Multi-Scale Model for Analyzing Disease States in Metabolic Syndrome

K. V. Venkatesh
Dept. of Chemical Engineering
IIT Bombay

Genotype to Phenotype

- Genome
- Transcriptome
- Proteome
- Metabalome
- Phenotype

Presence of genome does not ensure a phenotype
It requires a specific state in the hierarchical chain.

Central Dogma of Biology

Luciferase Gene — Genetic network

Luciferase gene decoded — RNA network

Catalyzed by Luciferase Enzyme — Protein network

Phosphorous release using ATP — Metabolic network

Physiological state

Firefly Glows
Transgenic Plant made to Glow

Quantification of Systems

- Engineering systems are quantified to a level that they are designed, optimized and optimally operated.
- Genetic, signaling/protein and metabolic networks are the result of reductionist approach of Molecular Biology.
- Bioinformatics has added more information to this approach.
- Principles of system science can be applied to component biology: **Systems Biology**

System Analysis and Quantification

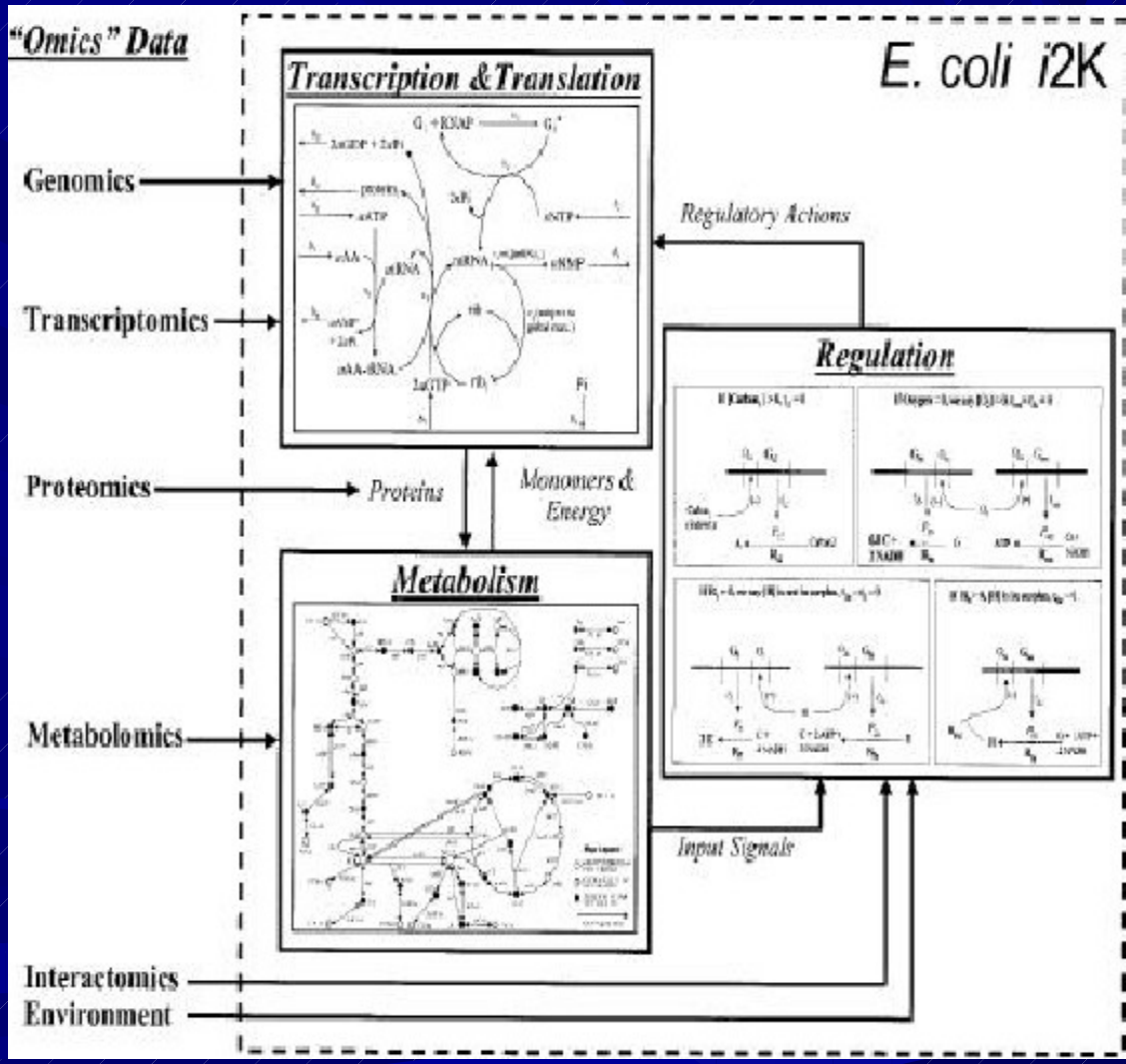
- Design
- Operation
- Control
- Fault Diagnosis
- Evolve

Bottom-up Design of a Complex System

- 1250 computers
- Hundreds of feedback loops
- Millions of components
- Design Manual Available

Design in Nature: Top-Down Approach (*Escherichia coli*)

- About 4400 genes
- Connectivity between genes, mRNA, proteins & metabolites
- Thousands of feedback loops
- No design principles available
- No computation – control & sensing achieved through interactions of biomolecules



Complexity in Engineered and Natural Systems

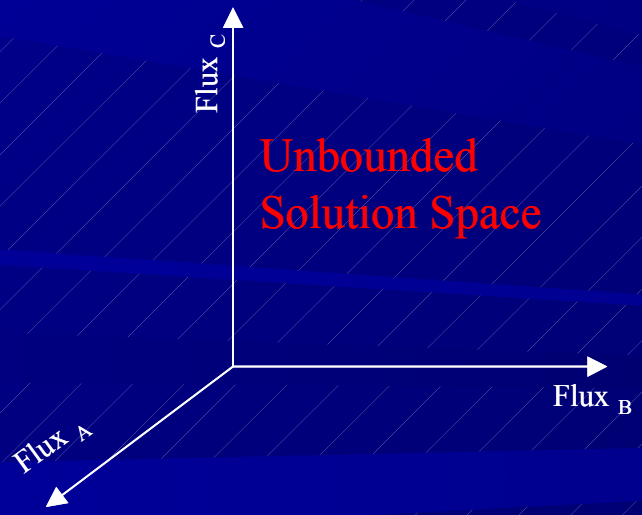
- Non-linear dynamics
- Multiple feedback loops
- Multiple interactions
- Cascade structures
- Feed forward loops
- Interactions between modules
- Timescale separation

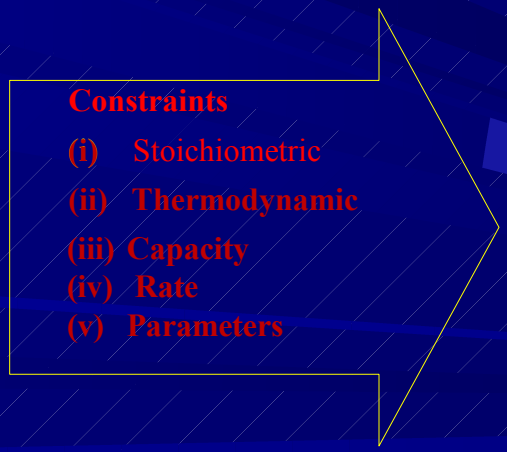
Resulting in a Complex system

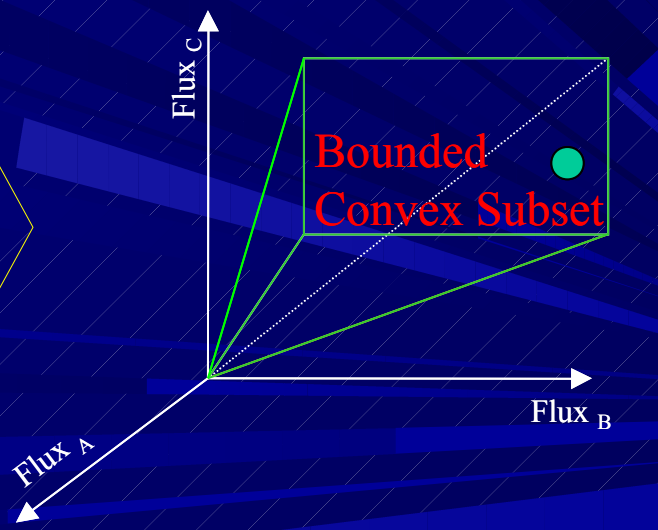
Constraint-based Analysis

How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?

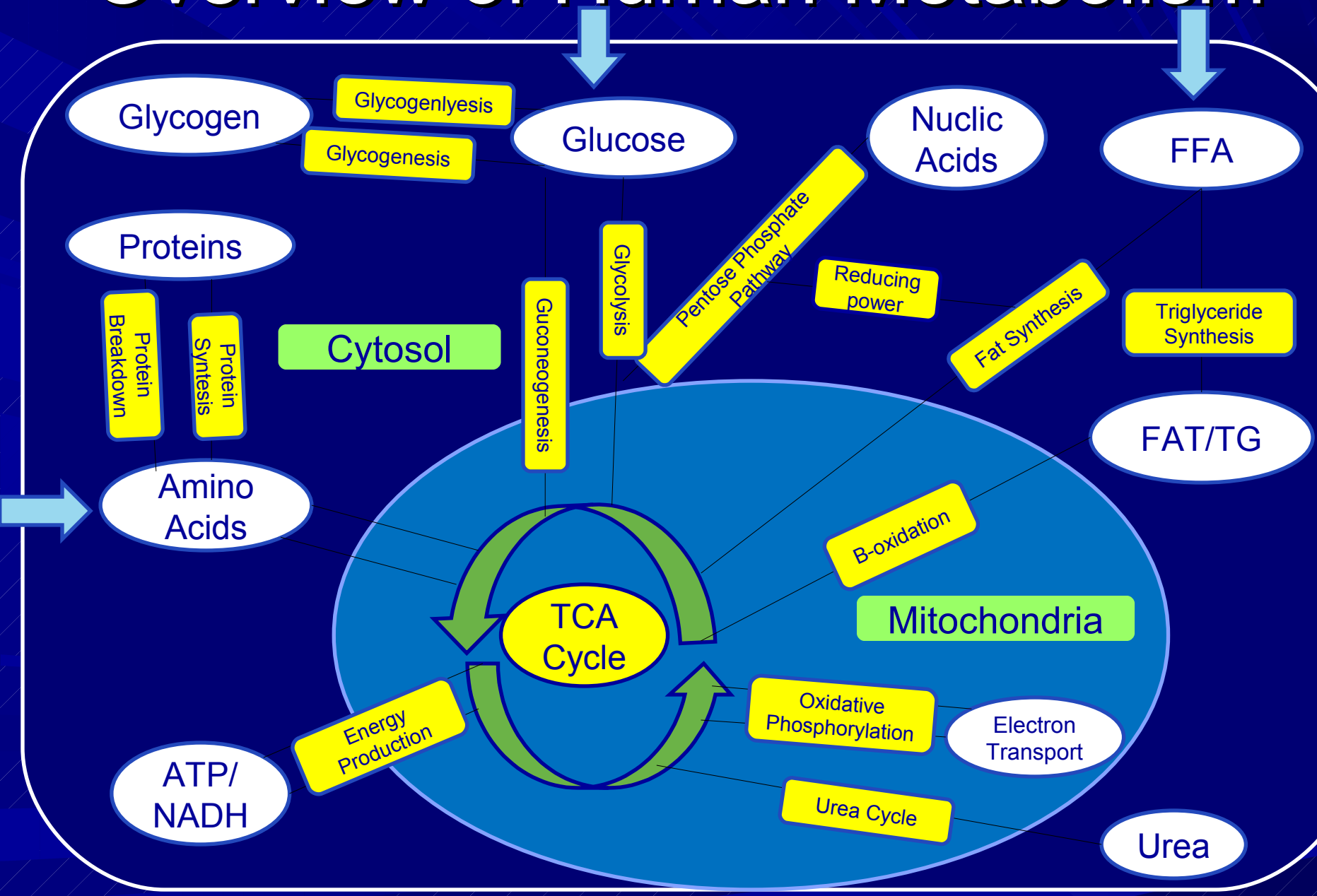
–Sherlock Holmes, A Study in Scarlet







Overview of Human Metabolism



Metabolic Regulation

Insulin (Anabolic)

