dehydrogenase               | 781         | mM hr$^{-1}$    | [2]       |
| 20     | $k_{GAPDH \text{gap}}^{m}$ | Rate constant for association of GAP with Glyceraldehyde phosphate dehydrogenase | 1.4         | mM              | [3]       |
|   |   |   |
|---|---|---|
| 21. | $k_{GAPDH_i (gap)}$ | Rate constant for dissociation of GAP from Glyceraldehyde phosphate dehydrogenase | $1.59 \times 10^{-16}$ | mM | [1] |
| 22. | $k_{GAPDH_{hi (h_2o_2)}}$ | Inhibition constant of H2O2 for Glyceraldehyde phosphate dehydrogenase | 21.044 | mM | Estimated |
| 23. | $k_{GAPDH_nad}$ | Rate constant for association of NAD with Glyceraldehyde phosphate dehydrogenase | 1.3 | mM | [3] |
| 24. | $l_{nad}$ | Rate of formation of intracellular NAD$^+$ from other internal sources | 12.5 | mM hr$^{-1}$ | Expected |
| 25. | $d_{nad}$ | Depletion of NAD$^+$ in other intracellular reactions | 0.5 | hr$^{-1}$ |
| 26. | $V_{PGK_m}$ | $V_{\text{max}}$ of Phosphoglycerate kinase | $2.21 \times 10^2$ | mM hr$^{-1}$ | [2] |
| 27. | $k_{PGK_{(1,3,3,pg)}}$ | Rate constant for dissociation of BPG from Phosphoglycerate kinase | 1.6 | mM | [1] |
| 28. | $k_{PGK_{adp}}$ | Rate constant for association of ADP with Phosphoglycerate kinase | 0.1 | mM | [1] |
| 29. | $d_{pg}$ | Natural decay of intracellular 3-phosphoglycerate | 1.8 | hr$^{-1}$ | Expected |
| 30. | $V_{PGCDH_m}$ | $V_{\text{max}}$ of Phosphoglycerate dehydrogenase | 0.0021 | mM hr$^{-1}$ | [4] |
| 31. | $k_{PGCDH_nad}$ | Rate constant for association of NAD with Phosphoglycerate kinase | 0.022 | mM | [5] |
| 32. | $k_{PGCDH_{3pg}}$ | Rate constant for association of PG with Phosphoglycerate kinase | 0.26 | mM | [5] |
| 33. | $k_{PGCDH_{i(3,pg)}}$ | Rate constant for dissociation of PG from Phosphoglycerate kinase | 20 | mM | Estimated |
| 34. | $d_{php}$ | Natural decay of intracellular phosphohydroxy phosphate | 0.005 | hr$^{-1}$ | Expected |
| 35. | $V_{PST_m}$ | $V_{\text{max}}$ of Phosphoserine transaminase | 0.081 | mM hr$^{-1}$ | [6] |
| 36. | $k_{PST_{i(glu)(l)}}$ | Rate constant for dissociation of Glutamate from Phosphoserine transaminase | 7.42 | mM | [6] |
| 37. | $k_{PST_{3php}}$ | Rate constant for association of PHP from Phosphoserine transaminase | 0.005 | mM | [6] |
| 38. | $k_{PST_{glut}}$ | Rate constant for association of Glutamate with Phosphoserine transaminase | 1.2 | mM | [6] |
| 39. | $d_{akg}$ | Utilization of $\alpha$-ketoglutarate into intracellular reactions | 0.8 | hr$^{-1}$ | Expected |
| 40. | $V_{PSP_m}$ | $V_{\text{max}}$ of Phosphoserine Phosphatase | 0.162 | mM hr$^{-1}$ | [7] |
|   |                      |                                                      |       |   |  |
|---|----------------------|------------------------------------------------------|-------|---|---|
| 41. | $k_{PSP}^{m}$        | $K_m$ of Phosphoserine transaminase                   | 0.1   | mM | [8] |
| 42. | $V_{m}^{GHMT}$       | $V_{max}$ of Glycine hydroxymethyltransferase         | 40    | mM $hr^{-1}$ | [9] |
| 43. | $k_{GHMT}^{thf}$     | Rate constant for association of THF with Glycine hydroxymethyltransferase | 0.05  | mM | [9, 10] |
| 44. | $k_{GHMT}^{ser}$     | Rate constant for association of Serine with Glycine hydroxymethyltransferase | 0.6   | mM | [9, 10] |
| 45. | $k_{GHMT}^{i(ser)}$  | Rate constant for dissociation of Serine from Glycine hydroxymethyltransferase | 14    | mM | Estimated |
