Systems Engineering Perspective of Human Metabolism

A Multi-scale Model for Disease Analysis

Modeling Metabolic Health and Disease

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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	Gene
↓	↓
Luciferase gene decoded	RNA
↓	↓
Catalyzed by Luciferase Enzyme	Protein
↓	↓
Phosphorous release using ATP	Metabolic Reaction
↓	↓
Firefly Glows Transgenic Plant made to Glow	Phenotype

Descriptional Science

- Historically Biology has been a descriptional science
- Molecular Biology has given molecular level description of the Hierarchical state.
- Genetic, signaling/protein and metabolic networks are the result of reductionism of Molecular Biology.
- Bioinformatics has added more information to this approach.
- Resulting in a highly interconnected network!

Quantification of Systems

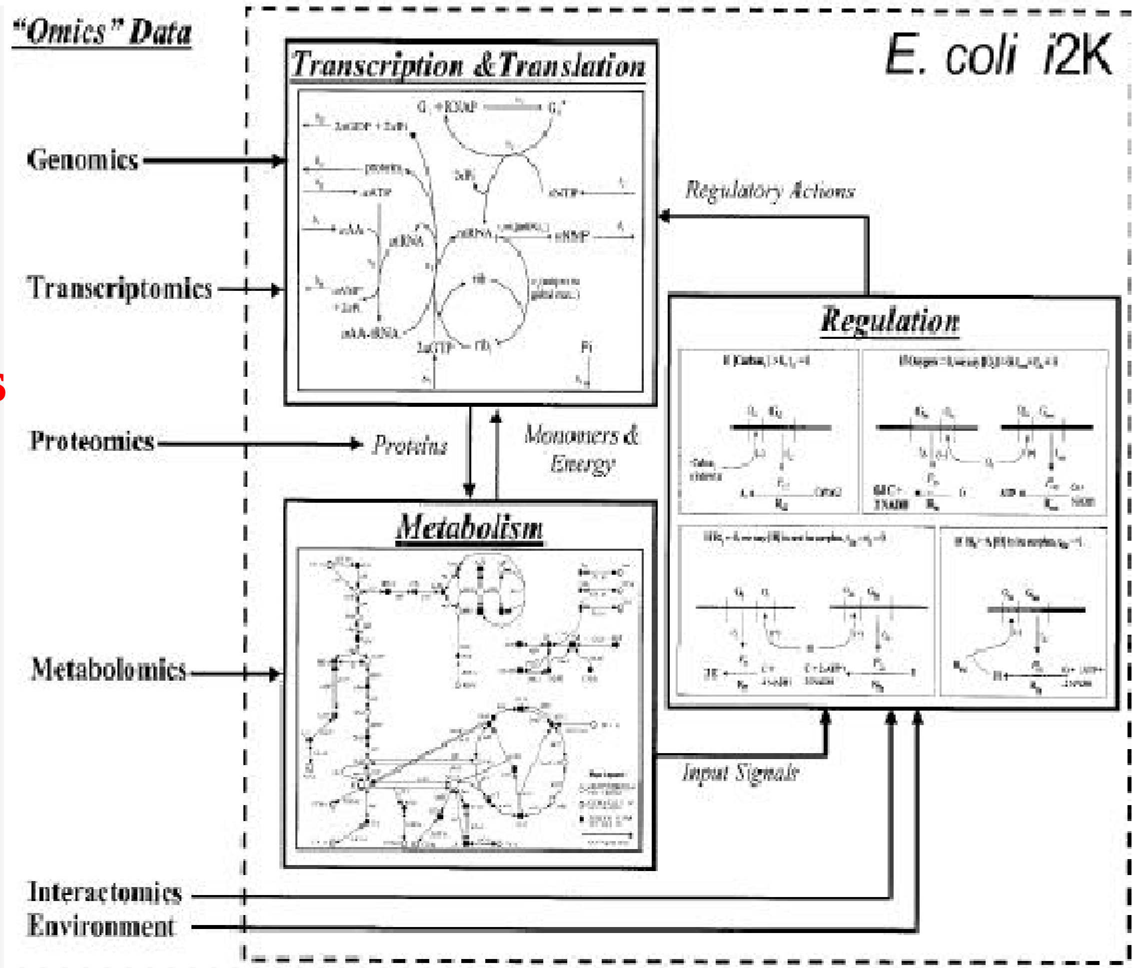
- Engineering systems are quantified to a level that they are designed, optimized and optimally operated.
- Biology is evolving to be a quantitative science.
- Principles of system science can be applied to biology: **Systems Biology**

Bottom-up Design of a Complex System

- 1250 computers
- Hundreds of feedback loops
- Millions of components
- Design Manual Available
- Only take off requires manual effort

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

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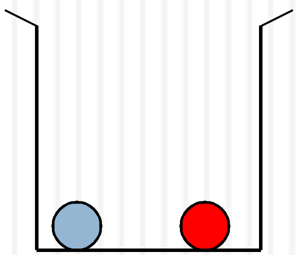
Resulting in a Complex system

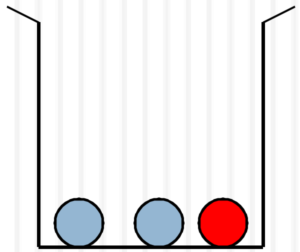
Example of a "Simple" Complex System

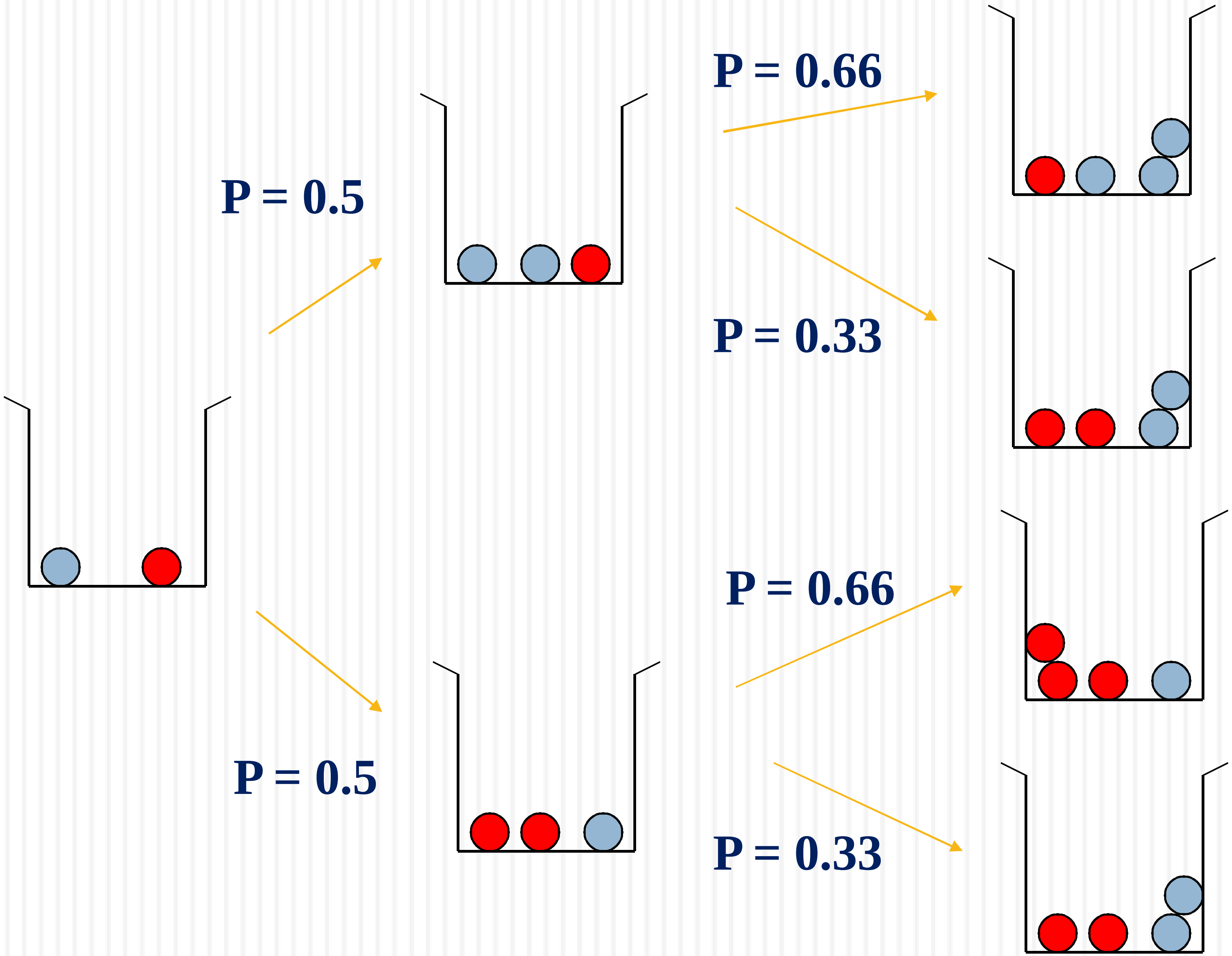
Experiment:

1. One **Red** and One **Green** Ball in a Box
2. Choose a ball randomly
3. Add and replace the same color ball into the box
4. What is the fraction of red balls after 50,000 steps

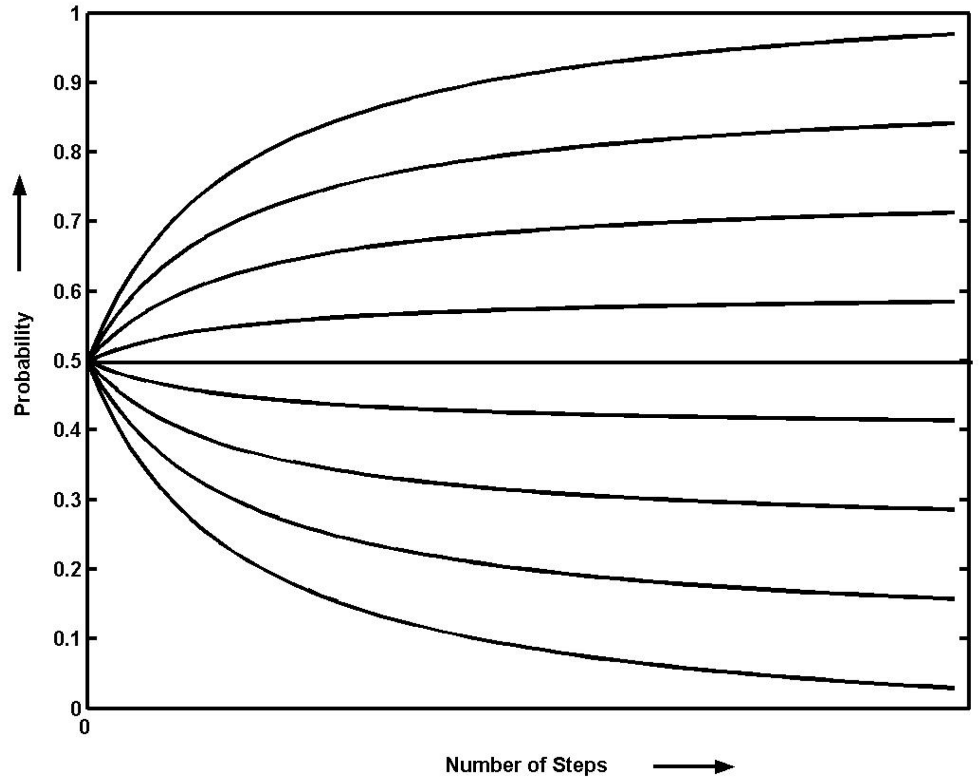


Picked Orange ball
Replaced the same
and added another
of same colour




P = 0.5
P = 0.5
P = 0.66
P = 0.33
P = 0.66
P = 0.33

Possible Outcomes in the Experiment



Multiple outcomes possible depending on initial few steps

Properties of Complexity

- Multiple Steady States
- Depends on History (Initial Condition)
- Parametric Sensitivity
- Bifurcation
- Robustness
- Adaptability
- Evolvability

Reconstructing Cellular Functions

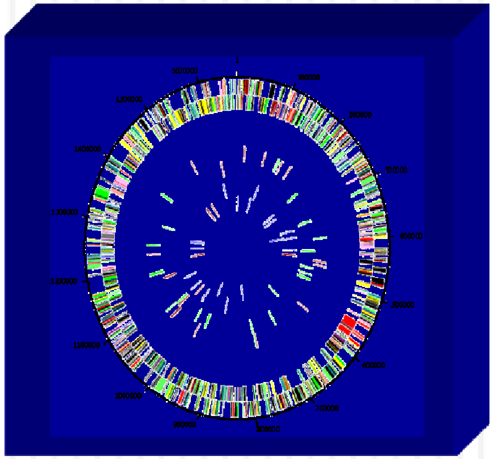
Palsson BO, Nature Biotech 18:1147 (2000)

Reductionistic Approach:

Components Biology

HT analytical chemistry:
genomics
transcriptomics
proteomics

20th Century Biology



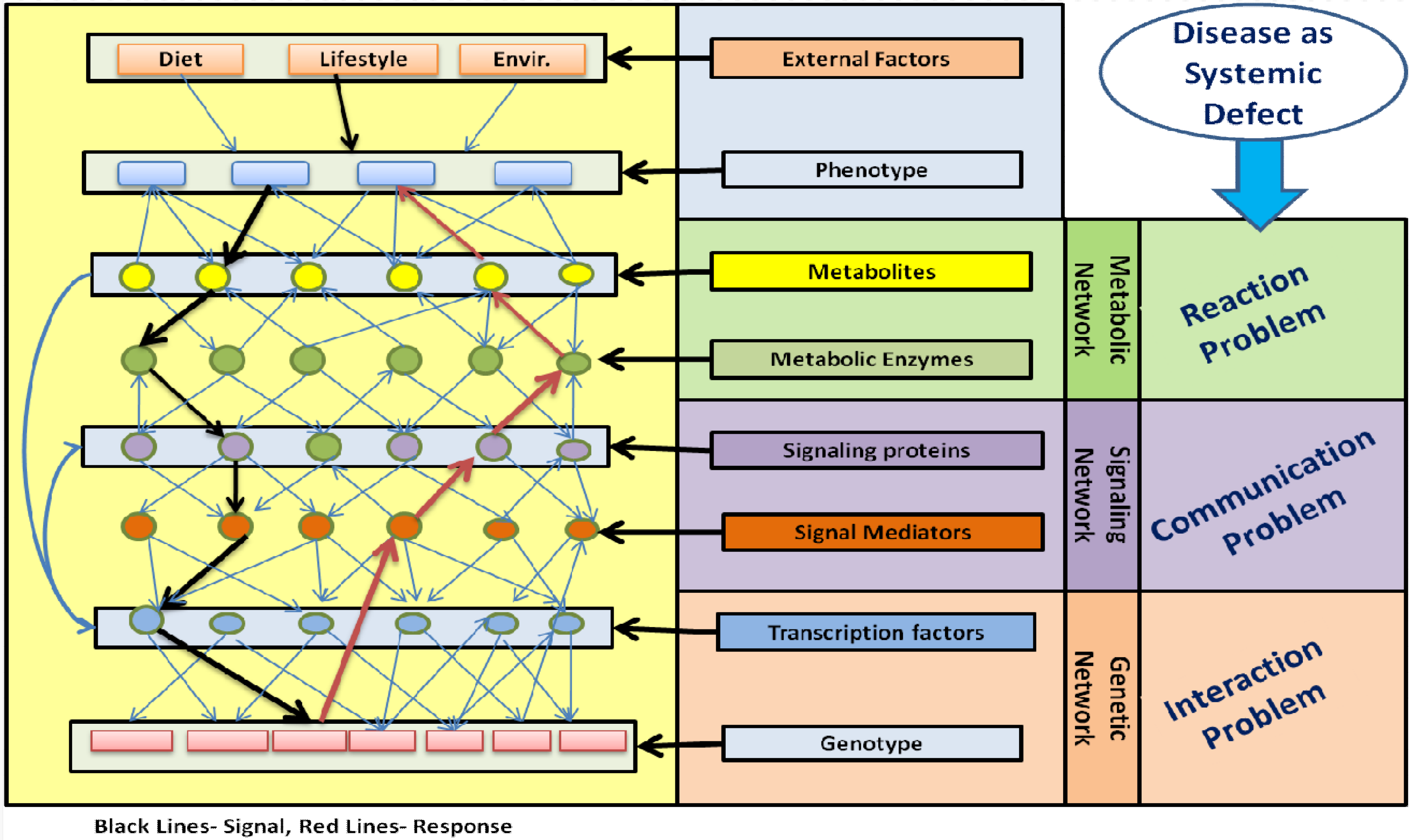
Integrative Approach:

Systems Biology

1. Components
2. Reconstruction
3. Modeling/simulation
4. Feedback analysis

21st Century Biology

Disease as Systemic Defect



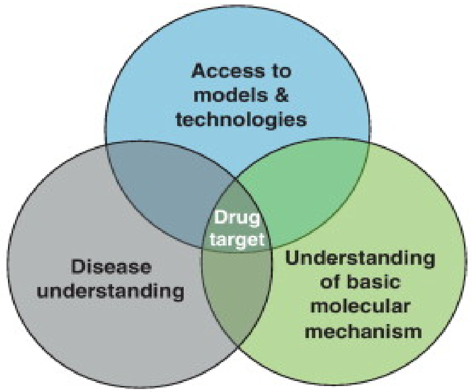
(Pramod and Venkatesh, 2013)

