Models of Glucose Metabolism and Control in Diabetes

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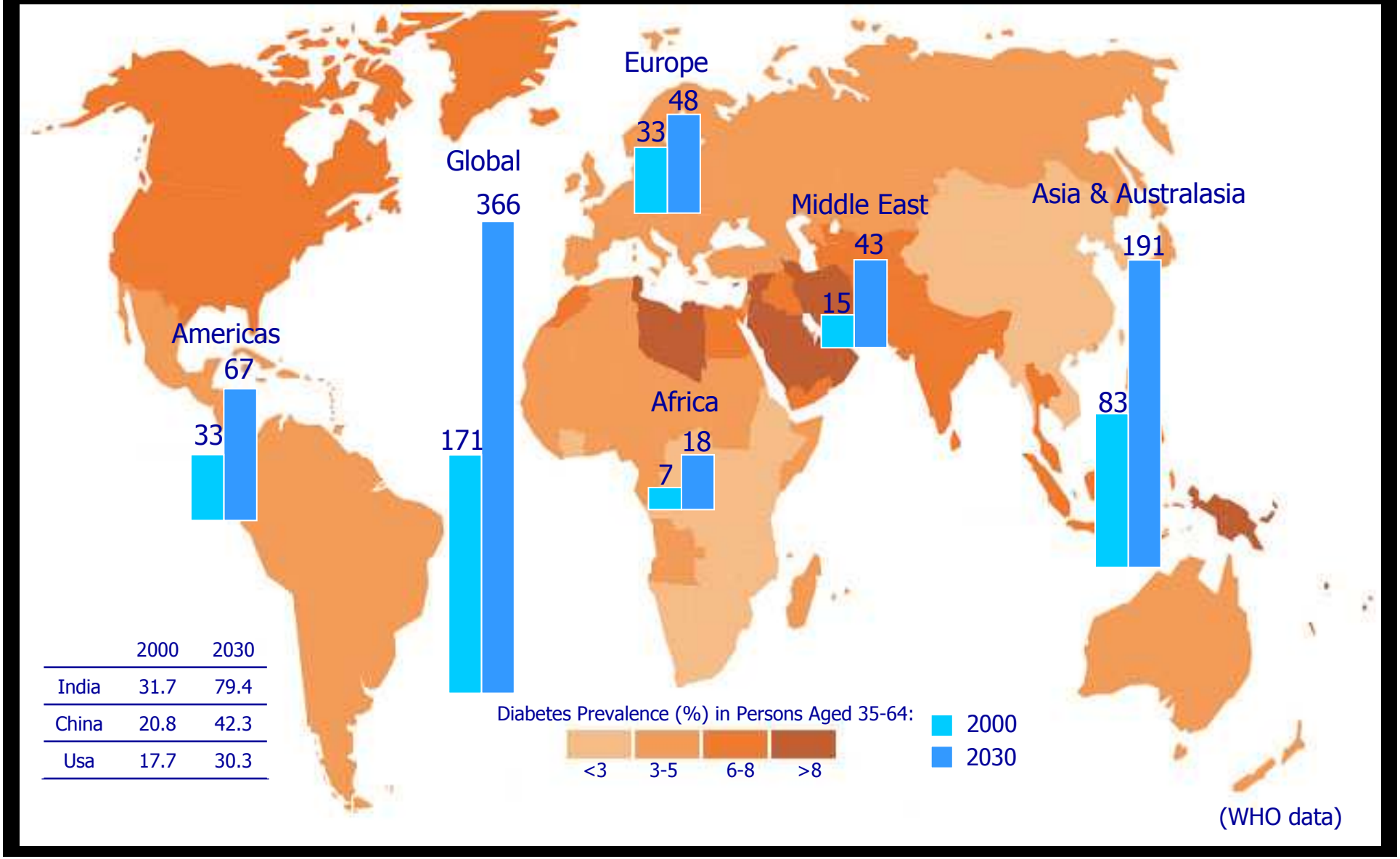
Department of Information Engineering
University of Padua, Italy

PAGE, Copenhagen, Denmark, 2007

The Diabetes World Epidemic

Millions with Diabetes 2000-2030



	2000	2030
India	31.7	79.4
China	20.8	42.3
Usa	17.7	30.3

American Diabetes Association

President, Medicine & Science Address

Robert Rizza, MD

66th ADA, June 9-13 2006, Washington, D.C.

The Problem

- 20 million people in the U.S. have diabetes
- 40 million people in the U.S. have prediabetes
- Diabetes costs the U.S. $132 billion per year
- Diabetes consumes 1 in 10 healthcare dollars
- Diabetes consumes 1 in 4 Medicare dollars

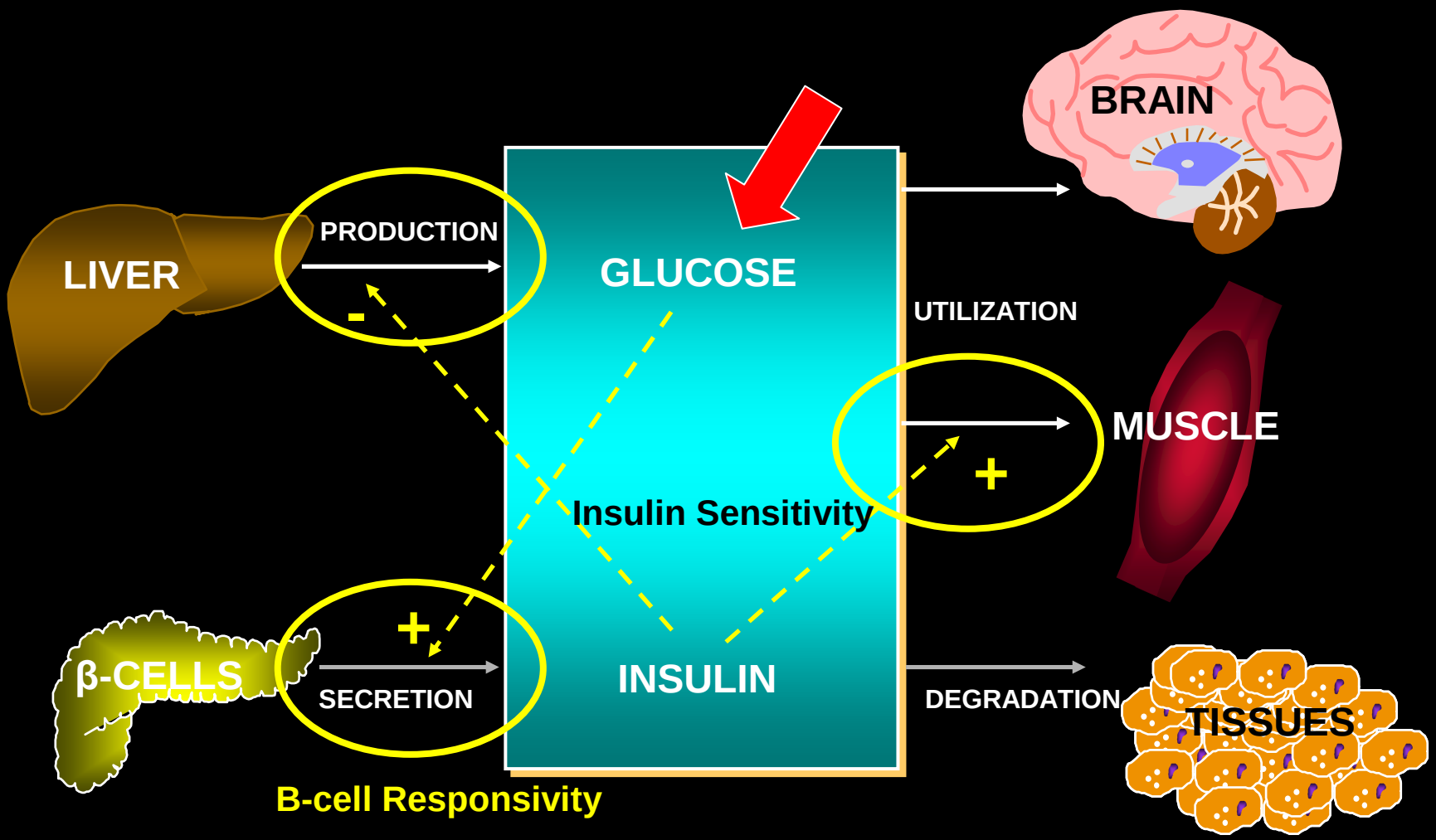
Diabetes:

- **#1 cause of new cases of blindness in adults**
- **#1 cause of end stage renal disease**
- **#1 cause of non-traumatic amputations**
- **#1 cause of neuropathy in adults**
- **And with prediabetes is present in two thirds of people who have had a heart attack**

Unless we do something to stop it

- 1 in 3 children born in the U.S. in the year 2000 will develop diabetes during their lifetime
- 1 in 2 children in high risk groups will develop diabetes in their lifetime
- Within the next 25 years a diabetes epidemic will occur in virtually every country in the world

The Glucose-Insulin System

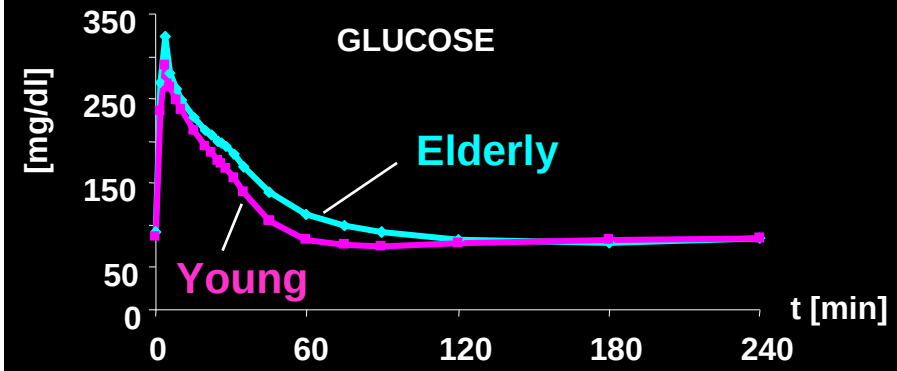


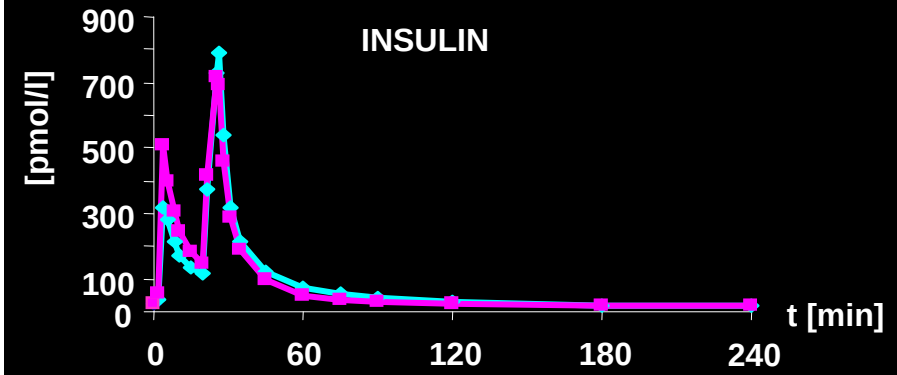
- **Models to Measure**
  - Whole Body
  - Organ/Tissue
- **Models to Simulate**
  - In Silico Whole-Body

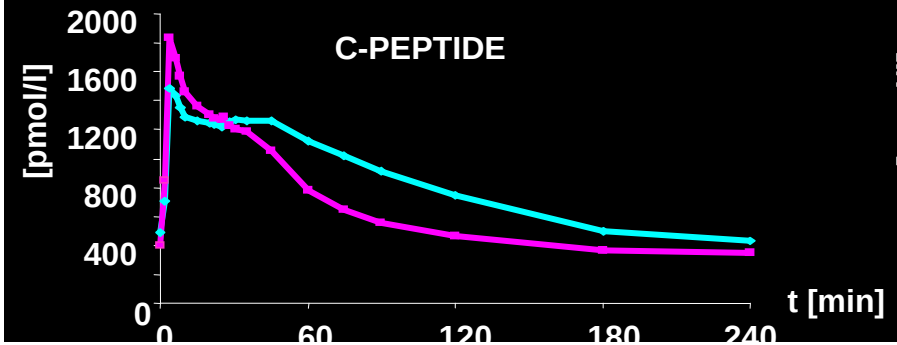
Young vs Elderly Subjects

N = 59 vs 145 (Basu et al, 2006)

