Supporting Information

1. Default model with α-ketoglutarate substrate inhibition

We have constructed a kinetic model which involves the mechanisms of α-ketoglutarate substrate inhibition. The model is schematically depicted in Fig. 1A and the kinetic parameters are listed in SI Table 1. The ordinary differential equations of the model are written below:

$$d[GDH.NADPH]/dt = k_1.[GDH].[NADPH]+k_4\,[GDH.NADPH.2OG]-k_2[GDH.NADPH]-k_3[GDH.NADPH].[2OG]$$

$$d[GDH.NADPH.2OG]/dt = k_3.[2OG].[GDH.NADPH]+k_6.[GDH.NADPH.2OG.NH_4^+\text{-}GDH.GLU.NADP^+]-k_4.[GDH.NADPH.2OG]\ -k_5.[NH_4^+].[GDH.NADPH.2OG]$$

$$d[GDH.NADPH.2OG.NH_4^+\text{-}GDH.GLU.NADP^+]/dt = k_5.[NH_4^+].[GDH.NADPH.2OG]+k_8.[GLU].[GDH.NADP^+] + k_9'.[NADP^+].[GDH.GLU]-(k_7+k_6+k_{10}')[GDH.NADPH.2OG.NH_4^+\text{-}GDH.GLU.NADP^+]$$

$$d[GDH.NADP^+]/dt = k_7.\,[GDH.NADPH.2OG.NH_4^+\text{-}GDH.GLU.NADP^+] +k_{10}.[NADP^+][GDH] + k_{12}\,[GDH.NADP^+.2OG]-k_8.[GLU].[GDH.NADP^+]-k_9[GDH.NADP^+]-k_{11}.[2OG].[GDH.NADP^+]$$

$$d[GDH.NADP^+.2OG]/dt = k_{11}.[2OG].[GDH.NADP^+] -k_{12}.[GDH.NADP^+.2OG]$$

$$d[GDH.GLU]/dt = k_{10}'[GDH.NADPH.2OG.NH_4^+\text{-}GDH.GLU.NADP^+] +k_8'[GLU][GDH]-k_9'.[NADP^+][GDH.GLU] -k_7'[GDH.GLU]$$

$$d[GDH]/dt = k_2\,[GDH.NADPH] + k_7'\,[GDH.GLU]+k_9\,[GDH.NADP^+]-k_1\,[NADPH].[GDH]-k_8'[GLU][GDH]-k_{10}\,[NADP^+][GDH]$$

$$d[GLU]/dt = k_7'[GDH.GLU]-k_8[GLU][GDH.NADP^+]-k_8'[GLU][GDH]$$

Equations 1: Ordinary Differential equations of the GDH system. The external inputs to the system are NADPH, ammonium and the α-ketoglutarate. The kinetic parameters used for numerical simulations are given in Table S1. Following the experimental kinetic study of Rife and Cleland (1980), concentrations of NADPH and $NADP^+$ have been fixed at 0.10 mM and 0.96 mM , respectively, at which α-KG substrate inhibition has observed. The system is being allowed to reach at feasible steady state while passing through at least 4000 time steps (i.e.,80 min) with different ammonium and α-ketoglutarate inputs.

This GDH system has been calibrated with the classis experimental results reported by Rife and Cleland (1980) which had experimentally probed and characterized the kinetic scheme considered here. This kinetic study reported that the ratio between the two ternary complexes, GDH-$NADP^+$-KG and GDH-NADPH-KG, remains constant under the variable substrate levels of ammonium and αKG. We have randomly supplied the ammonium and α-KG with uniform distribution in the range of 1-10 mM and 1-50 mM, respectively to estimate kinetic parameter values for which the ternary complex ratio has remained approximately constant throughout (Table 1). With this parameter setting, we have examined the sensitivity of GDH activities and regulation under variable substrate levels with different input conditions.

Table S1 Kinetic parameters. Listed are the kinetic parameters used for the simulations depicted in Fig.S1-S2. With this parameter setting, the ratio between the ternary complex GDH.$NADP^+$.αKG and GDH.NADPH. αKG remains constant (i.e., 0.1) under a wide range of variation in ammonium and αKG, as it is reported in the kinetic study of Rife and Cleland (1980):