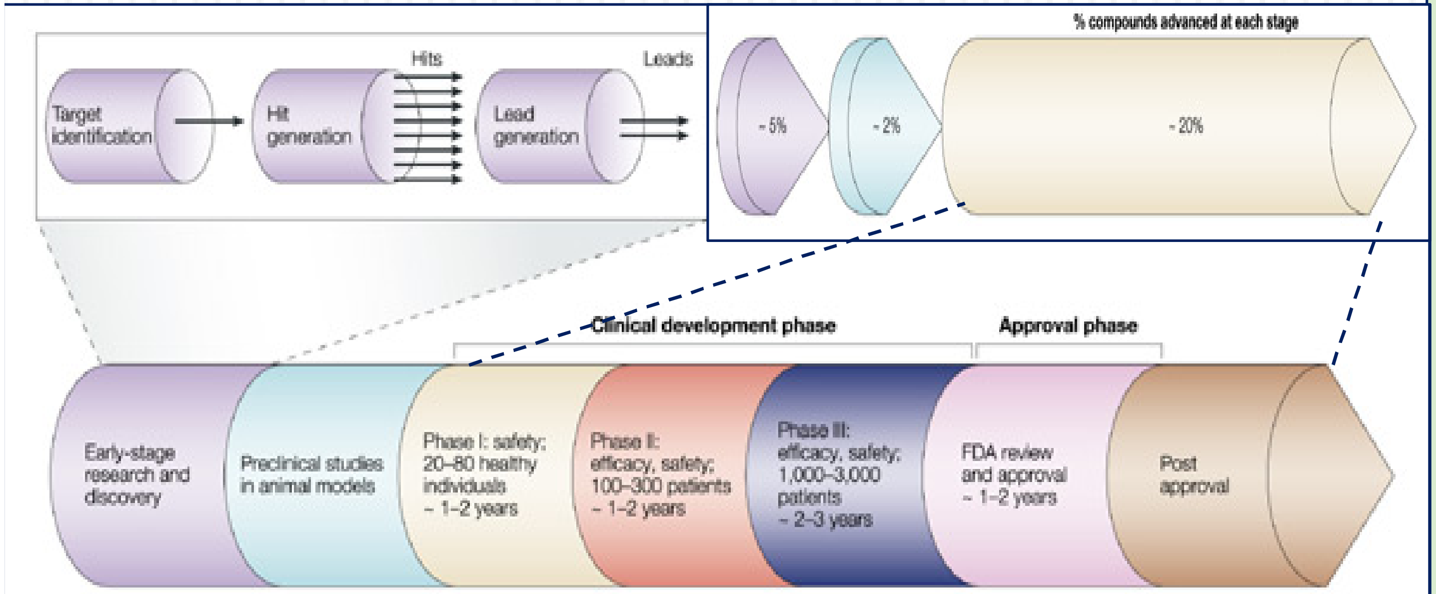
Challenges in Modeling Disease States

- Incomplete interaction map
- Incomplete Parametric space
- Ambiguity in data
- Difficult to validate model
- Need for a composite clinical data
- Validation is in the overall physiological response than quantitative
- Incomplete and ambiguous disease characterization

Systems Biology in Drug Discovery

- Basic research and Target Identification costs about 20-25 % of total drug development cost
- Only 2-5 Targets per 1000 targets reach the final stage of drug development
- Huge amount of work, time and money consumed





- Systems level insights
- Hypothesis generation
- Model testing
- Target identification/ validation
- Compound validation
- Lead optimization/SAR
- Disease indication/ trial design

(Eugene Butcher, Nature Biotech-2004)

Biochemical Networks-Structure and Dynamics

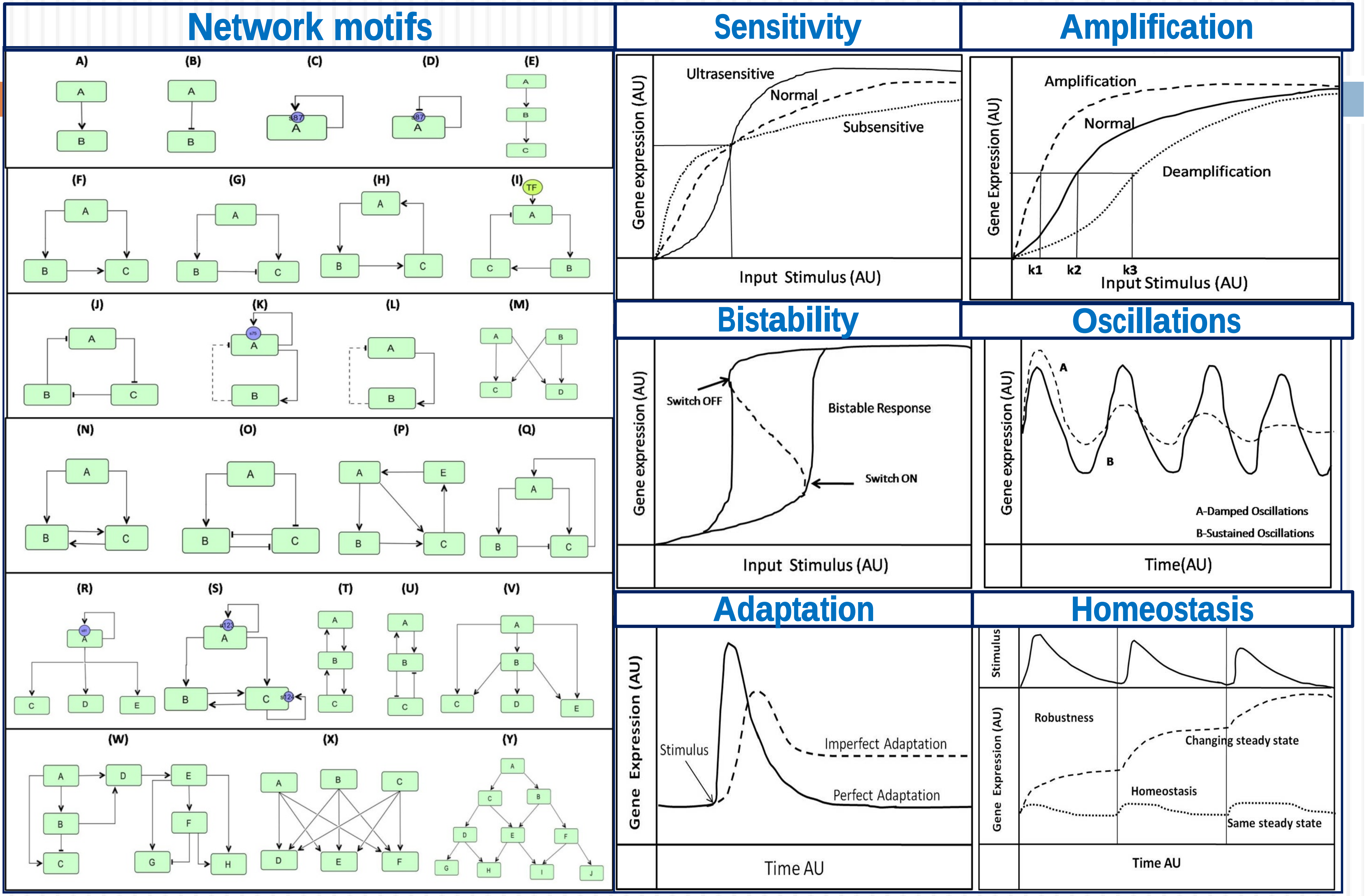
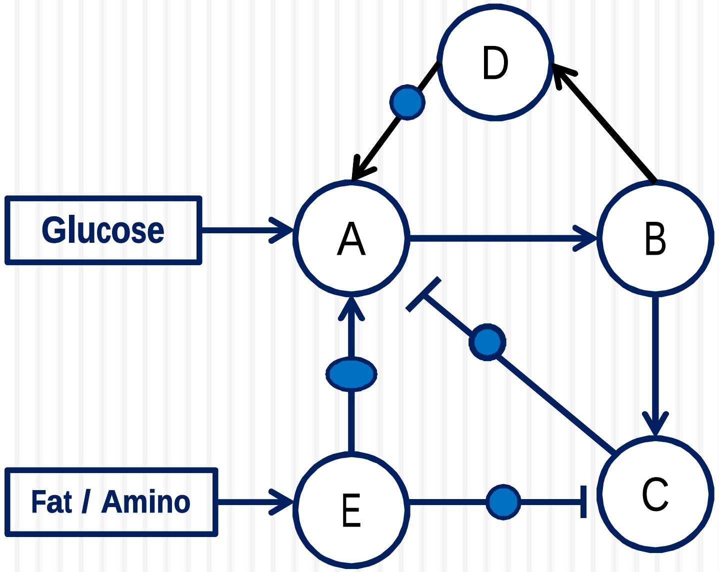


Illustration of Metabolic Regulatory Dynamics



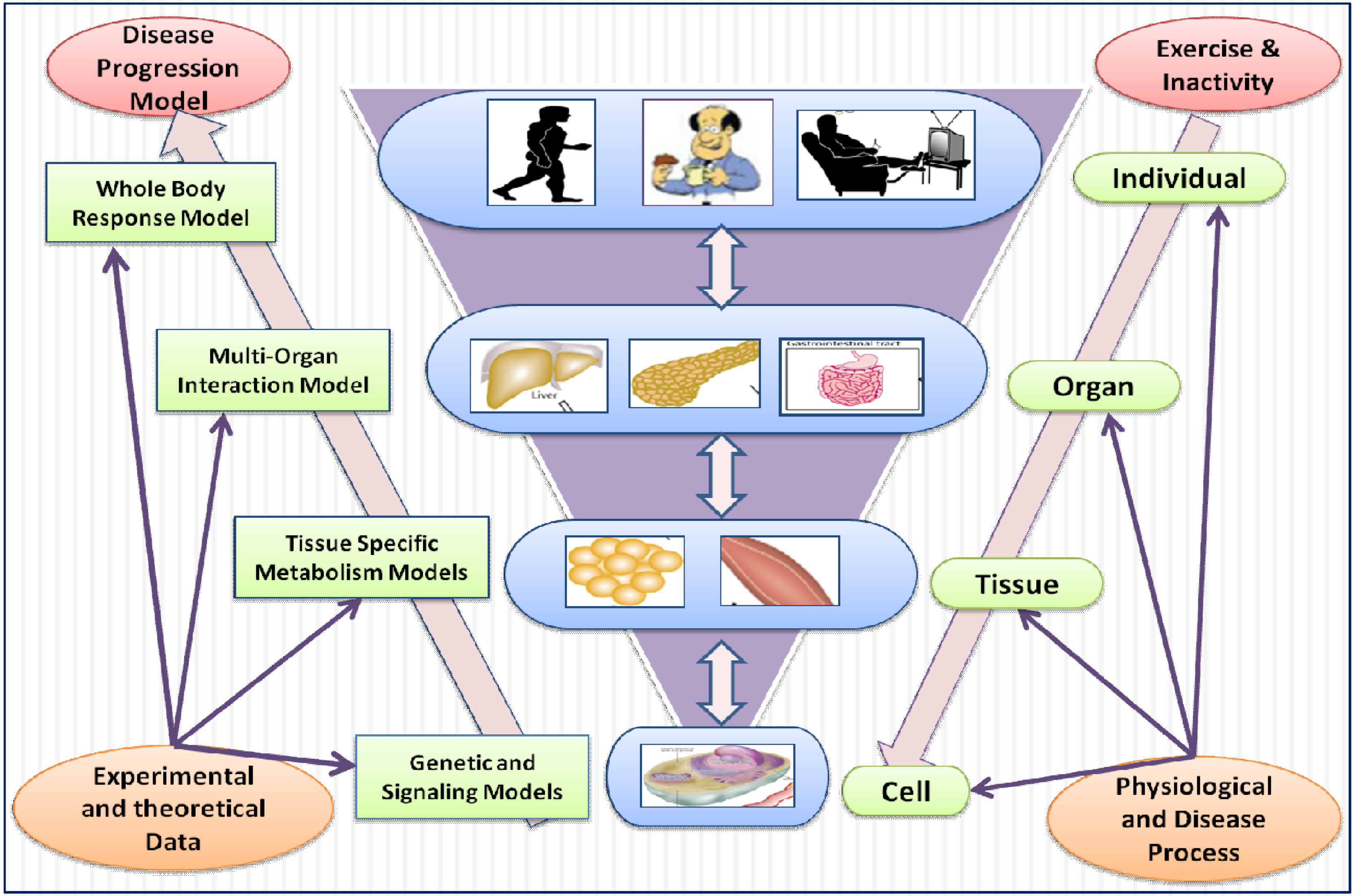
Case	Description	Response
1	C is sub sensitive to B	Adaptive
2	C is ultrasensitive to B	Homeostatic
3	B is ultrasensitive to A and A is sub sensitive to C	Oscillation
4	A is ultrasensitive to D and C	Robust
5	C is ultrasensitive to E	Bistable
6	A is amplified by D and E	Irreversible Bistable
7	C is deamplified by E	Damped Oscillation

Sensitivity and amplification are governed by the regulatory mechanisms (Signaling and trancription) and mutations, allosteric interactions, conformational changes etc.

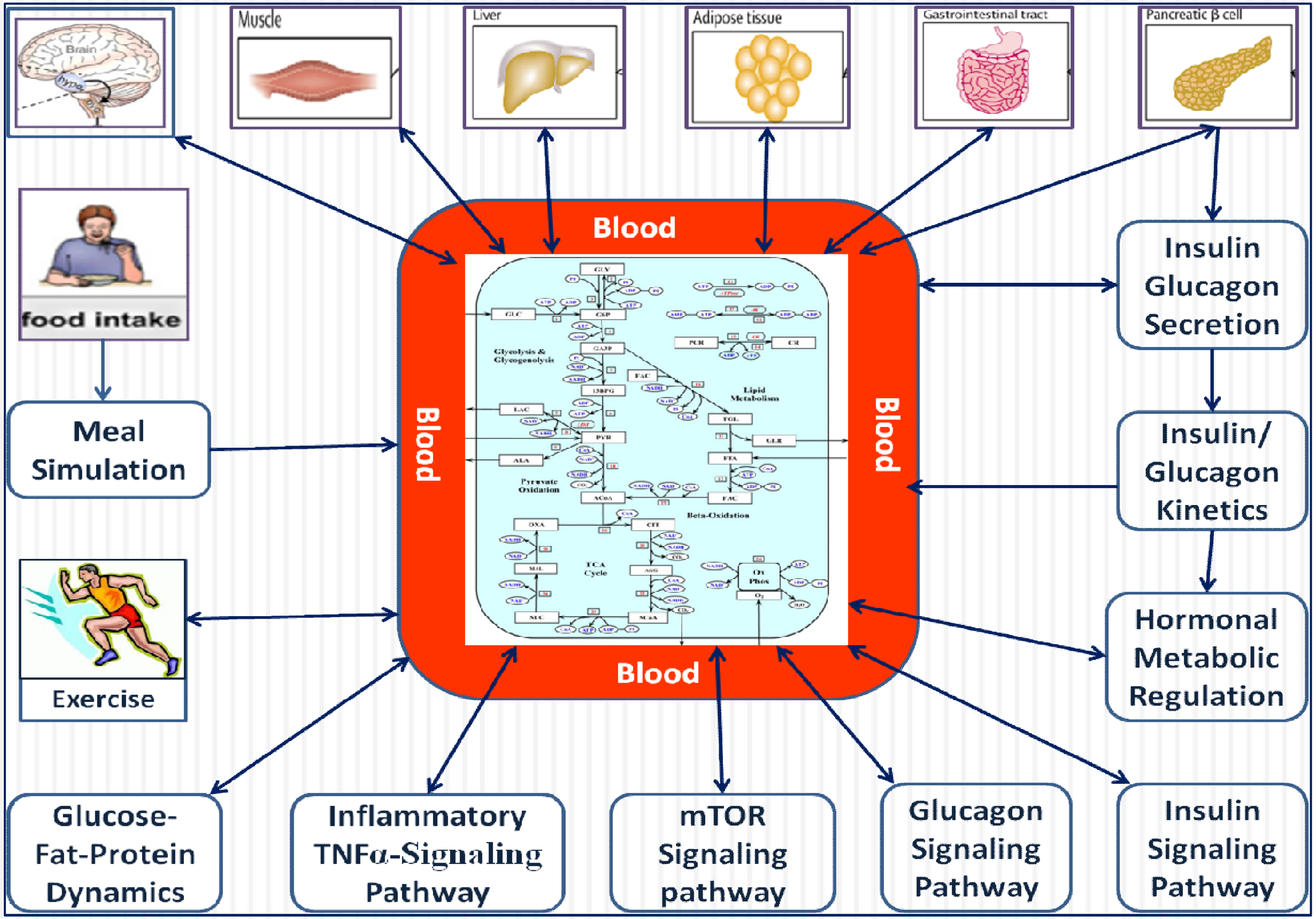
Introduction – modeling whole body metabolism

- A Multi-scale Composite model for whole-body Human Metabolism – incorporating tissue specific metabolism and regulation
- Incorporates Carbohydrate, proteins and Lipid metabolism including their regulation through signaling network
- Goal towards analyzing effect of lifestyle – such as diet and exercise on metabolism
- Deciphering design principles and control structures for healthy and disease states
- Analysis of disease states such as metabolic syndrome and cancer
- Sensitivity analysis towards rate limiting steps for therapeutics
- System level dynamic property evaluation of homeostatic variables