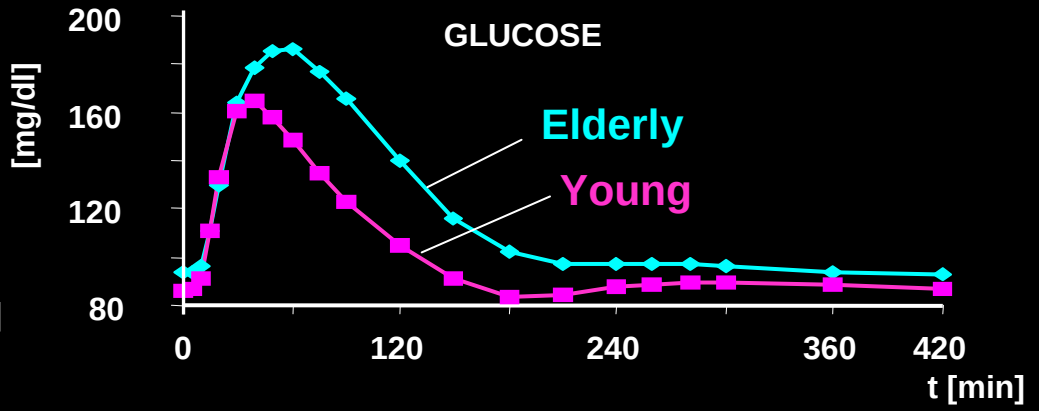
IVGTT

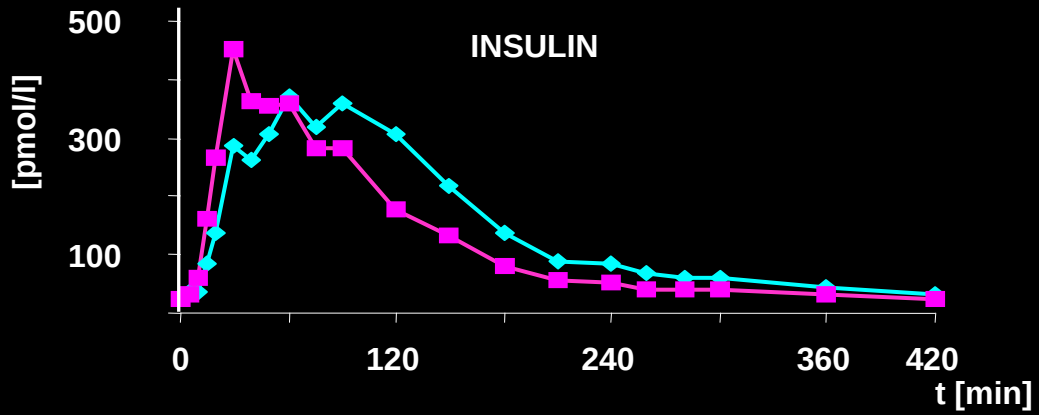


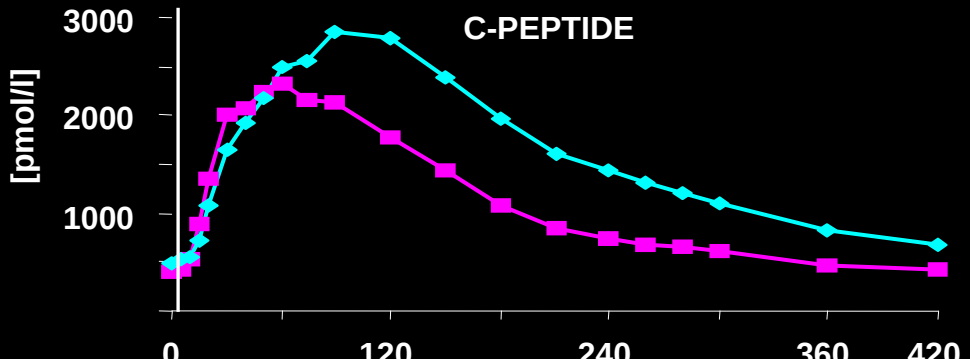




MEAL

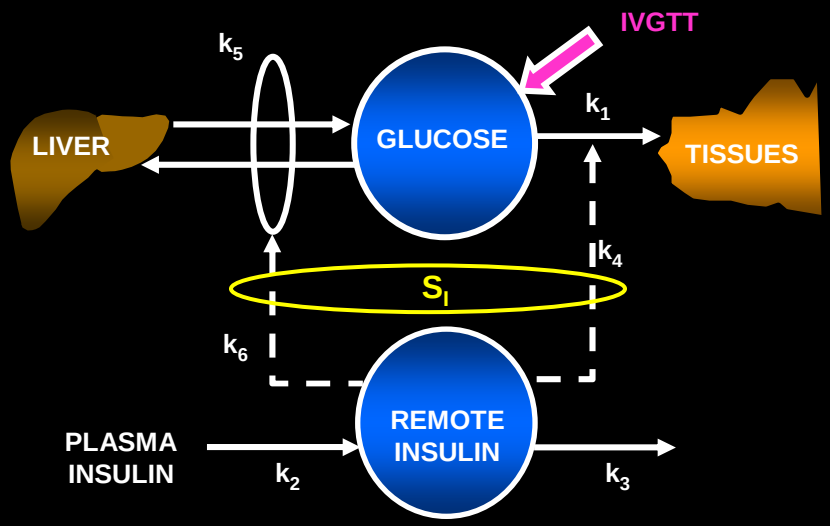




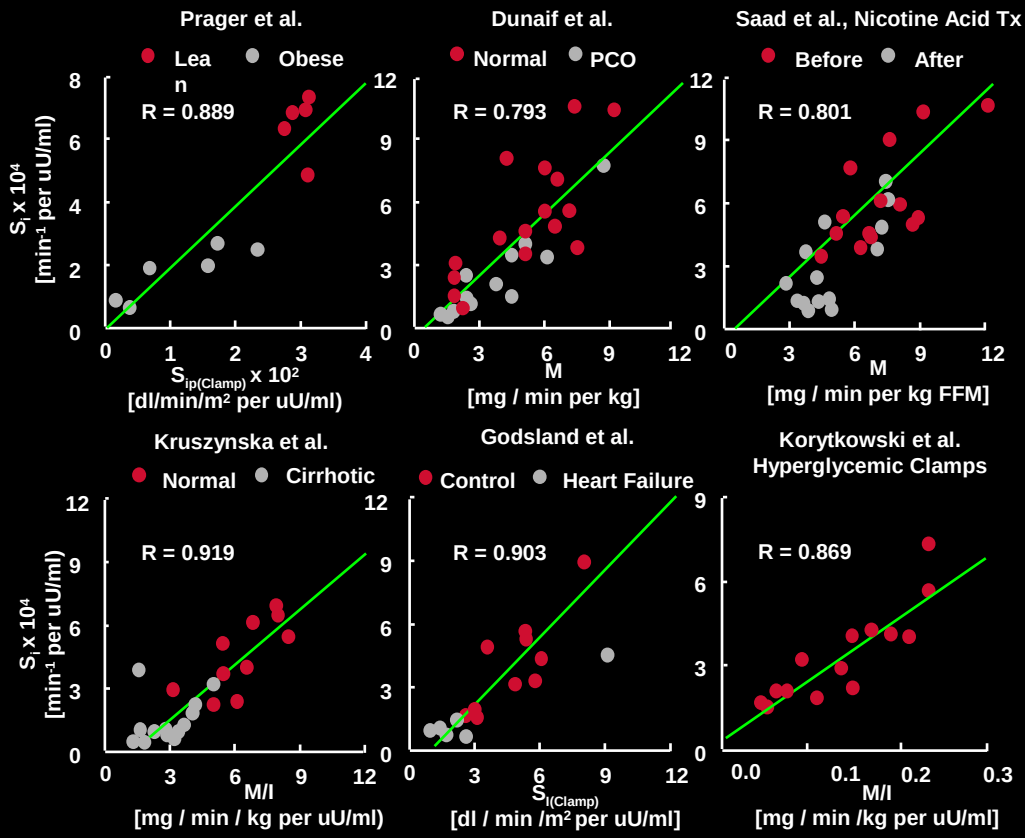


IVGTT Glucose Minimal Model

(Bergman & Cobelli, 1979)



S_I: Insulin Sensitivity (liver & periphery)



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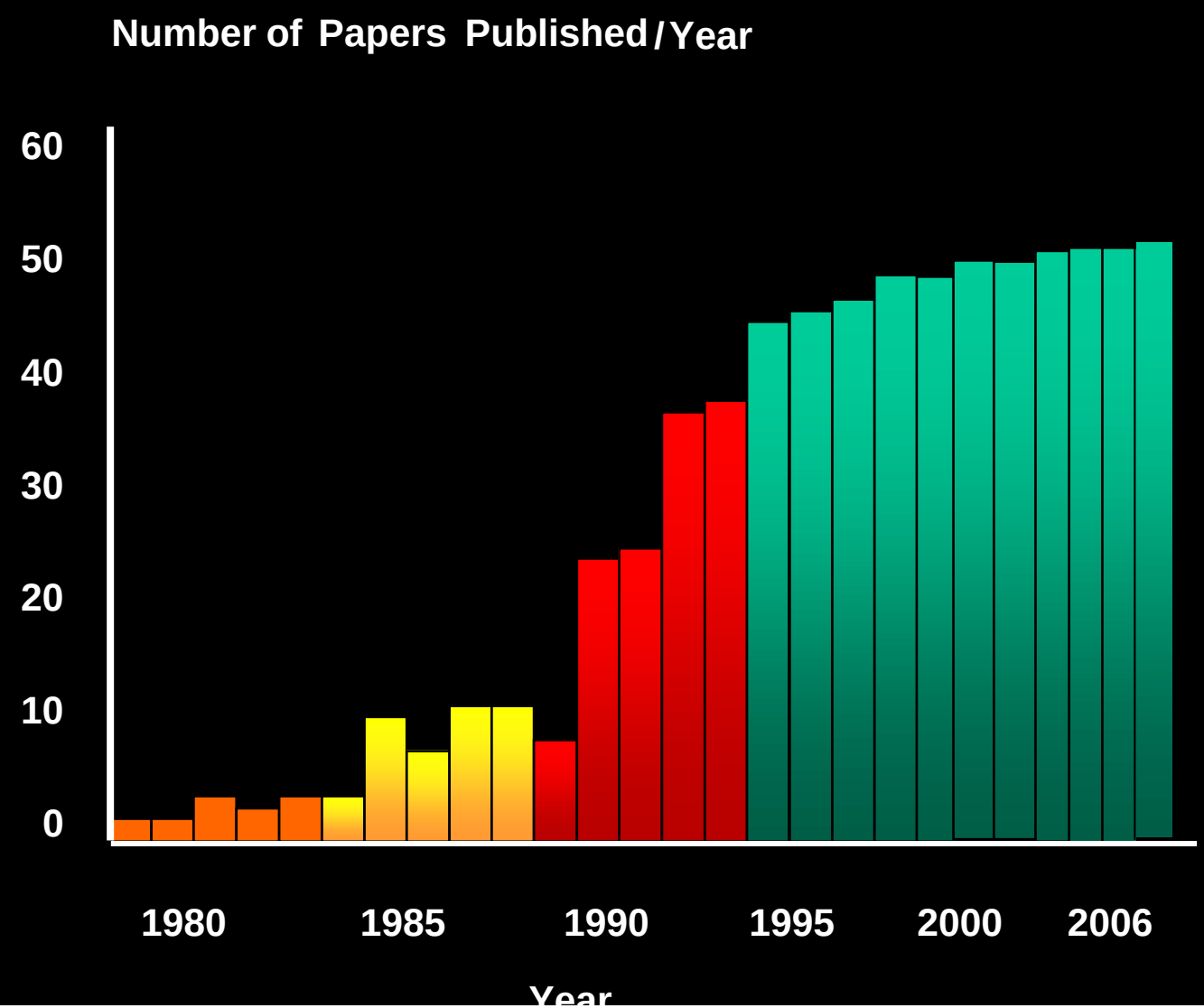
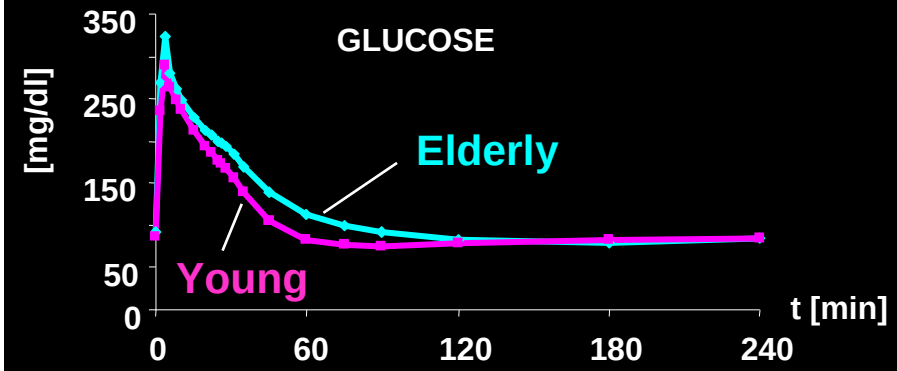
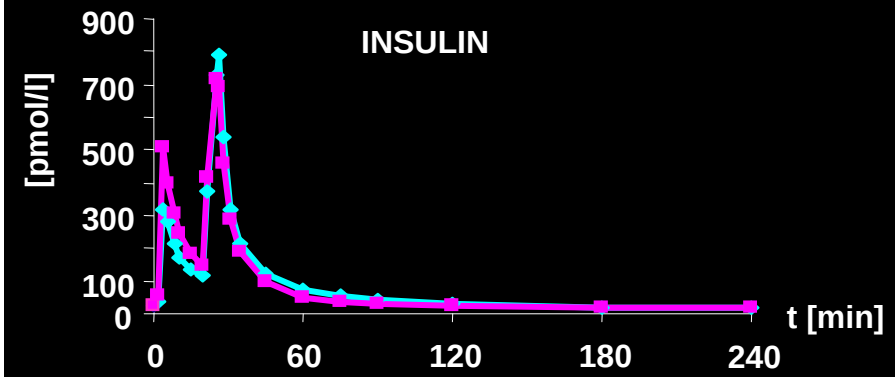


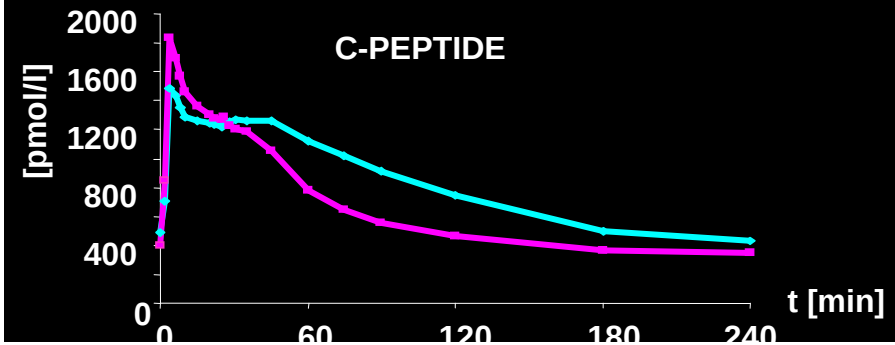
Young vs Elderly Subjects

N = 59 vs 145 (Basu et al, 2006)

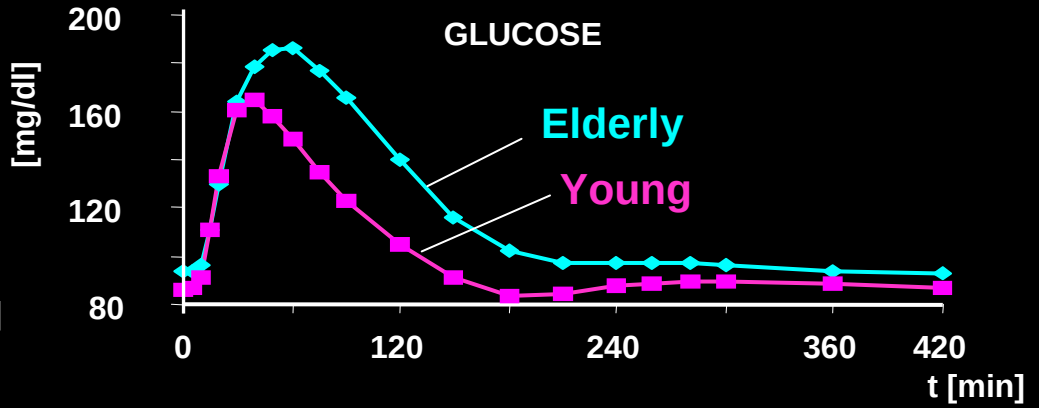
IVGTT

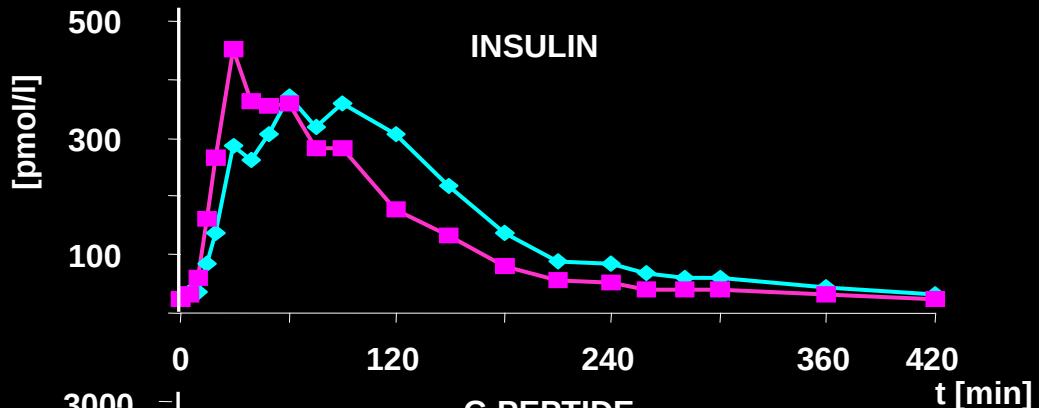


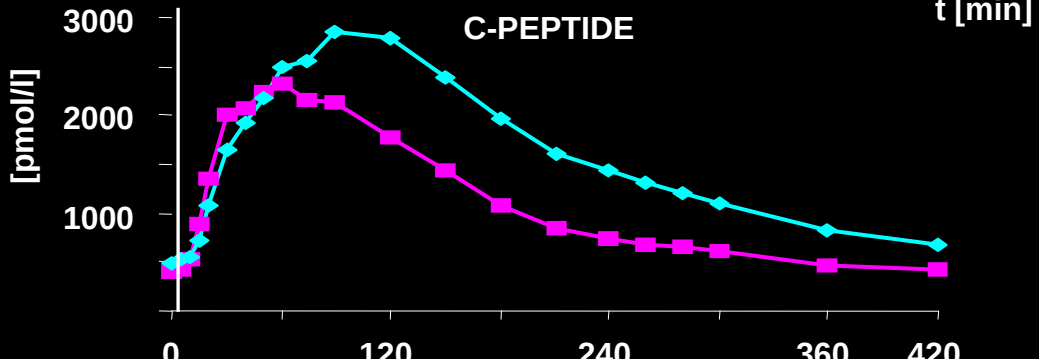




MEAL

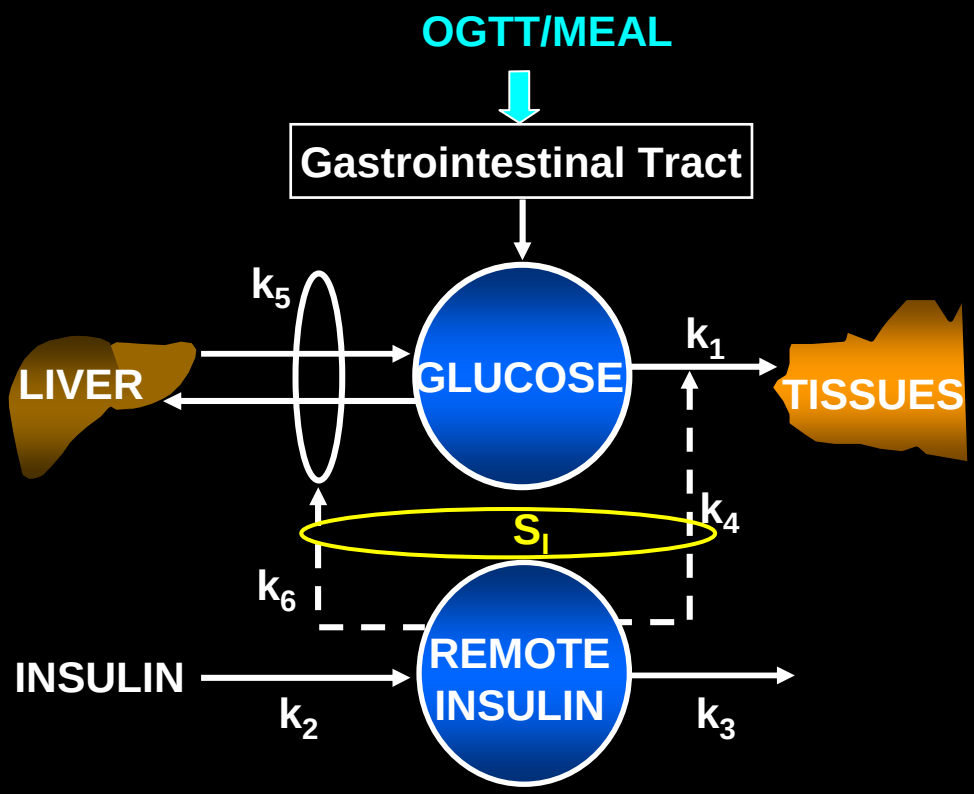






Oral Glucose Minimal Model

(Dalla Man & Cobelli, 2002)



