# Mathematical Modeling of the Gluconeogenesis Pathway in Hepatocytes

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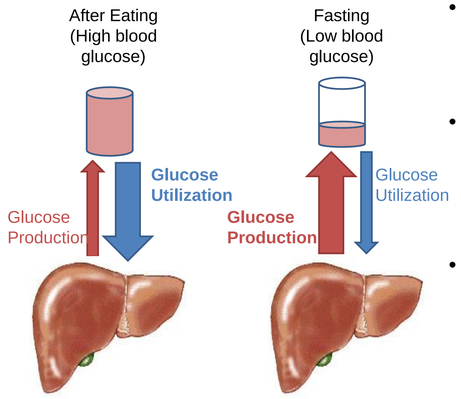
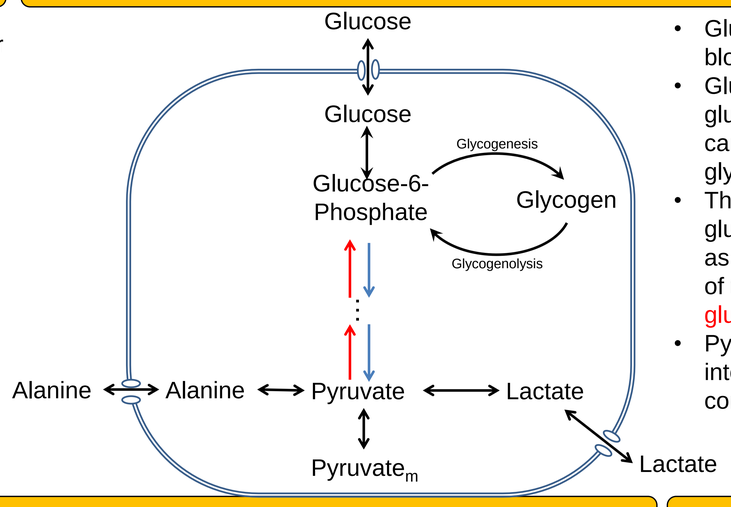
## Role of Liver in Glucose Homeostasis




- The type of liver cells responsible for maintaining blood glucose homeostasis are known as hepatocytes
- When blood glucose is high, hepatocytes can utilize glucose
  - Conversion to lactate and other metabolites
  - Storage as glycogen
- When blood glucose is low, hepatocytes produce glucose by breaking down glycogen and other metabolites

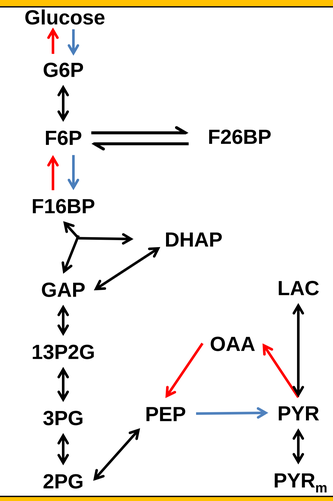
## Glucose Metabolism in Liver Cells




- Glucose transports from the blood into the cytosol
- Glucose is converted to glucose-6-phosphate, which can be converted into glycogen for storage
- The process of breaking down glucose into pyruvate is known as glycolysis, and the reverse of this process is gluconeogenesis
- Pyruvate can be transported into the mitochondria, and converted into lactate or alanine

## Detailed Glycolysis/Gluconeogenesis Pathway

- Many reactions are necessary for glycolysis or gluconeogenesis to occur
- Each reaction is catalyzed by a specific enzyme
- Glycolysis and gluconeogenesis share the same enzymes in the reversible (double arrow) steps

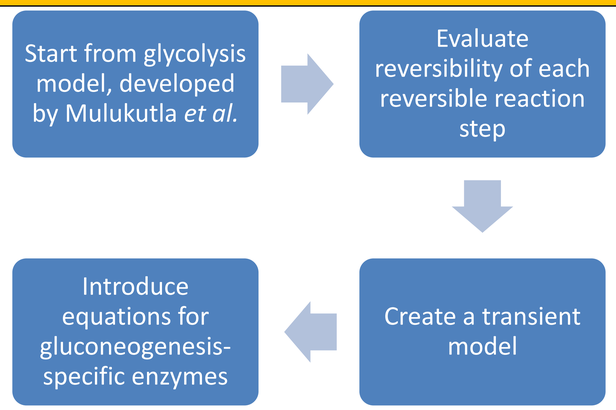



## Equations Used: Enzyme Kinetics and Mass Balance

$$\frac{dC}{dt} = \sum v_{production} - \sum v_{consumption}$$

- For each metabolite concentration, the time rate of change is determined by the total rate of production minus the total rate of consumption
- Enzyme kinetics/rates of reaction are determined by:
  - The mechanism of the enzyme catalyst
  - Concentration of substrates, products, co-factors, and allosteric regulators
  - Kinetic constants ($V_{max}$, $K_m$), determined experimentally