Modeling Strategy

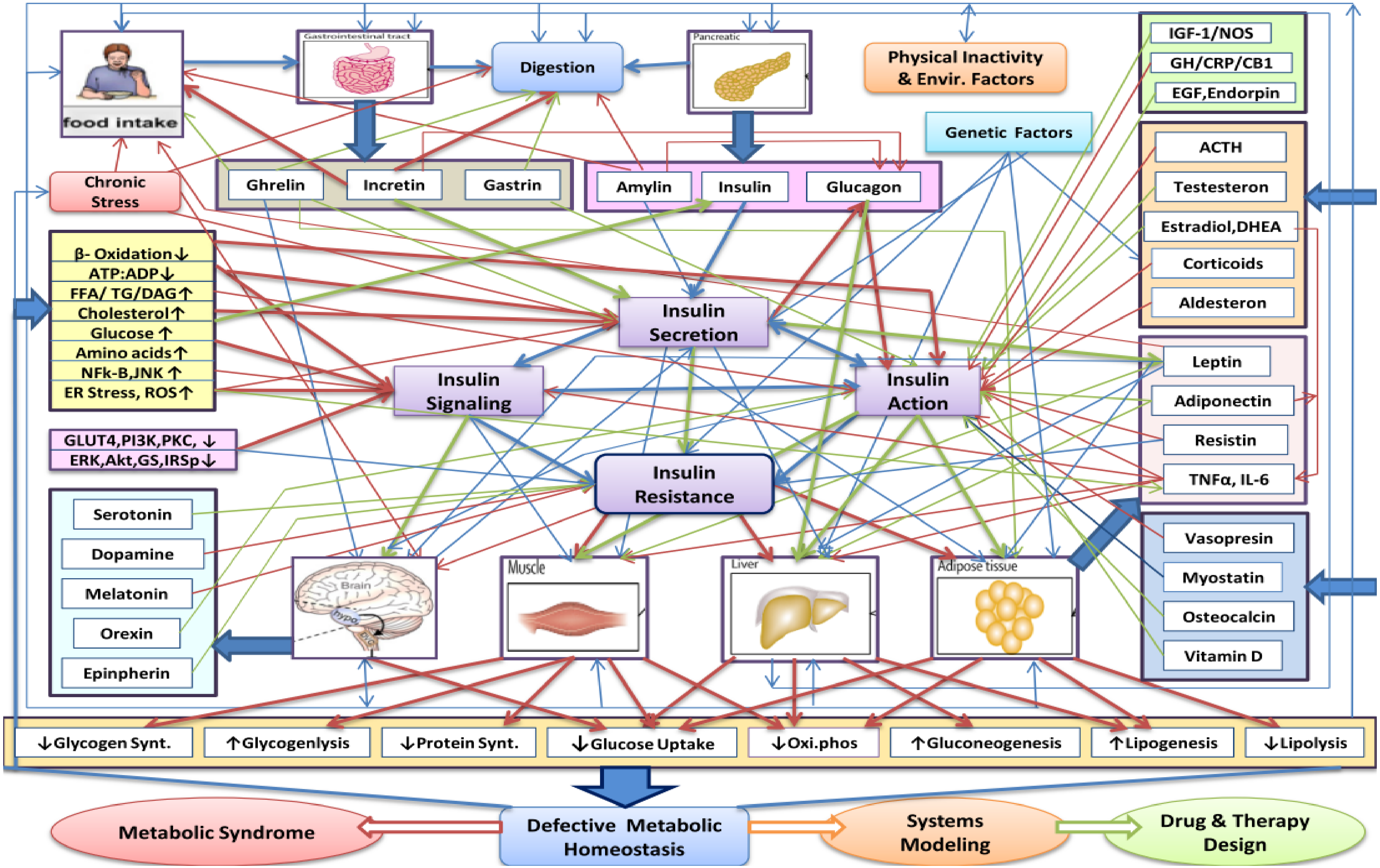


Composite Model



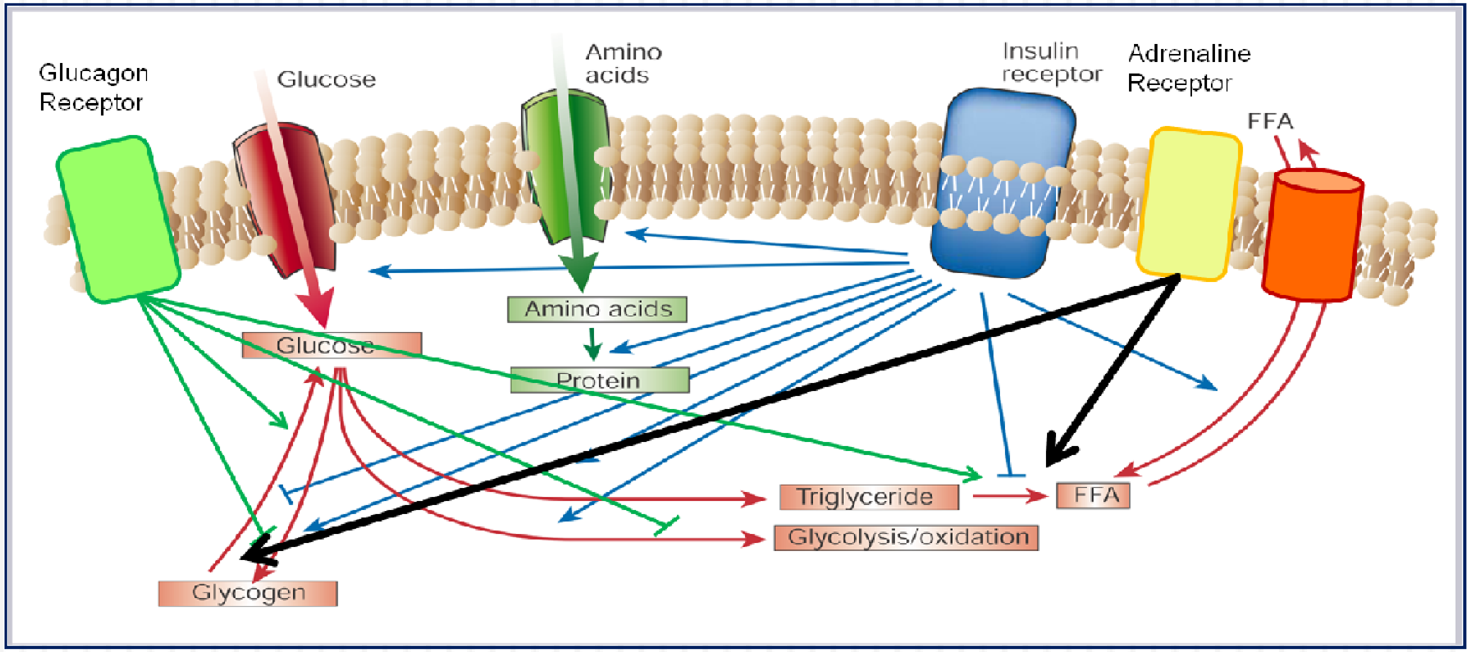
Insulin Resistance-Problem Complexity

Blue lines-Process Flow, Green lines-Positive Interactions, Red lines-Negative Interactions, Bold lines-Pathways and models available



Hormonal Metabolic Regulation

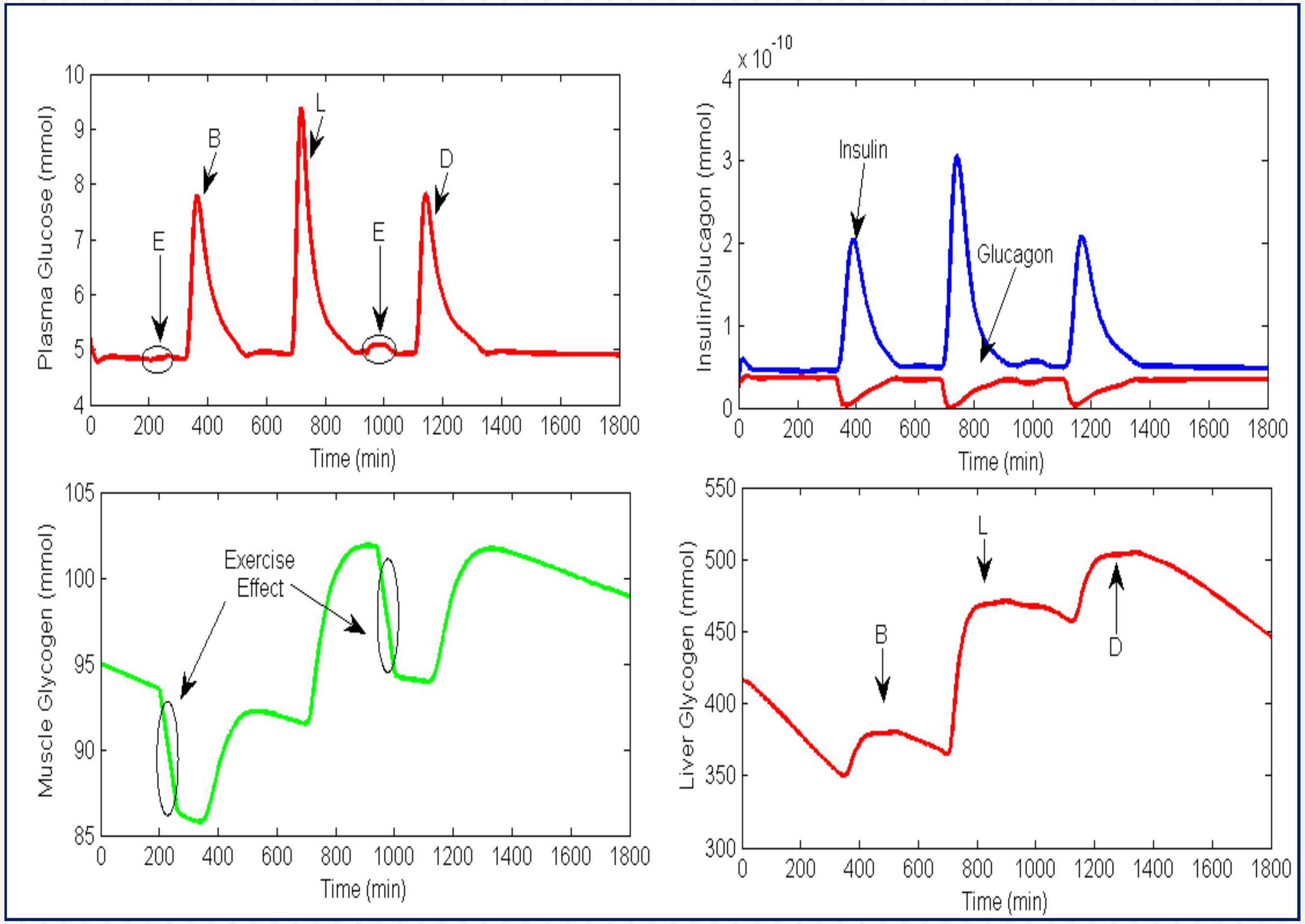
Insulin (Anabolic)	Glucagon (Catabolic)	Adrenaline (Neural)
➢ Glucose uptake	➢ Glycogenlysis	➢ Glycogen breakdown
➢ Glycolysis	➢ Gluconeogenesis	➢ Fat breakdown
➢ Glycogen synthesis	➢ Fat breakdown	➢ Increase in Blood flow
➢ Protein synthesis	➢ Proteolysis	(During Higher work rate and Exercise)
➢ Fat Synthesis	➢ Ketogenesis	



(Modified and adopted from Saltiel and Kahn 2001)

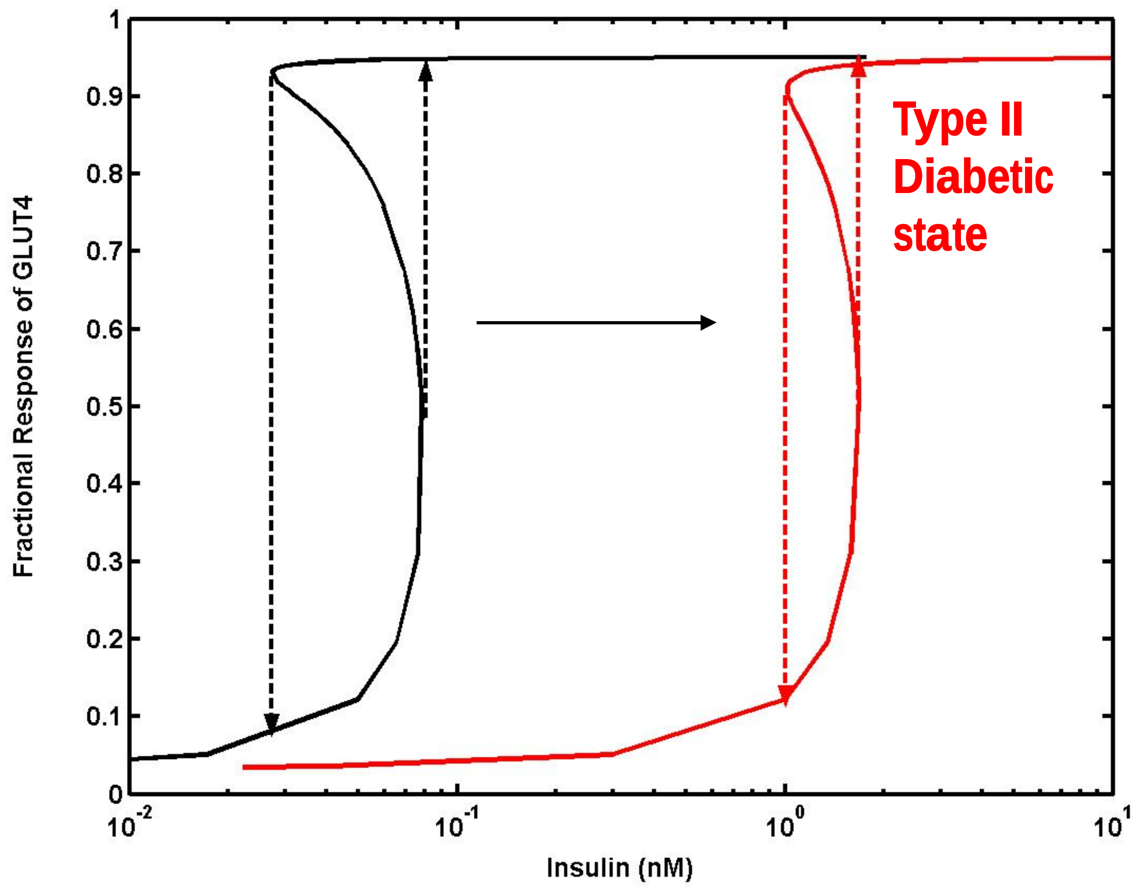
Typical Lifestyle Simulation

B-Breakfast, L-Lunch, D-Dinner, E-Exercise



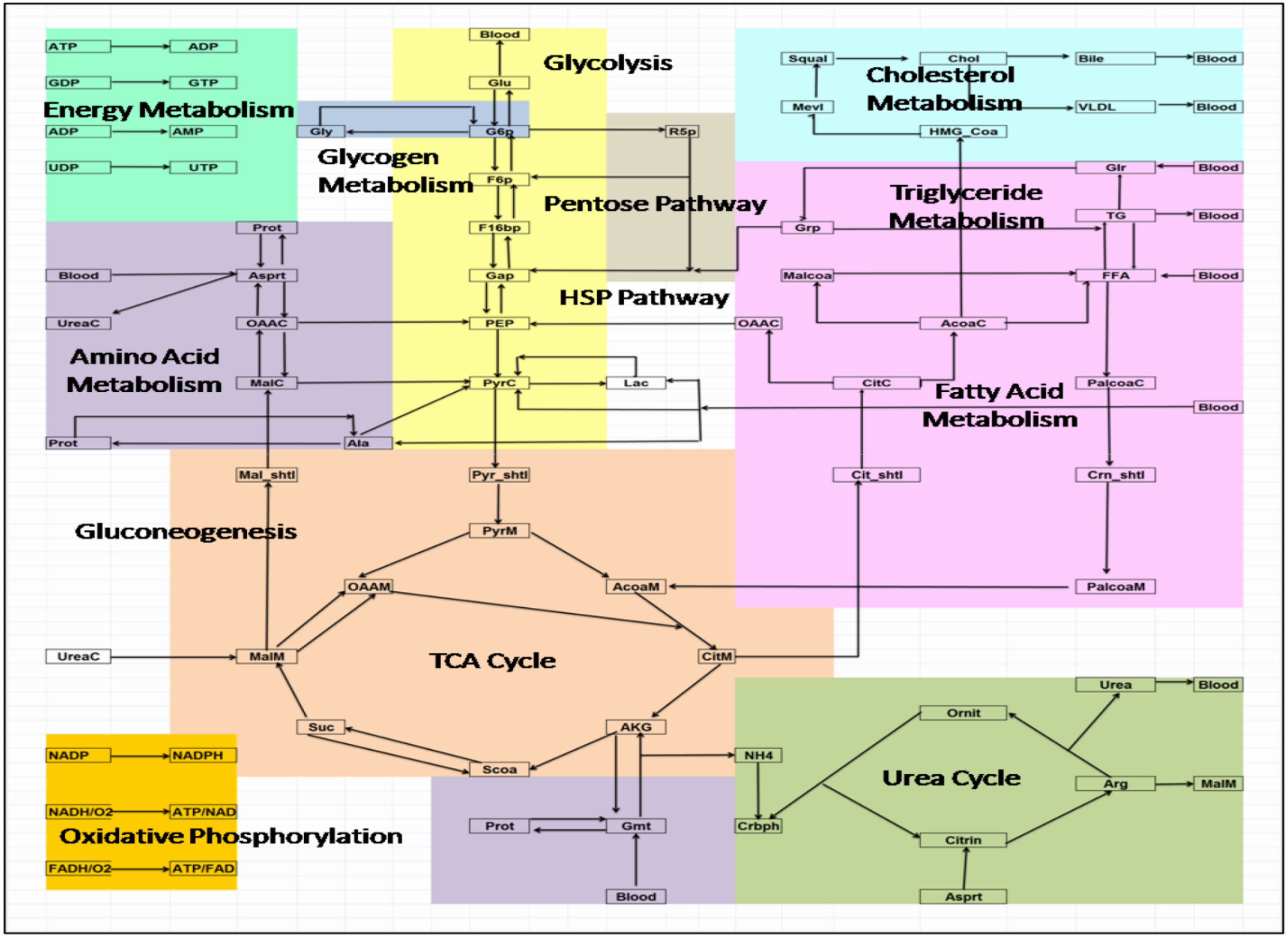
Input	Qty	Time
Exercise-1	1 hr	6 AM
Breakfast	50 g	8 AM
Lunch	100 g	2 PM
Exercise-2	1hr	6. PM
Dinner	50g	9 PM
Night-Rest	11 hr	