- Glucose uptake
- Glycolysis
- Glycogen synthesis
- Protein synthesis
- Fat Synthesis

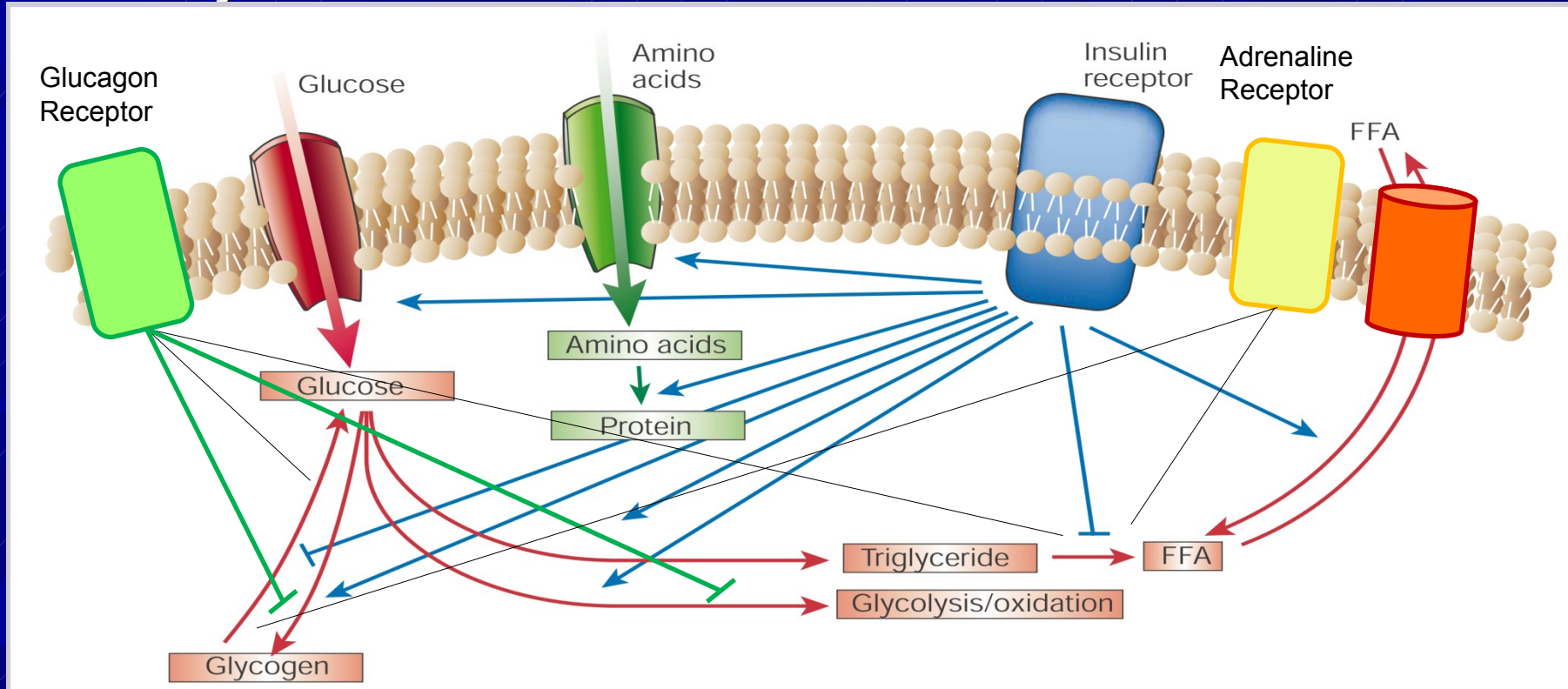
Glucagon (Catabolic)

- Glycogen breakdown
- Gluconeogenesis
- Fat breakdown
- Proteolysis
- Ketogenesis

Adrenaline

- Glycogen breakdown
- Fat breakdown

(During Higher work rate and Exercise)



Whole body Energy Balance

- Energy intake = total energy output

  (heat + work + energy storage)

- Average Energy Intake per day

  Carbohydrates-250 g, Fat-80 g, Protein-100 g

- Average Energy output

  Heat is usually about 60% - basal metabolic rate

  Excess energy is stored in the form of fat or glycogen

- Contribution to total Energy Expenditure

  Glucose -34% i.e. 130 mg/min @ 17 KJ/g

  Fat- 66% i.e. 112 mg/min @ 38 KJ/g

Metabolic Controllers

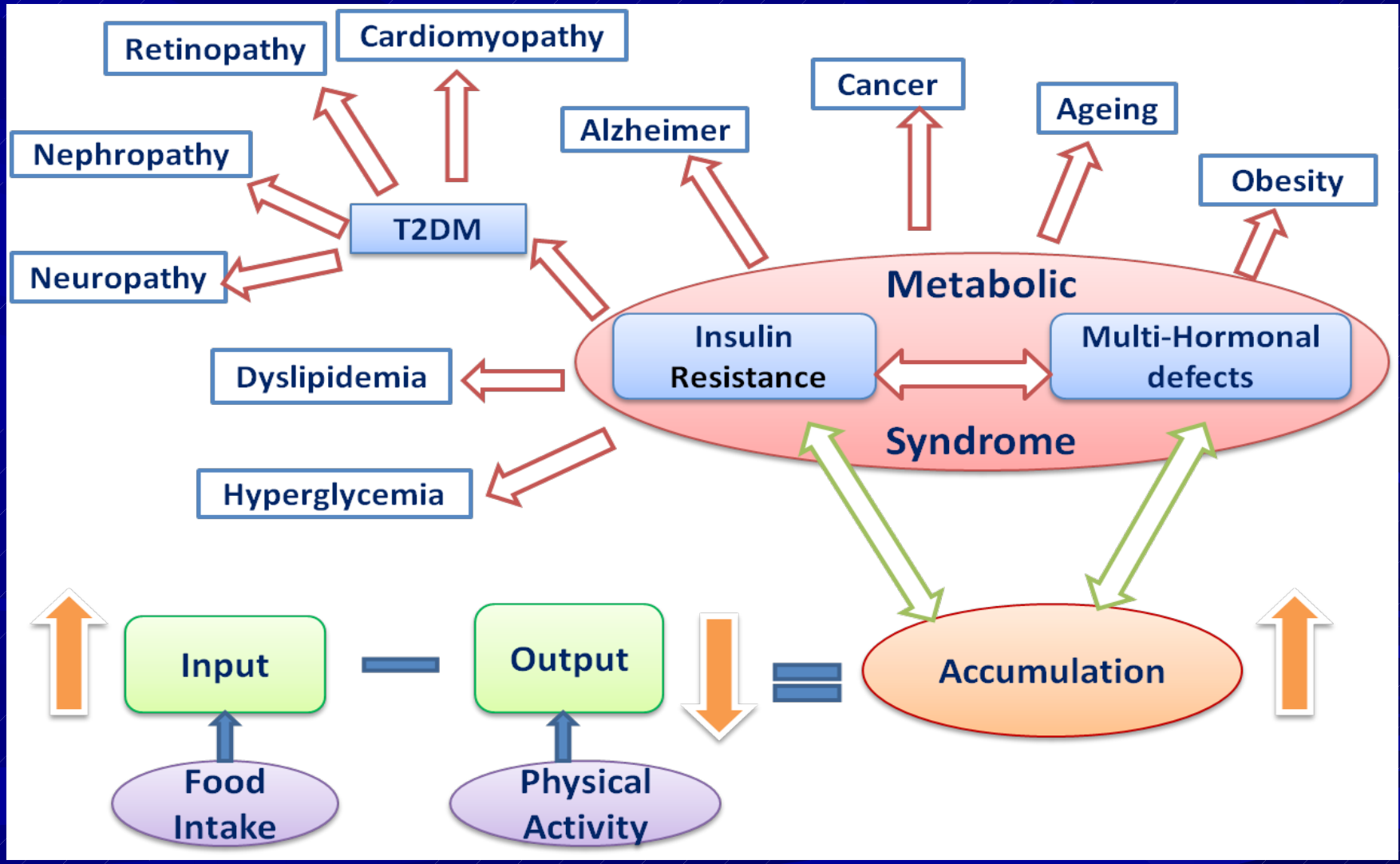
- Energy status of the cell controls metabolic fluxes
- Anabolic Pathways (after meal and storage) are controlled by
  - Phosphorylation state (Positive) = (ATP/ADP)
  - Redox State (Positive) = (NADH/NAD)
- Catabolic Pathways (while rest and Exercise) are controlled by
  - Phosphorylation state (Negative) = (ADP/ATP)
  - Redox State (Negative) = (NAD/NADH)
- Glucagon and Insulin works as a rein controller
  - Glucagon/Insulin ratio governs breakdown of Glycogen and Fat
- Adrenaline (Epinephrine)-Neural activation of Metabolic fluxes

During exercise or higher work rate Adrenaline effect Accelerates catabolism

- Blood flow to tissues changes with exercise and work rate

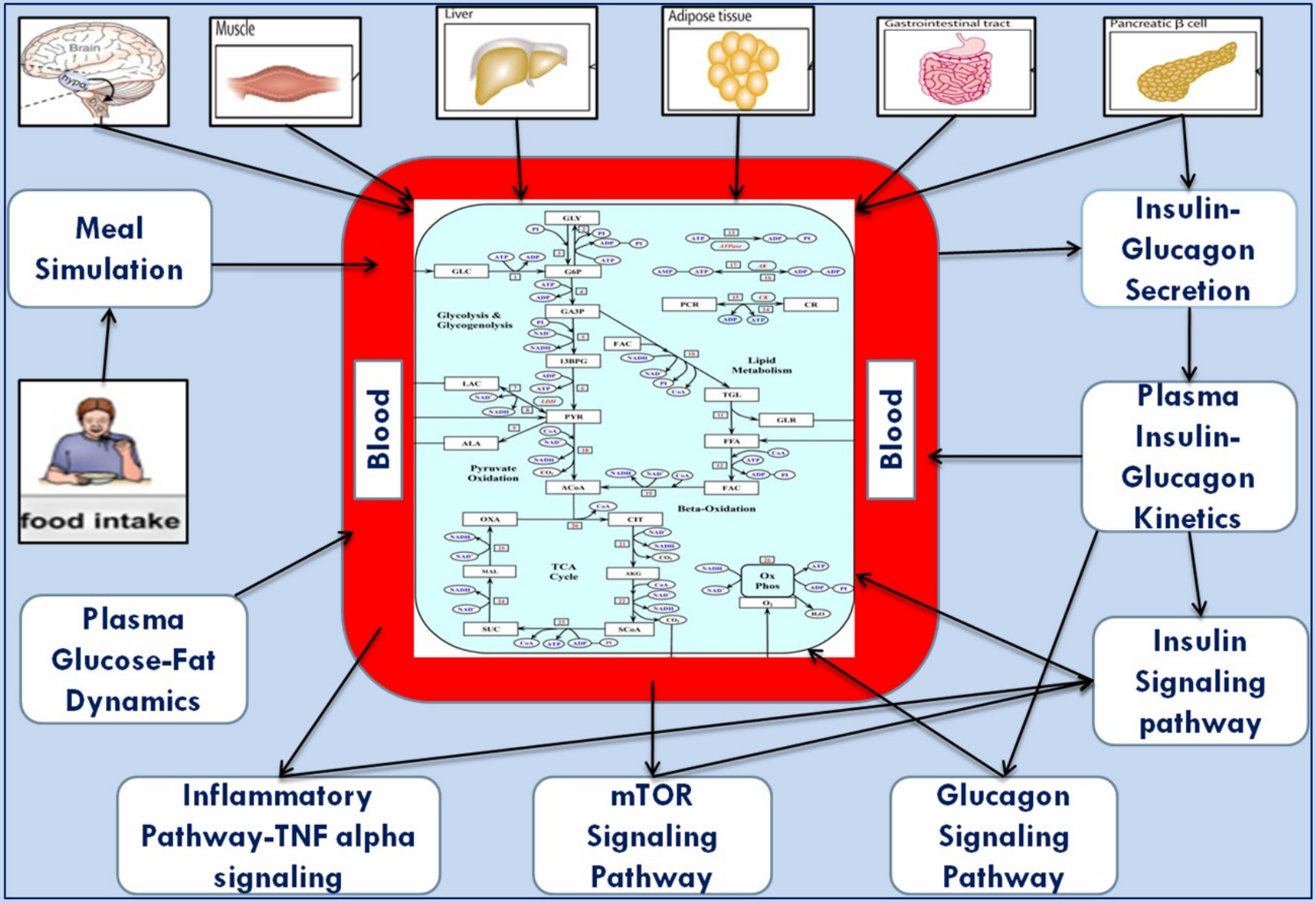
Blood flow increases in muscles and heart while decreases in GI track and Liver