Model Parameter(unit)	Description	Value
$k_1(mM^{-1}min^{-1})$	Rate constant of [GDH.NADPH] complex formation	5.7
$k_2(min^{-1})$	Rate constant of [GDH.NADPH] complex degradation	1.3669
$k_3(mM^{-1}min^{-1})$	Rate constant of [GDH.NADPH.KG] complex formation	5.5
$k_4(min^{-1})$	Rate constant of [GDH.NADPH.KG] complex degradation	2.81
$k_5(mM^{-1}min^{-1})$	Rate constant of (GDH.NADPH.KG.$+NH_4$ -GDH.Glu.$+NADP$) formation	0.05
$k_6(mim^{-1})$	Rate constant of (GDH.NADPH.KG.$+NH_4$ -GDH.Glu.$+NADP$) degradation	13.9439
$k_7(min^{-1})$	Rate constant of [GDH.$+NADP$] complex formation	0.48
$k_8(mM^{-1}min^{-1})$	Rate constant of [GDH.$+NADP$] complex degradation	5.77
$k_9(min^{-1})$	Rate constant of [GDH] come back	5.54
$k_{10}(mM^{-1}min^{-1})$	Rate constant of $+NADP$ associated with [GDH]	0.6964
$k_{11}(mM^{-1}min^{-1})$	Rate constant of [GDH. $\overset{+.KG}{NADP}$] complex formation	2.03
$k_{12}(min^{-1})$	Rate constant of [GDH. $\overset{+.KG}{NADP}$] complex degradation	1.45*k_{11}
$k_7'(min^{-1})$	Rate constant of release [Glu] product	1.13
$k_8'(mM^{-1}min^{-1})$	Rate constant of product [Glu] associated with enzyme [GDH]	1.4415
$k_9'(mM^{-1}min^{-1})$	Rate constant of [GDH.Glu] complex degradation	1.0
$k_{10}'(min^{-1})$	Rate constant of [GDH.Glu] complex formation	2.80

2. Simulated GDH kinetics:

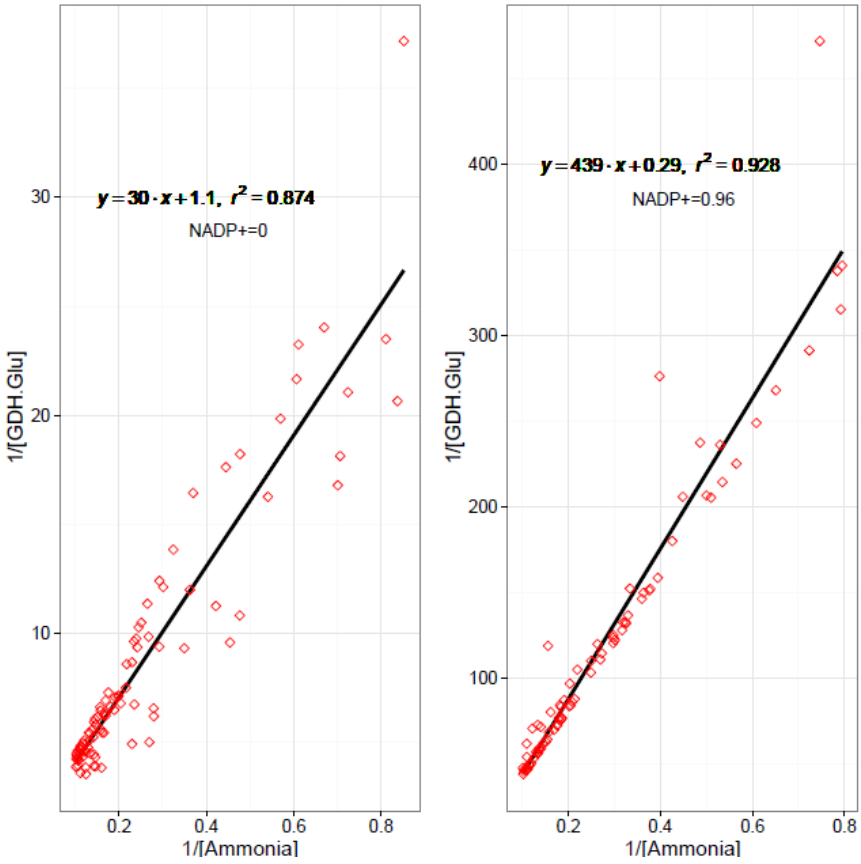
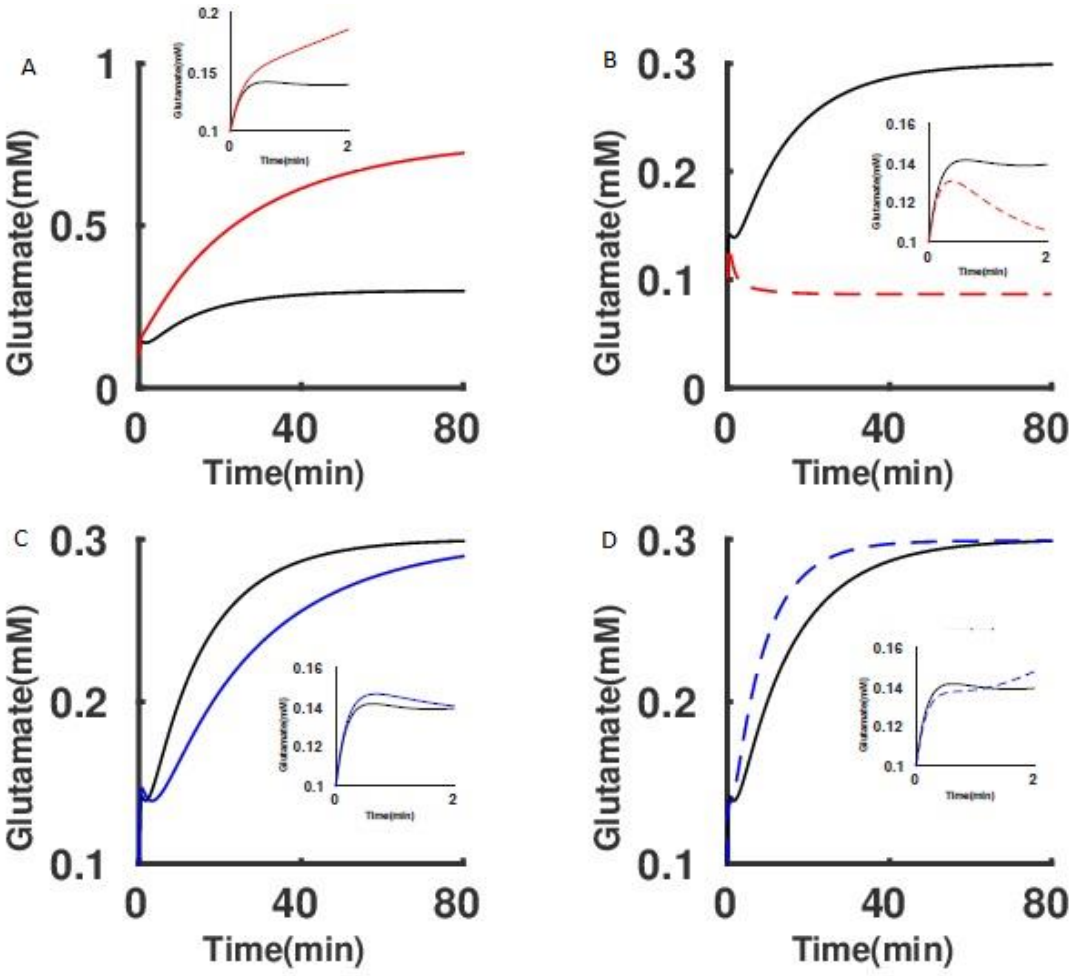