## Methodology – Overview

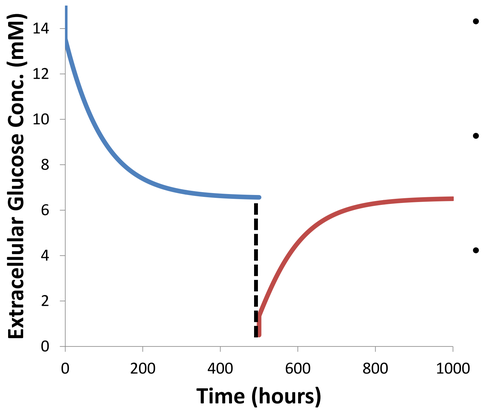



## Construction of Model

- Focus of model is how hepatocytes respond to prolonged fasting
  - Includes pathways for glycolysis and gluconeogenesis
  - Does not consider glycogen
- Model was constructed using Matlab
  - Ode23s solver used to solve the stiff system of differential equations
- Initial concentrations of metabolites were taken from the steady-state solution of the previous glycolysis model
- Cytosolic lactate concentration was fixed, representing a reservoir
- Extracellular glucose concentration was allowed to vary
- ATP, ADP, NAD, and NADH concentrations were kept constant

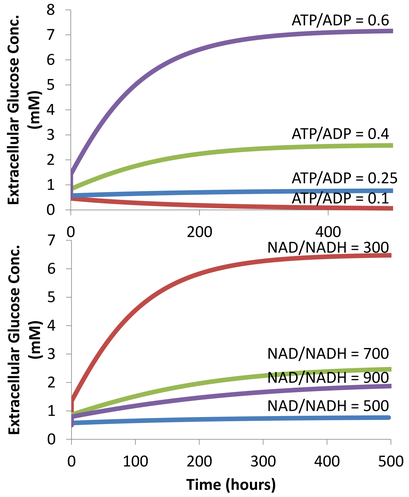
## Results

### Response to varying Extracellular Glucose



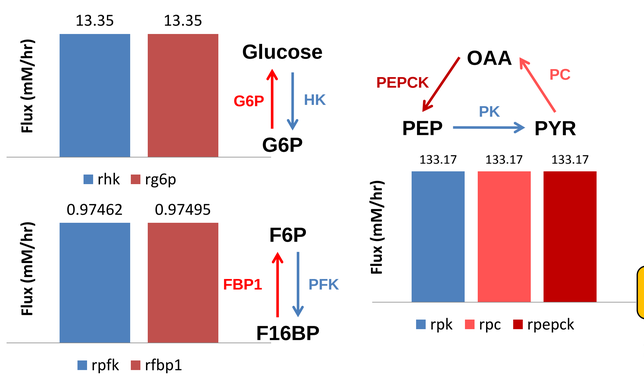

- Simulation of an elevated blood glucose level of 15 mM reached steady state through glycolysis in 500 hours
- From steady state, dropping blood glucose to 0.5 mM showed gluconeogenesis and return to steady state
- Steady state extracellular glucose was 6.5 mM
  - Within the range of normal blood glucose concentration (2-10 mM)

### Effect of ATP/ADP and NAD/NADH




- ATP/ADP ratio represents the energetic state of the cell
- At lower ATP/ADP ratios, gluconeogenesis is inhibited
- NAD/NADH ratio represents the redox state of the cell
- Mixed response to increased NAD/NADH ratio

### Fluxes of Enzymes in Futile Cycles




- Futile cycles occur when antagonistic enzymes operate simultaneously
- Result: little to no net flux, energy is wasted
- Other regulatory mechanisms should be considered to prevent this (e.g., phosphorylation of enzymes)

## Conclusion

The combined model, containing pathways for both glycolysis and gluconeogenesis, showed homeostatic response to changes in extracellular glucose. However, model can not yet be used to predict hepatocyte glycose metabolism, due to slow response. Possible future improvements include variable ATP/ADP concentrations and regulation to prevent futile cycles.

## References

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