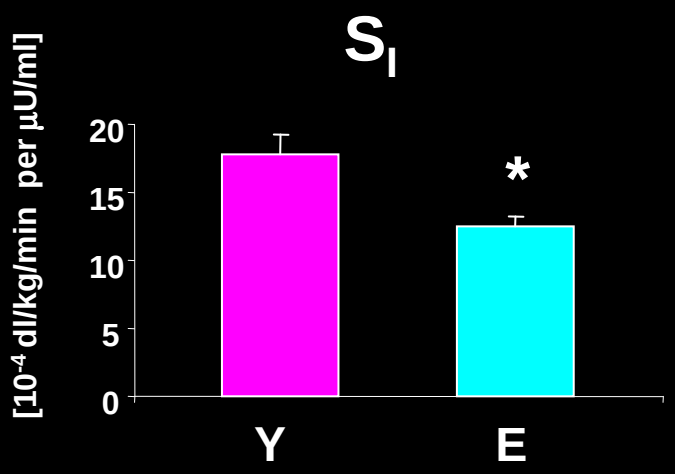
S_I: Insulin Sensitivity (liver & periphery)

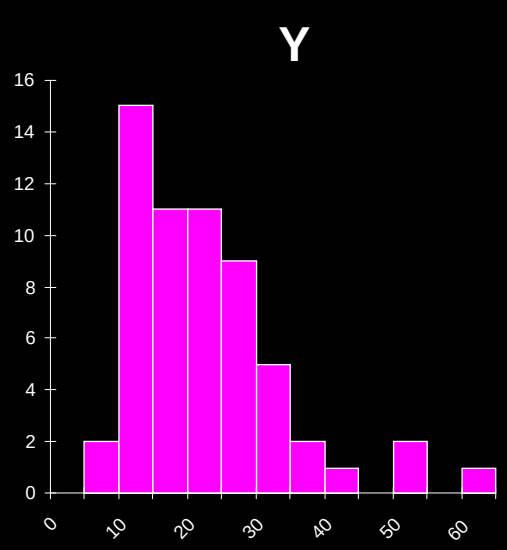
Validation: - Triple Tracer Meal (Dalla Man et al, 2004)
- Hyperinsulinemic Clamp (Dalla Man et al, 2005)

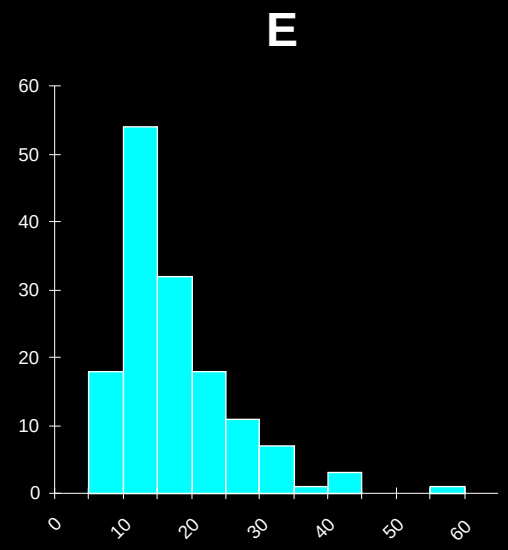
Insulin Sensitivity

59 Y vs 145 E

* p<0.05

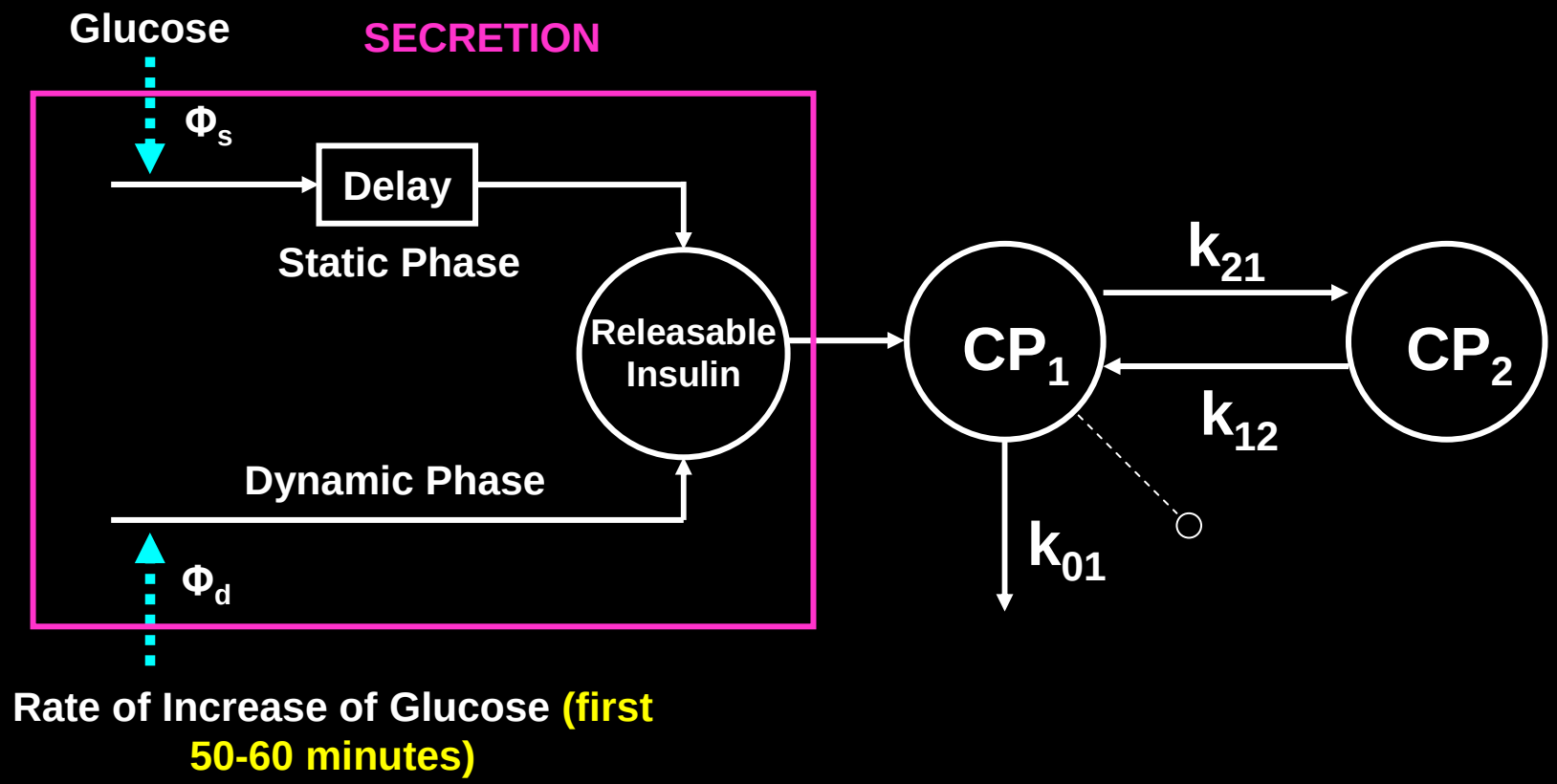






β-Cell Responsivity Minimal Model

(Toffolo et al, 2001; Breda et al, 2001, 2002)



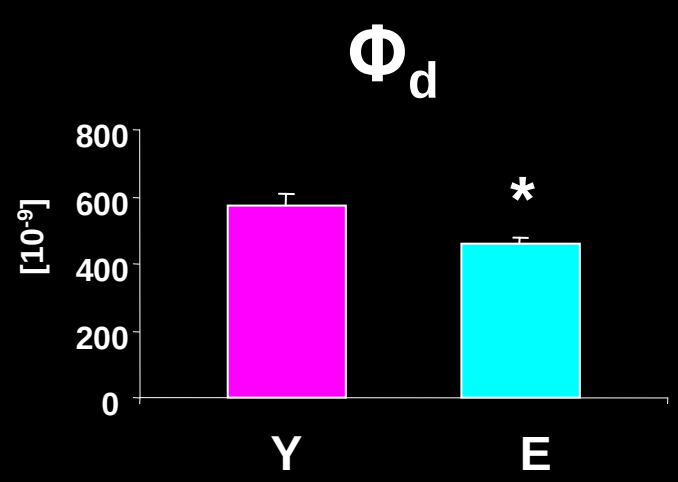
Φ_d: Dynamic Beta-Cell Responsivity

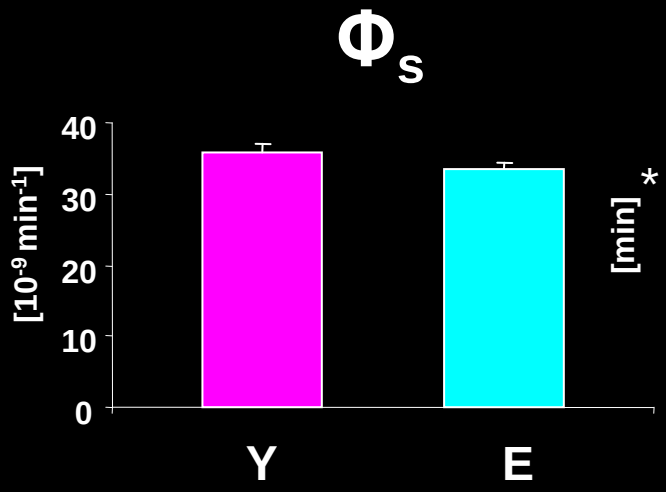
Φ_s: Static Beta-Cell Responsivity

Validation: Hyperglycemic Clamp (Steil et al, 2004)

β-Cell Responsivity Indices

59 Y vs 145 E





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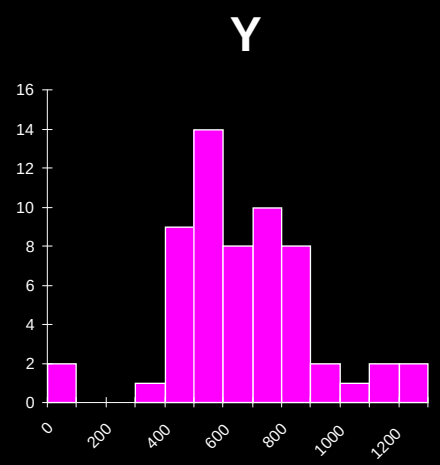
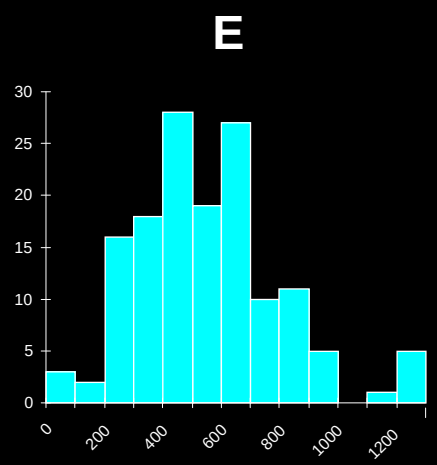
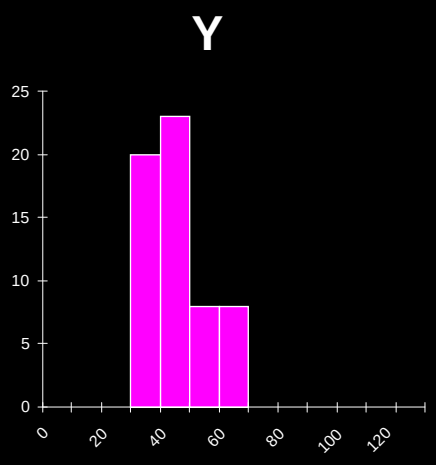
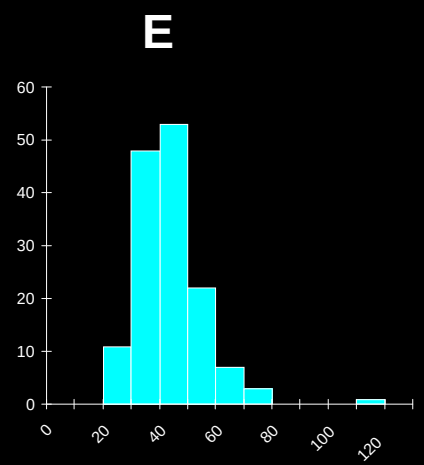
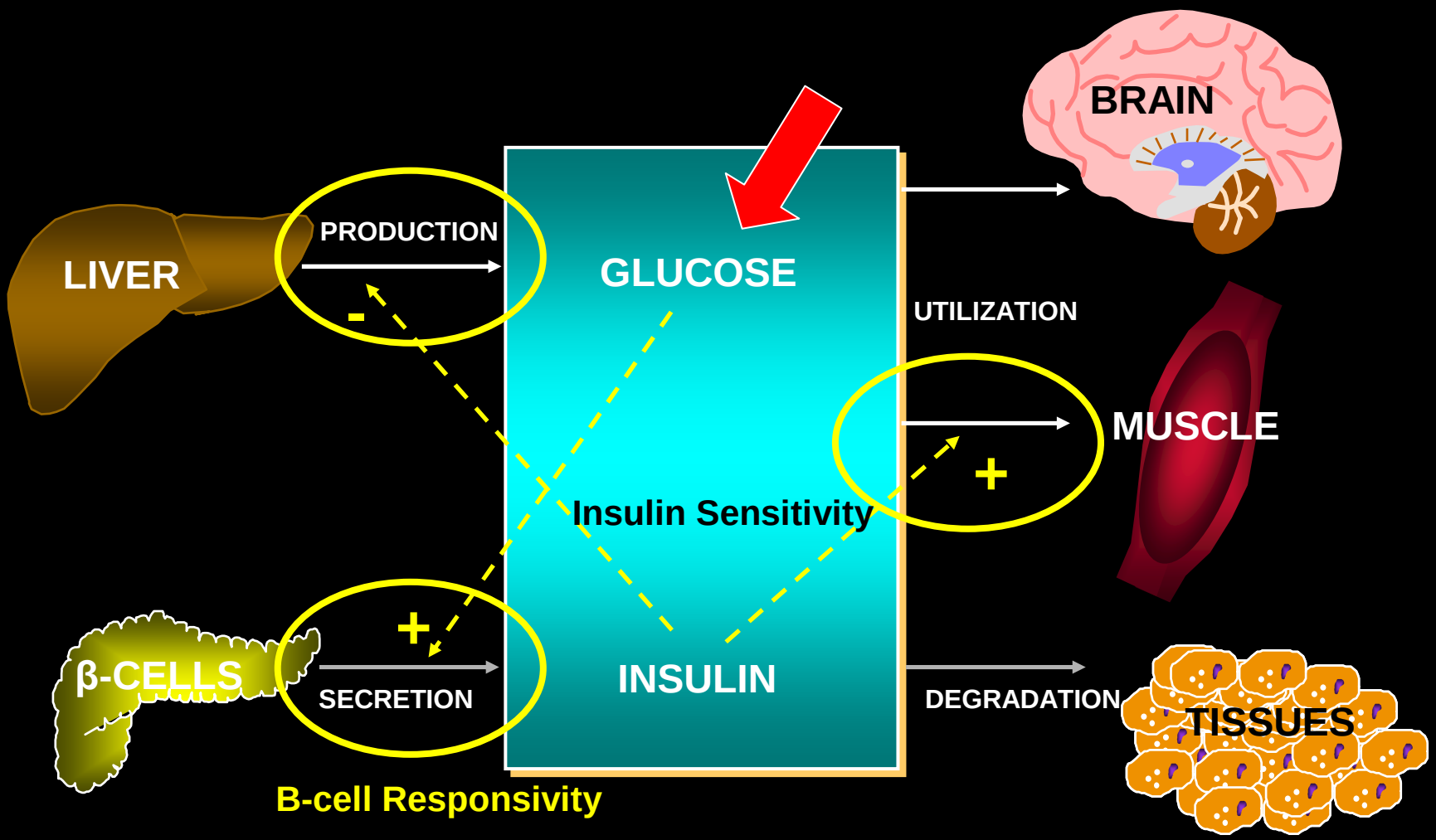