Fig.S1. A linear relationship between the product complex and ammonium under variable α-ketoglutarate (Table S1) is observed.

Table-S1: **Role of substrate inhibition:** simulated results of the GDH system under the substrate inhibition while a constant ratio between the obligatory ammonium binding complex and the inhibitory complex has been maintained within a wide range of ammonium and ketoglutarate variation

Variable substrate* (mM)		$NADP^+$ (mM)	Slope with respect to variable NH_4^+ .(R^2>0.85)(Fig.S1)	[GDH.$NADP^+$.αKG]/ [GDH.NADPH.αKG]	Robust ratio of [Glu]/NH_4^+
$NH4^+$	αKG	0.96	439.17	0.113 ± 0.010	0.037 ± 0.017
		0	30.037	0.004 ± 0.003	0.400 ± 0.046

**In silico* experiment was carried out with randomly supplied NH_4^+ and αKG from the uniform distribution in the range 1-10 mM and 1-50 mM respectively, while NADPH and initial GDH concentration were fixed at 0.10 mM and 0.088 mM, respectively.



FigS2. Transient dynamics of glutamate (GLU) synthesis with respect to the steady-state dynamics of GLU concentration (i.e.,0.299 mM) at the intracellular level of NH_4^+ and α-ketoglutarate, 10 mM and 20 mM, respectively (black line): it shows that the glutamate production is essentially depends on the ratio between NH_4^+ and αKG. (A) steady-state GLU level: 0.724 mM when NH_4^+: 20 mM, and αKG: 40 mM (red line), (B) steady-state GLU level: 0.087 mM when NH_4^+: 5 mM, and αKG: 10 mM (dotted red line), (C) steady-state GLU level: 0.290 mM when NH_4^+: 5 mM, and αKG: 40 mM (blue line), and (D) steady-state GLU level: 0.299 mM when NH_4^+: 20 mM, and αKG: 10 mM (dotted blue line).