Defective Metabolic Homeostasis



Whole Body Metabolic Model

- A kinetic model to represent metabolism integrated with signaling pathway
- Modular analysis towards *in silico* representation of different organ tissue types
- Metabolism connected to blood metabolite concentration
- Study the effect of perturbation in signaling pathway

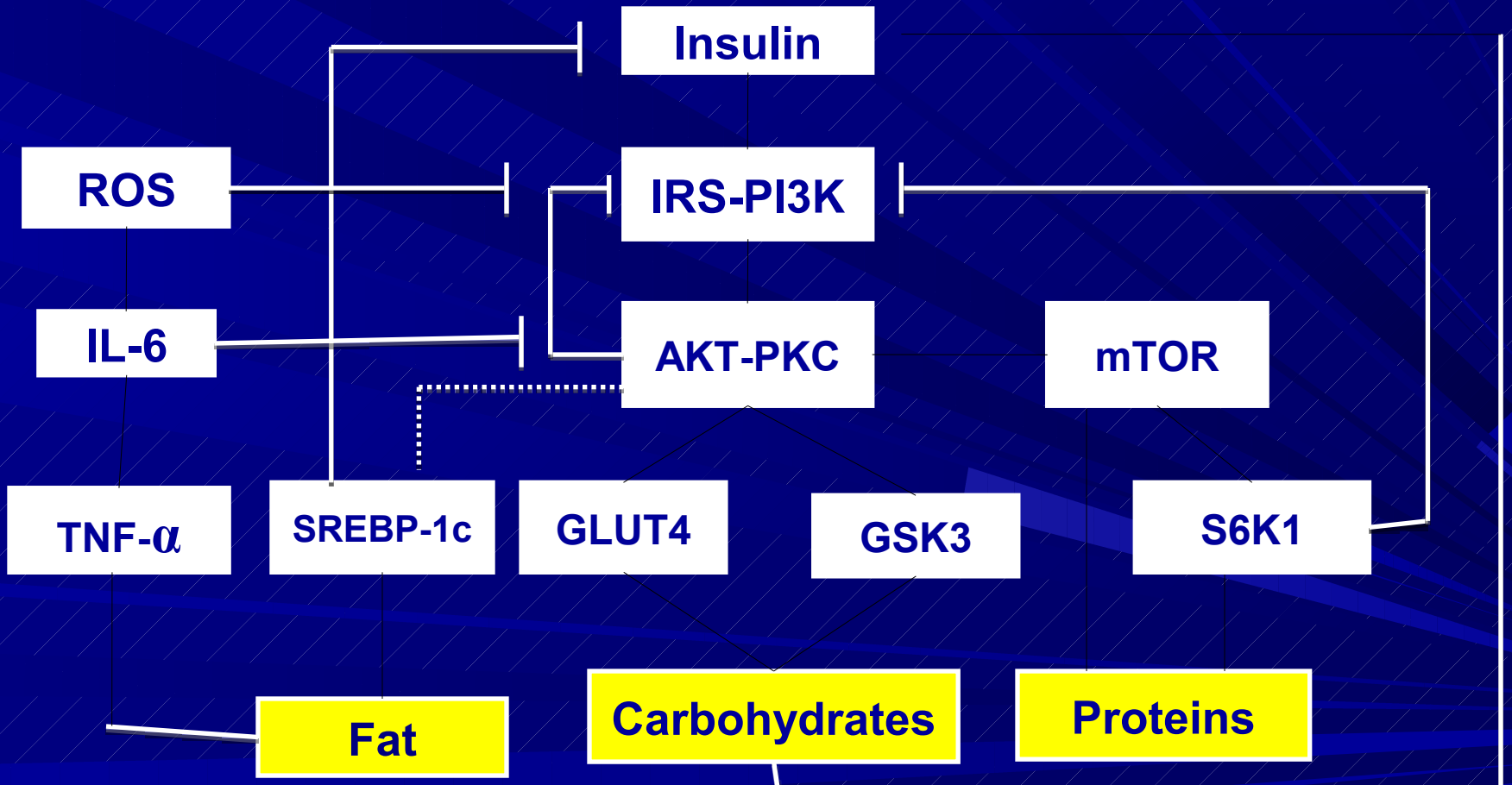

Brain
Muscle
Liver
Adipose tissue
Gastrointestinal tract
Pancreatic β cell
Meal Simulation
food intake
Plasma Glucose-Fat Dynamics
Blood
Blood
Glycolysis & Glycogenolysis
Lipid Metabolism
Pyruvate Oxidation
Beta-Oxidation
TCA Cycle
Ox Phos
Insulin-Glucagon Secretion
Plasma Insulin-Glucagon Kinetics
Insulin Signaling pathway
Inflammatory Pathway-TNF alpha signaling
mTOR Signaling Pathway
Glucagon Signaling Pathway

Integration of Models

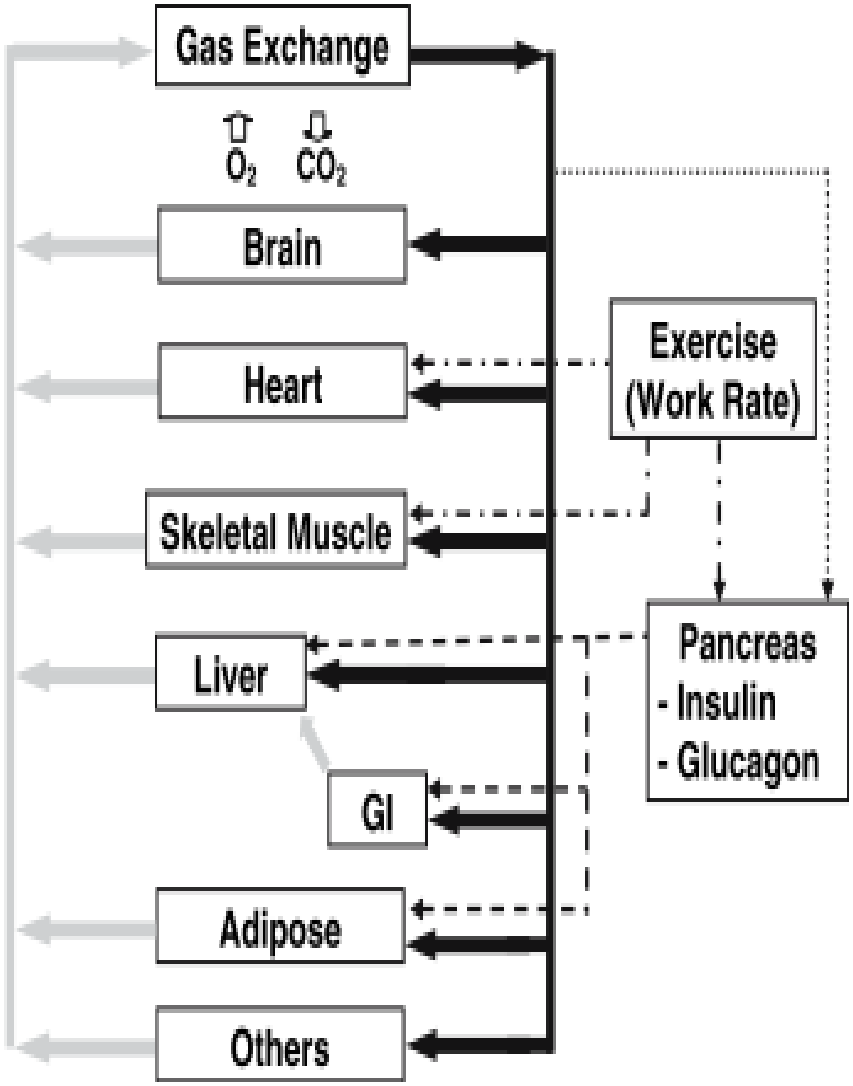
- The output of signaling pathways were given as the inputs for metabolic Network.
- Separate equations were modeled for Glucose transport through Glucose transporters, Fat transporters and Amino Acid transporters in different tissues.
- Around 600 rate equations including 300 odes & 1000 parameters

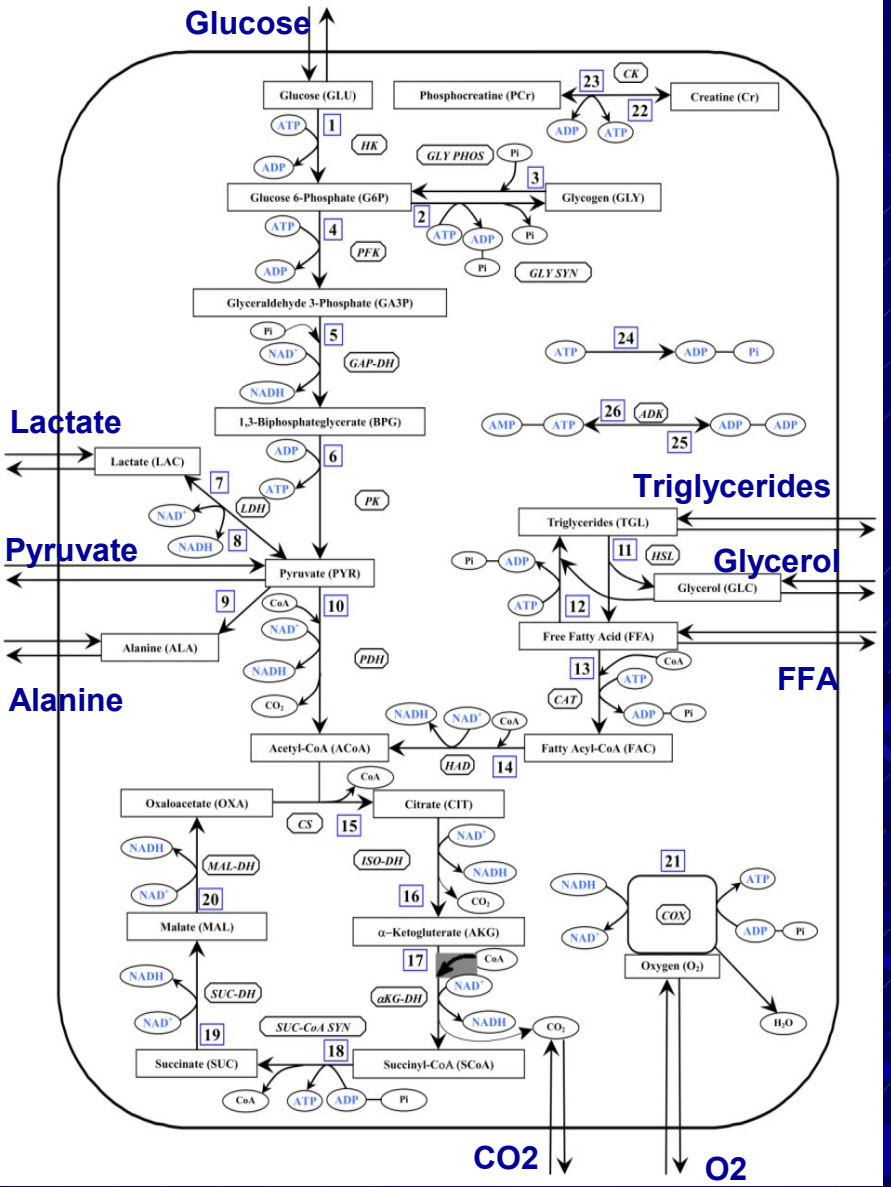
Organ/ Tissue	Glucose Transporter	Fat Transporter
Muscle	GLUT4	FATP1
Heart	GLUT4	FATP1
Adipocyte	GLUT4	FATP1
Liver	GLUT2	FATP5
GI track	GLUT3	FATP4
Brain	GLUT1	