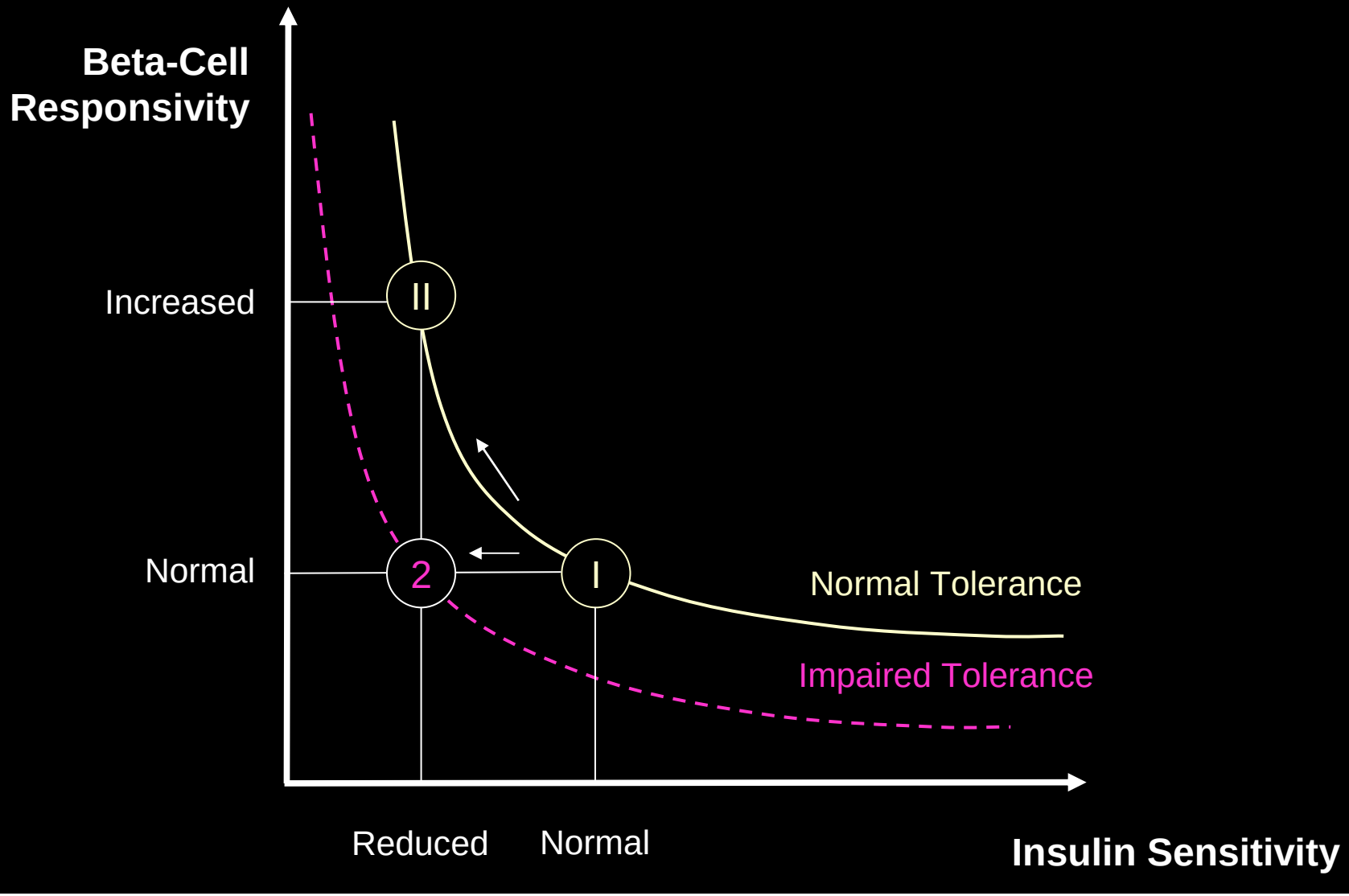
The Glucose-Insulin System



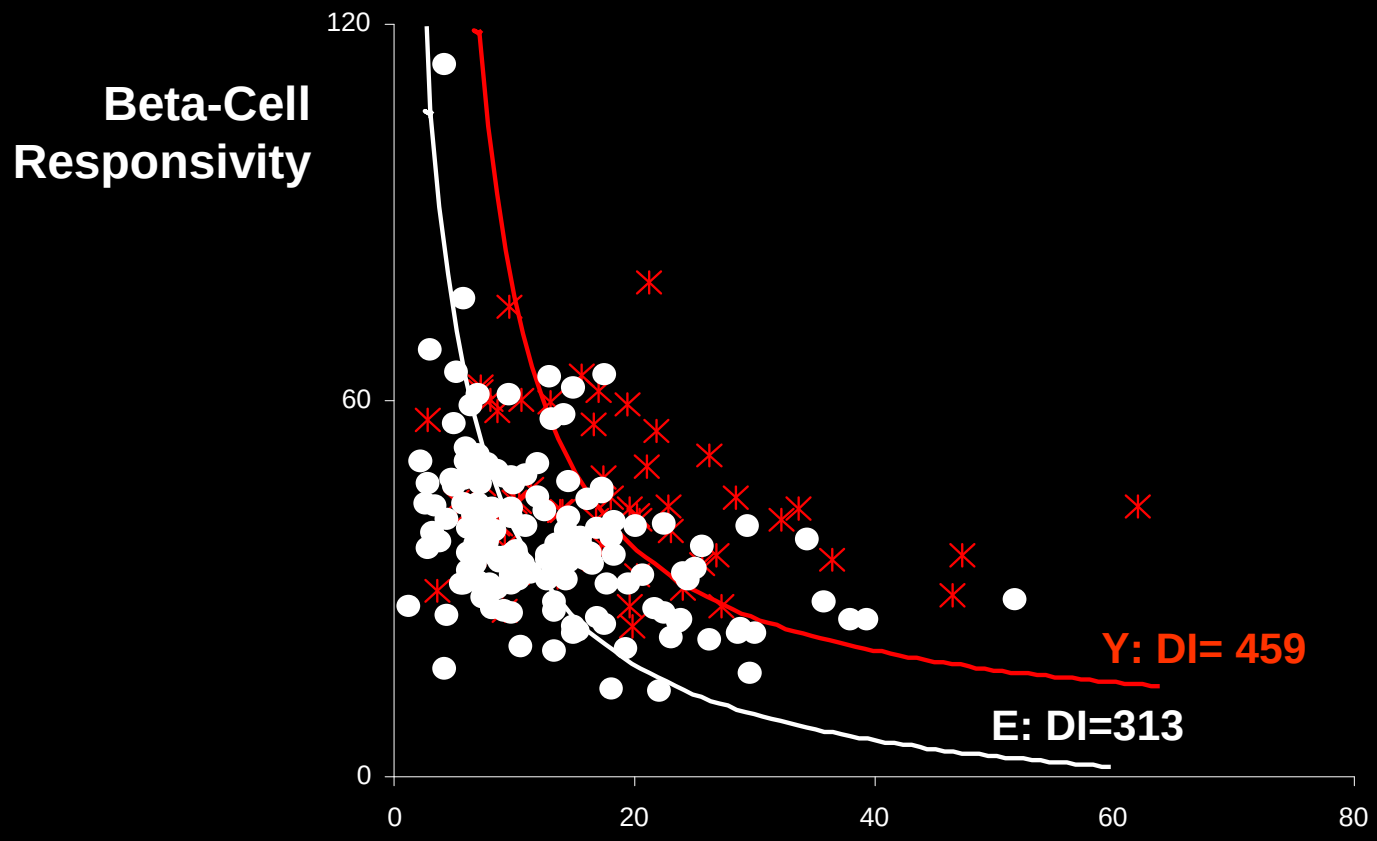
Efficiency of the Control: Disposition Index

(Bergman & Cobelli, 1981, Cobelli et at, 2007)

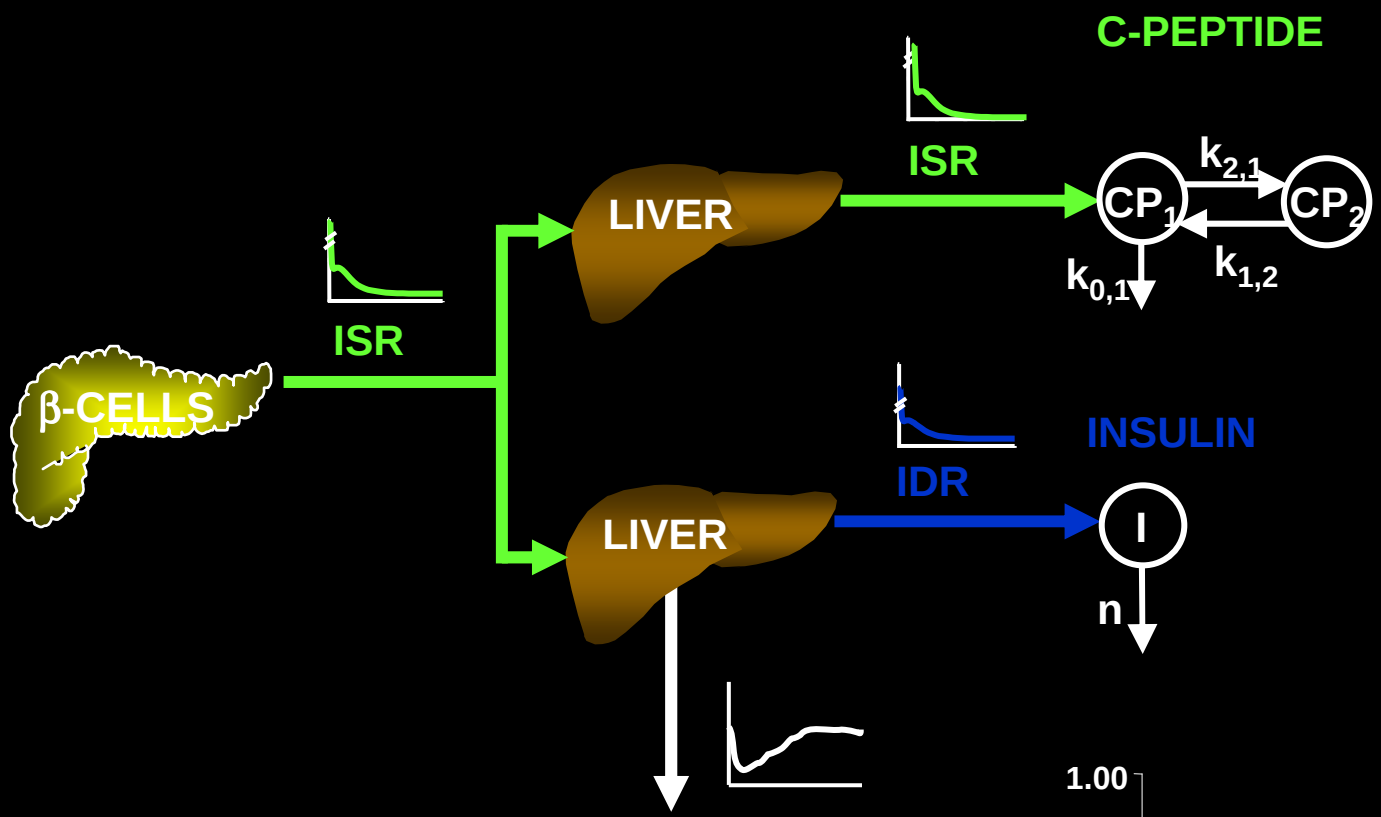
Insulin Sensitivity x Beta-Cell Function= Constant