| 46. | $V_{m}^{GLUTEX}$     | $V_{max}$ of Glutamate exchanger                     | 38.69 | mM $hr^{-1}$ | Estimated |
| 47. | $k_{m}^{GLUTEX}$     | $K_m$ of Glutamate exchanger                         | 0.097371 | mM | Estimated |
| 48. | $l_{thf}$            | Rate of formation of tetrahydofolate from internal reactions | 4    | mM $hr^{-1}$ | Expected*** |
| 49. | $d_{thf}$            | Depletion of tetrahydofolate in other intracellular reactions | 0.5  | hr$^{-1}$ | Expected |
| 50. | $l_{mthf}$           | Rate of formation of methyl-tetrahydofolate from other internal reactions | 6    | mM $hr^{-1}$ | Expected*** |
| 51. | $d_{mthf}$           | Depletion of methyl-tetrahydofolate in intracellular reactions | 0.5  | hr$^{-1}$ | Expected |
| 52. | $V_{m}^{GLUD}$       | $V_{max}$ of Glutamate dehydrogenase                 | $5.55 \times 10^3$ | mM $hr^{-1}$ | [1] |
| 53. | $k_{GLUD}^{i(glut)}$ | Rate constant for dissociation of Glutamate from Glutamate dehydrogenase | 3.5   | mM | [1] |
| 54. | $k_{GLUD}^{glut}$    | Rate constant for association of Glutamate with Glutamate dehydrogenase | 3.5   | mM | [1] |
| 55. | $k_{GLUD}^{nadp}$    | Rate constant for association of NADP with Glutamate dehydrogenase | 5.6   | mM | Estimated |
| 56. | $l_{glut}$           | Rate of glutamate influx into the ECM from other cellular processes | 3    | mM $hr^{-1}$ | Expected |
| 57. | $d_{glut}$           | Depletion of extracellular glutamate from other cellular processes | 0.3  | hr$^{-1}$ | Expected |
| 58. | $V_{m}^{GCL}$        | $V_{max}$ of Glutamyl-cysteine Ligase                | 14    | mM $hr^{-1}$ | Estimated |
| 59. | $k_{GCL}^{cysL}$     | Rate constant for association of Cysteine with Glutamyl-cysteine Ligase | 0.07  | mM | [11] |
| 60. | $k_{GCL}^{glut}$     | Rate constant for association of Glutamate with Glutamyl-cysteine Ligase | 0.46  | mM | [11] |
| 61. | $k_{GCL}^{atp}$      | Rate constant for association of ATP with Glutamyl-cysteine Ligase | 0.44  | mM | [11] |
|   |   | Rate constant for dissociation of ATP from Glutamyl-cysteine Ligase | 9.73 | \(\text{mM} \) | Estimated |
|---|---|---|---|---|---|
|   |   | Rate constant for dissociation of Glutamate from Glutamyl-cysteine Ligase | 9.72 | \(\text{mM} \) | Estimated |
|   |   | Natural decay of intracellular gamma-glutamyl cysteine | 0.08 | \(\text{hr}^{-1} \) | Expected |
|   |   | \(V^G_{\text{GS}} \) | \(V_{\text{max}}\) of Glutathione synthase | 0.1174 | \(\text{mM hr}^{-1}\) | [12]" |
|   |   | Rate constant for association of Glutamyl-cysteine with Glutathione synthase | 0.99 | \(\text{mM} \) | [13] |
|   |   | Rate constant for association of Glycine with Glutathione synthase | 1.37 | \(\text{mM} \) | [13] |
|   |   | Rate constant for association of ATP with Glutathione synthase | 0.23 | \(\text{mM} \) | [13] |
|   |   | Rate constant for dissociation of ATP from Glutathione Synthase | 11.8 | \(\text{mM} \) | Estimated |
|   |   | Rate constant for dissociation of Glycine from Glutathione Synthase | 6.0699 | \(\text{mM} \) | Estimated |
|   |   | \(V^N_{\text{NOX}} \) | \(V_{\text{max}}\) of NADPH Oxidase | 0.0468 | \(\text{mM hr}^{-1}\) | [14] |
|   |   | Rate constant for association of Oxygen with NADPH Oxidase | 0.22 | \(\text{mM} \) | [15] |
|   |   | Rate constant for association of NADPH with NADPH Oxidase | 0.055 | \(\text{mM} \) | [15] |
|   |   | Rate constant for dissociation of NADPH from NADPH Oxidase | 11.624 | \(\text{mM} \) | Estimated |