Interplay of ISP-mTOR-TNF Signaling for Anabolism



Whole body Metabolism

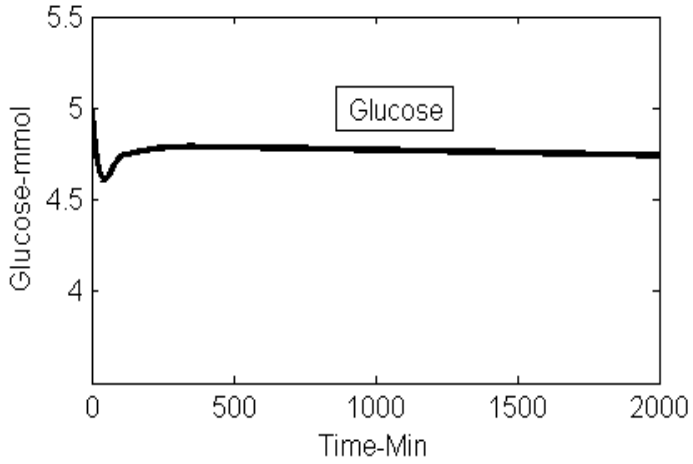


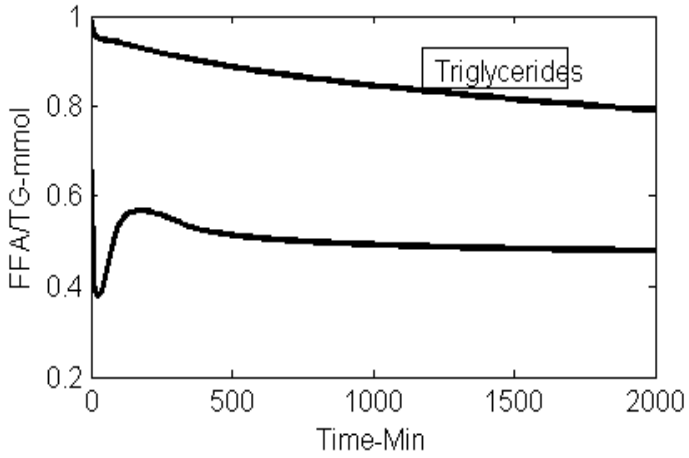


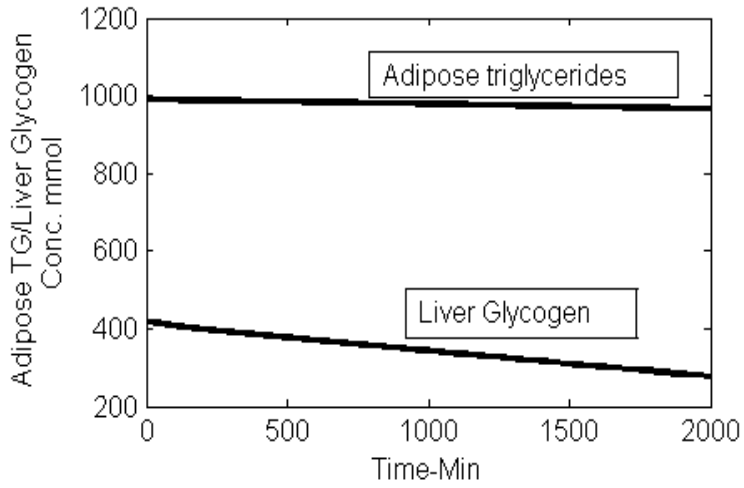
J.Kim et al. (2007)

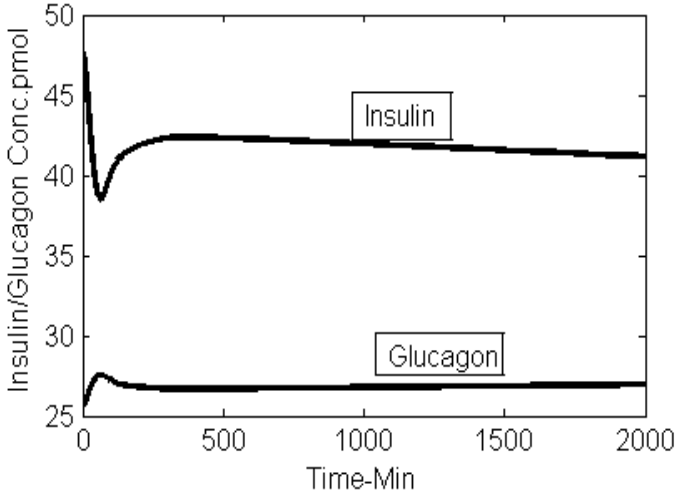
Results for Whole body Metabolism (While Rest-Plasma Conc.)

One and half day simulation of fasting dynamics



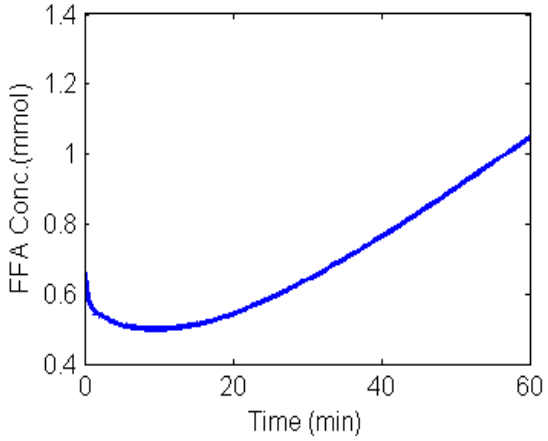


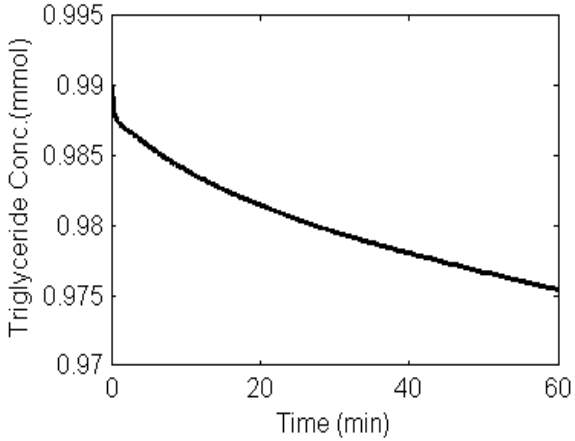


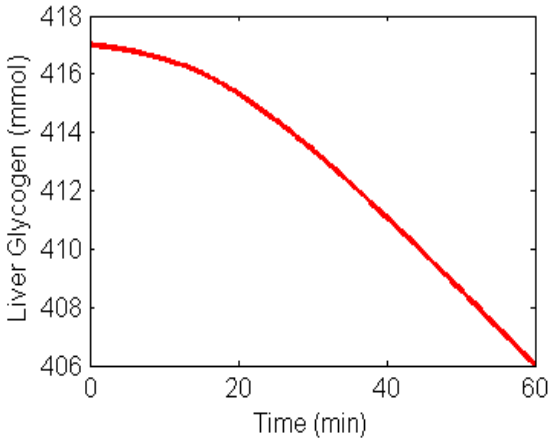


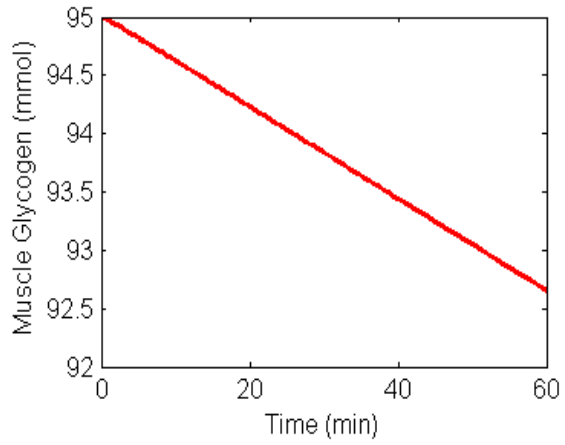
Results for Whole body Metabolism (While Exercise-Plasma conc.)

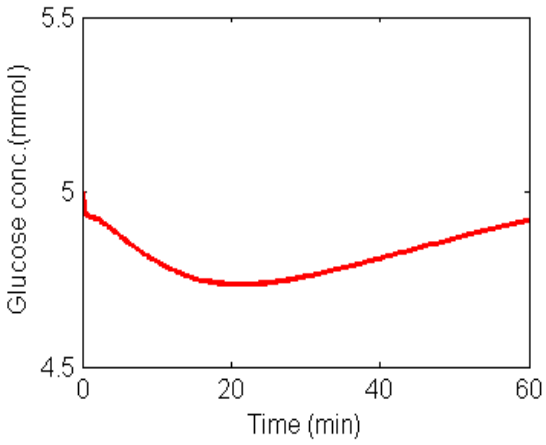
Response for One hour exercise at 150 watt work-load

