1 Supplementary File 1-

3 Figure 1* - The detailed molecular regulatory network comprising of the interactions between 2 metabolic hormones (insulin and glucagon), 3 macronutrients (glucose, amino acids and fatty acids), 4 signaling pathways (insulin signaling, mTOR signaling, Glucagon signaling and calcium signaling) along with major metabolic transcriptional factors and metabolic pathways.
Figure M1 The Hill fit curves for the data from literature reported for the plasma insulin levels with respect to (A) Plasma Glucose, (B) Plasma Amino Acids, (C) Plasma Fatty acids and (D) Blood flow with respect to plasma insulin levels.
Figure M2 (I) Validation of fluxes and metabolite profiles in liver for resting state. The solid line represents simulation profile and the ‘o’ markers represent the experimental data. (A) Hepatic glucose release profile validated with the data reported by König et al. 2012\(^1\), Edgerton et al 2006\(^2\) and Meyer et al 1998\(^3\) (B) Gluconeogenesis profile validated with data reported in König et al 2012\(^1\) and Edgerton et al 2006\(^2\) (C) Glycogen profile validated with data reported in König et al 2012\(^1\) (D) Triglycerides profile validated with data reported in Ferrell and Chiang et al. 2015\(^4\) and Ravi Kumar et al. 2004\(^5\).
**Figure M2(II)** Validation of resting hepatic metabolite profiles with the source models (Konig et al 2012 and Xu et al 2011). The solid line represents the simulation results and the dashed line represents the simulation profiles by the source models.
Figure M2(III) Validation of signaling and transcriptional profiles in liver while resting state with the source models. The solid line represents the simulation results and the dashed line represents the simulation profiles by the source models. The signaling components were validated by model profiles from Sedaghat et al. 2002 for AKT and PKC, Mutalik et al. 2007 and Xu et al. 2011 for GSK3, cAMP and PKA, Vinod and Venkatesh 2009 for mTOR. The transcription model represents the qualitative trends and the fold changes based upon the data reported in literature (refer to transcription module in methodology section).
Figure M3  The pyruvate transport flux for varying levels of plasma amino and fatty acids for four different glucose conditions. A positive value on the color bar represents the pyruvate uptake into the plasma from the liver, whereas a negative value represents the release of the pyruvate by hepatic tissues.
Figure M4  The Lactate transport flux varying levels of plasma amino and fatty acids for four different glucose conditions. A positive value on the color bar represents the lactate uptake into the plasma from the liver, whereas a negative value represents the release of the lactate by hepatic tissues.
Figure M5  The pyruvate carboxylase flux varying levels of plasma amino and fatty acids for four different glucose conditions.
Figure M6 The ratio of ATP breakdown [Adenylate kinase flux] to ATP production (oxidative phosphorylation flux) for varying levels of plasma amino and fatty acids for four different glucose conditions. The ratio below one represents that the ATP production flux is higher than the ATP lysis flux.
Figure M7  The rate of pentose phosphate pathway represented Glucose 6 phosphate dehydrogenase flux that is abstracted for conversion of G6p to ribulose 5 phosphate for varying levels of plasma amino and fatty acids for four different glucose conditions.
Figure M8 The triglyceride transport flux for varying levels of plasma amino and fatty acids for four different glucose conditions. The value below one represents the net flux is towards triglyceride release and vice versa.
Figure M9  The amino acid uptake flux from the liver, for varying levels of plasma amino and fatty acids for four different glucose conditions.
Figure M10 The steady state fold change in ammonia levels in liver for varying levels of plasma amino and fatty acids for four different glucose conditions.
Steady States of Signaling and Transcription factors

Steady state responses for some of the key signaling regulators and transcription factors with respect of varying levels of amino acids and fatty acids for four different glucose levels [low, normal, moderately high, very high] are shown in the Figures below [Fig..S1 to Fig..S12]. The trends observed in the above mentioned metabolic fluxes are resultant effects of the states of signaling and transcriptional molecules. AKT, mTOR, S6K1p, CHREBP, SREBP and PPARγ are the anabolic regulators activated by glucose, insulin, amino acids and fatty acids. PKA, PKC, AMPK, FOXO, PPARα and TRB3 are the catabolic regulators activated by the glucagon, amino acids and fatty acids. The interplay of these regulators at signaling and transcriptional levels under different dietary conditions yield the specific metabolic state of the tissue. These metabolic states decide upon the healthy or disease condition of the tissue.

