Multi-Scale Model for Analyzing Disease States in Metabolic Syndrome

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Genotype to Phenotype

- Genome
- Transcriptome
- Proteome
- Metabolome
- Phenotype

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

<table>
<thead>
<tr>
<th>Luciferase Gene</th>
<th>Genetic network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luciferase gene decoded</td>
<td>RNA network</td>
</tr>
<tr>
<td>Catalyzed by Luciferase Enzyme</td>
<td>Protein network</td>
</tr>
<tr>
<td>Phosphorous release using ATP</td>
<td>Metabolic network</td>
</tr>
<tr>
<td>Firefly Glows Transgenic Plant made to Glow</td>
<td>Physiological state</td>
</tr>
</tbody>
</table>
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
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
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)

Glucagon Receptor

Glucose

Amino acids

Insulin receptor

Adrenaline Receptor

FFA

Glycogen

Protein

Triglyceride

Glycolysis/oxidation
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
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

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Glucose Transporter</th>
<th>Fat Transporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>GLUT4</td>
<td>FATP1</td>
</tr>
<tr>
<td>Heart</td>
<td>GLUT4</td>
<td>FATP1</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>GLUT4</td>
<td>FATP1</td>
</tr>
<tr>
<td>Liver</td>
<td>GLUT2</td>
<td>FATP5</td>
</tr>
<tr>
<td>GI track</td>
<td>GLUT3</td>
<td>FATP4</td>
</tr>
<tr>
<td>Brain</td>
<td>GLUT1</td>
<td></td>
</tr>
</tbody>
</table>
Interplay of ISP-mTOR-TNF Signaling for Anabolism

- Insulin
- IRS-PI3K
- AKT-PKC
- mTOR
- SREBP-1c
- GLUT4
- GSK3
- S6K1

- ROS
- IL-6
- TNF-\(\alpha\)

- Fat
- Carbohydrates
- Proteins

- TNF-\(\alpha\)
- Carbohydrates
- Proteins
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: 4.9 mmol,
Diabetic Blood Glucose level above: 7 mmol
## Sensitive Nodes In Insulin Pathway


<table>
<thead>
<tr>
<th>Rank</th>
<th>Node</th>
<th>U/D</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>AKT-nP</td>
<td>↓</td>
</tr>
<tr>
<td>2</td>
<td>GSK3-P</td>
<td>↑</td>
</tr>
<tr>
<td>3</td>
<td>PTP</td>
<td>↑</td>
</tr>
<tr>
<td>4</td>
<td>IRS-1-nP</td>
<td>↓</td>
</tr>
<tr>
<td>5</td>
<td>IRp- nB</td>
<td>↑</td>
</tr>
<tr>
<td>6</td>
<td>PI3K-nA</td>
<td>↑</td>
</tr>
<tr>
<td>7</td>
<td>PKC-P</td>
<td>↑</td>
</tr>
</tbody>
</table>

ODEs: 23  
Parameters: 47
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

Fold change in response to carbohydrate intake

Fold Change Values

0 0.5 1 1.5 2 2.5 3 3.5 4

Carbohydrate Intake (gm)

0 200 400 600 800

Blood Glucose peak value

Time required to reach Normal BG
Number of meals per Day

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

Number of meals/Day for 200g of Carbohydrate Intake

Time required to reach normal BG

Maximum BG Peak value

Optimum lies around 3 meals/day

Normalized values

Number of meals per Day

Number of meals

Normalized values

0 1 2 3 4 5 6 7 8 9

0 0.5 1 1.5 2 2.5 3 3.5
Optimal Meal Distribution per Day

Breakfast-50 g, Lunch-100-140 g, and dinner-10-50 g

Mean Peak value Normalized-7.83, Tss normalized-215 m

<table>
<thead>
<tr>
<th>No.</th>
<th>B</th>
<th>L</th>
<th>D</th>
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<tbody>
<tr>
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<td>50</td>
<td>150</td>
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<tr>
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<td>10</td>
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<tr>
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<tr>
<td>11</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>
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 $\alpha$-ketoglutarate levels

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

- All past and current students
- Pramod Somvanshi (PhD student)
- Prof. PJ Bhat – GAL system, cancer & metabolism
- Prof. Sharad Bhartiya – Yeast systems biology
- Prof. Mahesh T – Chemotaxis and Rheology of cell suspension