|   |   | Rate of formation of intracellular NADPH from other internal sources | 8 | \(\text{mM hr}^{-1}\) | Expected |
|   |   | Depletion of NADPH in other intracellular reactions | 0.8 | \(\text{hr}^{-1}\) | Expected |
|   |   | \(V^S_{\text{SOD}} \) | \(V_{\text{max}}\) of Superoxide Dismutase | \(11.4*10^3\) | \(\text{mM hr}^{-1}\) | [16] |
|   |   | Rate constant for association of free oxygen radical with Superoxide Dismutase | 0.054 | \(\text{mM} \) | [16] |
|   |   | \(V^G_{\text{GTHP}} \) | \(V_{\text{max}}\) of Glutathione Peroxidase | 0.438 | \(\text{mM hr}^{-1}\) | [17, 18] (ranges: 0.2874 to 2.697 mM/hr) |
|   |   | Rate constant for association of GSH with Glutathione Peroxidase | 0.2 | \(\text{mM} \) | [19] |
|   |   | Natural decay of intracellular reduced glutathione | 0.00016 | \(\text{hr}^{-1}\) | Expected |
|   |   | Rate constant for association of H$_2$O$_2$ with Glutathione Peroxidase | 0.45 | mM | [19] |
|---|---|---|---|---|---|---|
| 82. | $k_{	ext{GTNP}}^{	ext{h}_2\text{O}_2}$ |   |   |   |   |   |
|   |   | Rate constant for dissociation of H$_2$O$_2$ from Glutathione Peroxidase | 5.3677 | mM | Estimated |
| 83. | $k_{i(h_2o_2)}^{	ext{GTNP}}$ |   |   |   |   |   |
|   |   | Decay of intracellular hydrogen peroxide in other cellular processes | 0.001 | hr$^{-1}$ | Expected |
| 84. | $d_{h_2\text{O}_2}$ |   |   |   |   |   |
|   | $V_m^{	ext{GTPO}}$ | V$_{\text{max}}$ of Glutathione Oxidoreductase | 0.00216 | mM hr$^{-1}$ | [20] |
| 85. |   |   |   |   |   |   |
|   |   | Rate constant for association of NADPH with Glutathione Oxidoreductase | 0.063 | mM | [21] |
| 86. | $k_{\text{GTPO}}^{	ext{nadph}}$ |   |   |   |   |   |
|   |   | Rate constant for association of GSSG with Glutathione Oxidoreductase | 0.154 | mM | [21] |
| 87. | $k_{\text{GTPO}}^{	ext{gssg}}$ |   |   |   |   |   |
|   |   | Rate constant for dissociation of GSSG from Glutathione Oxidoreductase | 5.05 | mM | Estimated |
| 88. | $k_{i(gssg)}^{	ext{GTPO}}$ |   |   |   |   |   |
|   |   | Natural decay of intracellular oxidized glutathione | 0.00020 | hr$^{-1}$ | Expected |
| 89. | $d_{\text{gssg}}$ |   |   |   |   |   |
|   | $V_m^{	ext{XCT}}$ | V$_{\text{max}}$ of Cystine-glutamate antiporter | 0.001272 | mM hr$^{-1}$ | [22] |
| 90. |   |   |   |   |   |   |
|   |   | Rate constant for dissociation of Cystine from Cystine-glutamate antiporter | 0.0249 | mM | [23] |
| 91. | $k_{i(cys)}^{	ext{XCT}}$ |   |   |   |   |   |
|   |   | Rate constant for association of Glutamate with Cystine-glutamate antiporter | 0.084 | mM | [24] |
| 92. | $k_{\text{glut}}^{	ext{XCT}}$ |   |   |   |   |   |
|   |   | Rate constant for association of Cystine with Cystine-glutamate antiporter | 0.084 | mM | [24] |
| 93. | $k_{i(cys)}^{	ext{XCT}}$ |   |   |   |   |   |
|   |   | Rate of cystine influx into the ECM via other cellular processes | 3 | mM hr$^{-1}$ | Expected |
| 94. | $l_{\text{cys}}$ |   |   |   |   |   |
|   |   | Depletion of extracellular cystine into other cellular processes | 0.6 | hr$^{-1}$ | Expected |
| 95. | $d_{\text{cys}}$ |   |   |   |   |   |
|   |   | Rate of Oxygen diffusing into the ECM and available for cellular uptake | 10 | mM hr$^{-1}$ | Expected |
| 96. | $L_{\text{oxy}}$ |   |   |   |   |   |
|   |   | Utilization of Oxygen by other cell types | 0.7 | hr$^{-1}$ | Expected |
| 97. | $d_{\text{oxy}}$ |   |   |   |   |   |
|   |   | V$_{\text{max}}$ of external Oxygen uptake | 15.278 | mM hr$^{-1}$ | [25] |