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

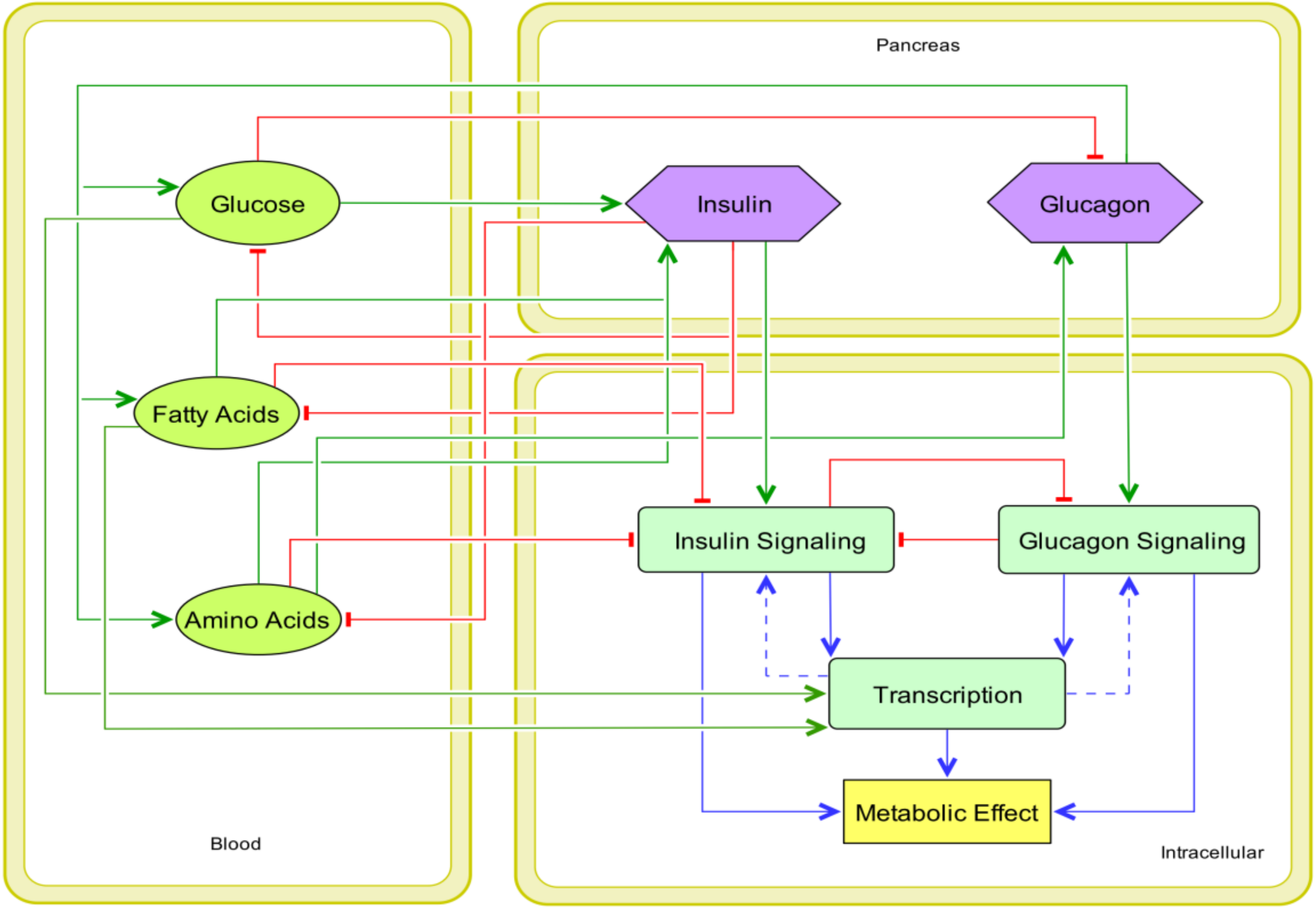


Giri, Mutalik, Venkatesh, BMC Theoretical Biology & Medical Modeling

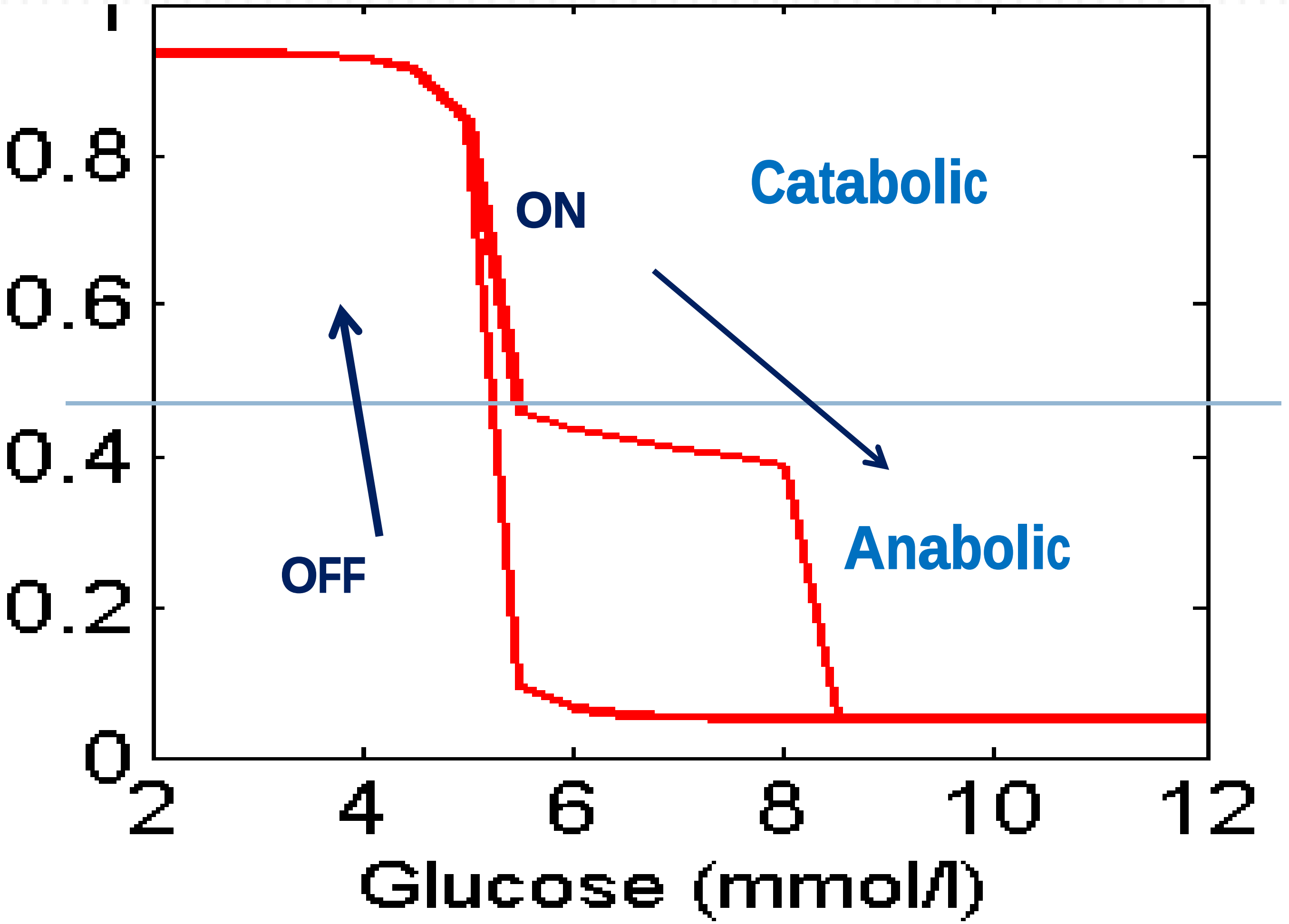
Hepatic Metabolic Network



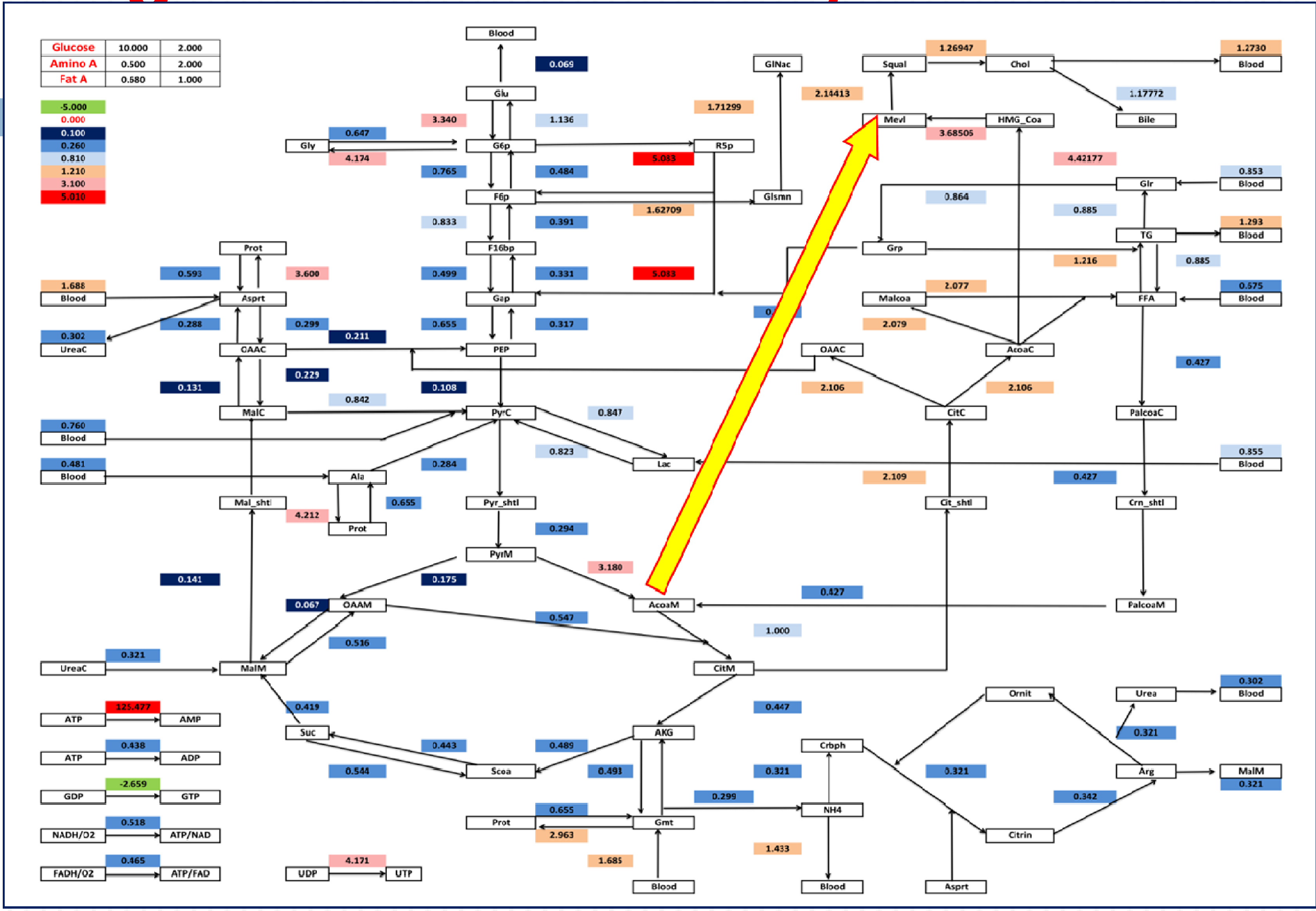
Linking metabolism and signaling



Steady state response for Glucose and Glucagon



High CH and Protein, normal fat



The yellow arrow shows the diversion of the metabolic flux towards the lipogenesis.

Significance of Disease Modeling

Rational Drug Design

Early diagnosis of diseases

Clinical Trials

Targeted therapeutic treatment

Drugs without side effects

Reliable diagnosis

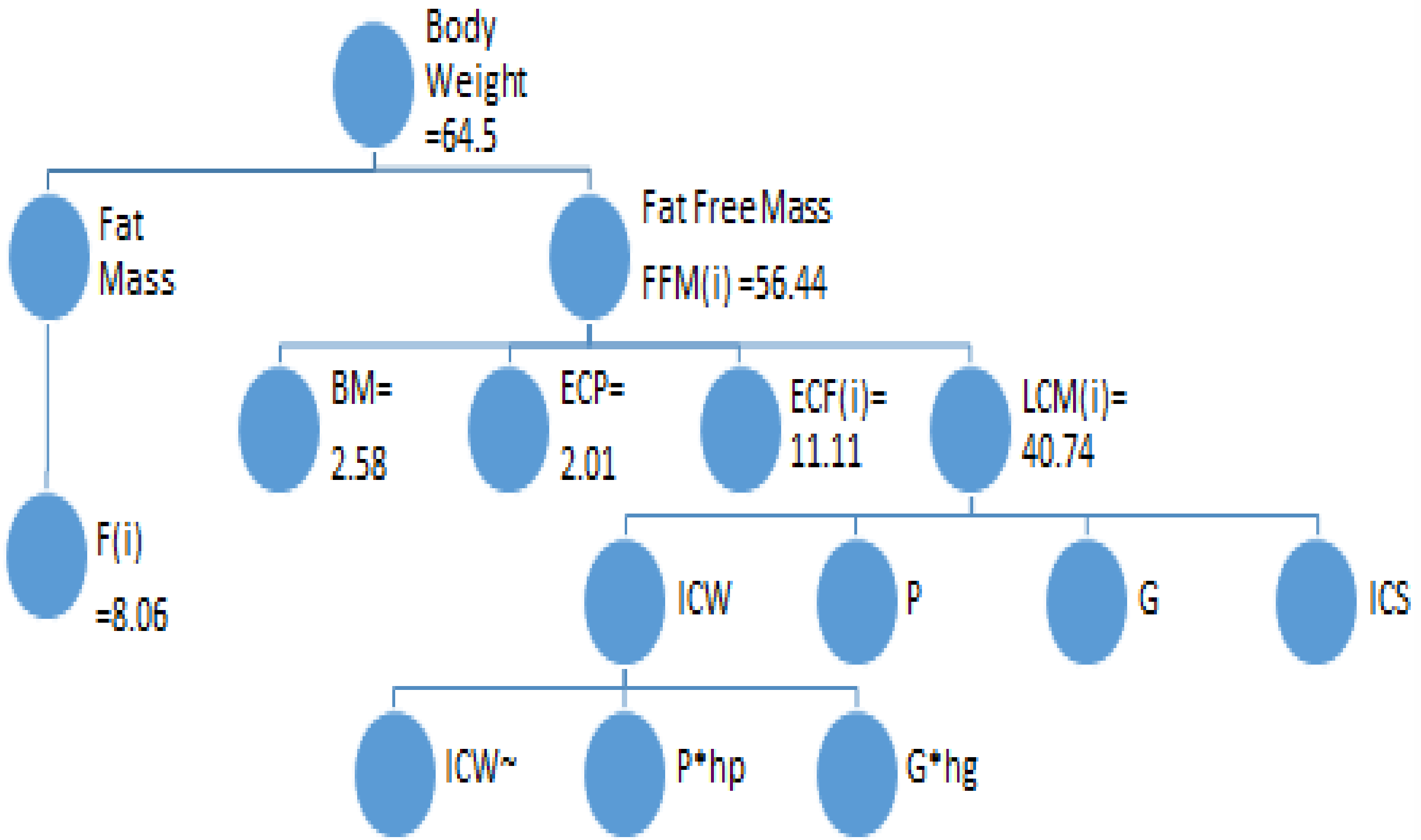
Rational Therapy Design

Improved Healthcare

How Diet Affects Human Body Weight

Abhishek Koshta and K V Venkatesh
Department of Chemical Engineering

Constituents of Body Weight (in Kg)

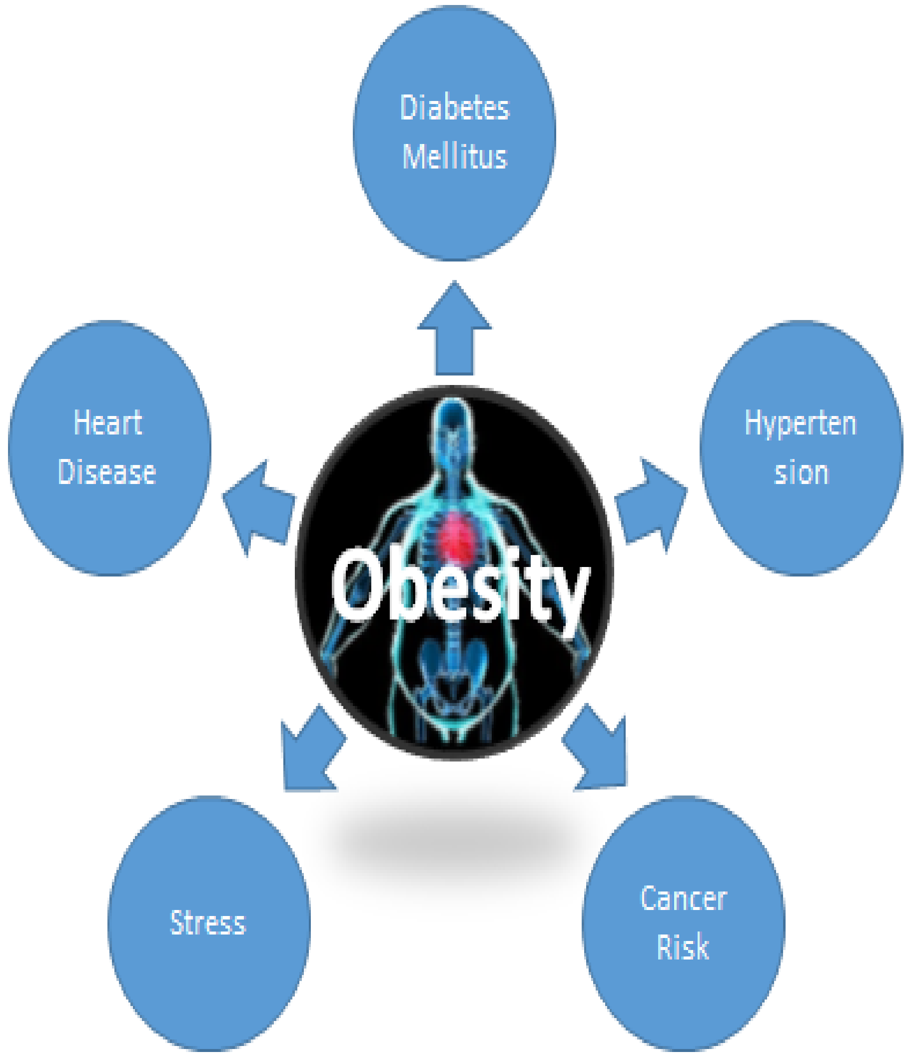


BM - Bone mineral mass, ECF- Extracellular Fluid, ECP – Extracellular Protein,
LCM – Lean cell mass, ICW – Intracellular water, P – Protein, G – Glycogen, ICS – Intracellular solids
$I\tilde{CW}$ - Initial constant intracellular water, hp and hg are hydration coeff. For protein and glycogen

Background

Obesity is being an epidemic in the current world. Obesity causes many fatal diseases. The prevalence of obesity is alarmingly high, and the proportion of adults who are overweight and obese in the developed country like US continues to increase.

The complexity of interactions among dietary and genetic factors is becoming more appreciated, and much research has been undertaken in recent years to probe various interactions between diets and its effect, which has allowed for a greater understanding of the intricacy of this field of research. Body weight depends upon dietary intake, surrounding and physical activity. Body weight can be controlled by changing our dietary intake and daily life style.