**Figure N1** The steady state response of AKT phosphorylation for varying levels of plasma amino and fatty acids for four different glucose conditions. AKT increases with increasing glucose levels and decreases with increasing amino and fatty acid levels. AKT is highest at high glucose and low amino fatty acid conditions and lowest at very high amino fatty acid conditions.
The steady state response of PKA activation for varying levels of plasma amino and fatty acids for four different glucose conditions. PKA increases with increasing amino and fatty acid levels and decreases with increasing glucose levels. PKA is highest at low glucose and low amino fatty acid conditions and lowest at very high glucose conditions.
Figure N3 The steady state response of PKC activation for varying levels of plasma amino and fatty acids for four different glucose conditions. PKC increases with increasing glucose and fatty acid levels and decreases with increasing amino acid levels. However under high glucose conditions, it increases with fatty acid levels and decreases with decreasing fatty acids.
Figure N4 The steady state response of AMPK activation for varying levels of plasma amino and fatty acids for four different glucose conditions. AMPK increases with low glucose and high amino acid levels and decreases with increasing fatty acid levels. However, under high glucose condition it increases with increasing fatty acids and decreases with lower amino acid levels. It is mostly inhibited at high amino fatty acid levels.
Figure N5 The steady state response of CHREBP activation for varying levels of plasma amino and fatty acids for four different glucose conditions. CHREBP increases with increasing glucose and decreases with increasing fatty acids at normal glucose levels, due to inhibition of AKT. It is inhibited at high amino fatty acid levels.
The steady state response of TRB3 activation for varying levels of plasma amino and fatty acids for four different glucose conditions. TRB3 increases with increasing fatty acids and decreases with increasing glucose levels. However at lower glucose levels it also decreases with increasing amino acid levels, whereas, at higher glucose levels, it increases with increasing amino fatty acids.
Figure N7 The steady state response of PPARγ activation for varying levels of plasma amino and fatty acids for four different glucose conditions. PPARγ expression increases with increasing fatty acid levels. Under normal glucose levels, it is inhibited at low amino acid and low fatty acid and at high glucose condition it is reduced with increasing amino acid levels.
Figure N8 The steady state response of FOXO activation for varying levels of plasma amino and fatty acids for four different glucose conditions. FOXO increases at very low glucose fat amino acid condition. At normal glucose levels it increases with high fatty acid levels. At high glucose levels, it is highest at moderate amino acids conditions. However at very high glucose, its activation decreases due to increasing levels of AMPK and PPARγ that are inhibitors of FOXO.
Figure N9 The steady state response of PPARα activation for varying levels of plasma amino and fatty acids for four different glucose conditions. It increases with increasing fatty acid levels and decreases with increasing glucose levels. However, under high glucose levels it increases with high amino fatty acid condition. PPARα is activated by fatty acids and PKA and deactivated by AKT.
Figure N10 The steady state response of SREBP activation for varying levels of plasma amino and fatty acids for four different glucose conditions. SREBP increases with increasing amino acid and decreasing fatty acid conditions under normal glucose levels. However, it is contrast under high glucose conditions.
Figure N11 The steady state response of mTOR activation for varying levels of plasma amino and fatty acids for four different glucose conditions. mTOR increases with increasing amino acid and glucose levels and decreases with lower amino acid levels. The Figure shows sensitivity of mTOR to amino acids decrease with increasing fatty acid levels. Therefore, it is highest at high amino glucose and low fatty acid condition.
Figure N12 The steady state response of S6K phosphorylation for varying levels of plasma amino and fatty acids for four different glucose conditions. This follows the trend similar to mTOR.