| 98. | $V_m^{O_2}$ |   |   |   |   |   |
|   |   | K$_m$ of external Oxygen uptake | 164 | mM | [2] |
| 99. | $k_m^{O_2}$ |   |   |   |   |   |
|   |   | Utilization of Oxygen in other intracellular reactions | 50.313 | hr$^{-1}$ | Estimated |
| 100. | $d_m$ |   |   |   |   |   |
|   |   | Rate of glycine influx into the ECM via other cellular processes | 4 | mM hr$^{-1}$ | Expected |
| 101. | $l_{\text{gly(e)}}$ |   |   |   |   |   |
|   |   | Depletion of extracellular glycine into other cellular processes | 0.5 | hr$^{-1}$ | Expected |
| 102. | $d_{\text{gly(e)}}$ |   |   |   |   |   |
| 103. | \( V_{\text{GLYex}}^{m} \) | \( V_{\text{max}} \) of Glycine Exchanger | 0.0287 | \( \text{mM hr}^{-1} \) | [26] |
| 104. | \( k_{\text{GLYex}}^{m} \) | \( K_{m} \) of Glycine Exchanger | 0.029 | \( \text{mM} \) | [26, 27] |
| 105. | \( d_{\text{gly}} \) | Natural decay of intracellular glycine | 0.0586 | \( \text{hr}^{-1} \) | Expected |
| 106. | \( V_{\text{G6PDH}}^{m} \) | \( V_{\text{max}} \) of Glucose-6-phosphate dehydrogenase | 5.337 | \( \text{mM hr}^{-1} \) | Estimated |
| 107. | \( k_{\text{G6PDH}}^{i(g6p)} \) | Rate constant for dissociation of G6P from Glucose-6-phosphate dehydrogenase | 6.904 | \( \text{mM} \) | Estimated |
| 108. | \( k_{\text{G6PDH}}^{nadp} \) | Rate constant for association of NADP with Glucose-6-phosphate dehydrogenase | 4.9725 | \( \text{mM} \) | Estimated |
| 109. | \( k_{\text{G6PDH}}^{g6p} \) | Rate constant for association of G6P with Glucose-6-phosphate dehydrogenase | 6.627 | \( \text{mM} \) | Estimated |
| 110. | \( k_{\text{G6PDH}}^{ii(atp)} \) | Inhibition constant of ATP for Glucose-6-phosphate dehydrogenase | 6.0885 | \( \text{mM} \) | Estimated |
| 111. | \( l_{\text{nadp}} \) | Rate of formation of intracellular NADP+ from other internal sources | 6 | \( \text{mM hr}^{-1} \) | Expected |
| 112. | \( d_{\text{nadp}} \) | Depletion of NADP+ in other intracellular reactions | 0.5 | \( \text{hr}^{-1} \) | Expected |
| 113. | \( V_{\text{CR}}^{m} \) | \( V_{\text{max}} \) of Cystine Reductase | 12 | \( \text{mM hr}^{-1} \) | Estimated |
| 114. | \( k_{\text{CR}}^{i(cys)} \) | Rate constant for dissociation of Cystine from Cystine Reductase | 10 | \( \text{mM} \) | Estimated |
| 115. | \( k_{\text{CR}}^{nadph} \) | Rate constant for association of NADPH with Cystine Reductase | 5.536 | \( \text{mM} \) | Estimated |
| 116. | \( k_{\text{CR}}^{cys} \) | Rate constant for association of Cystine with Cystine Reductase | 5.1175 | \( \text{mM} \) | Estimated |
| 117. | \( d_{\text{cysl}} \) | Natural decay of intracellular cysteine | 0.0517 | \( \text{hr}^{-1} \) | Expected |
| 118. | \( l_{\text{atp}} \) | Rate of formation of intracellular ATP from other internal reactions | 8 | \( \text{mM hr}^{-1} \) | [28] |
| 119. | \( d_{\text{atp}} \) | Depletion of ATP in other intracellular reactions | 0.5 | \( \text{hr}^{-1} \) | Expected |
| 120. | \( l_{\text{adp}} \) | Rate of formation of intracellular ADP from other internal reactions | 0.8 | \( \text{mM hr}^{-1} \) | [29] |
| 121. | \( d_{\text{adp}} \) | Depletion of ADP in other intracellular reactions | 0.4 | \( \text{hr}^{-1} \) | Expected |
| 122. | \( l_{\text{nadh}} \) | Rate of formation of intracellular NADH from other internal sources | 5 | \( \text{mM hr}^{-1} \) | Expected |
| 123. | \( d_{\text{nadh}} \) | Depletion of NADH in other intracellular reactions | 0.7 | \( \text{hr}^{-1} \) | Expected |