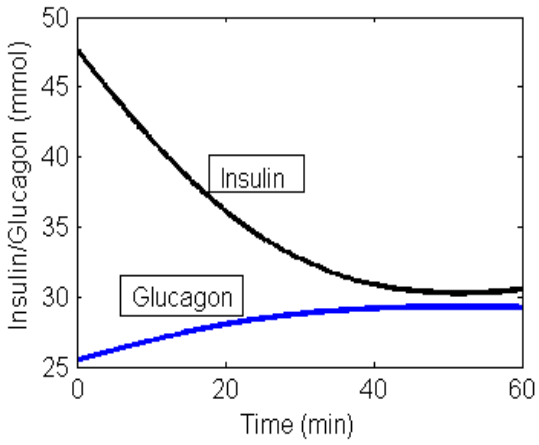






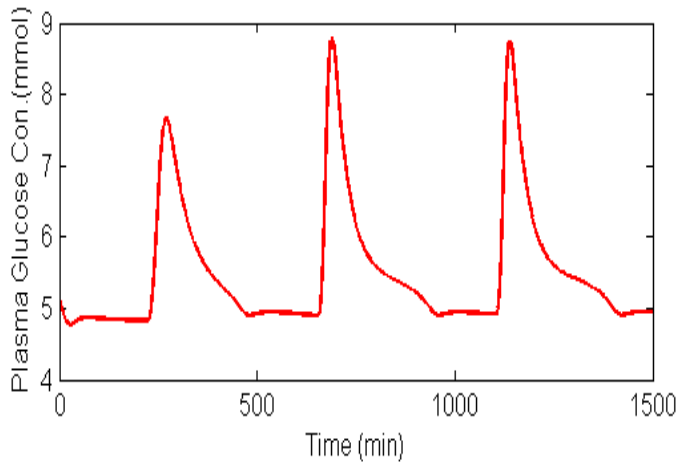


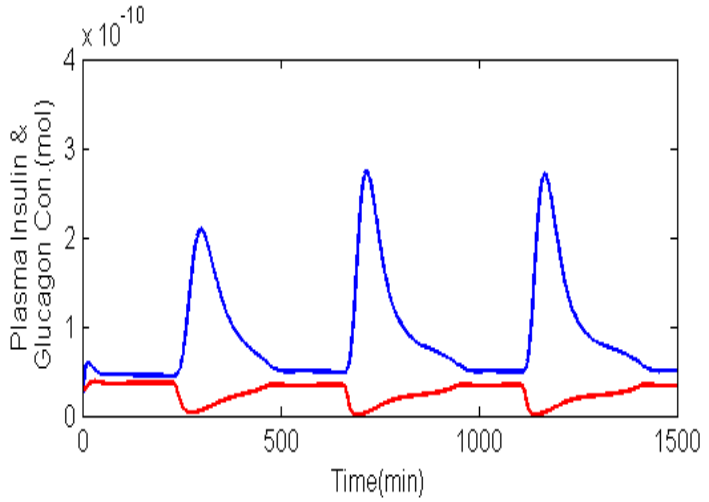


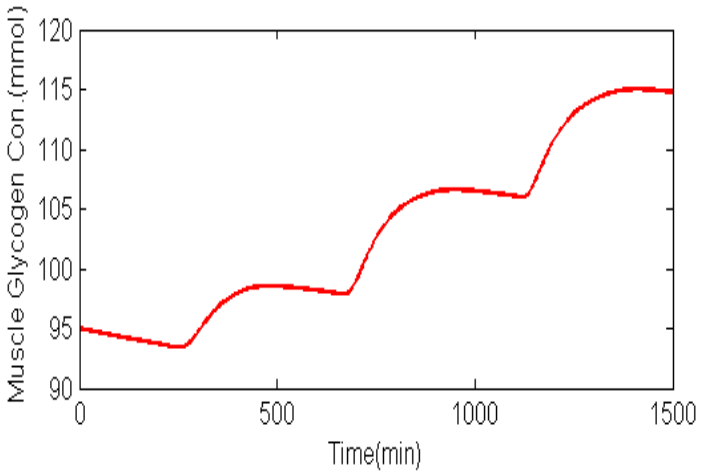


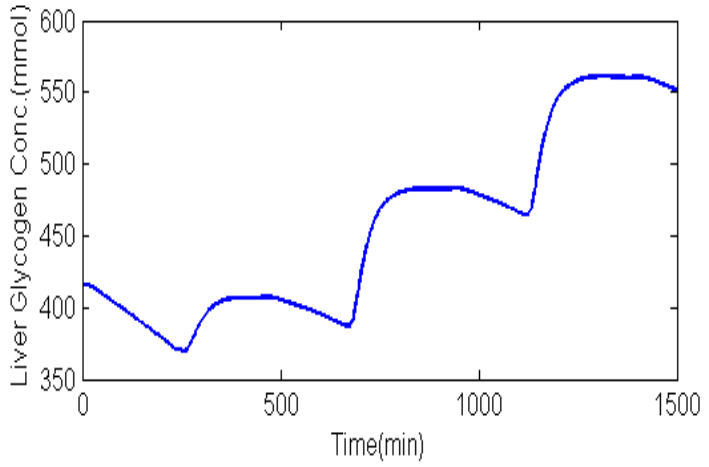
Results for Whole body Metabolism (Postprandial-Plasma conc.)

Meal – 50, 75, 75 g of Carbohydrate



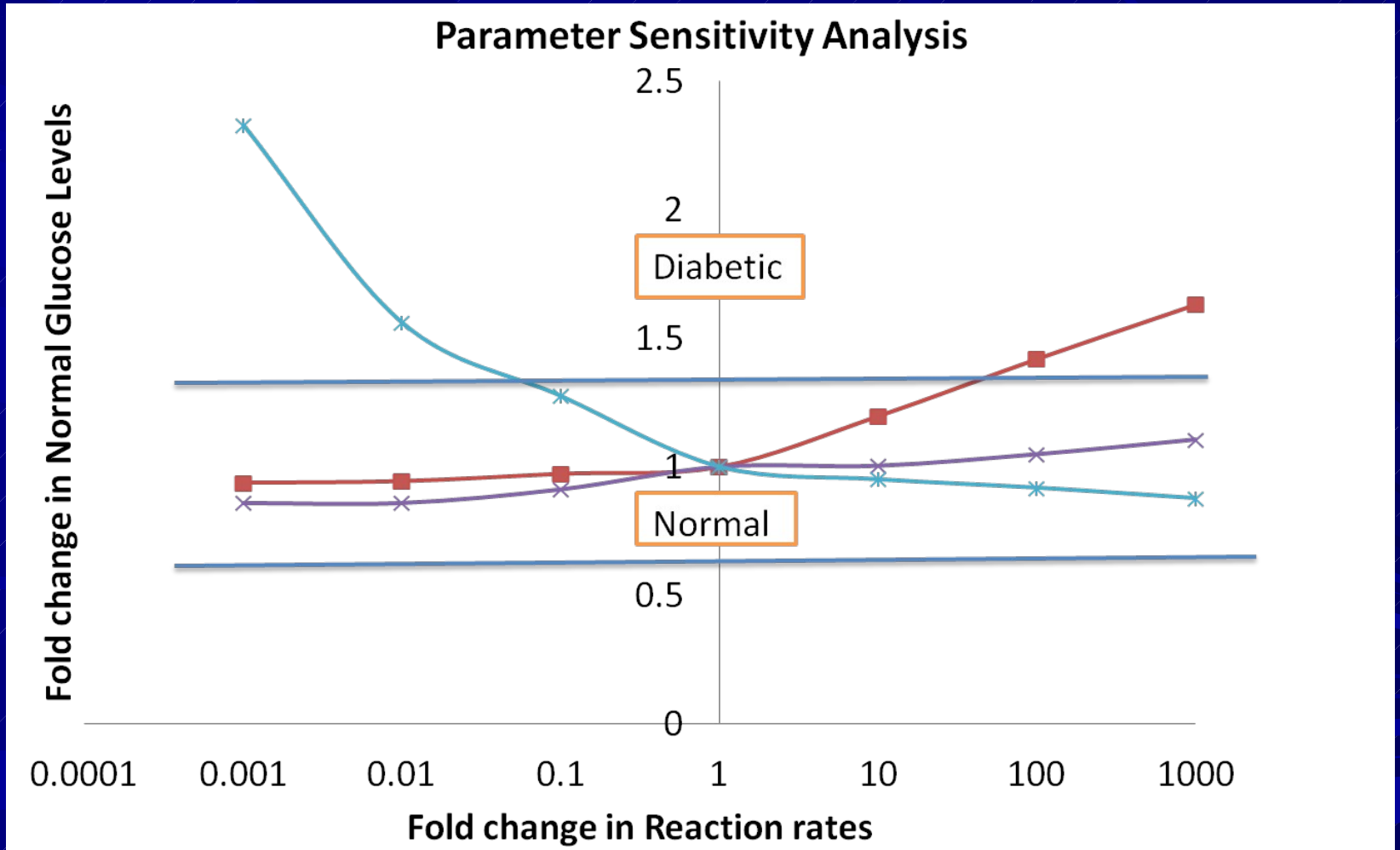






Parametric Sensitivity for Insulin Signalling Pathway

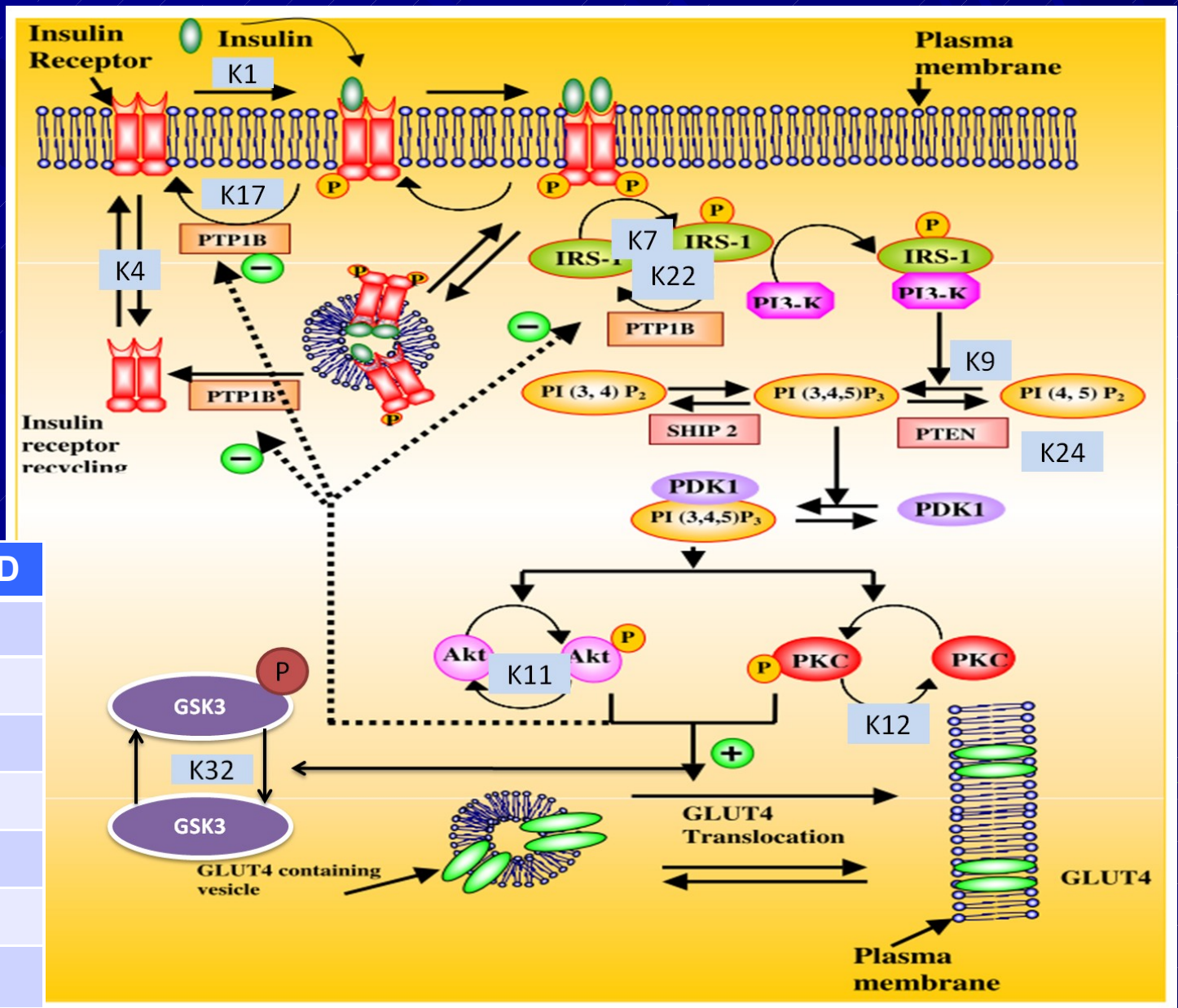
Blue – GSK3, Red – PI3K, Violet – PTEN
Normal Blood Glucose level-4.9mmol,
Diabetic Blood Glucose level above-7mmol