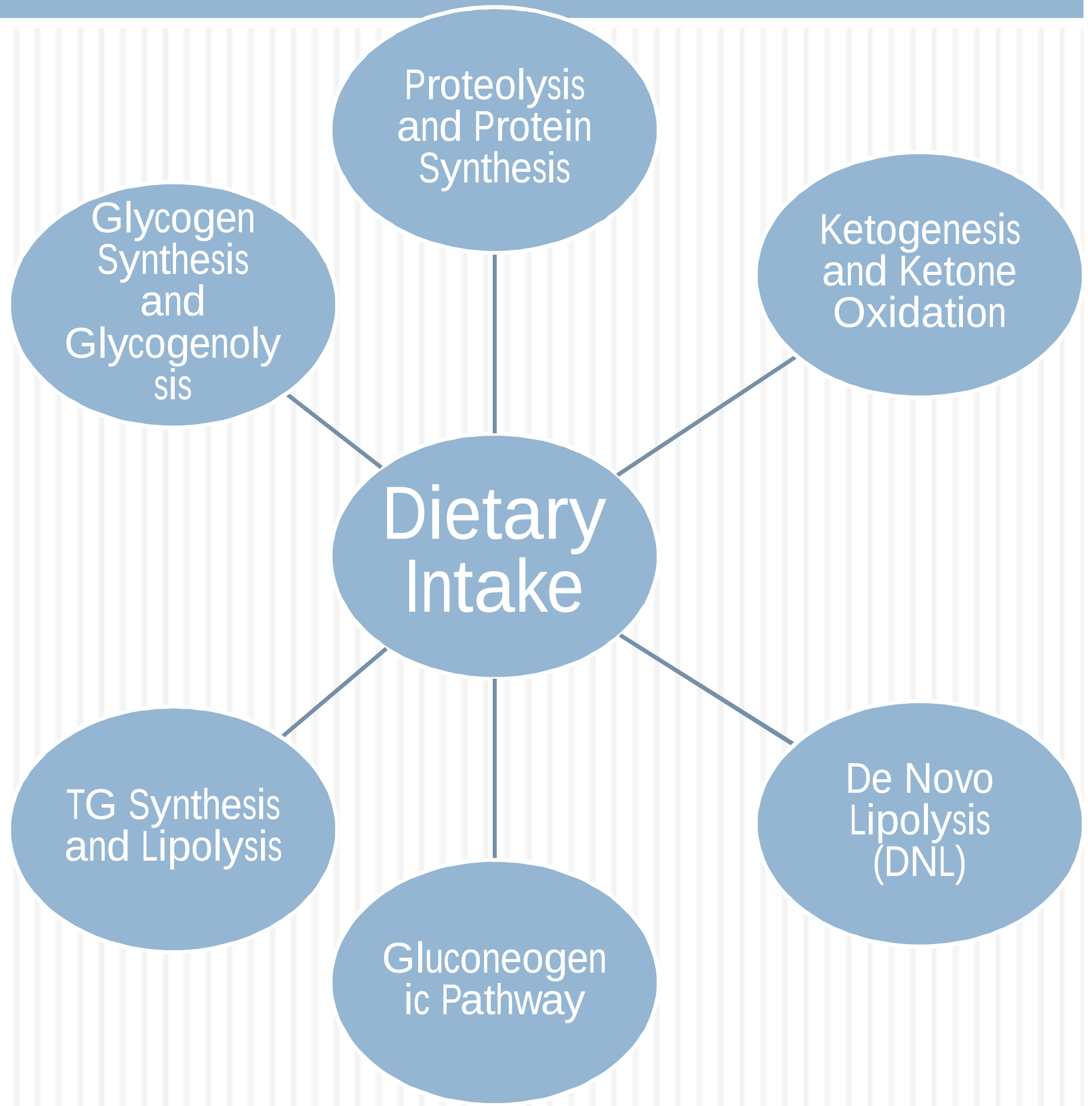


Dietary Intake

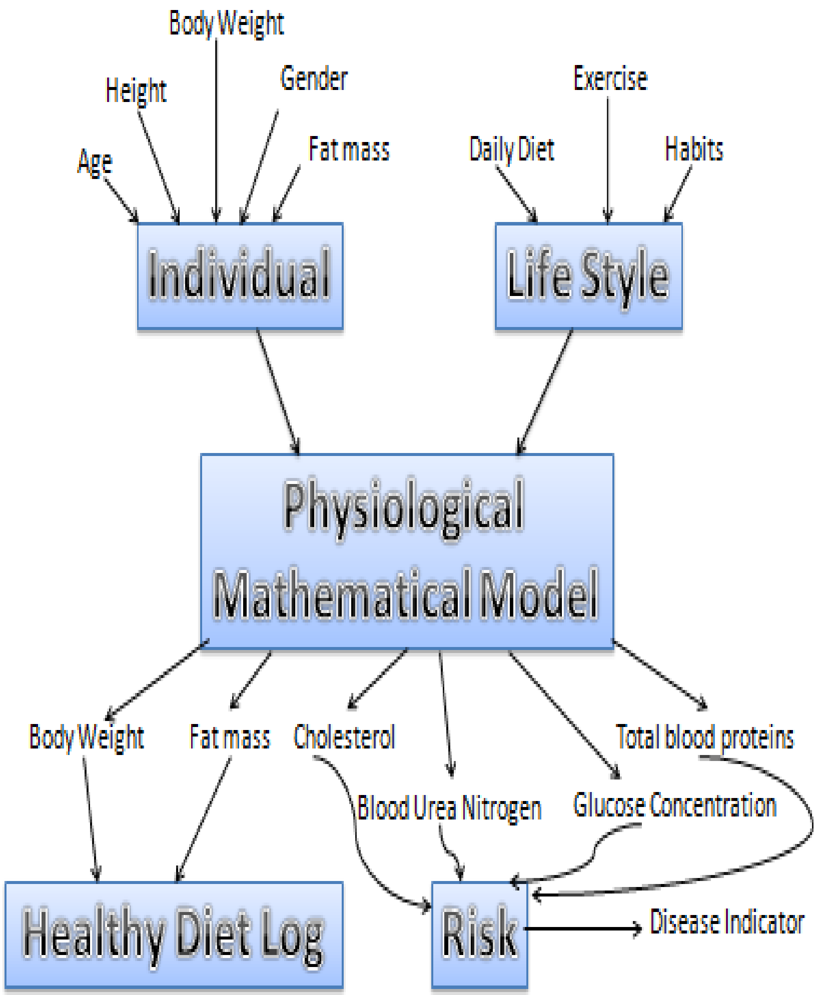
Carbohydrate, fat and protein goes for different metabolic pathways.

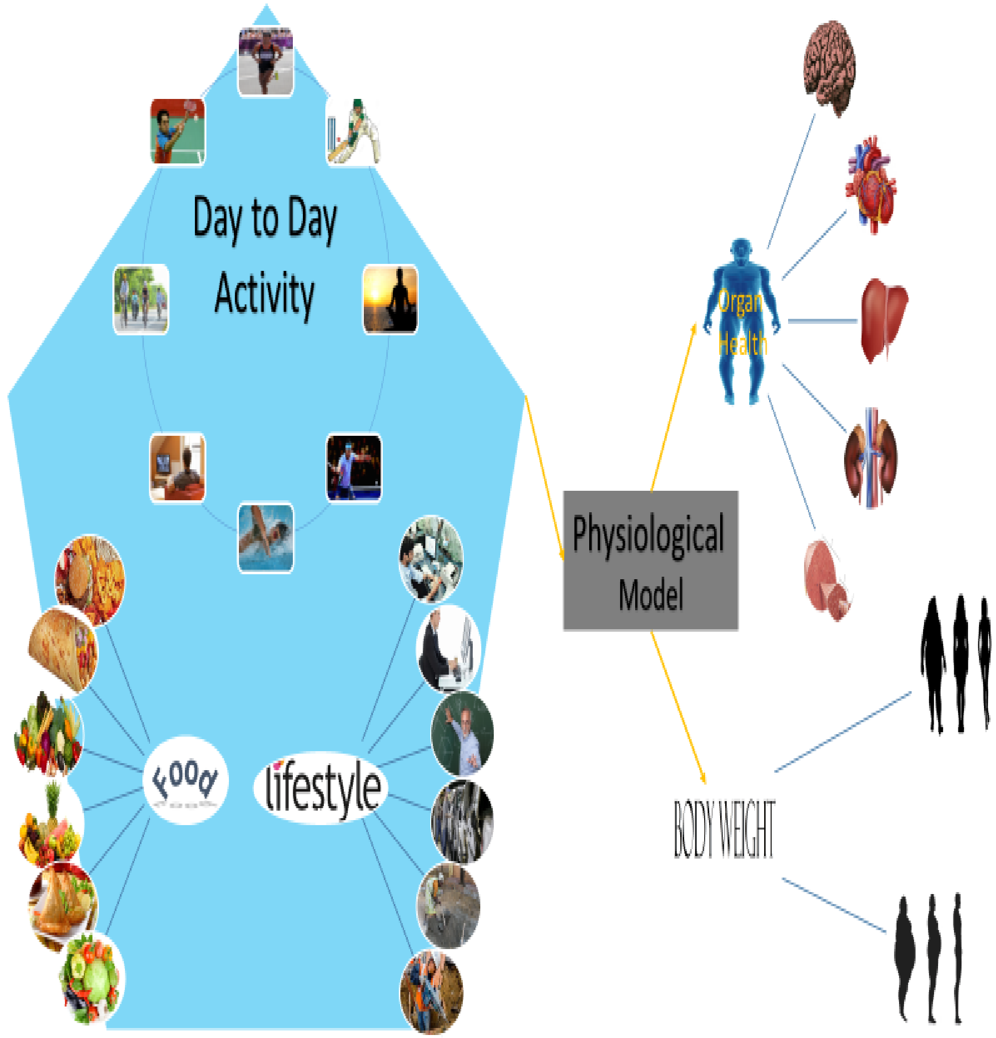
Glucose can be made by fat and protein as well for energy requirement, using the gluconeogenic pathway.

Carbohydrate can be converted to fats using De Novo Lipogenesis metabolic pathway.

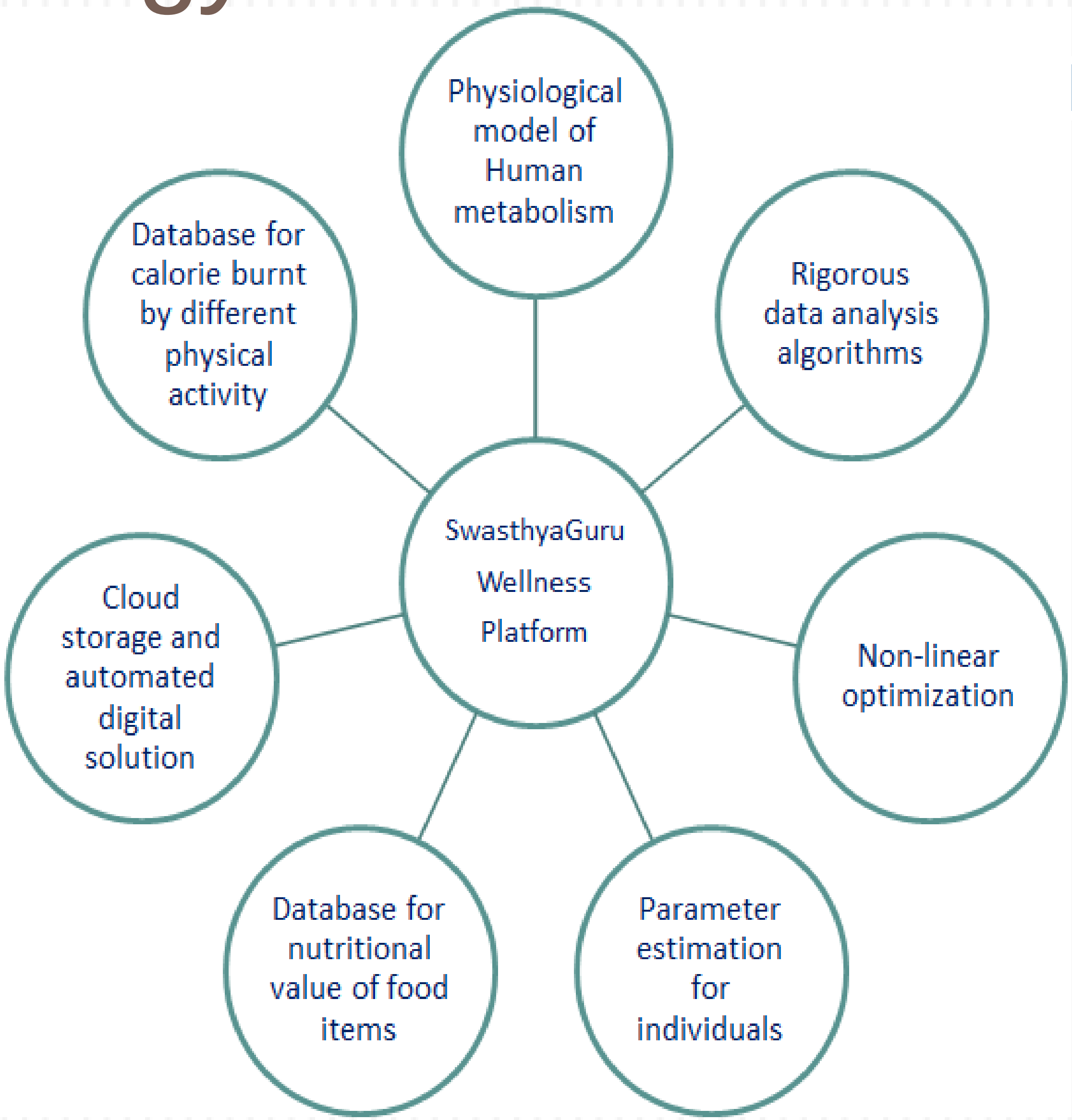


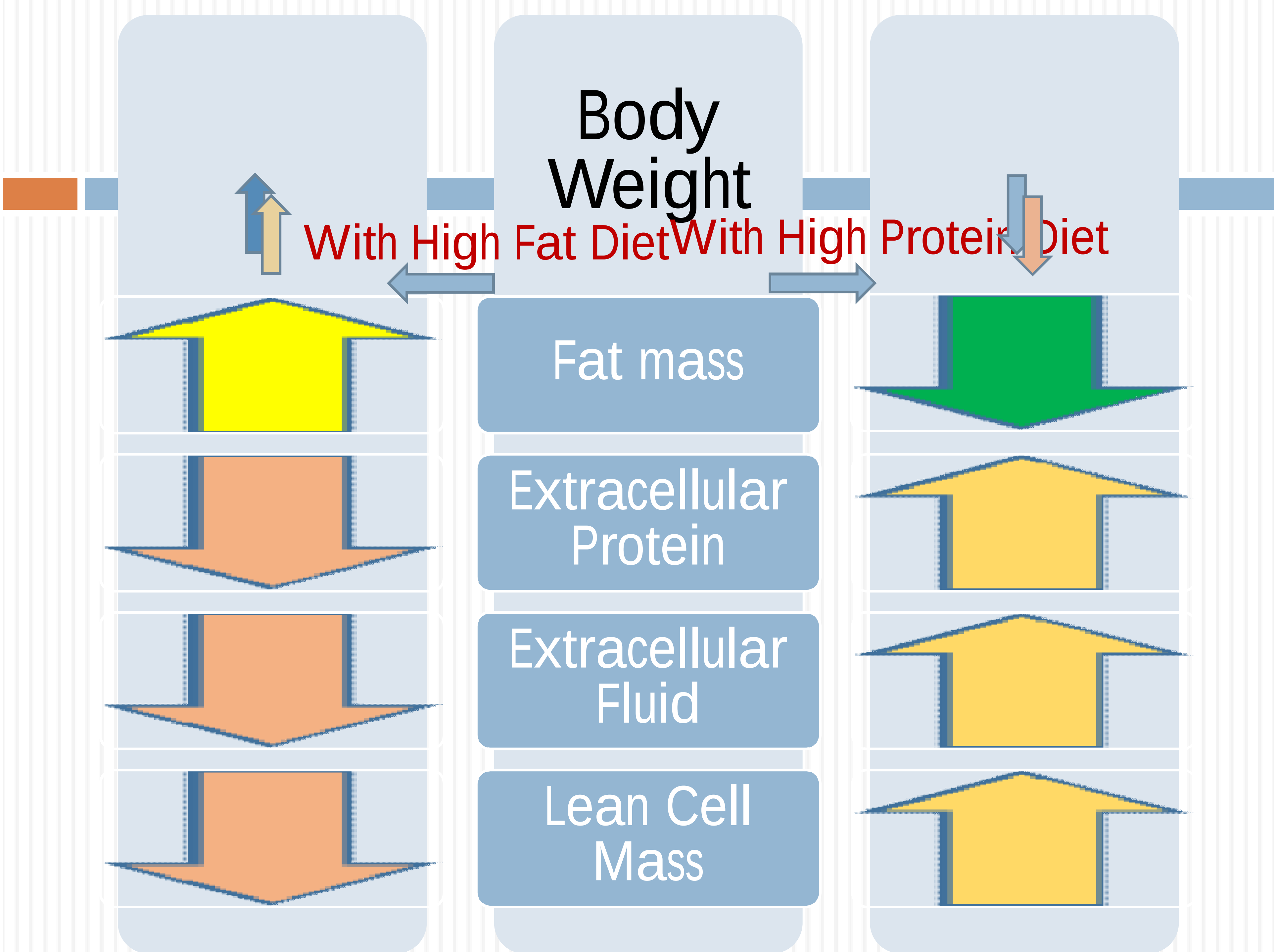
Input output flow to the model





Technology used



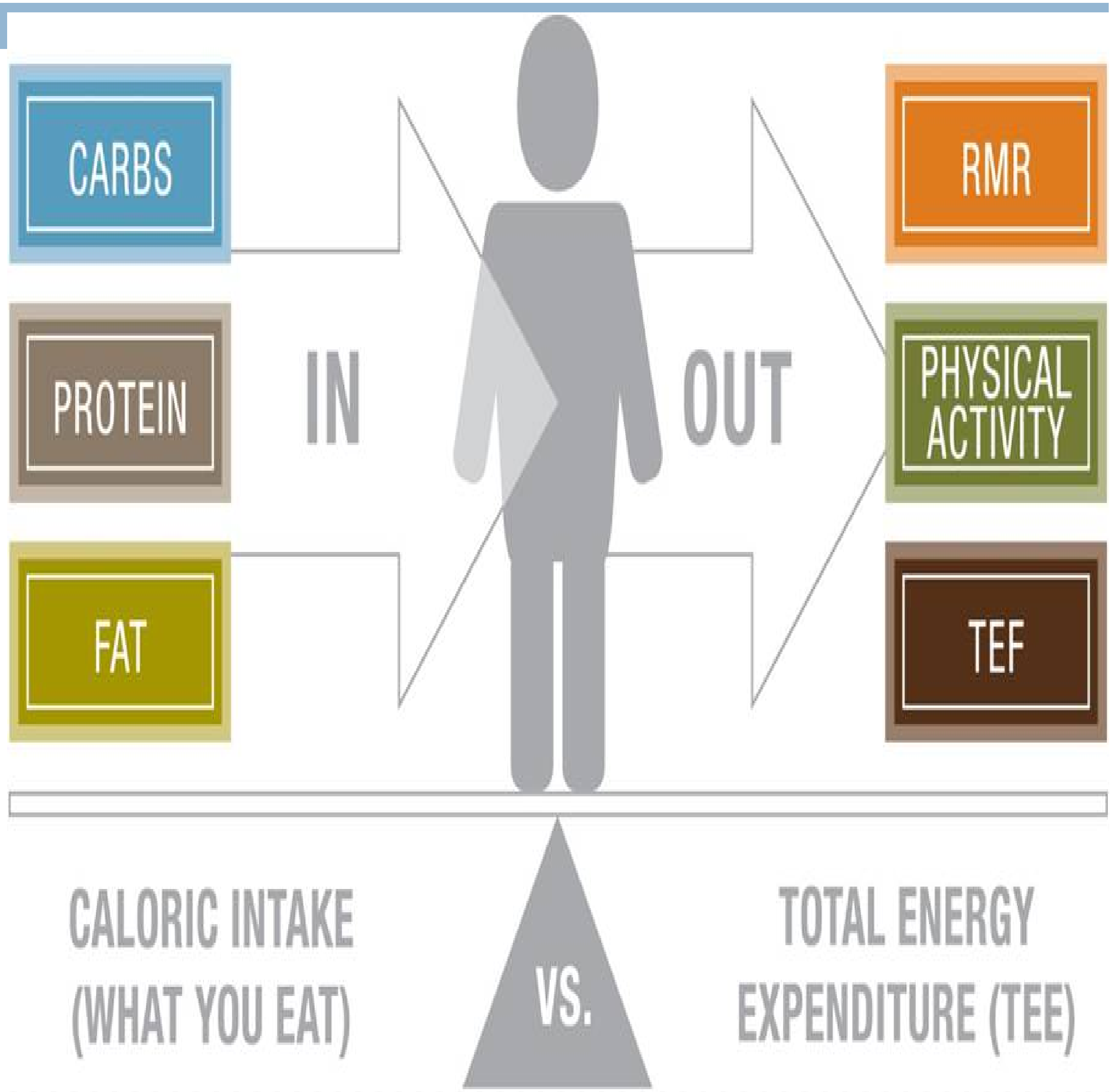


Body Weight
With High Fat Diet
With High Protein Diet
Fat mass
Extracellular Protein
Extracellular Fluid
Lean Cell Mass