* Assumptions to the values of rate of influx of glucose and depletion from the extracellular matrix are assumed such that they yielded an extracellular concentration of around 3.9 to 5.4 mM.
** The value has been taken from Brenda and it ranges between 0.37 mM to 0.76 mM [30, 31]
*** The values are assumed based on the reported value of $V_{\text{DHFR}}^\text{m}$ and $V_{\text{MTHFR}}^\text{m}$ to be 5000 μM/hr (or 5 mM/hr) [32].
# The value ranges around the reported value.

Table S2: Initial values to all the variables considered in the model and their reported range in the biological systems have been listed below.

| Variable | Description | Reported Range | Initial Value | Reference |
|----------|-------------|----------------|---------------|-----------|
| $g_{lc_e}$ | Extracellular Glucose | 2.0 – 4.0 mM | 4 mM | [33] |
| $g_{lc_c}$ | Cytoplasmic Glucose | 1.0 – 7.0 mM | 4 mM | [34] |
| $g_{6p}$ | Glucose-6-phosphate | ~ 0.12 mM | 0.38 mM | [35] |
| $f_{6p}$ | Fructose-6-phosphate | ~ 0.016 mM | 0.016 mM | [36] |
| $f_{16bp}$ | Fructose-1,6-bisphosphate | ~ 0.0076 mM | 0.0076 mM | [36] |
| $g_{ap}$ | Glyceraldehyde Phosphate | ~ 0.0076 mM | 0.0076 mM | [36] |
| $d_{hap}$ | Dihydroacetone phosphate | ~ 0.14 mM | 0.14 mM | [36] |
| $1,3\text{bgp}$ | 1,3-bisphosphoglycerate | ~ 0.0004 mM | 0.0004 mM | [36] |
| $3_{pg}$ | 3-phosphoglycerate | ~ 0.045 mM | 0.045 mM | [36] |
| $3_{php}$ | 3-Phosphohydroxypyruvate | 0.01 to 0.4 mM | 0.45 mM | [37] |
| $p_{ser}$ | Phosphoserine | ~ 0.446 mM | 0.446 mM | [38] |
| $s_{er}$ | Serine | 0.5 – 1.0 mM | 0.7 mM | [34] |
| $g_{ly}$ | Cytoplasmic Glycine | 4.4 – 8.4 mM | 5 mM | [34] |
| $t_{hf}$ | Tetrahydrofolate | 2.5 mM | Expected |
| $m_{thf}$ | Methyl-tetrahydrofolate | 2.5 mM | Expected |
| $g_{lut}$ | Extracellular Glutamate | 0.00002 - 0.02 mM | 0.02 mM | [39] |
| $g_{lut}$ | Cytoplasmic Glutamate | 2.6 – 4.6 mM | 2.5 mM | [34] |
| $c_{ys_e}$ | Extracellular Cystine | ~1.6 mM | 1.5 mM | [40] |
| $c_{ys}$ | Cytoplasmic Cystine | 3.6 mM | Expected |
| $c_{ysL}$ | Cysteine | 0.5 – 5 mM | 1.6 mM | [34] |
| $g_{lucys}$ | γ-glutamyl cysteine | 2.5 mM | Expected |
| $g_{sh}$ | Reduced Glutathione | 2.0 – 3.0 mM | 3.83 mM | [41] |
| $g_{ssg}$ | Oxidised Glutathione | 0.024 – 3.0 mM | 0.5 mM | [42] |
| $h_{o2}$ | Hydrogen peroxide | 0.01 – 2 mM | 1.55 mM | [43, 44] |
| $o_{xrad}$ | Oxygen free radicals | | 0.05 mM | Expected |
| $a_{tp}$ | Adenosine tri-phosphate | 1.5 – 6.0 mM | 1.54 mM | [35] |
| $a_{dp}$ | Adenosine di-phosphate | ~ 0.27 mM | 2.7 mM | [36] |
| $n_{ad}$ | Nicotinamide adenine Dinucleotide (oxidized) | ~ 0.05840 mM | 0.0584 mM | [36] |
| $n_{adh}$ | Nicotinamide adenine Dinucleotide (reduced) | ~ 0.03060 mM | 0.03060 mM | [36] |
| $n_{adp}$ | Nicotinamide adenine dinucleotide phosphate | ~ 0.0002 mM | 0.0002 mM | [36] |
|        | (oxidized)                                                                 | ~ 0.0658 mM | 0.0658 mM | [36] |
|--------|----------------------------------------------------------------------------|-------------|-----------|------|
| *nadph*| Nicotinamide adenine dinucleotide phosphate (reduced)                      |             |           |      |
| *akg*  | α-ketoglutarate                                                            | ~ 0.157 mM | 1.4 mM    | [38] |
| *O_{i(ex)}* | Extracellular oxygen               | 12 - 22 mM | 15 mM    | [25] |
| *O_{i}*  | Intracellular oxygen                                                        |             | 5 mM      |      |
| *gly_{ex}* | Extracellular glycine                  | 0.2-2 mM   | 0.2 mM    | [26] |