Sensitive Nodes In Insulin Pathway

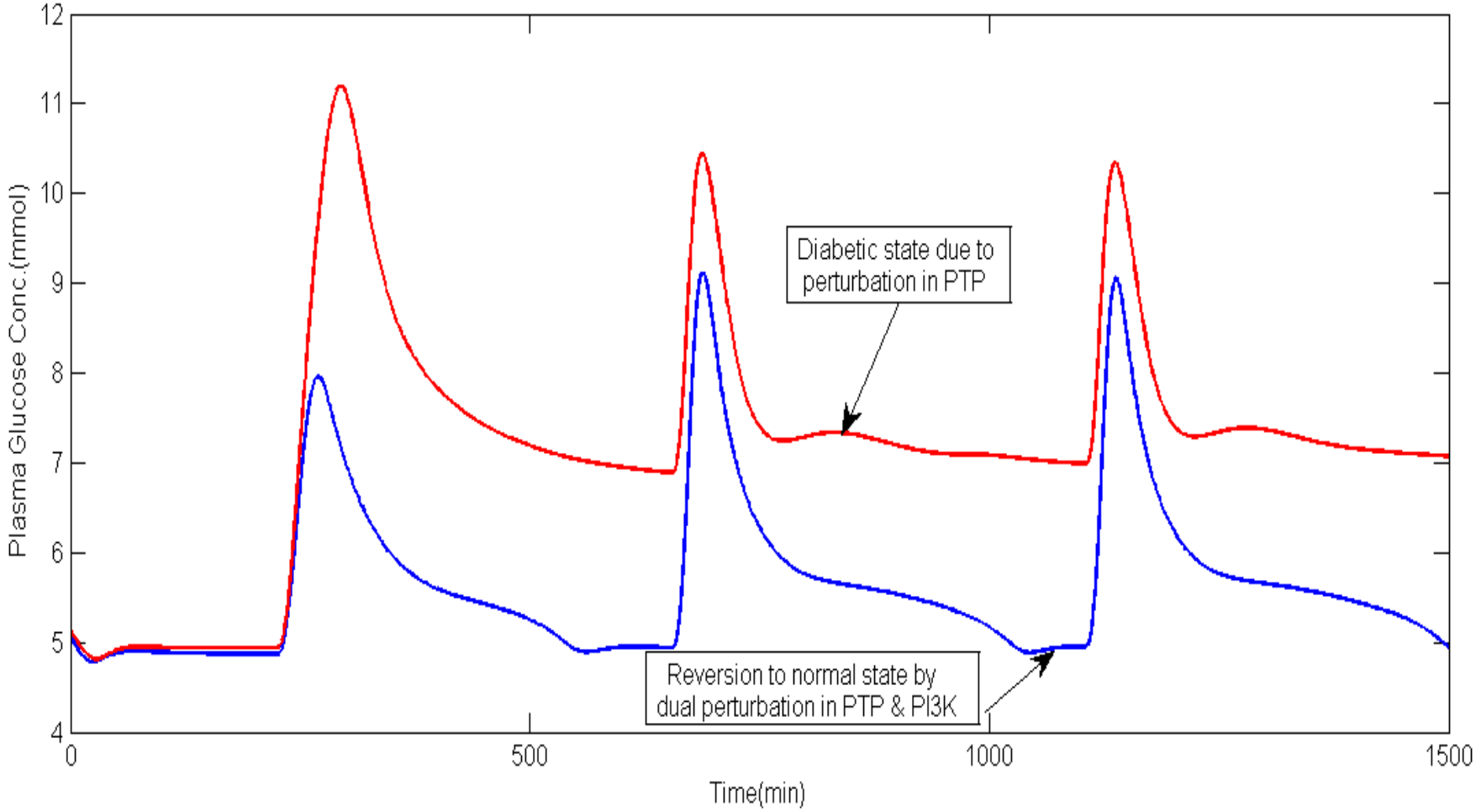
ODEs: 23
Parameters:47

Rank	Node	U/D
1	AKT-nP	↓
2	GSK3-P	↑
3	PTP	↑
4	IRS-1-nP	↓
5	IRp- nB	↑
6	PI3K-nA	↑
7	PKC-P	↑

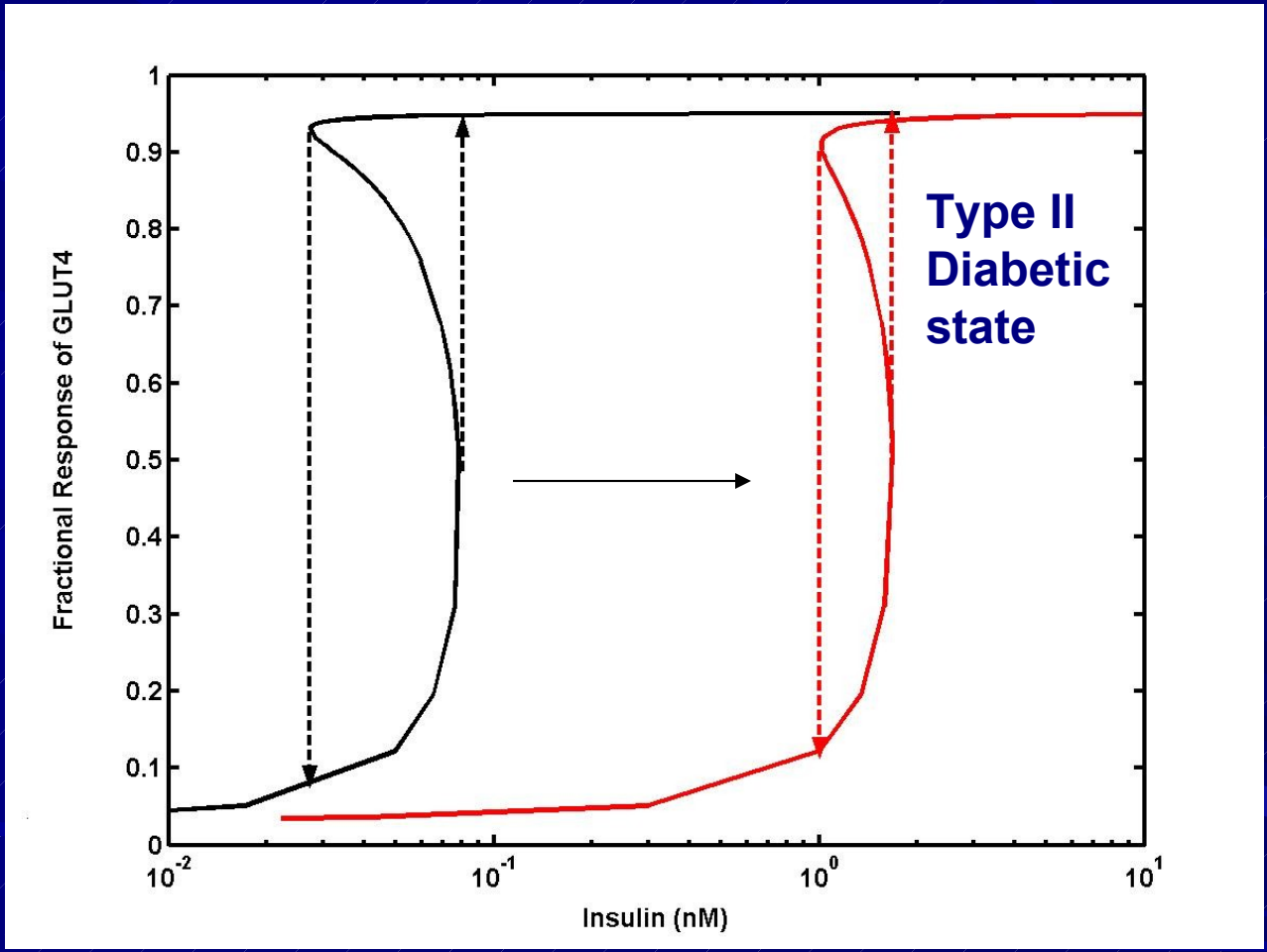


Parameter perturbation

Dual perturbations in both PTP and PI3K can restore normalcy



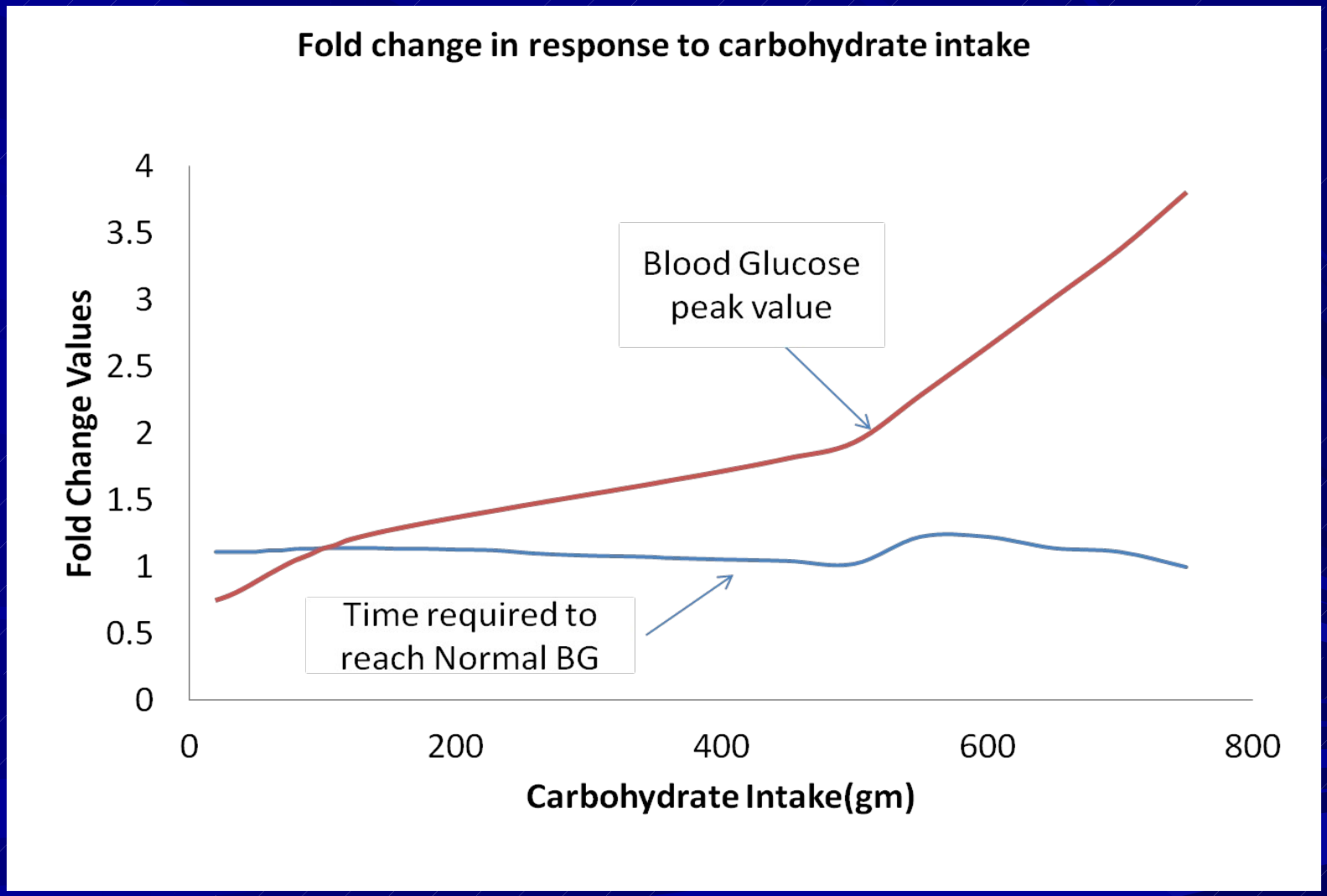
Bistability in Insulin Signaling Pathway Type-II Diabetic State – Effect of PTP