Energy Intake and Expenditure

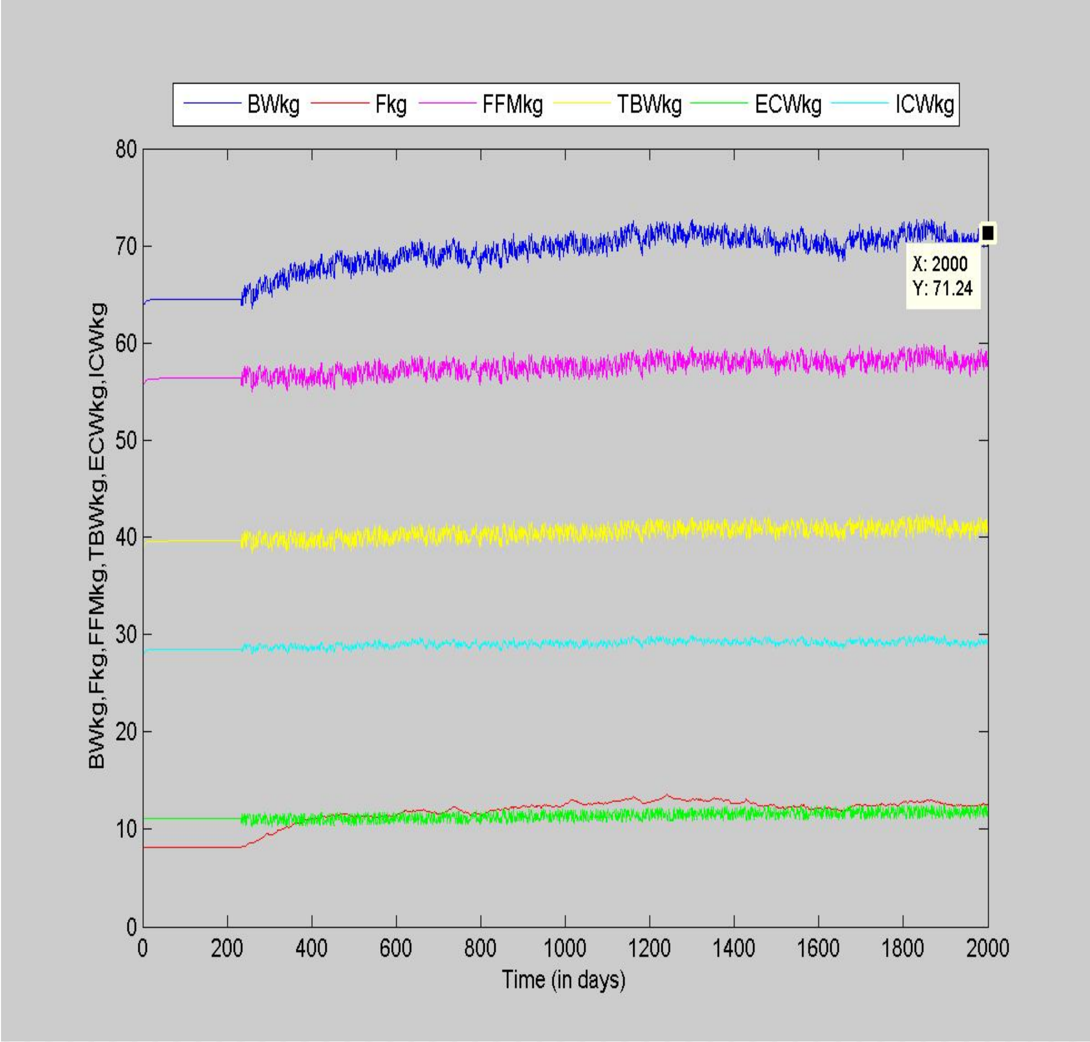
Thermic effect of food (TEF), also known as specific dynamic action (SDA) of a food or dietary induced thermogenesis (DIT), is the amount of energy expenditure above the resting metabolic rate due to the cost of processing food for use and storage.

Resting metabolic rate (RMR) is the minimum number of calories your body needs at **rest** to fuel its **metabolic** activity, for example to maintain functions such as heart beat, breathing and temperature.



Fluctuations in body weight while diet remains in between ±50% of normal diet

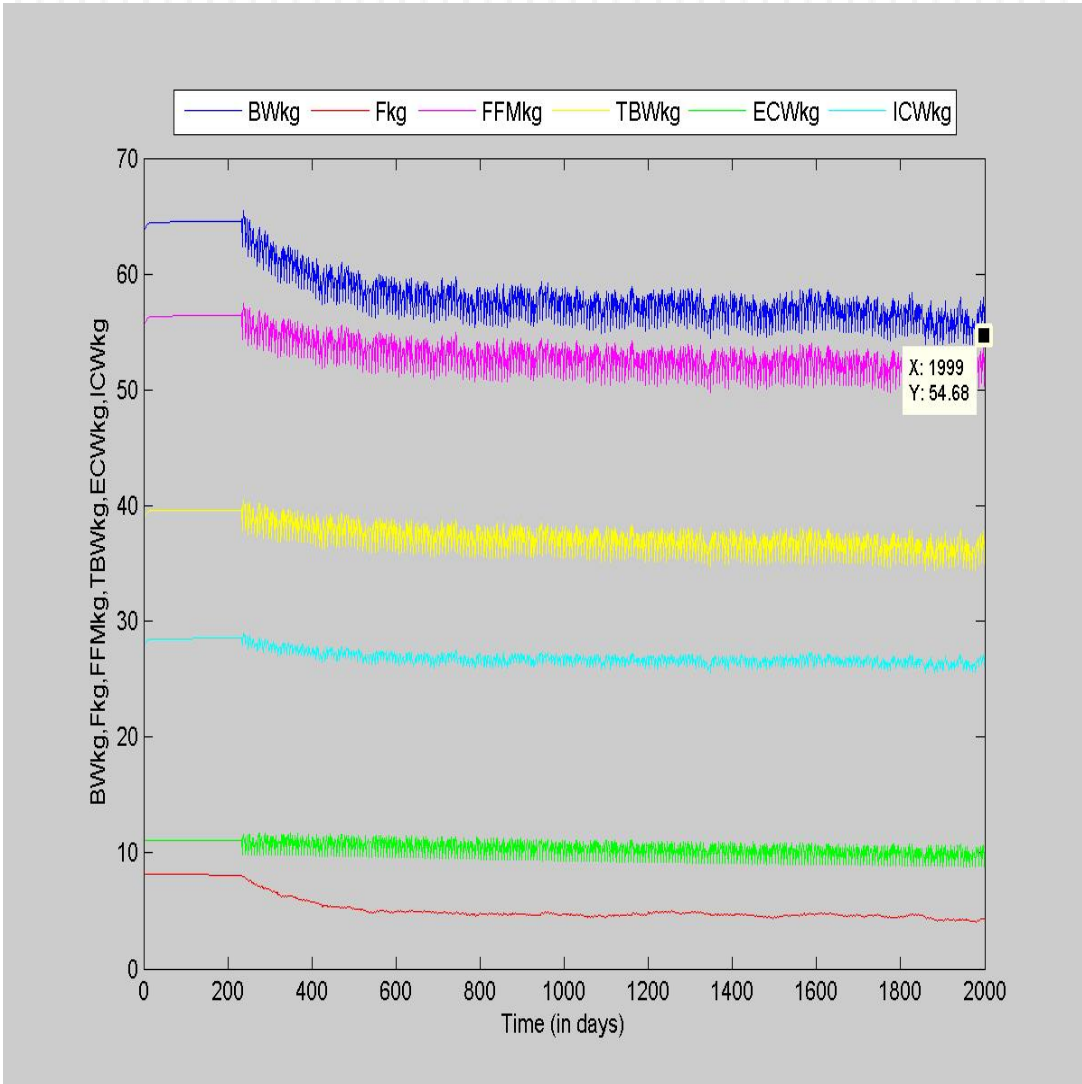
Body weight increases by consuming random diet. Random diet is not advisable to maintain the body weight. Carbohydrate oxidation is observed to be increased. While increased fat oxidation helps in reducing/maintaining the body weight. We can increase fat oxidation by fasting a day in a week.



Body weight with fast a day in a week with diet remains between ±50% of normal diet

I simulated the model with zero calorie on the day of fast. Body weight These results are for sedentary person like office worker.

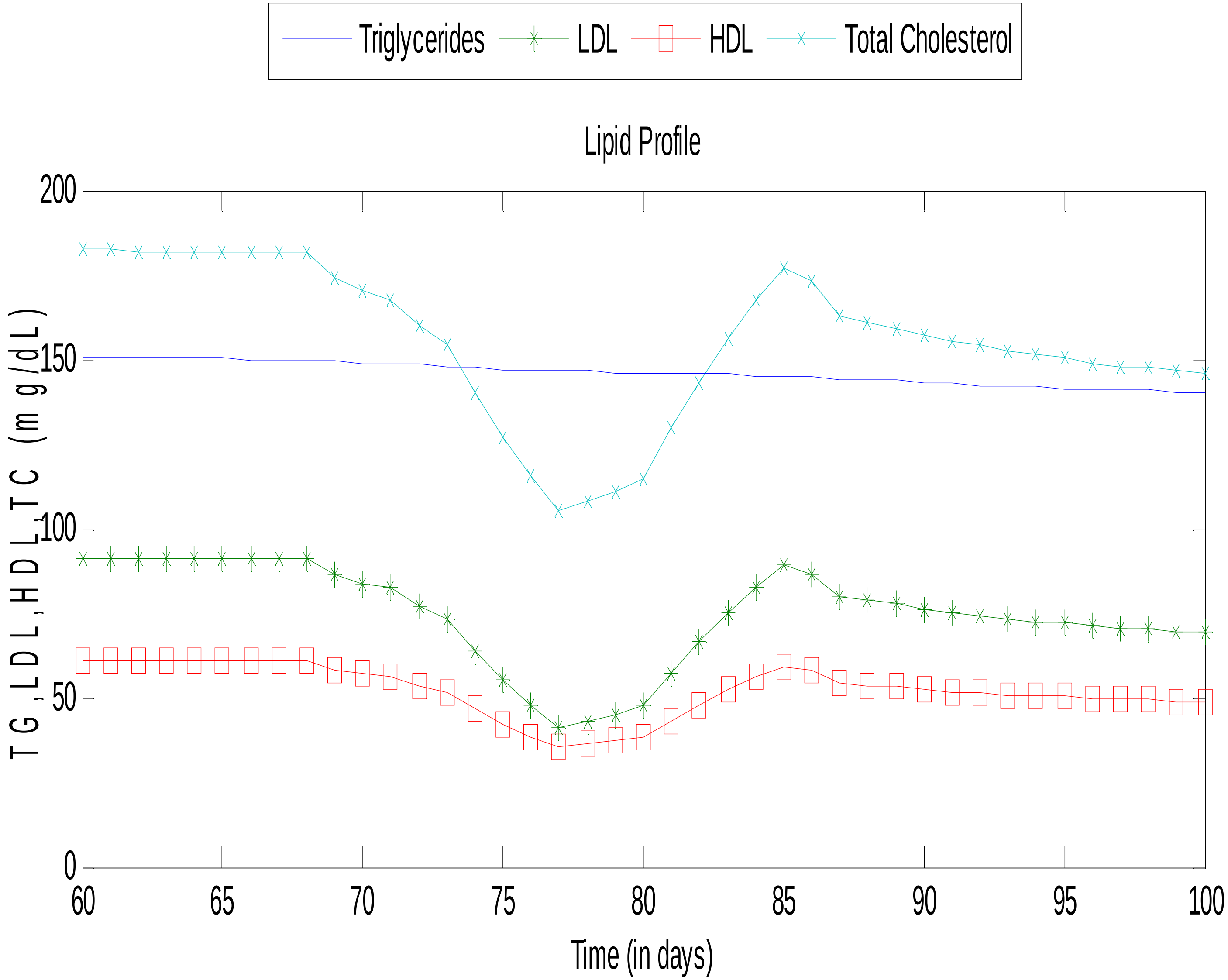
Body weight can be reduced by following this schedule. Fat oxidation increases which reduces the fat mass.



Ode used for TC, TG, Nitrogen, Urea

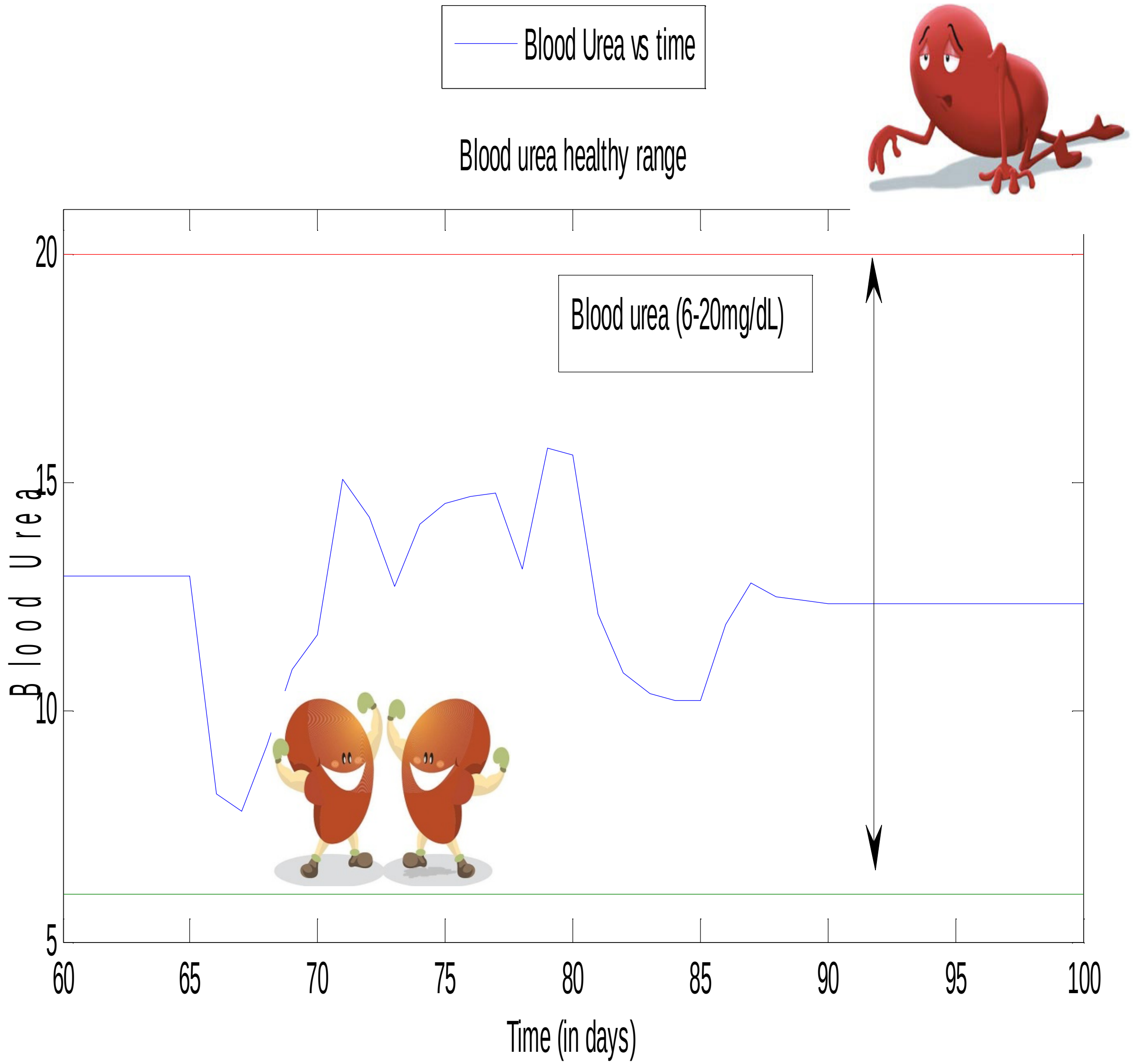
- $\frac{D[Chol]}{dt} = \eta_{chol} * k_{Chol\_synth} - k_{util} * Chol + k_{abs} * Chol_{food}$
- $\frac{D[TG]}{dt} = k_{TG_{synth}} * \eta_{TG} - k_{brk_{dwn}} * TG$
- $\frac{D[N]}{dt} = k_{basal} - k_{des_N} * N - k_{net} * Prot_{diet}$
- $\frac{D[U]}{dt} = k_{synth} * \eta_u - k_{brk} * U$