5. **Parameter estimation:**

Parameter estimation of 23 unknown parameters was done using the Delayed Rejection Adaptive Metropolis (DRAM) algorithm of Markov Chain Monte Carlo (MCMC) Toolbox in MATLAB 2017a. The parameter distribution plot of the 23 parameters has been shown in Figure S1A and the trace plot till 5 lakh chains has been shown in Figure S1B. The model was re-evaluated for available data for glutamate exchange in astrocytes [45] to estimate the value of parameters $V_{m}^{GLUTEX}$ and $k_{m}^{GLUTEX}$. The predictive plot for the same has been provided in Figure S2A and the distribution plot and trace plot of estimated parameters have been shown in Figure S2B and S2C respectively.
**Figure S1:** A. Parameter distribution plot of the estimated parameters within the minimum and maximum range provided for the simulations, B. Trace plots of the estimated parameters generated after 5 lakh chains of MCMC DRAM.
Figure S2: A. Predictive plot demonstrating the fitted model for glutamate exchange and uncertainty regions; B. Parameter distribution curve of the estimated parameters; C. Trace plots of the estimated parameters generated after 5 lakh chains of MCMC DRAM.

6. Sensitivity Analysis:
Extended Fourier Amplified Sensitivity Test (eFAST) algorithm was used for identifying sensitive parameters to the system. The sensitivity analysis was carried out using the whole set of parameters [k=123]. 150 samples were chosen per search curve and the resampling of the search curves was carried out 5 times [NS =150, NR =5]. Hence, the total number of model simulations N=(k+1)*Ns*NR=93000. Sensitivity analyses were performed for normal glial, hypoxic and glioma scenarios created in the model. Supplementary Figure 3 shows the sensitivity index (Si) of the sensitive parameters for the variables gsh (A-C), gssg (D-F), h_{2}O_{2} (G-I) and oxrad (J-L)
under normal glial, hypoxic and glioma scenarios respectively. The sensitivity indices of the parameters were captured for multiple time points (1hr, 2hrs, 4hrs, 8hrs, 16hrs, 20hrs, 24hrs, 32hrs, 50hrs, 100hrs, 150hrs, and 200hrs) and the difference in Si (if any) was taken into account.