Giri, Mutalik, Venkatesh, BMC Theoretical Biology & Medical Modeling

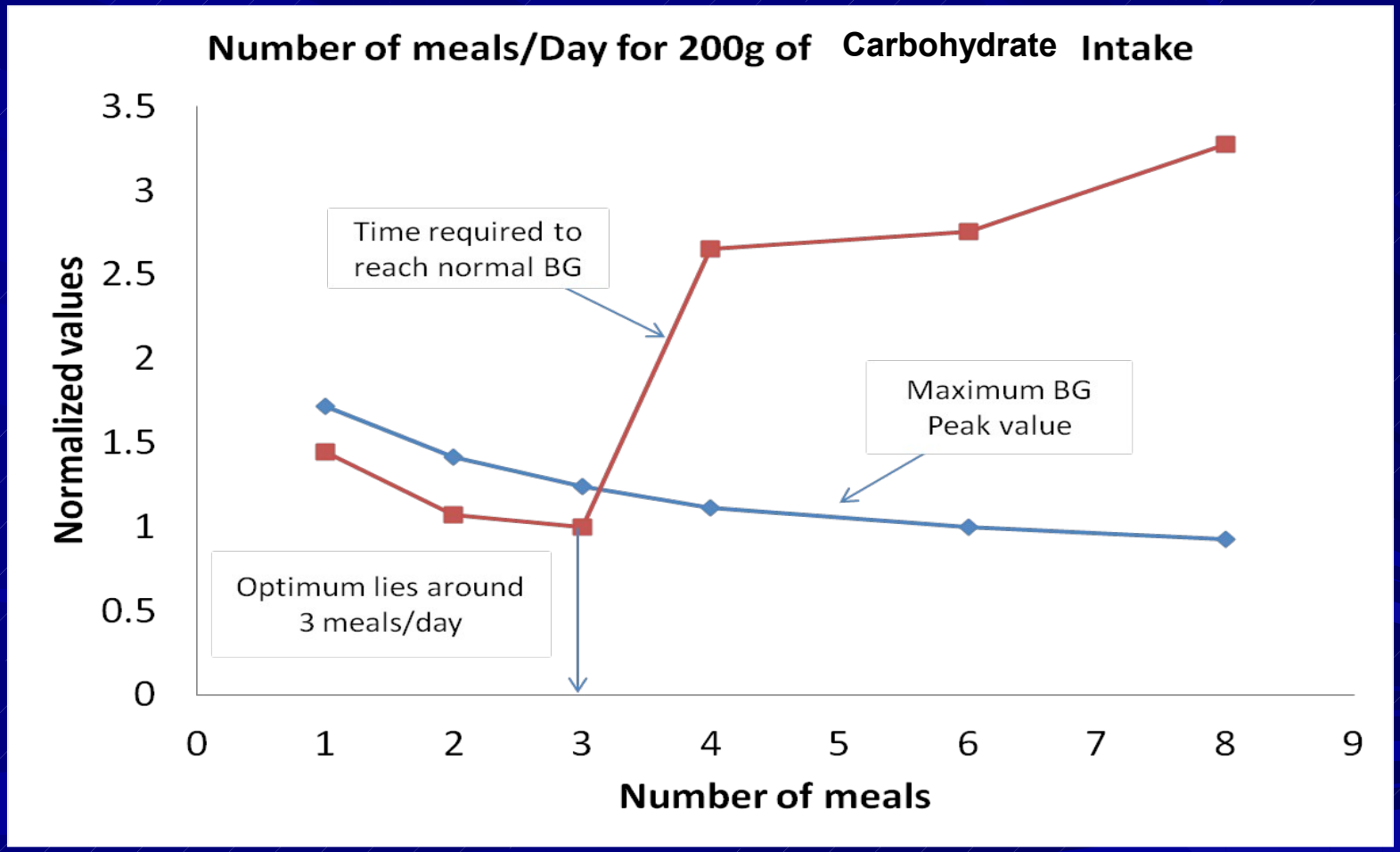
Carbohydrate Intake-Response

BG Peak value normalised by 8.78, Tss value normalised by 180 min



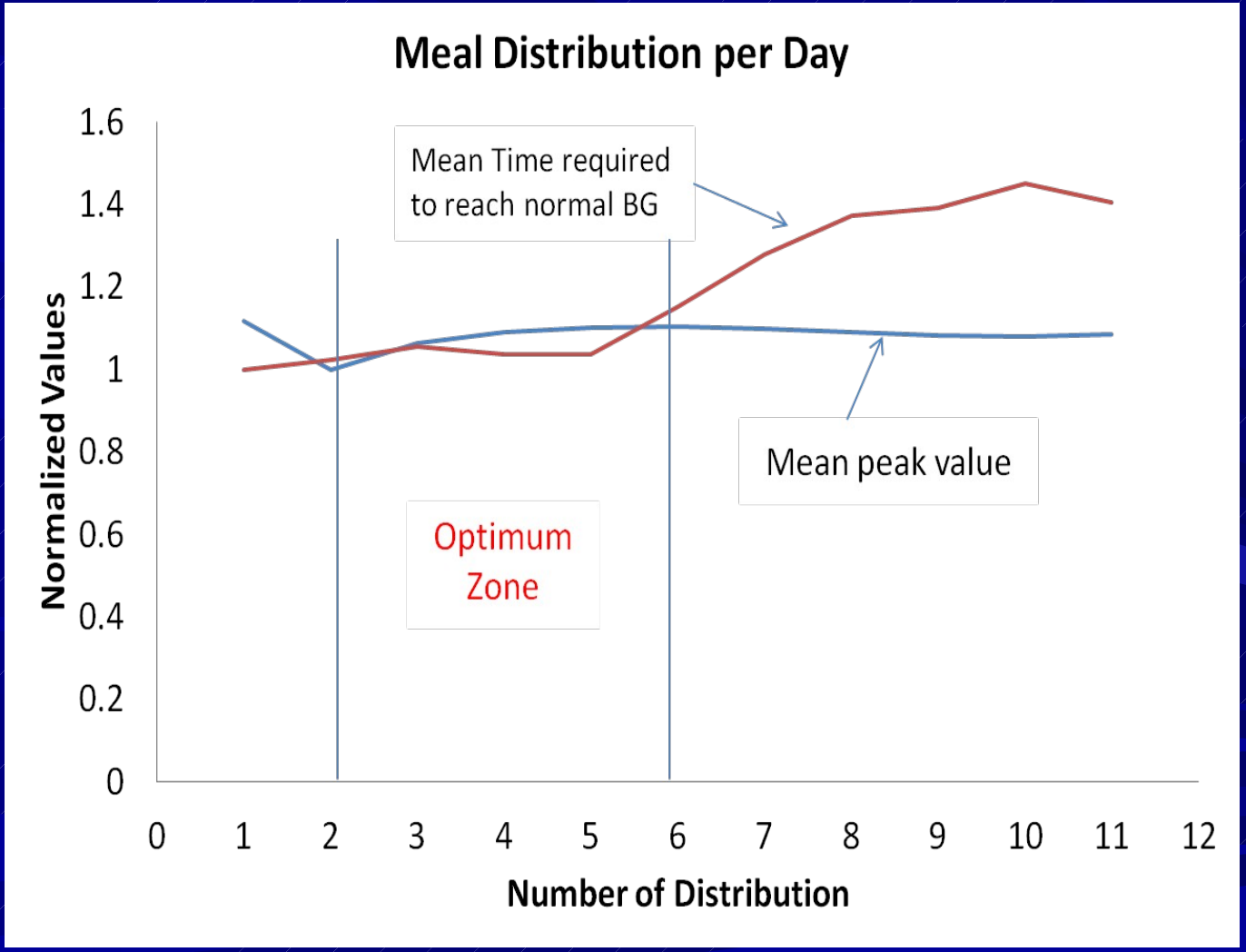
Number of meals per Day

Peak BG value normalized-7, Tss value normalized-290



Optimal Meal Distribution per Day

Break fast-50 g, Lunch-100-140 g, and dinner-10-50 g
Mean Peak value Normalized-7.83,Tss normalized-215 m



No.	B	L	D
1	50	150	0
2	50	140	10
3	50	130	20
4	50	120	30
5	50	110	40
6	50	100	50
7	50	90	60
8	50	80	70
9	50	70	80
10	50	60	90
11	50	50	100

Conclusions

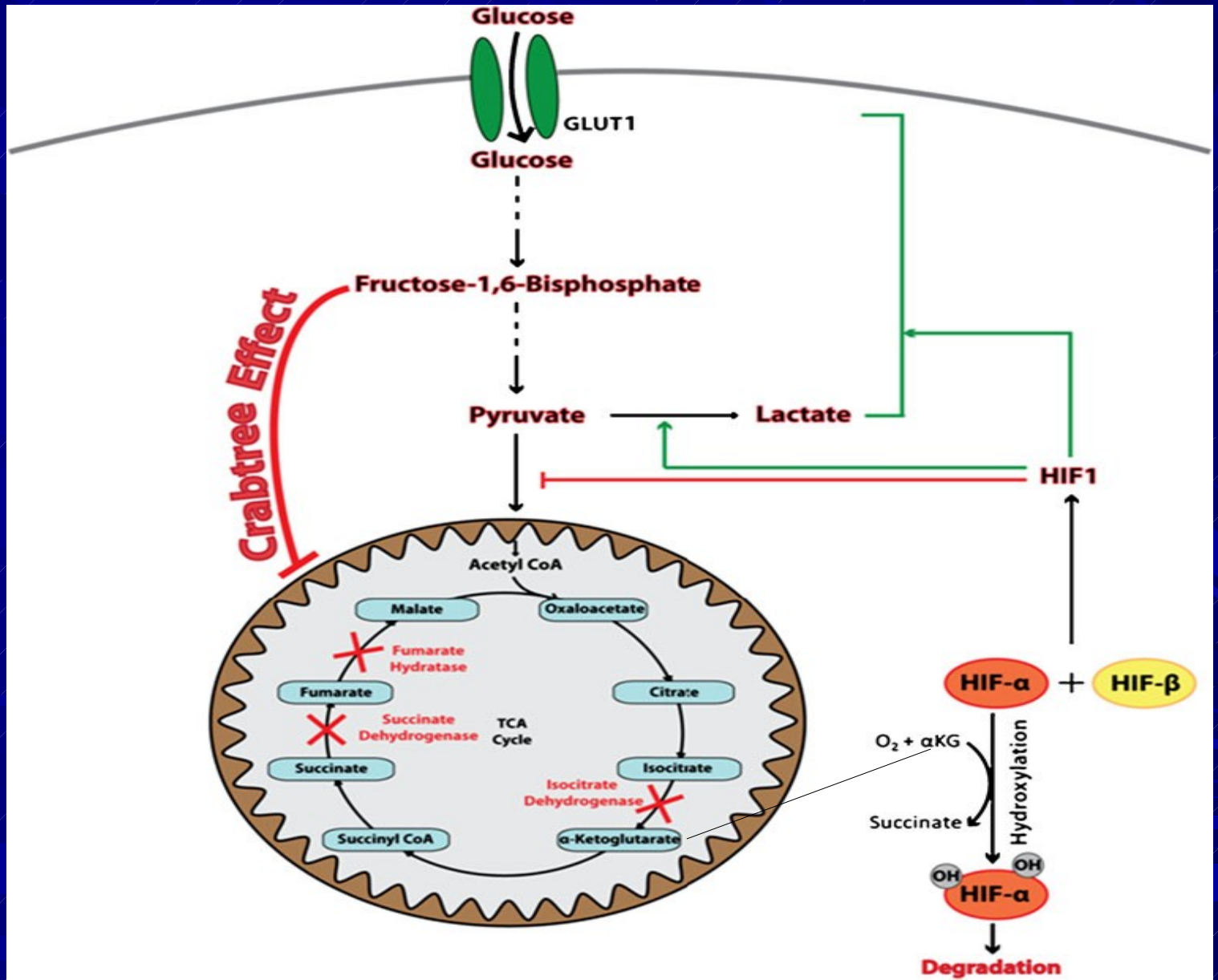
- Simulations of lifestyle and obesity conditions possible
- Effect of Perturbations under low calories was less compared to high calorie diet
- Effect of exercise can be studied, effects are slow and long term simulations needed
- More data to fine tune the model
- Data from Indian population for healthy and diabetic conditions is a lacuna
- In future, model should be linked to clinical data