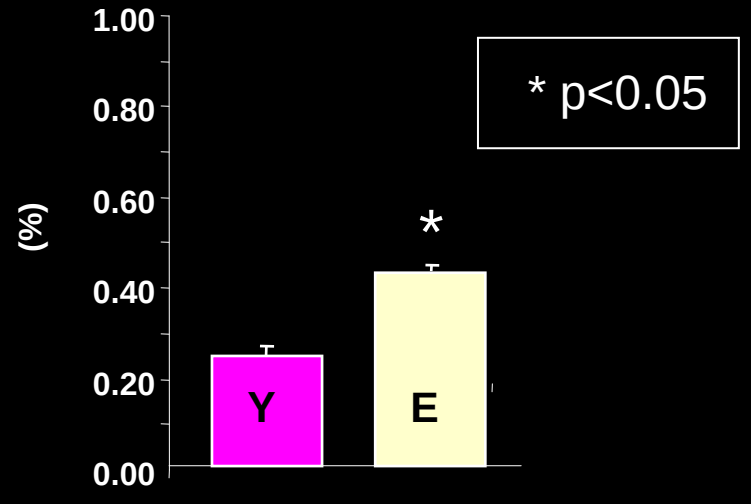
Disposition Index



Hepatic Insulin Extraction

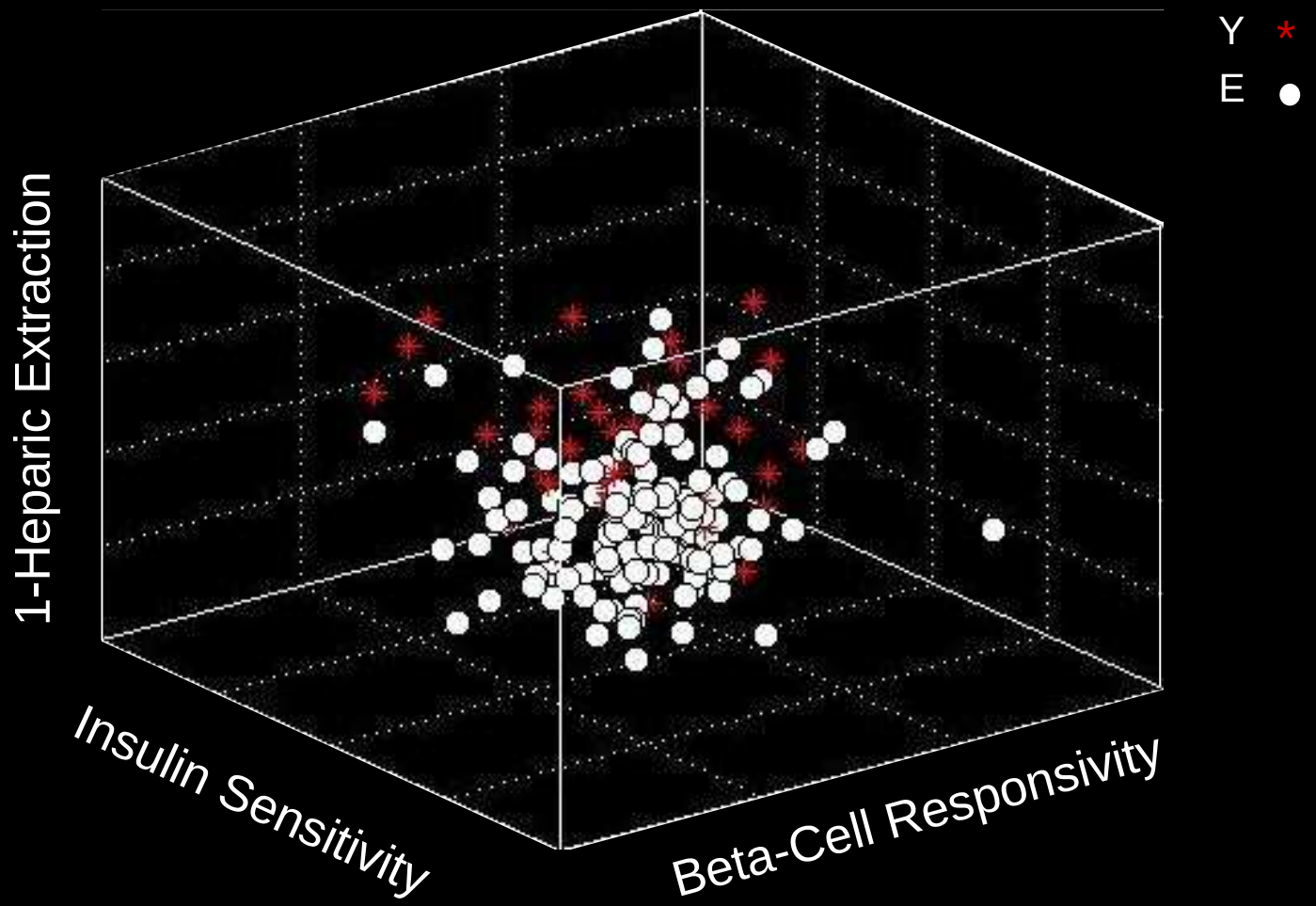


$$HE = \frac{\int_0^T ISR(t)dt - \int_0^T IDR(t)dt}{\int_0^T ISR(t)dt}$$



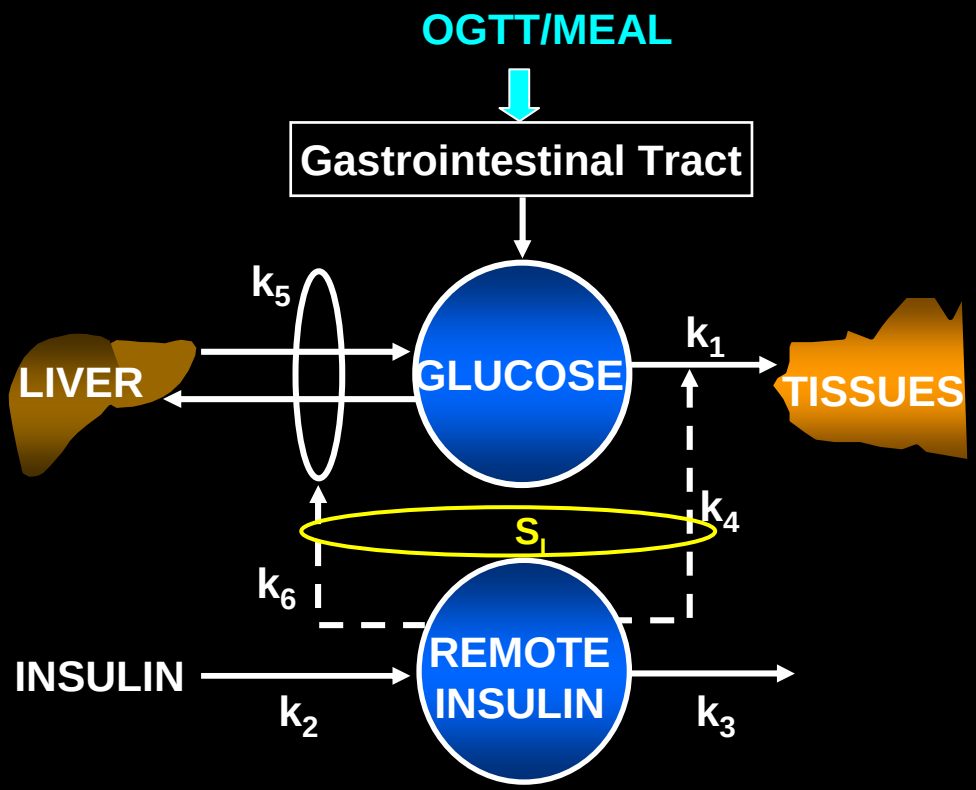
Disposition Index

From 2 to 3D



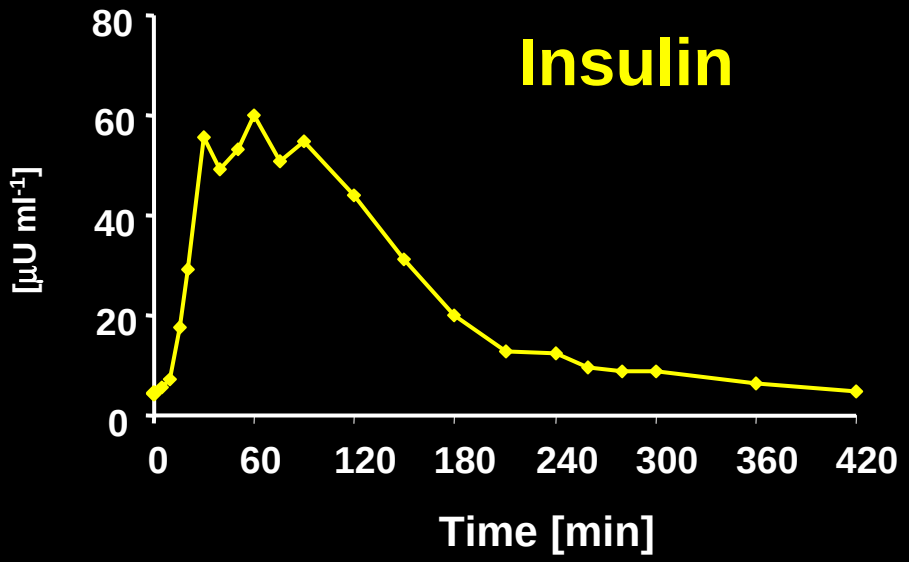
Oral Glucose Minimal Model

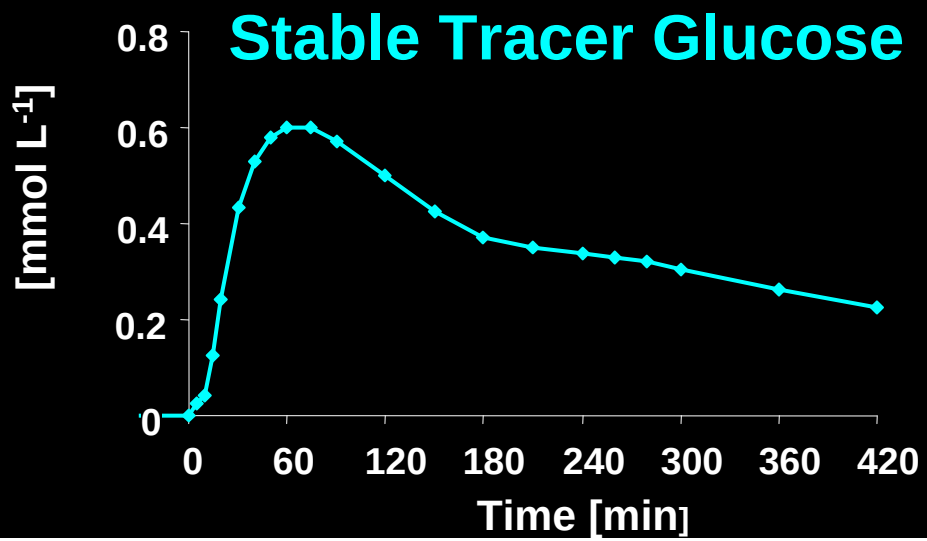
(Dalla Man & Cobelli, 2002)



S_I: Insulin Sensitivity (liver & periphery)

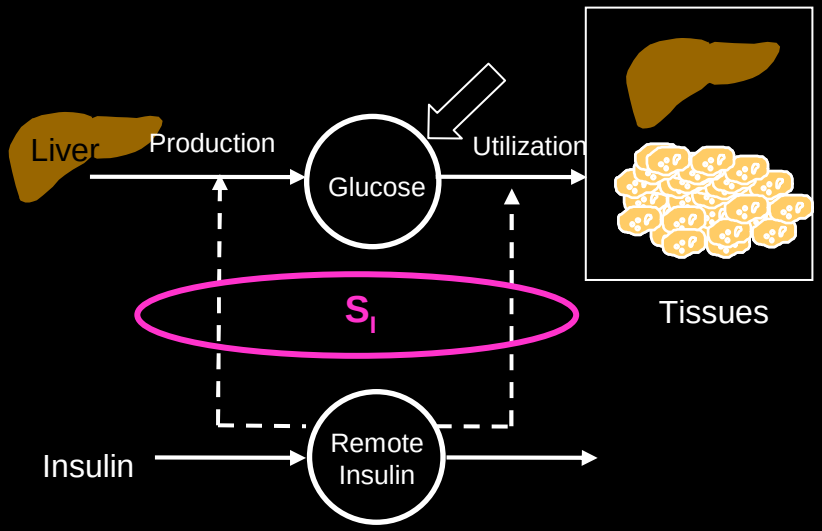
Labelled Meal



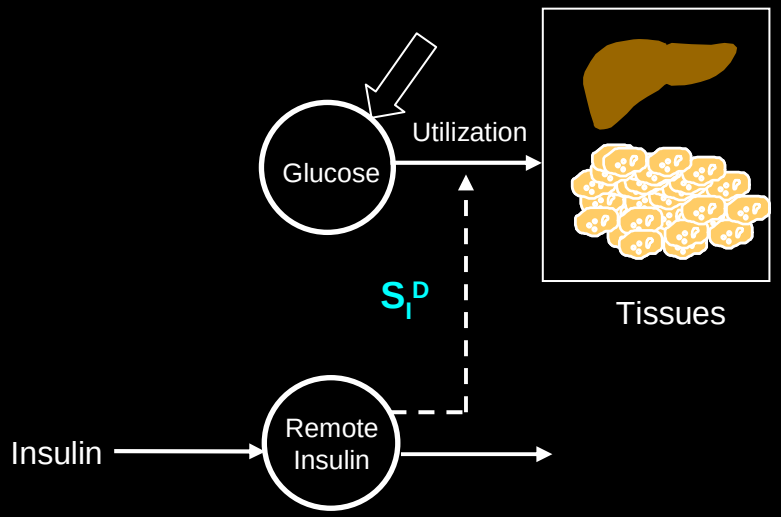


Disposal Insulin Sensitivity

“COLD” MINIMAL MODEL



“HOT” MINIMAL MODEL



S_I: Insulin Sensitivity

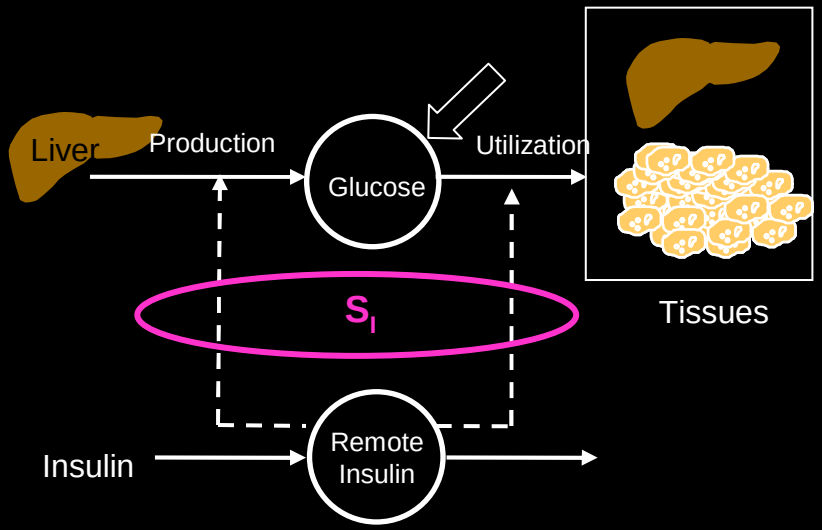
(Utilization + Production)

S_I^D: Disposal Insulin Sensitivity

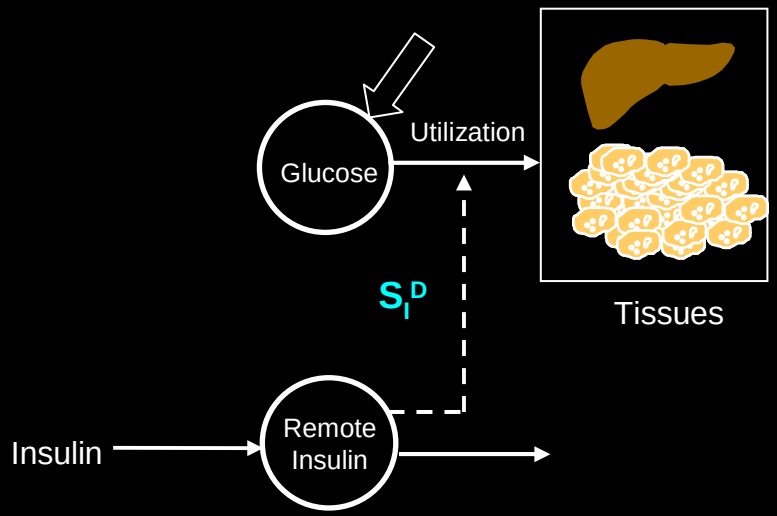
(Utilization Only)

Hepatic Insulin Sensitivity

“COLD” MINIMAL MODEL

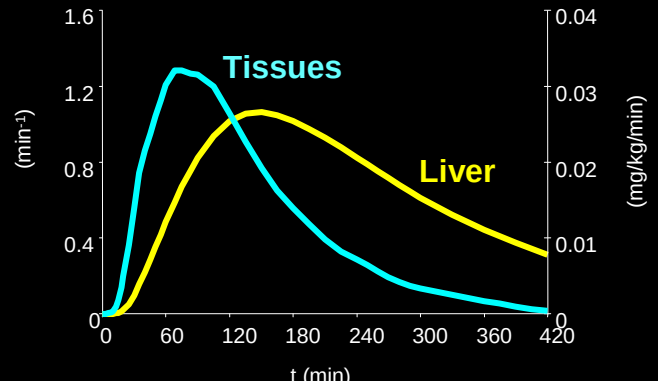


“HOT” MINIMAL MODEL

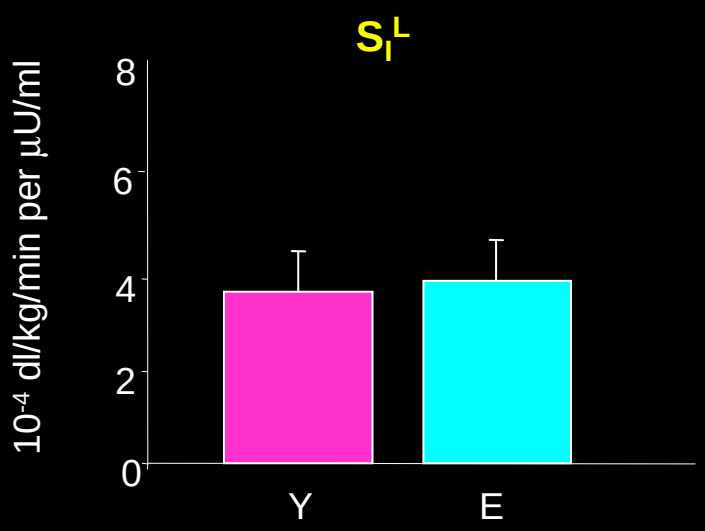


From S_I and S_I^D ⟶ $S_I^L = S_I - S_I^D$

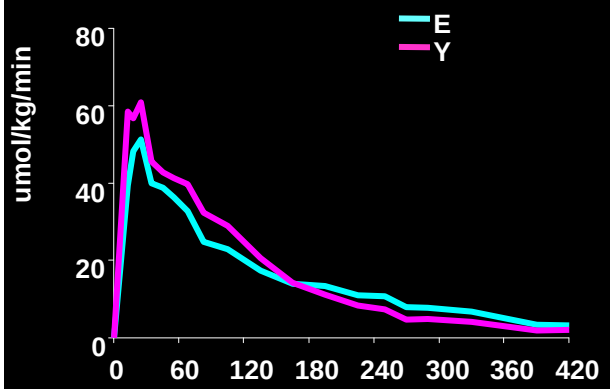
Remote Insulin



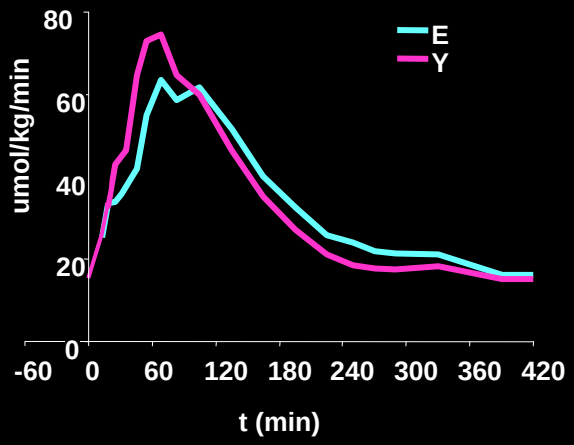
Labelled Meal: Additional Information



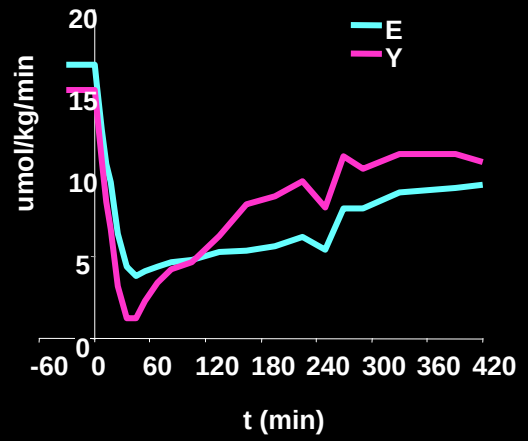
Rate of Appearance



Rate of Disappearance



Endogenous Production



Use in Pathophysiology

1) **Role of age and gender** (Basu et al, **Diabetes** 2006)

2) **Pathogenesis of Prediabetes** (Bock et al, **Diabetes** 2006)

3) **OGTT vs Meal** (Bock et al, **Diabetes** 2007)

4) **Diurnal Variation of Glucose Tolerance** (Dr. E. Van Cauter, University of Chicago, Chicago, IL)

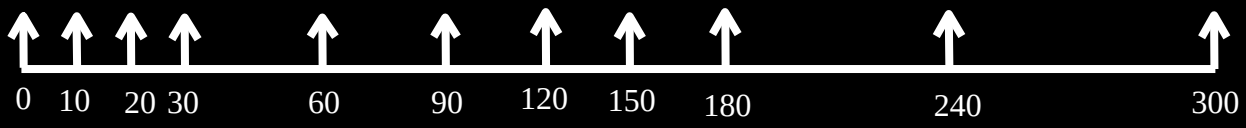
5) **Role of Race** (Petersen et al, **Proceedings of the National Academy of Science** 2006)

6) **Children and Adolescent** (Dr. S. Caprio, Yale University, New Haven, CT)