Plasma metabolite concentration

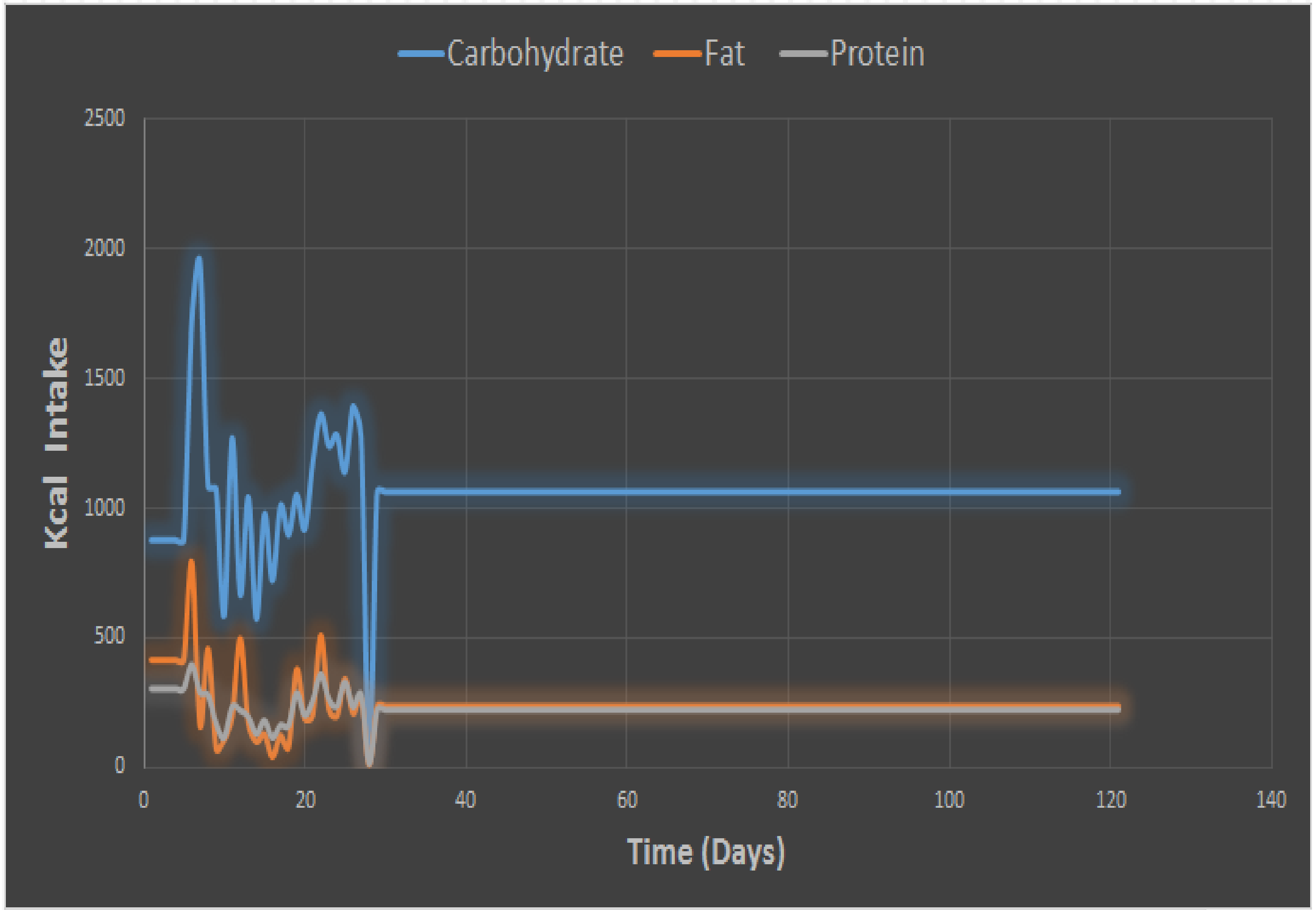


Predicting health of Kidney

- High BUN means kidney is injured which might be caused by diabetes or high blood pressure.
- Low BUN represents low protein intake

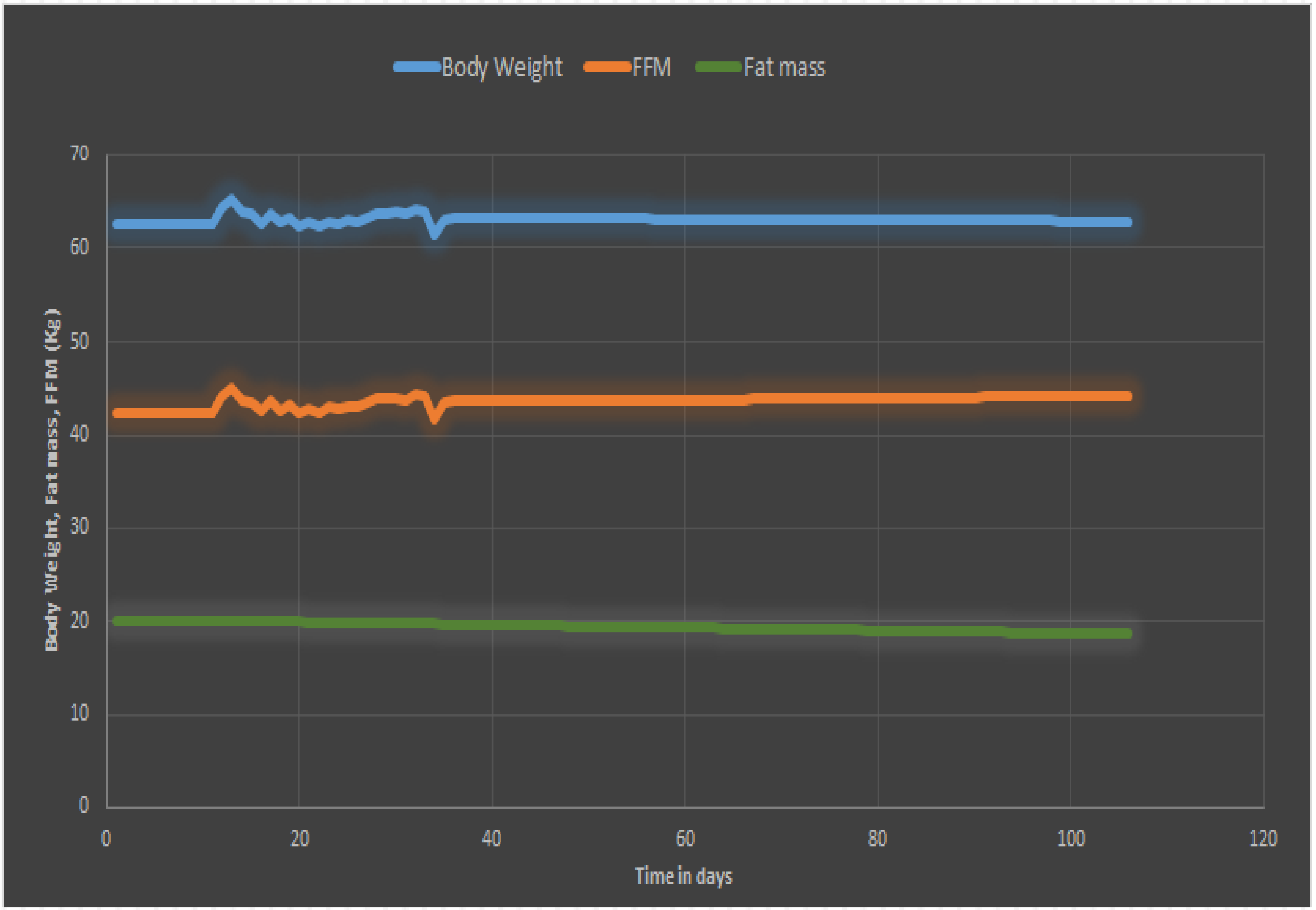


Kcal Intake

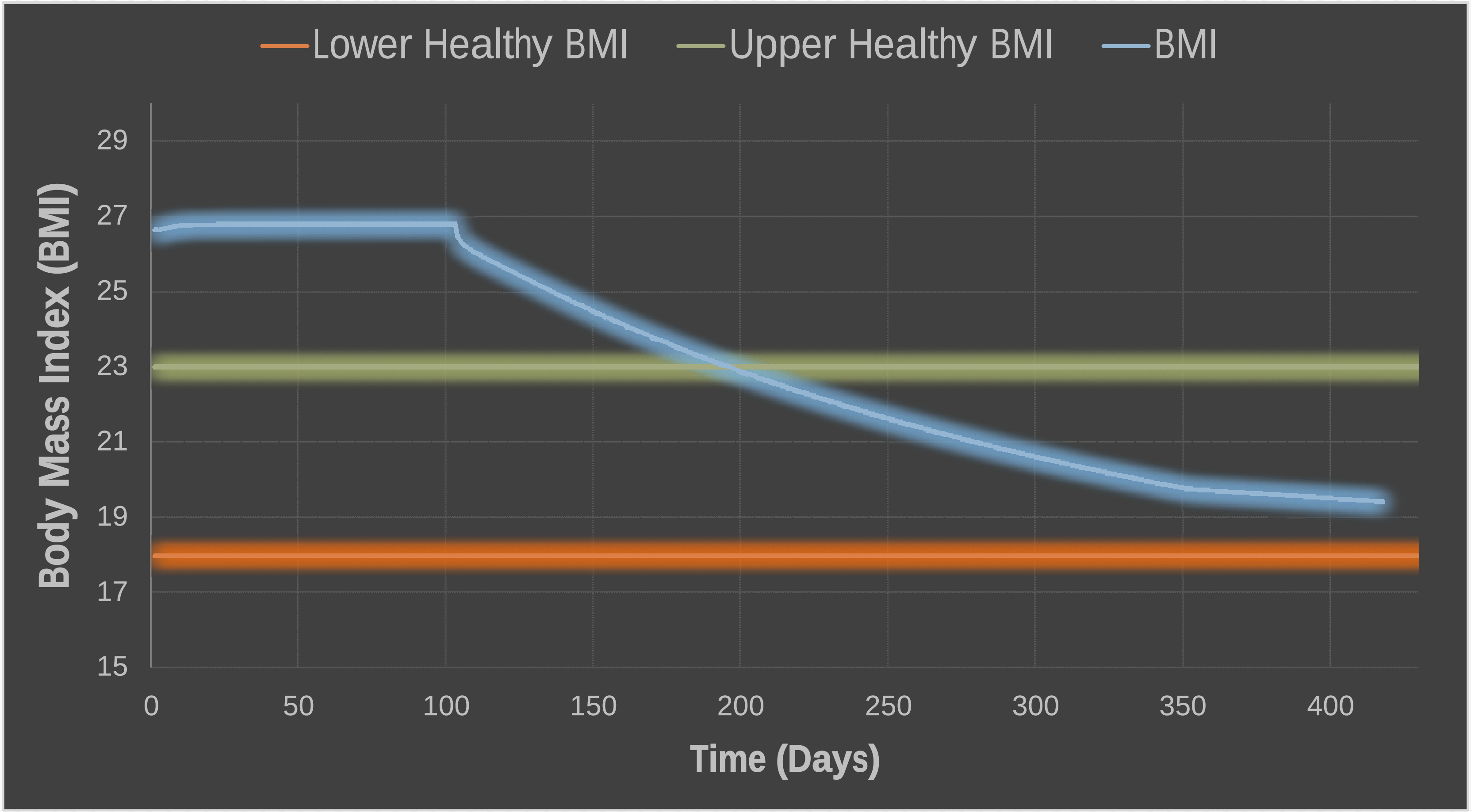


Carbohydrate
Fat
Protein
2500
2000
1500
1000
500
0
Kcal Intake
0
20
40
60
80
100
120
140
Time (Days)