Metabolism and Cancer

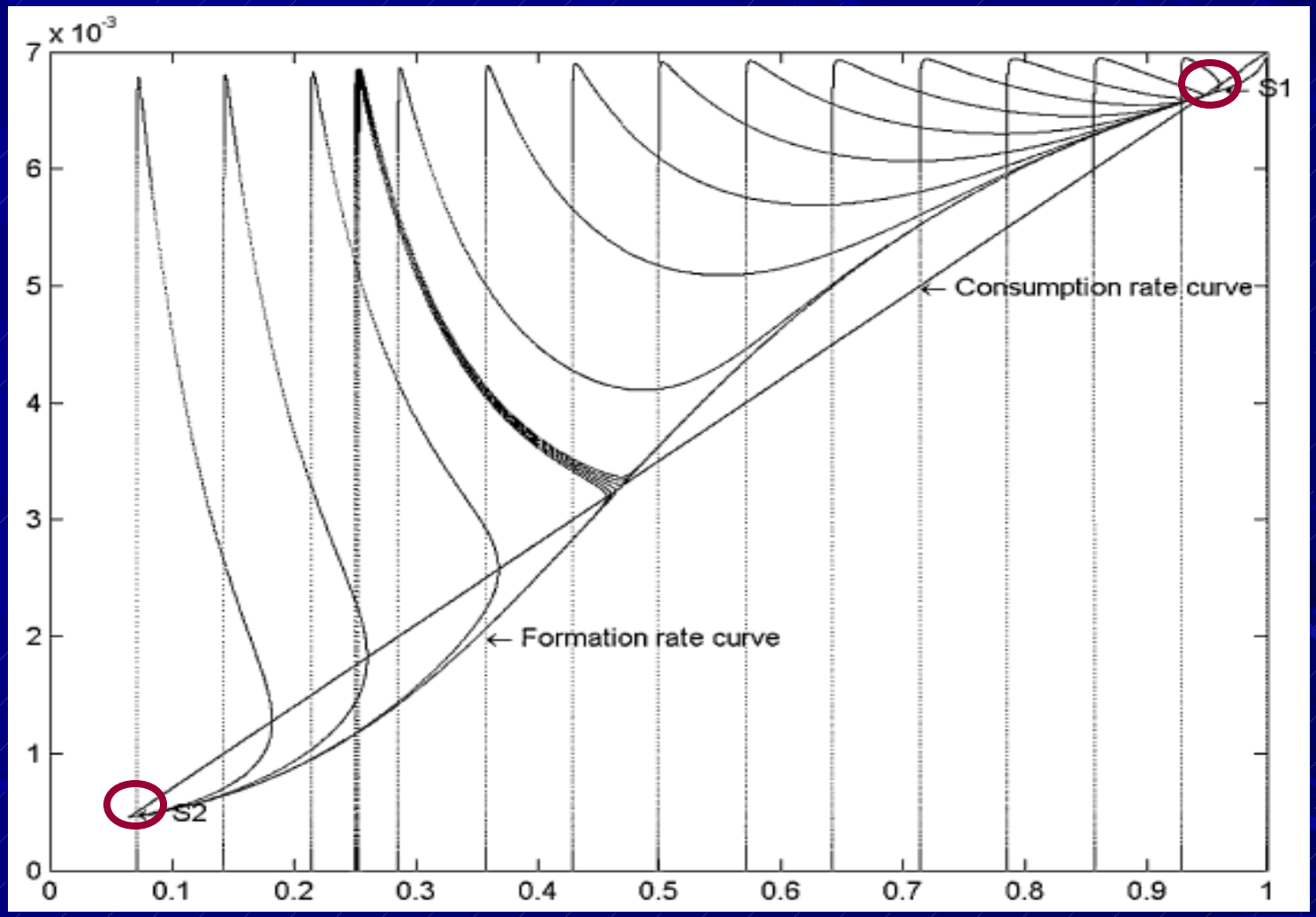
High alpha-KG maintains normal growth

Low alpha-KG Activates HIFI leading to lactate formation and higher uptake of glucose

HIF – Hypoxia Inducing Factor



Bistability of α-ketoglutarate levels



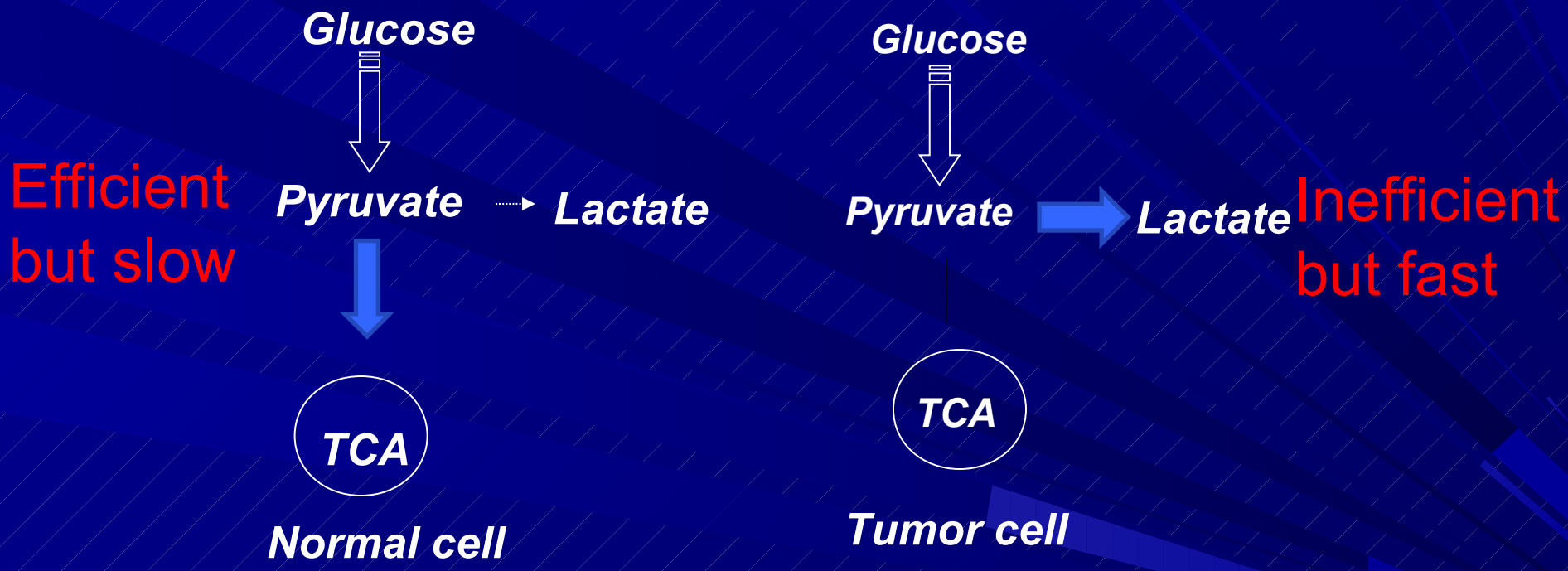
Rate of formation and consumption of α-ketoglutarate

Concentration of α-ketoglutarate

A concentration less than 35% of the maximum will shift the steady state from normal to fermentative

Metabolism and Cancer

Metabolic Transition: *Oxidation to fermentation*



This transition also occurs under normal conditions, whenever rapid proliferation is required, such as wound healing

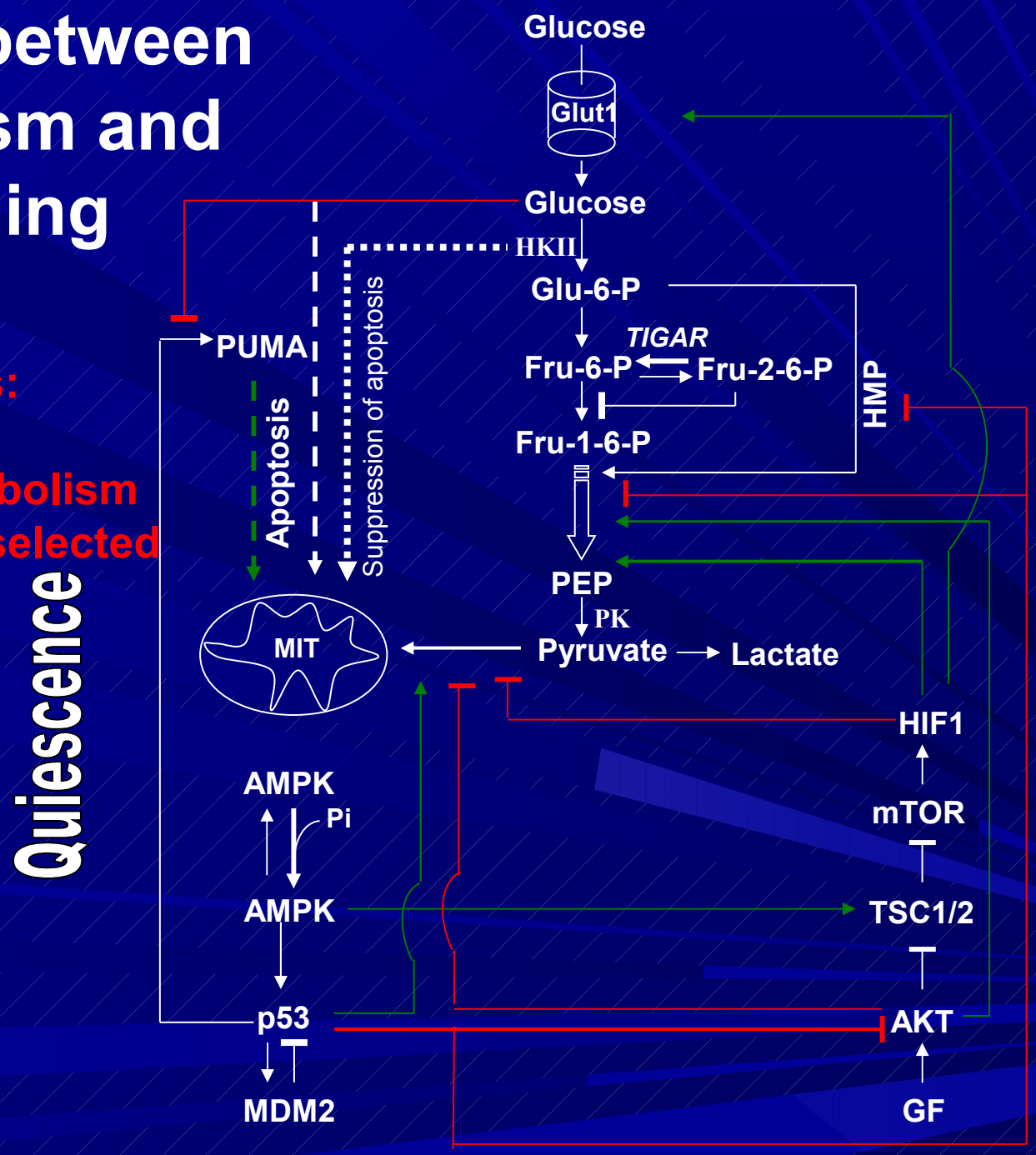
Interplay between Metabolism and signaling

Sequence of events:

First defect in metabolism and mutations are selected

or

Other way around



Conclusions

- Quantification is key to Systems Biology
- Design principles inherent in Biological structure
- System analysis to elucidate role of structure and connectivity
- Operational characteristics of networks
- Fault-diagnosis for characterization of disease state
- Possible sites in the network as drug targets
- Modular analysis towards *in silico* cellular representation

Acknowledgements

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