OGTT Protocol

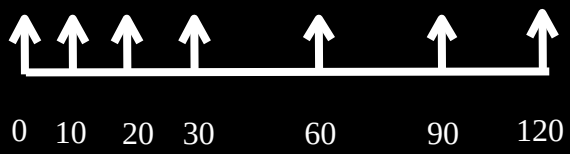
FULL

300 min – 11 samples



REDUCED

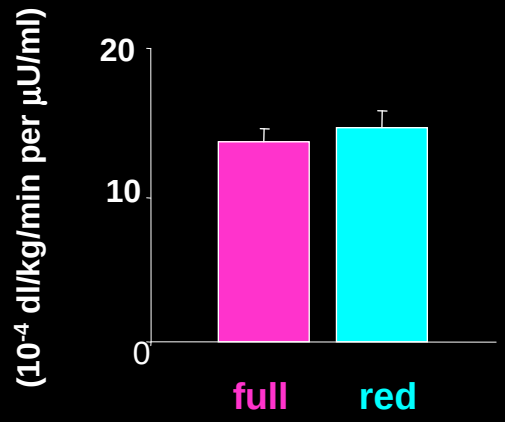
120 min – 7 Samples

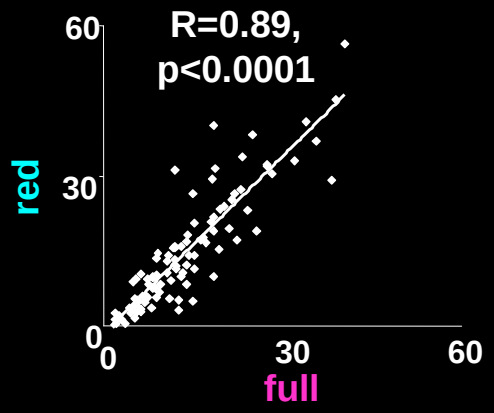


OGTT

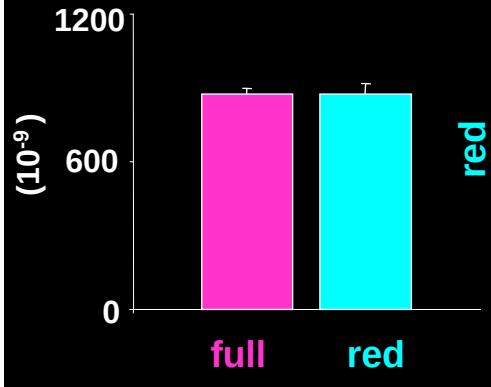
(N=100)

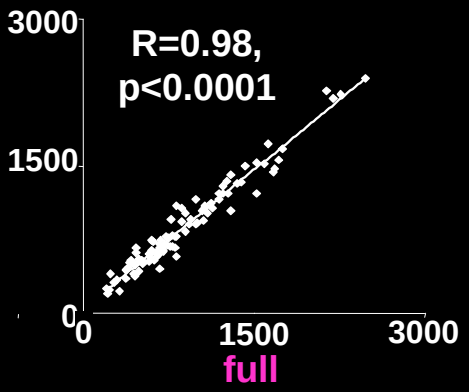
SI



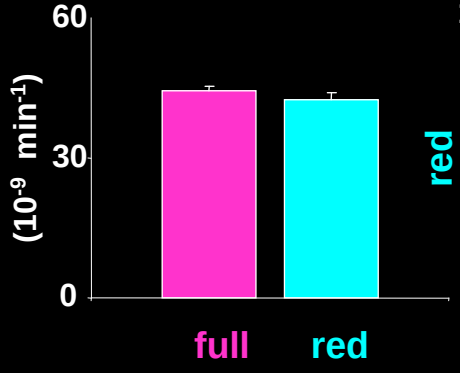


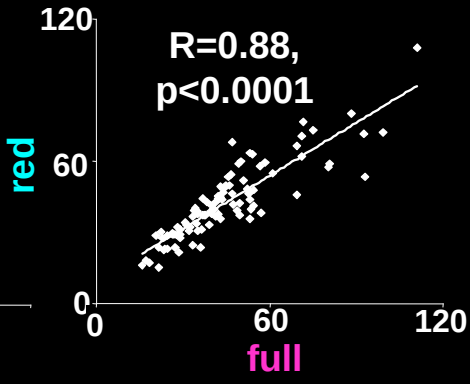
Φ_d





Φ_s





Use in Pathophysiology

1) **Role of age and gender** (Basu et al, **Diabetes** 2006)

2) **Pathogenesis of Prediabetes** (Bock et al, **Diabetes** 2006)

3) **OGTT vs Meal** (Bock et al, **Diabetes** 2007)

4) **Diurnal Variation of Glucose Tolerance** (Dr. E. Van Cauter, University of Chicago, Chicago, IL)

5) **Role of Race** (Petersen et al, **Proceedings of the National Academy of Science** 2006)

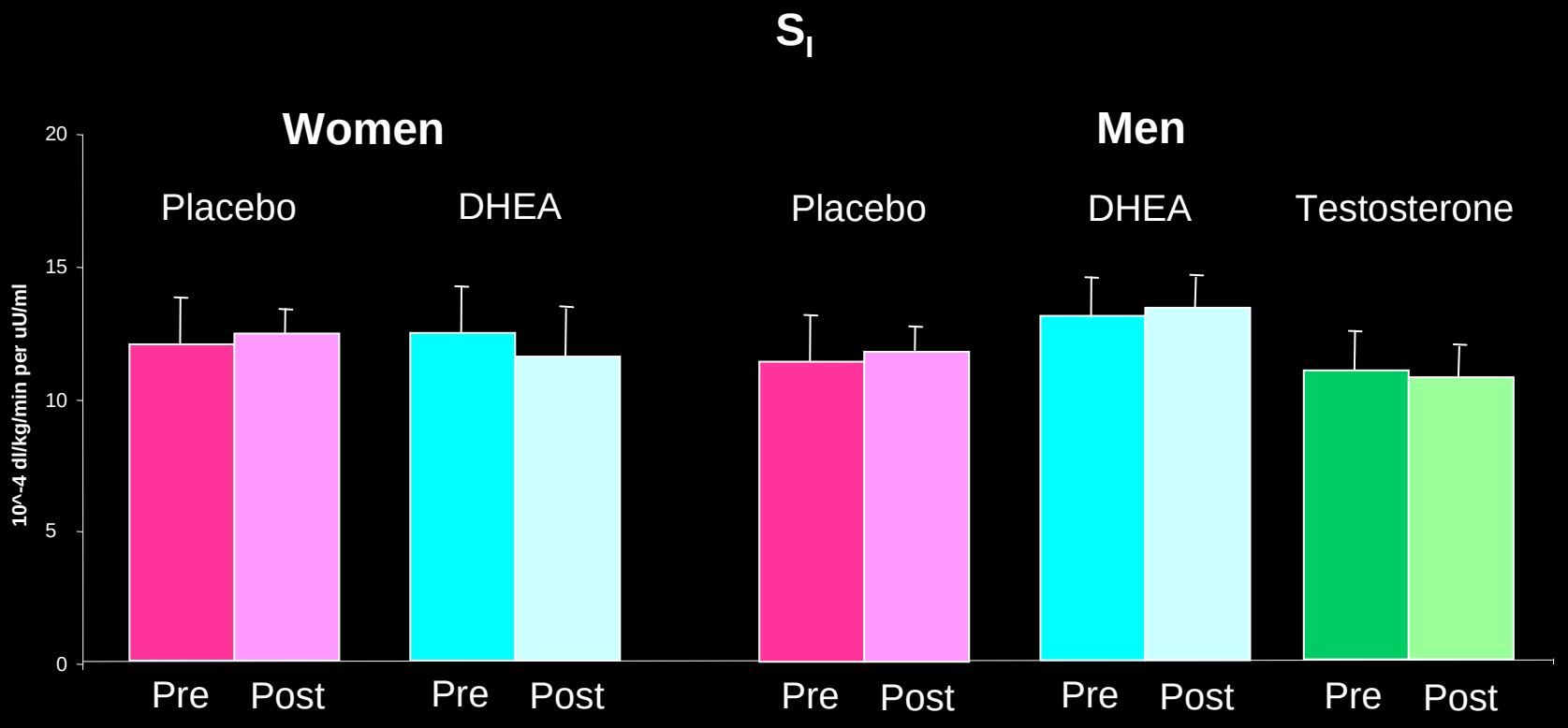
6) **Children and Adolescent** (Dr. S. Caprio, Yale University, New Haven, CT)

7) **Efficiency of Anti-aging Drugs** (Nair et al, **New England Journal of Medicine** 2006)

Efficiency of Anti aging Drug

- 87 elderly men e 57 elderly women underwent a mixed meal test

- After a 2 yr DHEA or Testosterone same test



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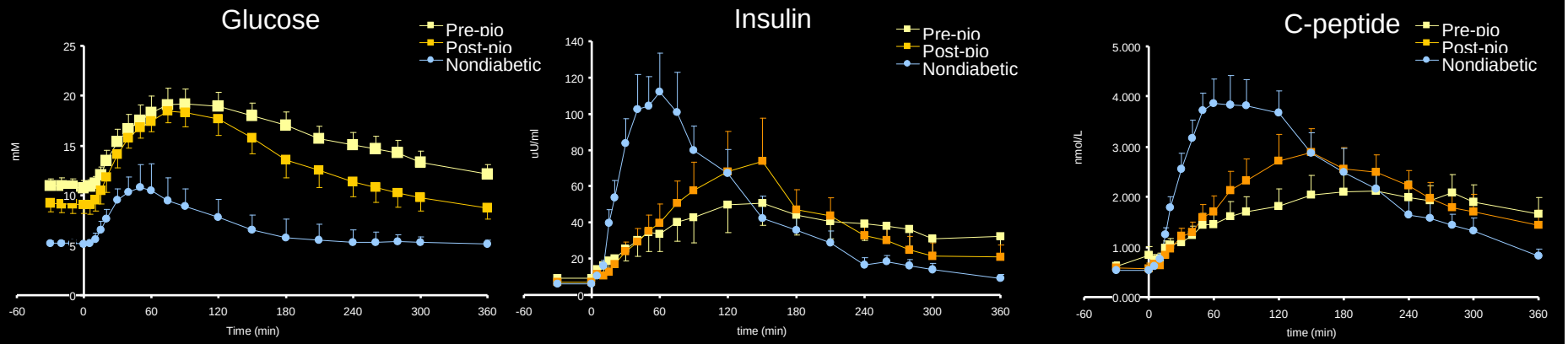
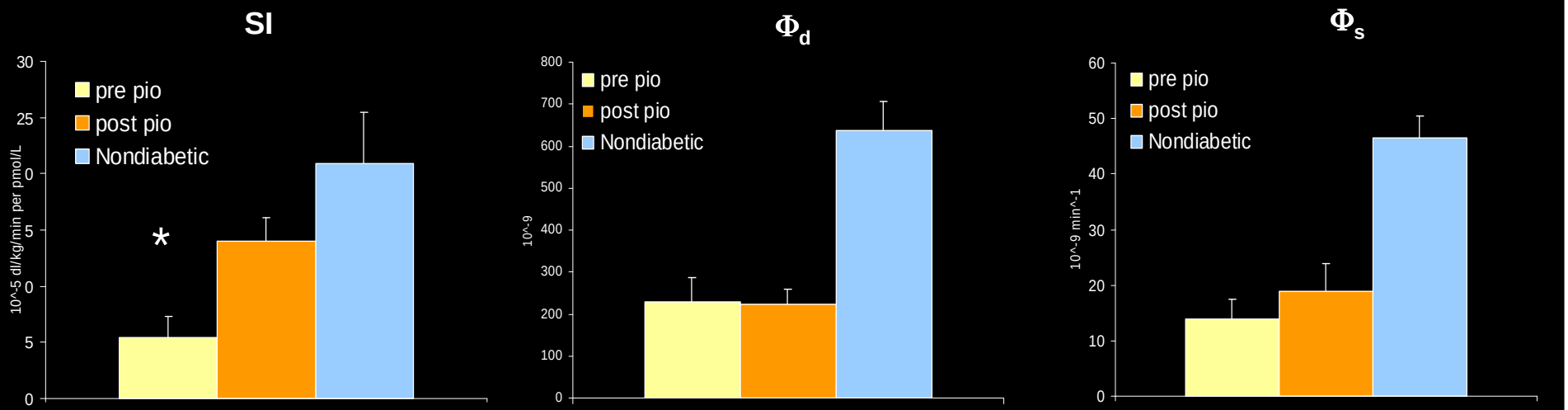
8) **Type 2 Diabetes** (Dr. A. Basu, Mayo Clinic Rochester, MN)

Type 2 Diabetes: Effect of Pioglitazone

(Basu A. et al submitted)



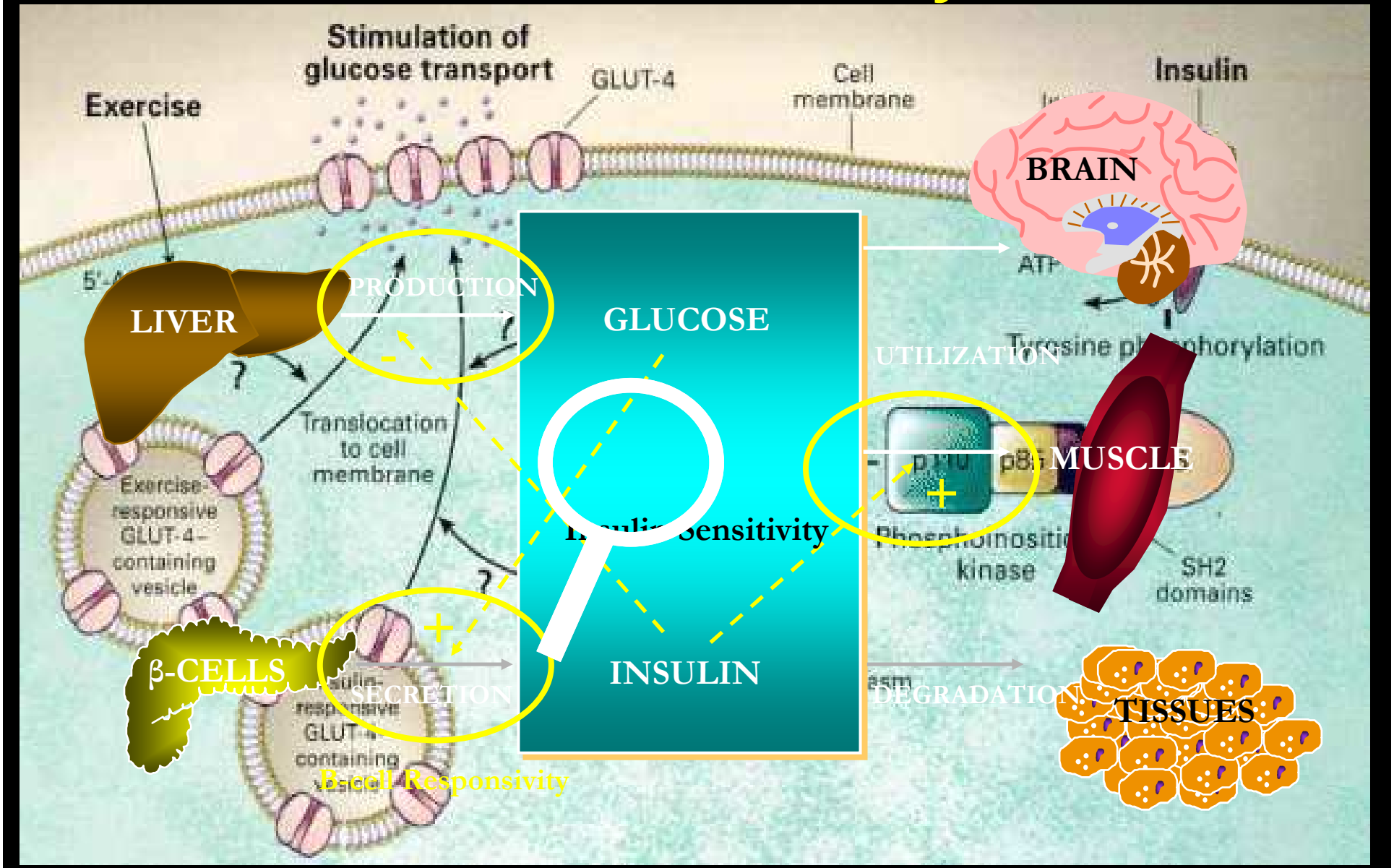


* p<0.05 pre vs post treatment

^ p<0.05 post treatment vs nondiabetic

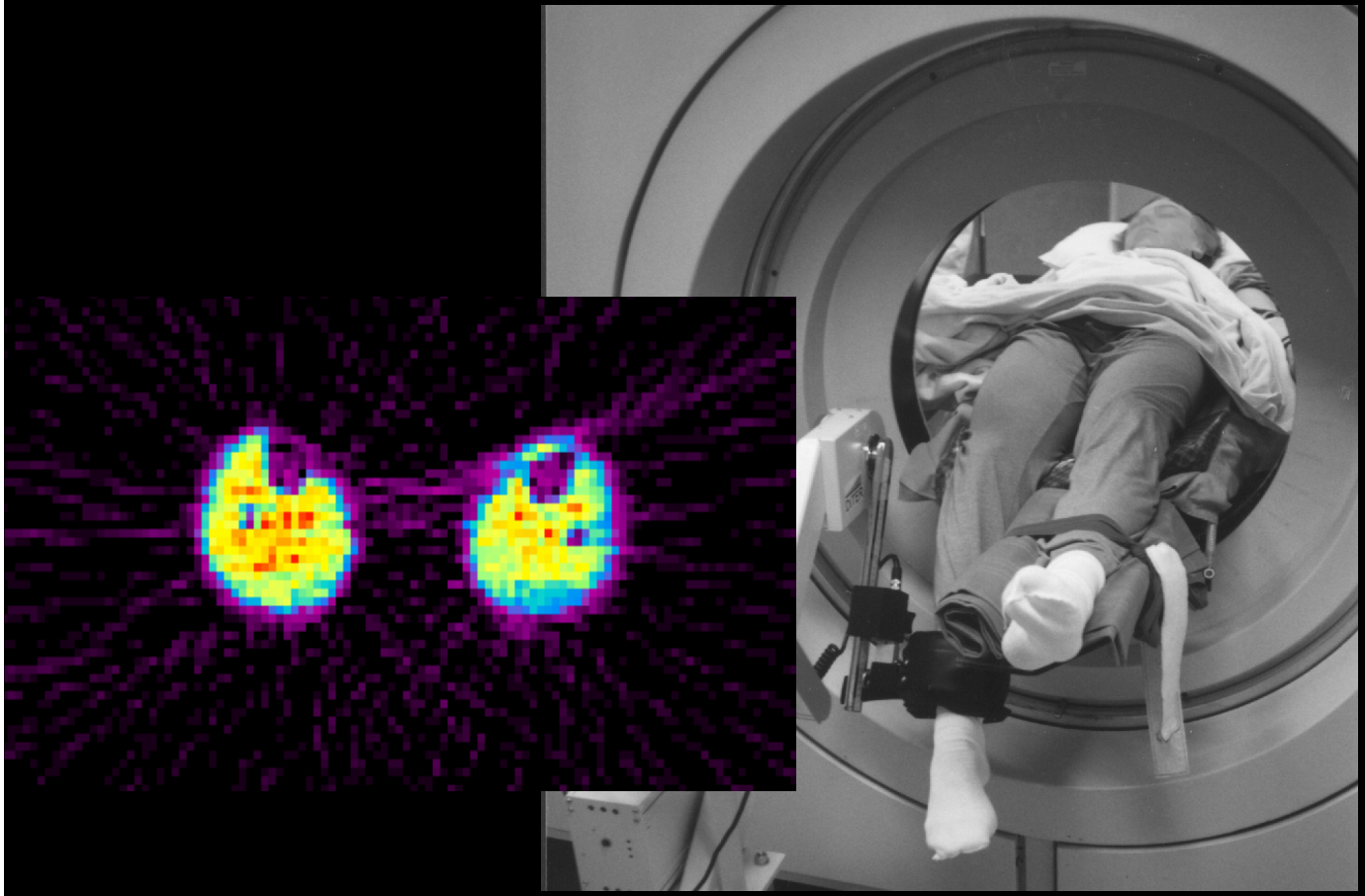
- **Models to Measure**
  - Whole Body
  - Organ/Tissue
- **Models to Simulate**
  - In Silico Whole-Body