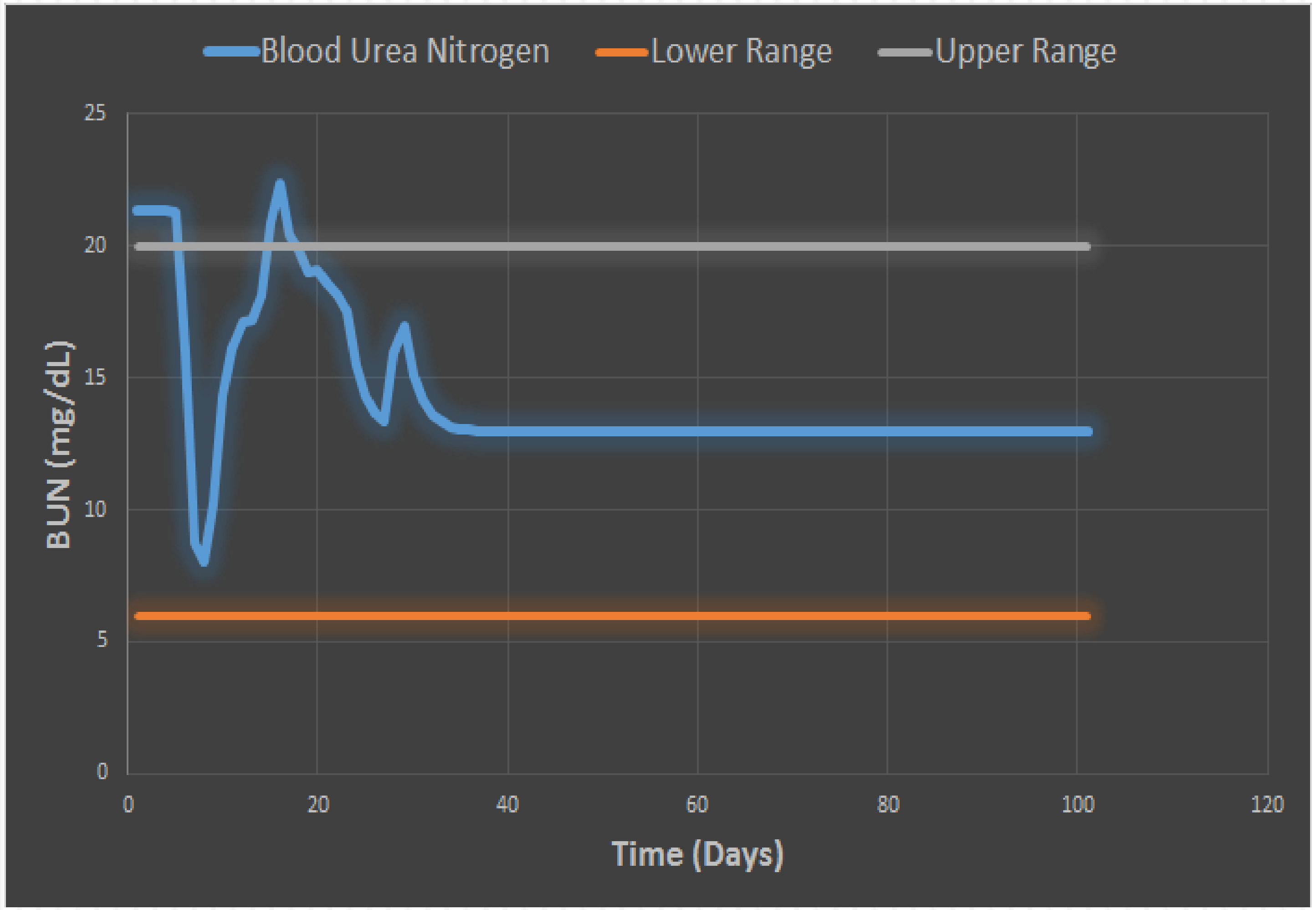
Output: - Body weight dynamics



Body mass index

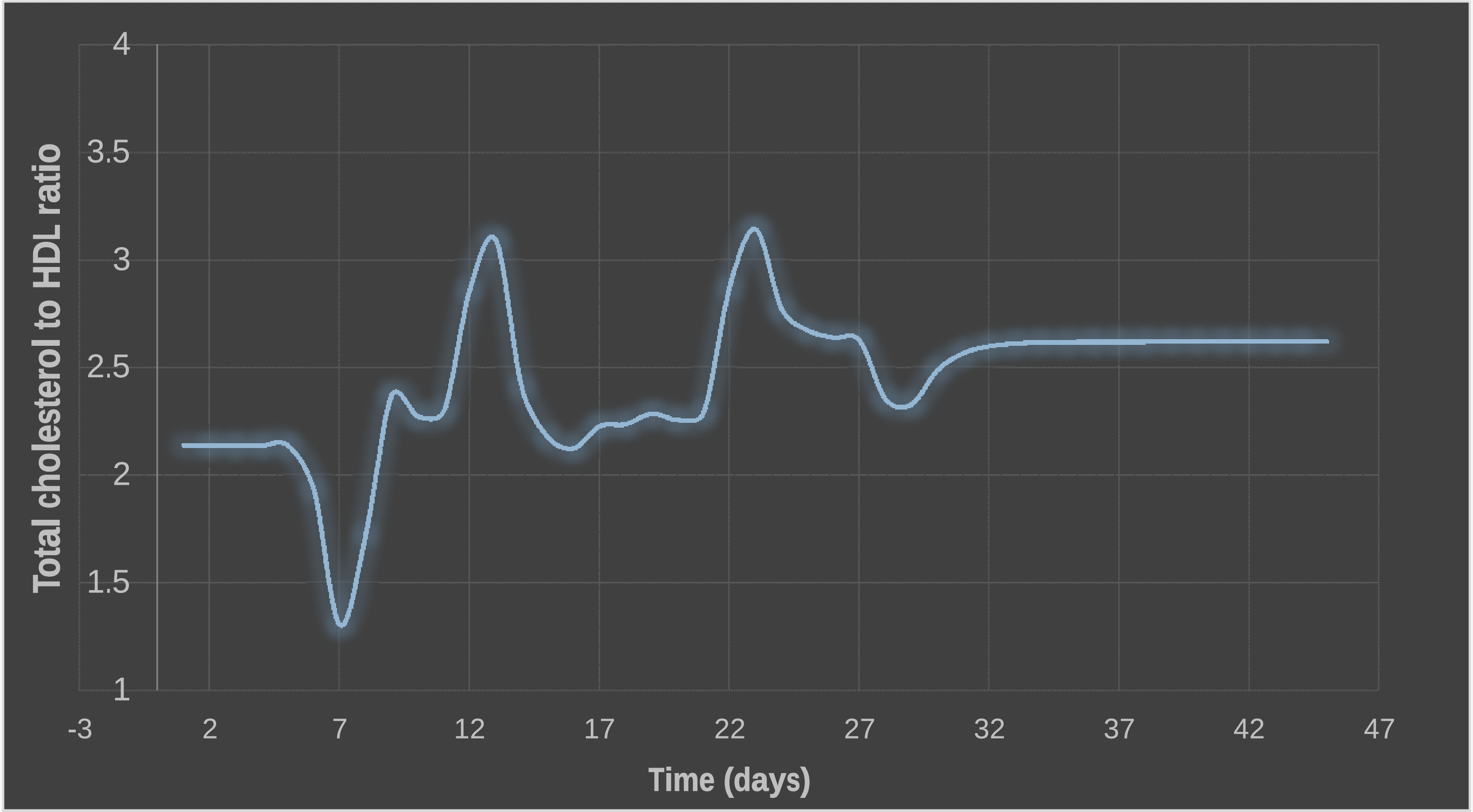


Blood urea nitrogen

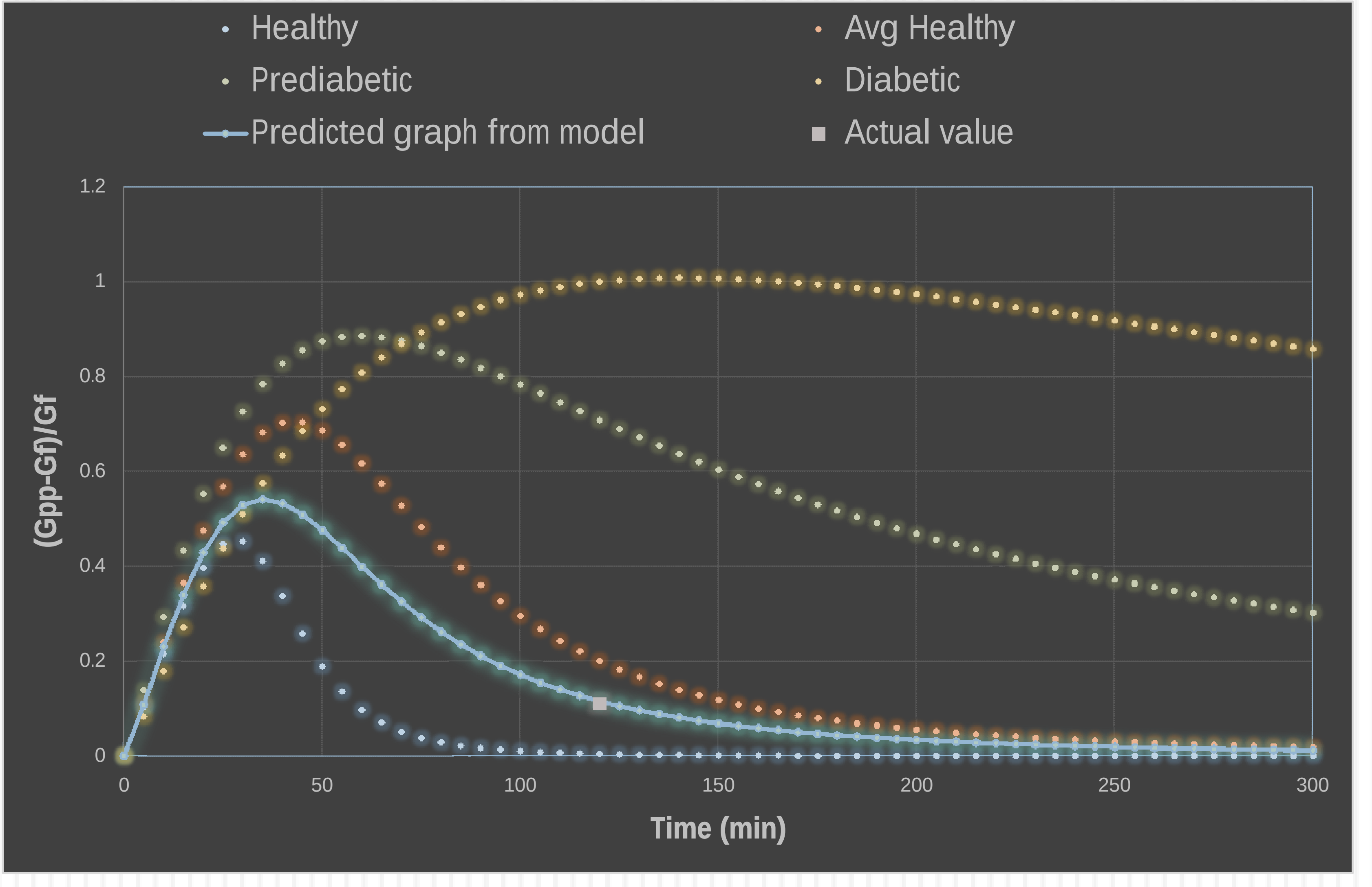


Risk for diabetes

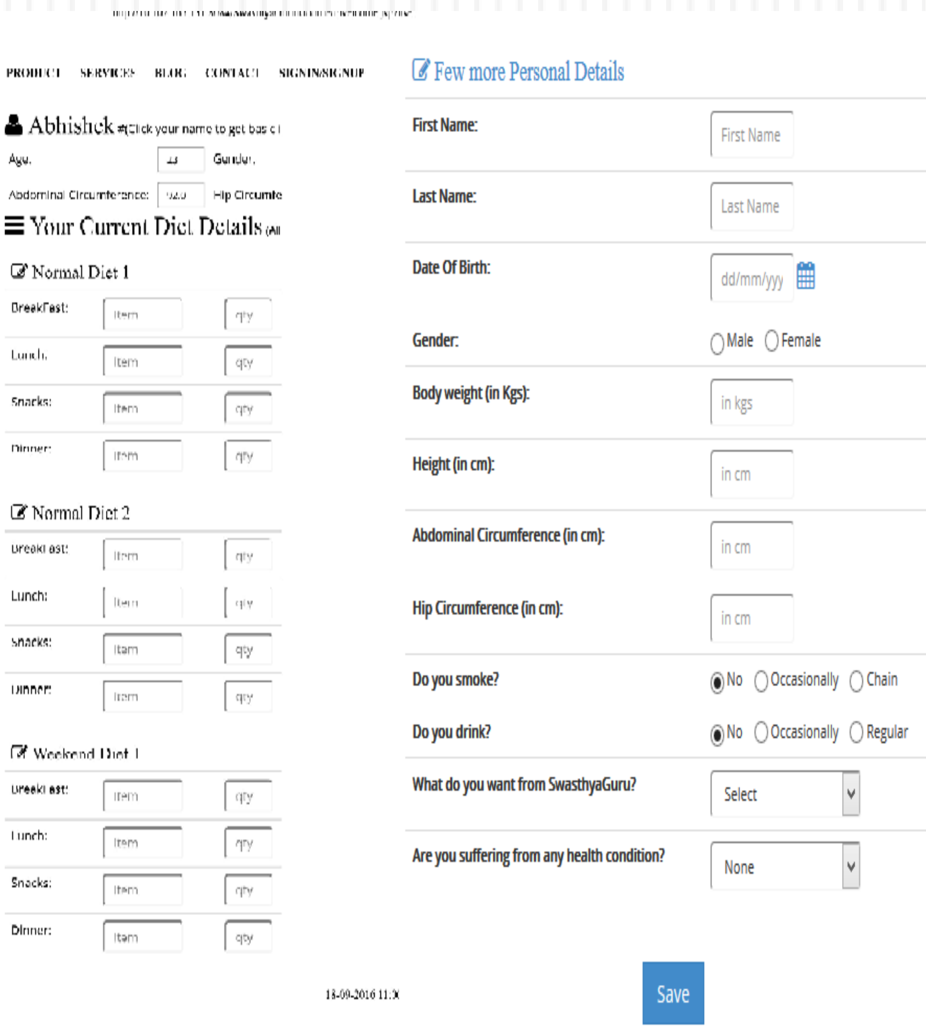
Total to HDL ratio should be in between 3.5 to 1.
A ratio greater than 3.5 exhibits risk of diabetes



Glucose dynamics for diabetes prediction



Input to model and predicted output



SwasthyaGuru
Your Personal Healthcare Companion

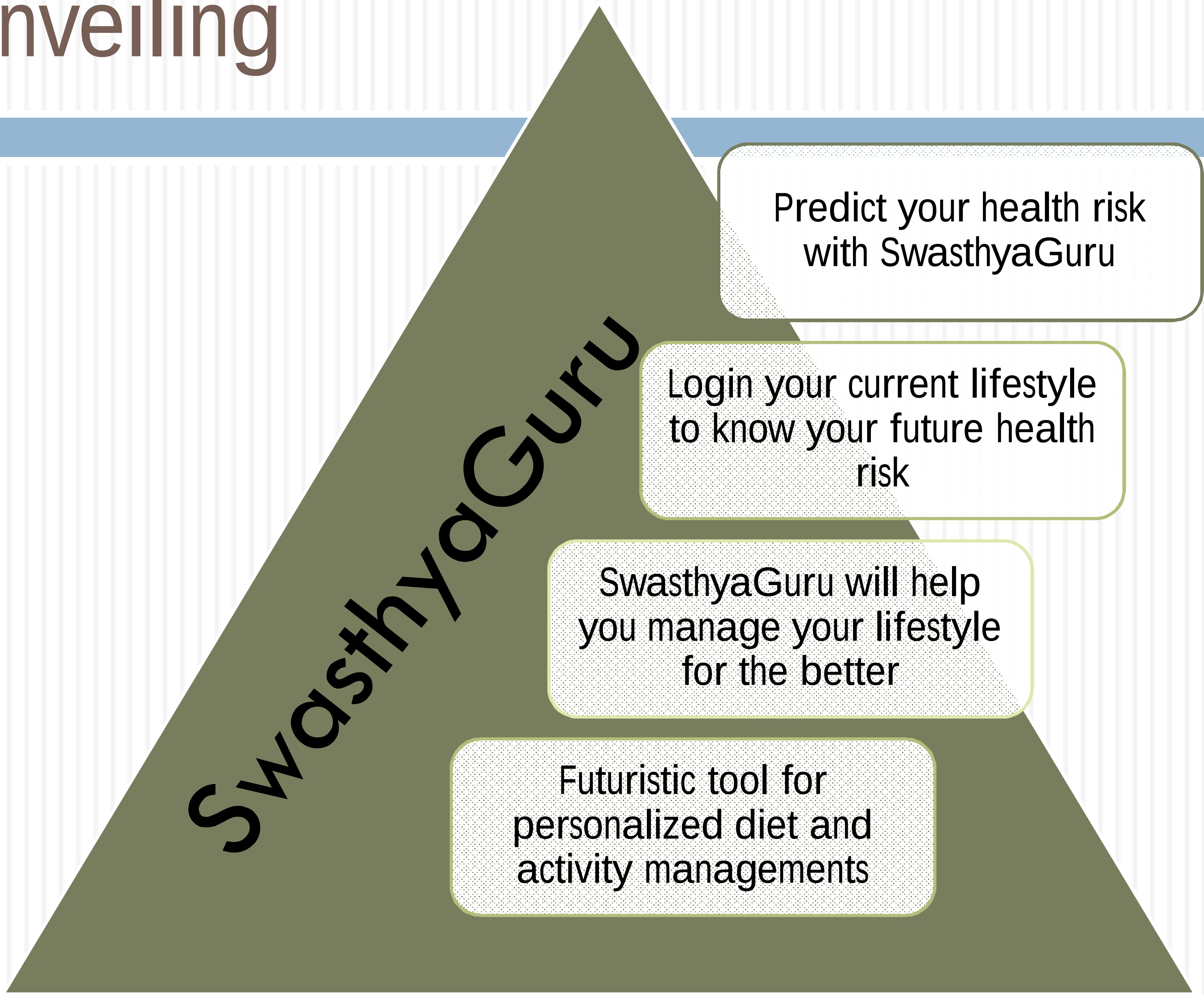
Name	Abhishek		Weight (Kg)	68
Age (years)	23		Height (cm)	176
What do you eat?				
Average Diet Composition (In %)				
	Carbohydrate	Protein	Fat	
	74.46	13.46	12.08	
Calories Taken (In %)				
Break Fast	Lunch	Snacks	Dinner	Total kcal/day
26.74	48.00	4.26	21.00	2261
Body Composition Dynamics		Current	Healthy	After 1 year
	Body Weight	68	50.5-66.6	69.3
	Fat Mass	19.5	11.2-15.5	21.2
	Body Mass Index	21.9	18-21.5	22.4
	% Fat	28.7	15-25	30.6
	Lean Muscle Mass	48.5	48.8-43	48.1
Blood Profile				
	HDL	67	30-70	52
	LDL	71.2	<130	87
	Triglyceride	104	25-160	110.2
	Total Cholesterol	159	140-250	161
	Blood Urea Nitrogen	14	6.0-23.0	12.9
	Total Blood Protein	7.2	6.0-8.0	7.6
	Haemoglobin	14.4	13-18	14.5
Disease Risk				
	Diabetes Risk	6%	Very low risk	
	Heart Risk	1%	Very low risk	
	Health of Kidney	5%	Good condition	

Optimized Suggested Plan for ideal body weight

Recommended Plan:	0.5 Kg loss per month
Desired final weight	66 Kg (BMI: 21.5)
With Diet only Plan:	2020 (241 Kcal reduction per day)
With exercise only Plan	35 minutes of cycling per day with original 2261 Kcal intake

PS: Above plan can be modified to suite your choice (combination of diet and exercise)

Unveiling


SwasthyaGuru
Predict your health risk with SwasthyaGuru
Login your current lifestyle to know your future health risk
SwasthyaGuru will help you manage your lifestyle for the better
Futuristic tool for personalized diet and activity managements

Our capabilities

- **Digital holistic lifestyle management application**

System level human metabolic model to predict future physiological parameters based on current lifestyle inputs specifically for Indians.

- **Adaptive weight-loss/gain management**

Maintain and sustain weight with ideal fat mass/lean muscle mass through optimized diet and exercise routine

- **Food and physical activity diary**

Day to day diet and physical activity log to help balance calorie intake and expenditure

Our capabilities

- **Micro-nutrient balanced diet (Calcium, iron, vitamins)**

Minimize deficiency in micronutrient for better health and active lifestyle

- **Reduce disease risk (diabetes and cardio-vascular health)**

Predict and control physiological parameters (Blood glucose, cholesterol, urea etc.) towards reduced risk of diabetes, cardiovascular, PCOS

- **Medical Repository**

Store your medical history (Blood profile, X-ray, ECG, Pathlab reports) at one place for better future health management

Unique Selling Point

- Knowledge based human physiological model for predicting health parameters
- Individualized recipe for weight management through an automatic optimized solution platform based on a database of Indian foods
- Personalized plans based on the choice of the individual
- Disease management solutions for lifestyle diseases such as diabetes, heart disease, PCOS etc.
- Predict and maintain blood plasma metabolite profiles for better organ health
- Micronutrient balanced diet
- Platform for infants and children (a solution for the whole family)

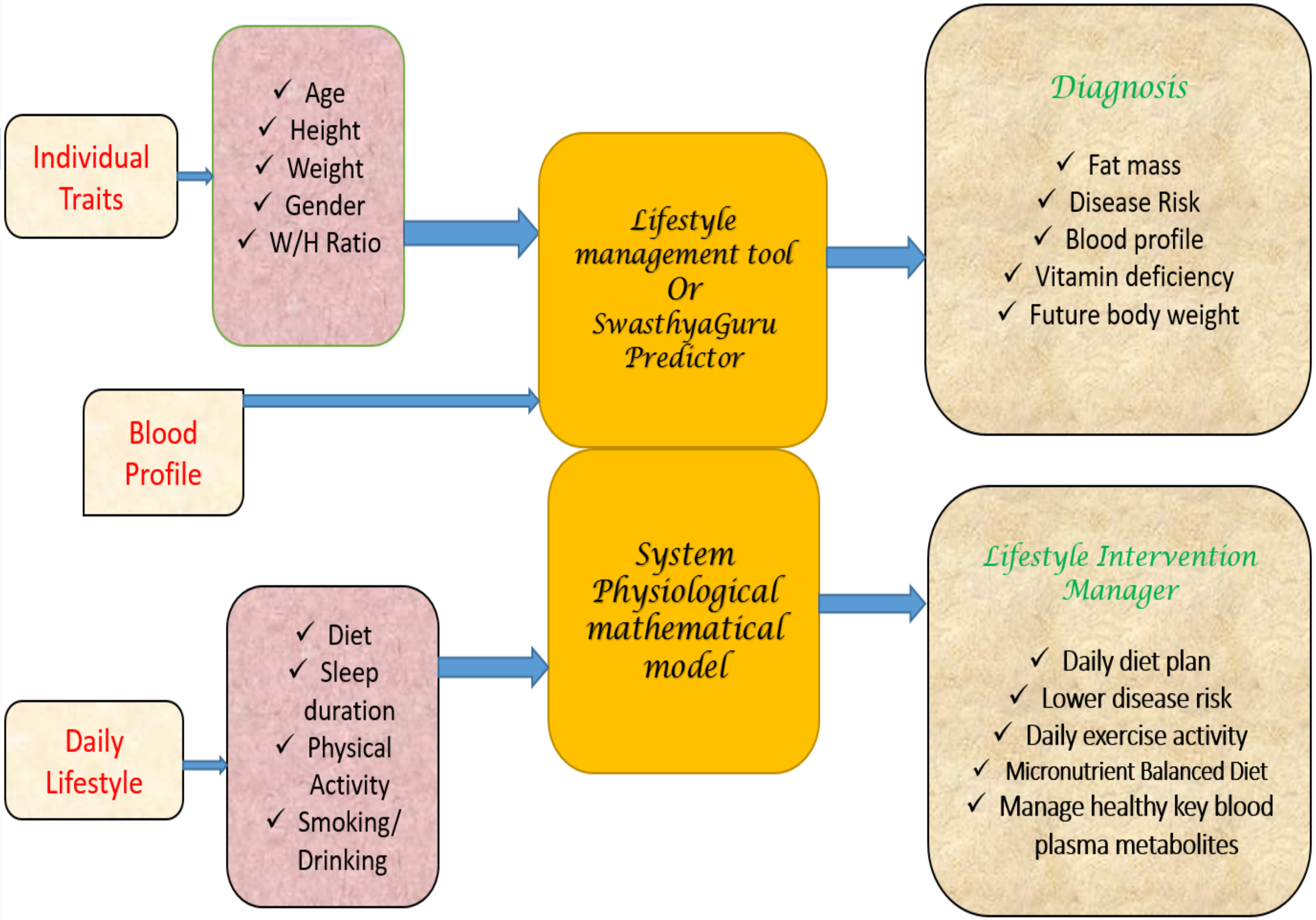
Capabilities of the Platform

Micro-Scale Model:

1. Quantification of metabolism and signaling for individual organ
2. Effect of diet and lifestyle on intracellular pathways
3. Analyzing disease progression and diagnostics
4. Effect of active metabolite/compound on whole body physiology

Macro-Scale Model:

1. Prediction of body weight and fat percentage
2. Individualize the model for person specific through parameter estimation
3. Disease risk analysis based on lifestyle inputs
4. Optimized diet for both macro and micro nutrients and physical activity chart
5. Lifestyle intervention for disease management
6. Medical Data repository for individuals


Individual Traits
✓ Age
✓ Height
✓ Weight
✓ Gender
✓ W/H Ratio
Blood Profile
Daily Lifestyle
✓ Diet
✓ Sleep duration
✓ Physical Activity
✓ Smoking/ Drinking
Lifestyle management tool Or SwasthyaGuru Predictor
System Physiological mathematical model
Diagnosis
✓ Fat mass
✓ Disease Risk
✓ Blood profile
✓ Vitamin deficiency
✓ Future body weight
Lifestyle Intervention Manager
✓ Daily diet plan
✓ Lower disease risk
✓ Daily exercise activity
✓ Micronutrient Balanced Diet
✓ Manage healthy key blood plasma metabolites

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THANK YOU