Figure S3: Plots of sensitive parameters for different variables obtained for the three scenarios - normal, hypoxia and hypoxia with multiple mutations respectively: (A-C) gsh; (D-F) gssg; (G-I) h_2o_2; (J-L) oxrad

7. Effect of changing $k_\omega$ on uptake of Oxygen:

$k_\omega$ represents the cellular affinity for external oxygen. The model was simulated for different values of $k_\omega$. A lowering in the value of $k_\omega$ shows a reduction in the concentration of external oxygen representing an increasing affinity for external oxygen. The changing concentration of external oxygen with changing values of $k_\omega$ has been shown in Figure S4.
8. Effect of changing $V^{GTHO}_m$ on $\text{nadph}/\text{nadp}^+$ ratio:
A change in the $\text{nadph}/\text{nadp}^+$ ratio was observed depending on the changing value of $V^{GTHO}_m$. This change is captured in Figure S5. A dip in the $\text{nadph}/\text{nadp}^+$ ratio is observed for all the values of $V^{GTHO}_m$. However, with increasing value of $V^{GTHO}_m$, the decline in the $\text{nadph}/\text{nadp}^+$ ratio increases which is regained back to normal and the dynamics depend on the value of $V^{GTHO}_m$ and the persisting amount of oxidant ($\text{HO}_2$) concentration at any point of time.

Figure S5: Temporal plot of Varying $V^{GTHO}_m$ and $k^O_m$ at 1mM over time and its effect on the $\text{nadph}/\text{nadp}^+$ ratio
9. **Combinatorial targets for pro- and anti-oxidant therapy:**

Glioma scenario was created in the model by incorporating changes in the parameter values $V_{m}^{NOX}$, $V_{m}^{GTHO}$, $V_{m}^{GTHP}$ and $k_{m}^{O_{2}}$ which were changed to $1 \text{ mM} \ hr^{-1}$, $0.2 \text{ mM} \ hr^{-1}$, $0.19 \text{ mM} \ hr^{-1}$ and $1 \text{ mM}$ from $0.0468 \text{ mM} \ hr^{-1}$, $0.5 \text{ mM} \ hr^{-1}$, $0.00216 \text{ mM} \ hr^{-1}$ and $164 \text{ mM}$ respectively. Combinatorial variations of sensitive parameters reported in the glioma scenario G11 specified in Table 1 of the main text were made. The values of the parameters were varied between a wide range (0.0001 to 100 units) and changes were observed. Here we have reported the temporal variation in the $h_{2}o_{2}$, $gsh/gssg$ and $nadph/nadp^{+}$ profiles for a particular value of the parameters. The values of the parameters have been specified in Table S2 and the temporal plots have been shown in Figure S6.

**Table S3:** Values of parameters for which pro- and anti-oxidant effects are obtained in the glioma scenario.

| Sr. No. | Parameter 1 | Parameter 2 | Value of Parameter 1 | Value of Parameter 2 | Effect |
|---------|-------------|-------------|----------------------|----------------------|--------|
| 1.      | $k_{i}^{NOX}^{(nadph)}$ | $k_{i}^{CR}^{nadph}$ | $1 \text{ mM}$ | $15 \text{ mM}$ | Pro-oxidant |
| 2.      | $k_{i}^{NOX}^{(nadph)}$ | $k_{i}^{NOX}^{nadph}$ | $20 \text{ mM}$ | $10 \text{ mM}$ | Anti-oxidant |
| 3.      | $L_{oxy}$ | $k_{i}^{CR}^{nadph}$ | $20 \text{ mM} \ hr^{-1}$ | $15 \text{ mM}$ | Pro-oxidant |
| 4.      | $k_{i}^{NOX}^{(nadph)}$ | $l_{atp}$ | $0.5 \text{ mM}$ | $20 \text{ mM} \ hr^{-1}$ | Pro-oxidant |
| 5.      | $V_{m}^{FBA}$ | $L_{oxy}$ | $0.0001 \text{ mM} \ hr^{-1}$ | $5 \text{ mM} \ hr^{-1}$ | Anti-oxidant |
| 6.      | $k_{i}^{GS}^{glucys}$ | $k_{i}^{CR}^{nadph}$ | $0.0001 \text{ mM}$ | $0.5 \text{ mM}$ | Pro-oxidant |
Figure S6: Temporal area plots of changing \( \text{nadhph/nadp}^+ \) and \( \text{gsh/gssg} \) ratios along with the change in \( \text{h}_2\text{o}_2 \) concentration with a combinatorial variation of parameters made in glioma scenario.
10. References

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