The Glucose-Insulin System

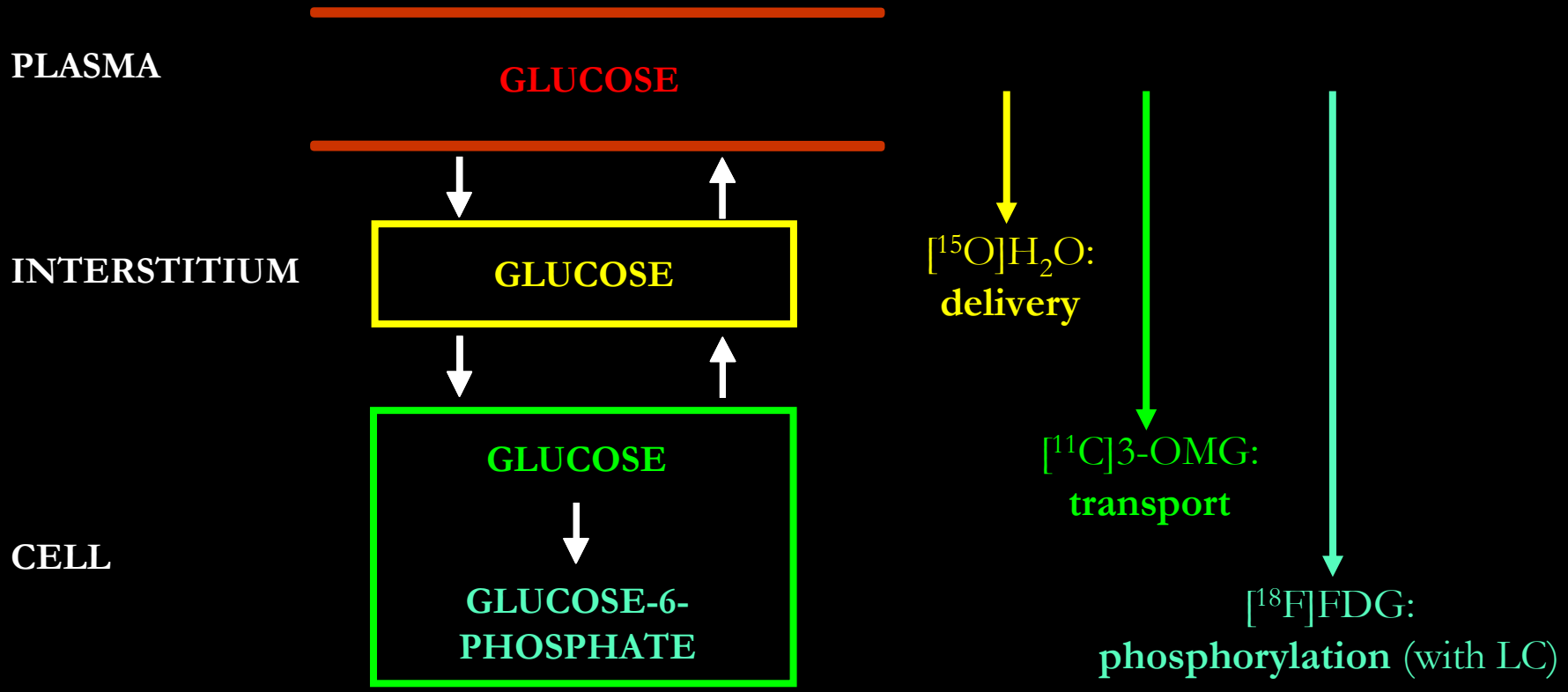


Using PET to Study Insulin Action on Glucose Delivery, Transport and Phosphorylation

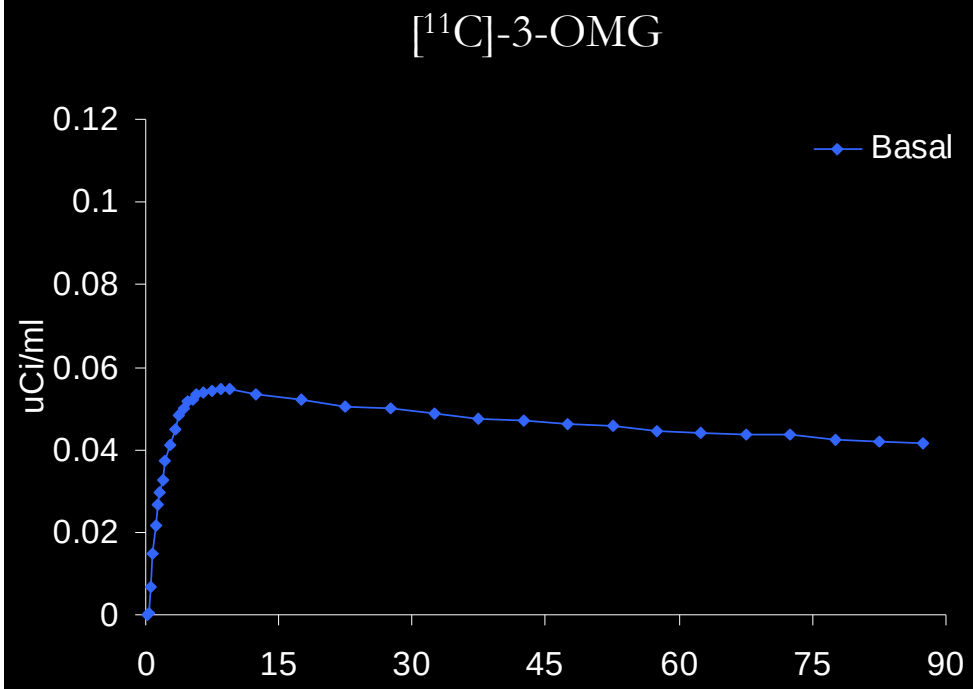
(Dr. David Kelley, University of Pittsburgh, Pittsburgh, PA)

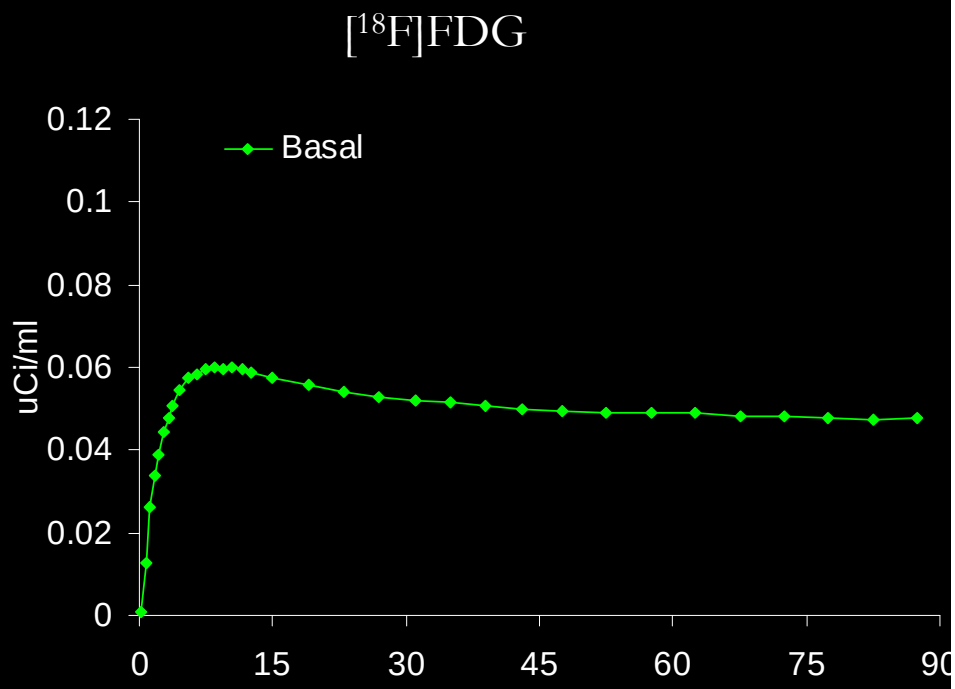


Triple-Tracer PET Imaging



Basal & Insulin Study





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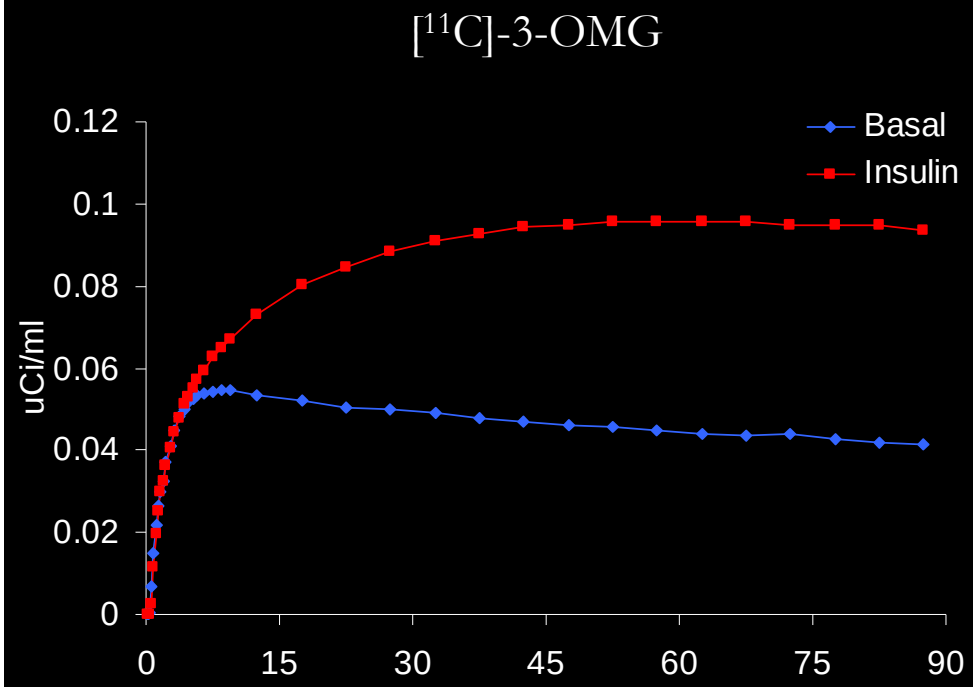
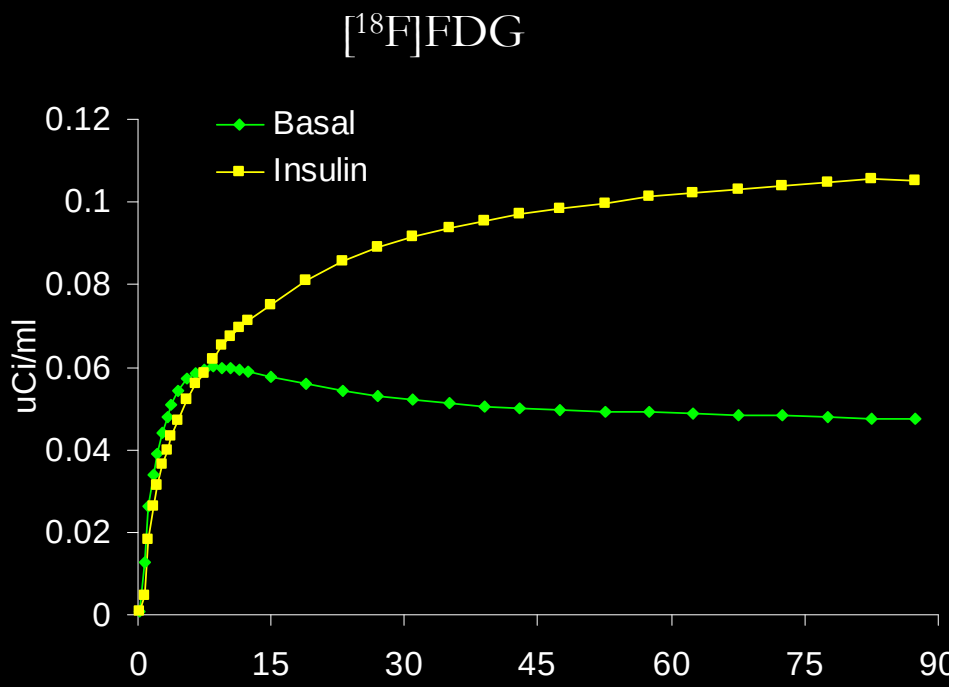
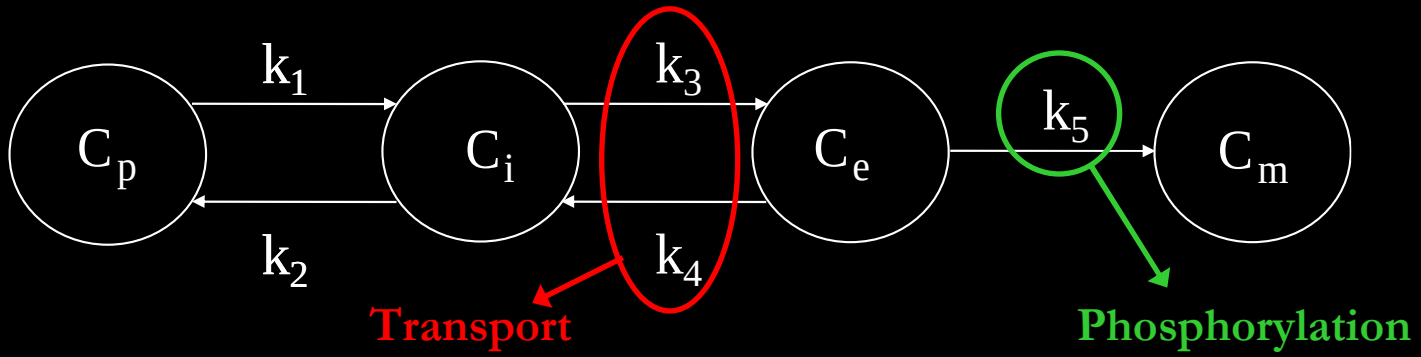
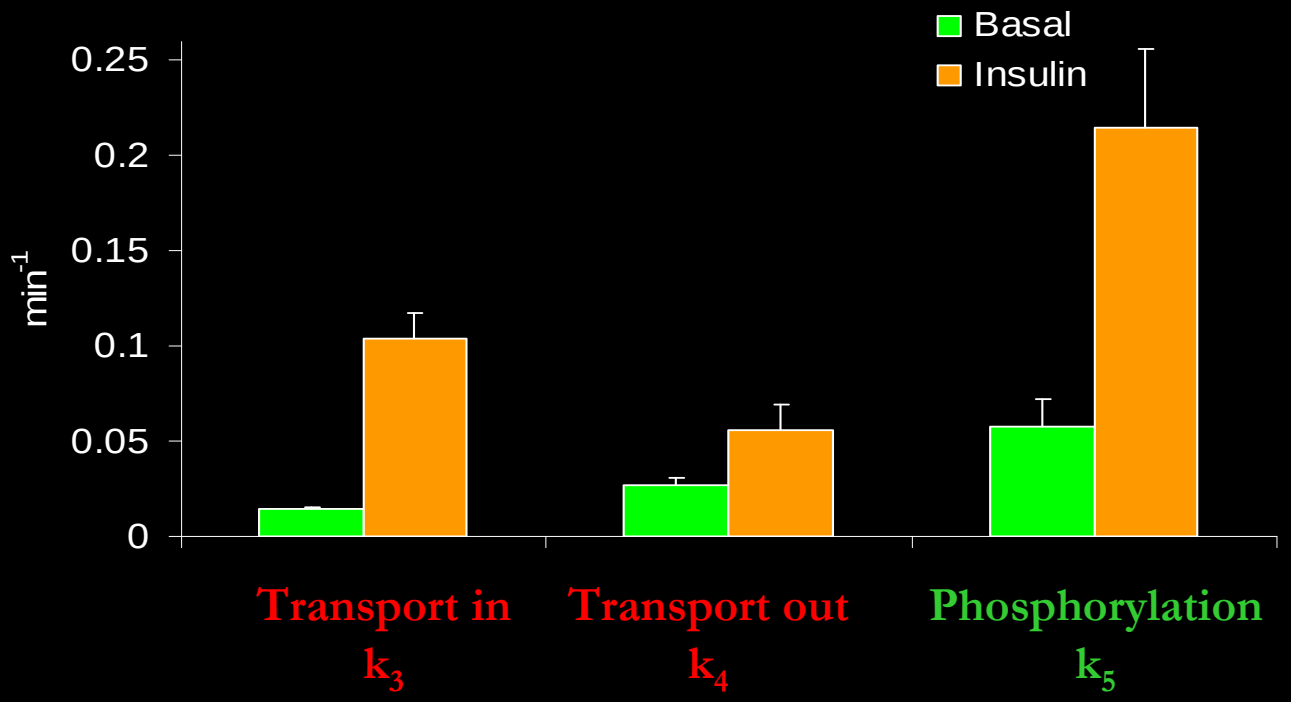




The 5K model

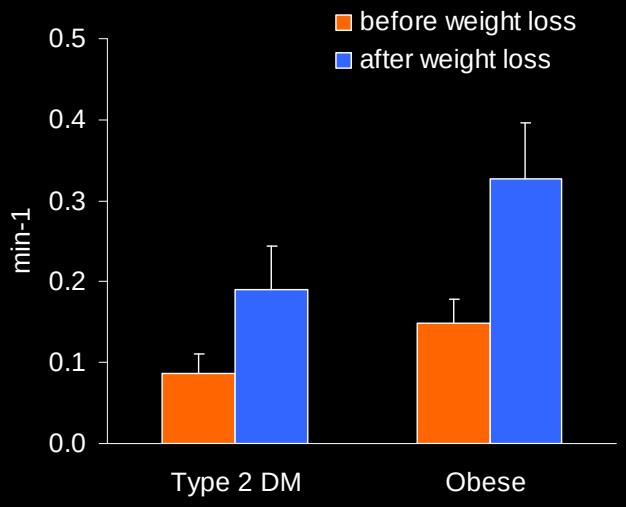
(Bertoldo et al, 2001)



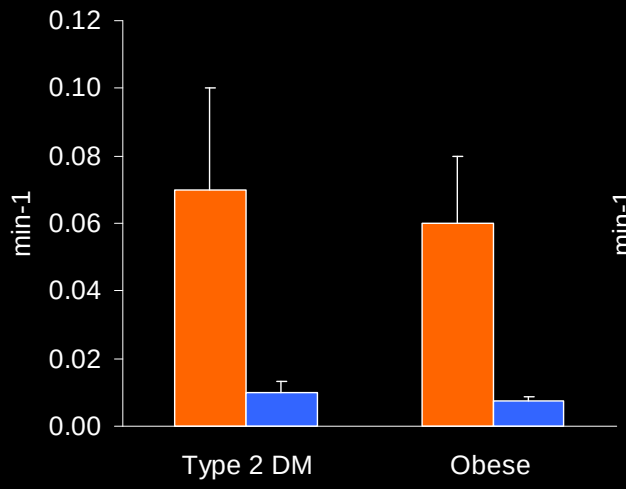


Weight Loss Impact on Glucose Transport & Phosphorylation in Obesity & Type 2 Diabetes

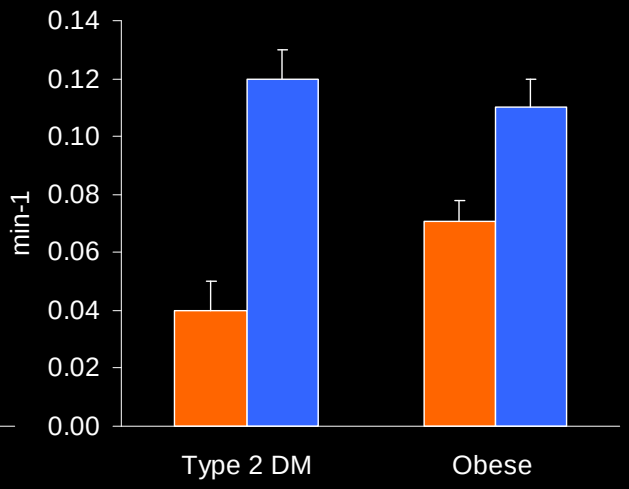
(Williams et al, 2003)



Transport in
k_3



Transport out
k_4



Phosphorylation
k_5

- **Models to Measure**
  - Whole Body
  - Organ/Tissue
- **Models to Simulate**
  - In Silico Whole-Body

Background

- Models to Simulate:

  often not possible, appropriate, convenient or desirable to perform experiments in humans, e.g. testing of glucose sensors and insulin infusion algorithms for closed loop control during normal life condition

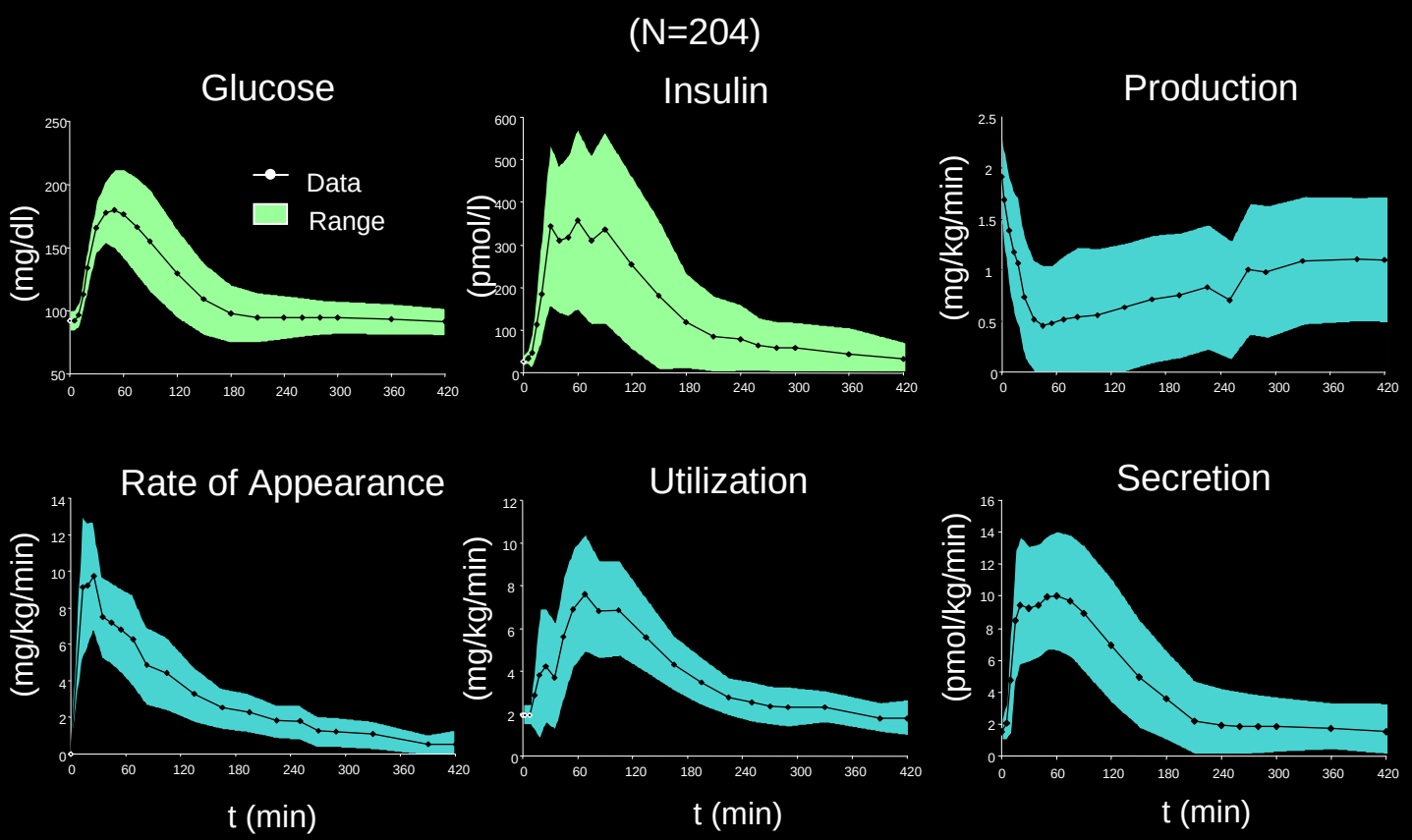
- Can Models to Measure be used as Models to Simulate?

No

Models to Measure need to be minimal (parsimonious)
Models to Simulate need to be maximal (large scale)

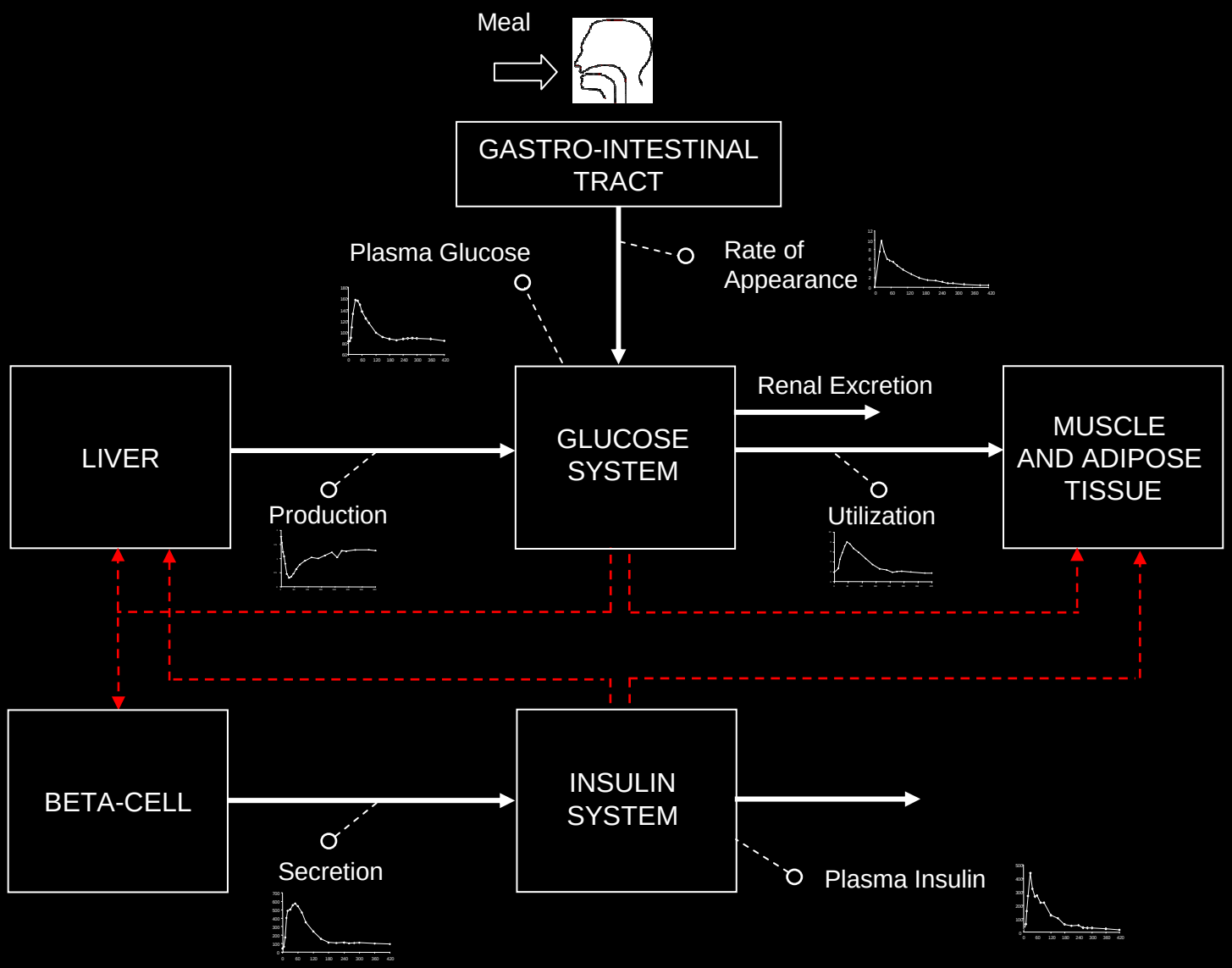
New Generation of In Silico Models

Fluxes, in addition to concentrations, available

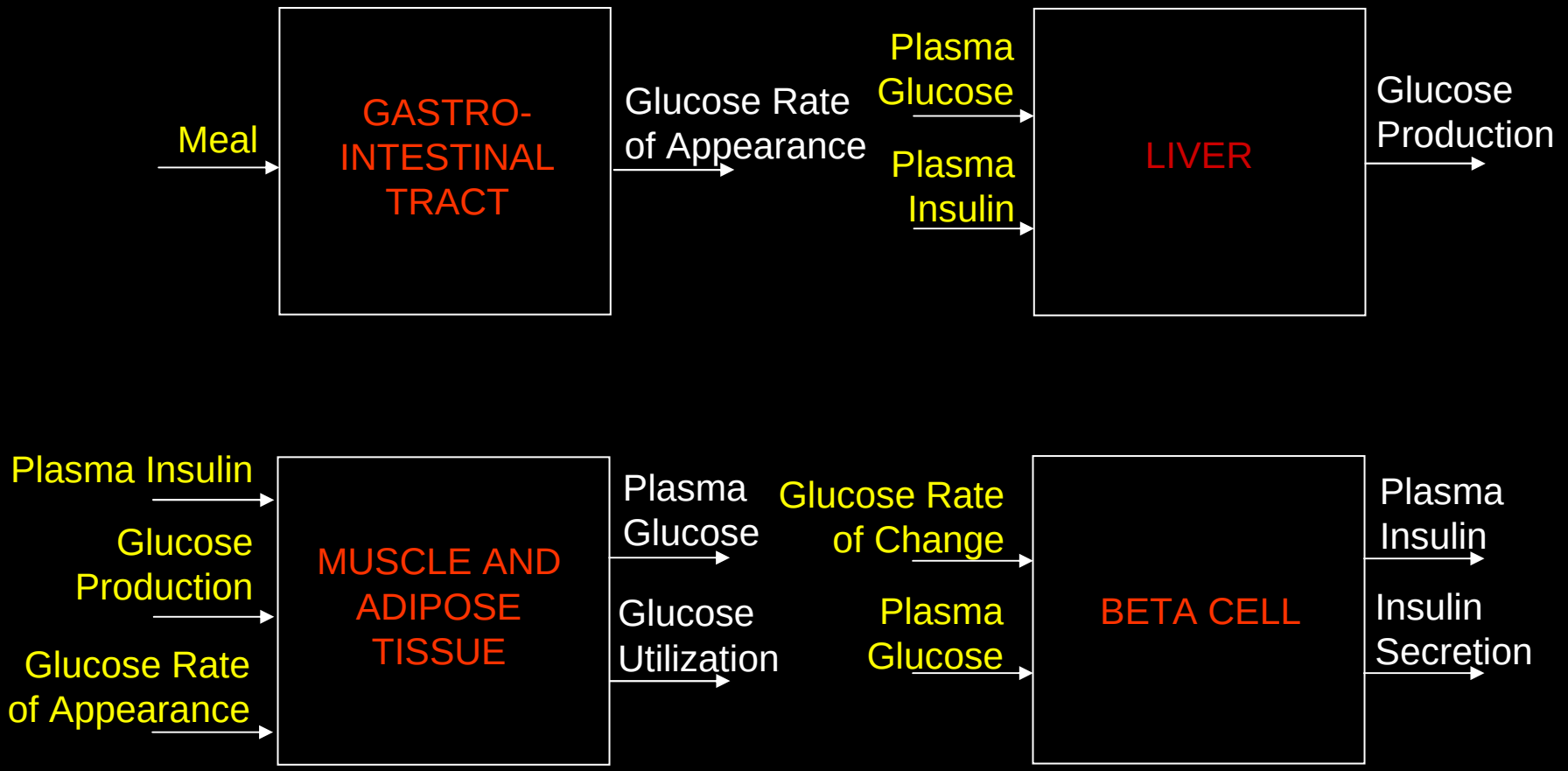


In Silico Meal Model

(Dalla Man et al, 2007)

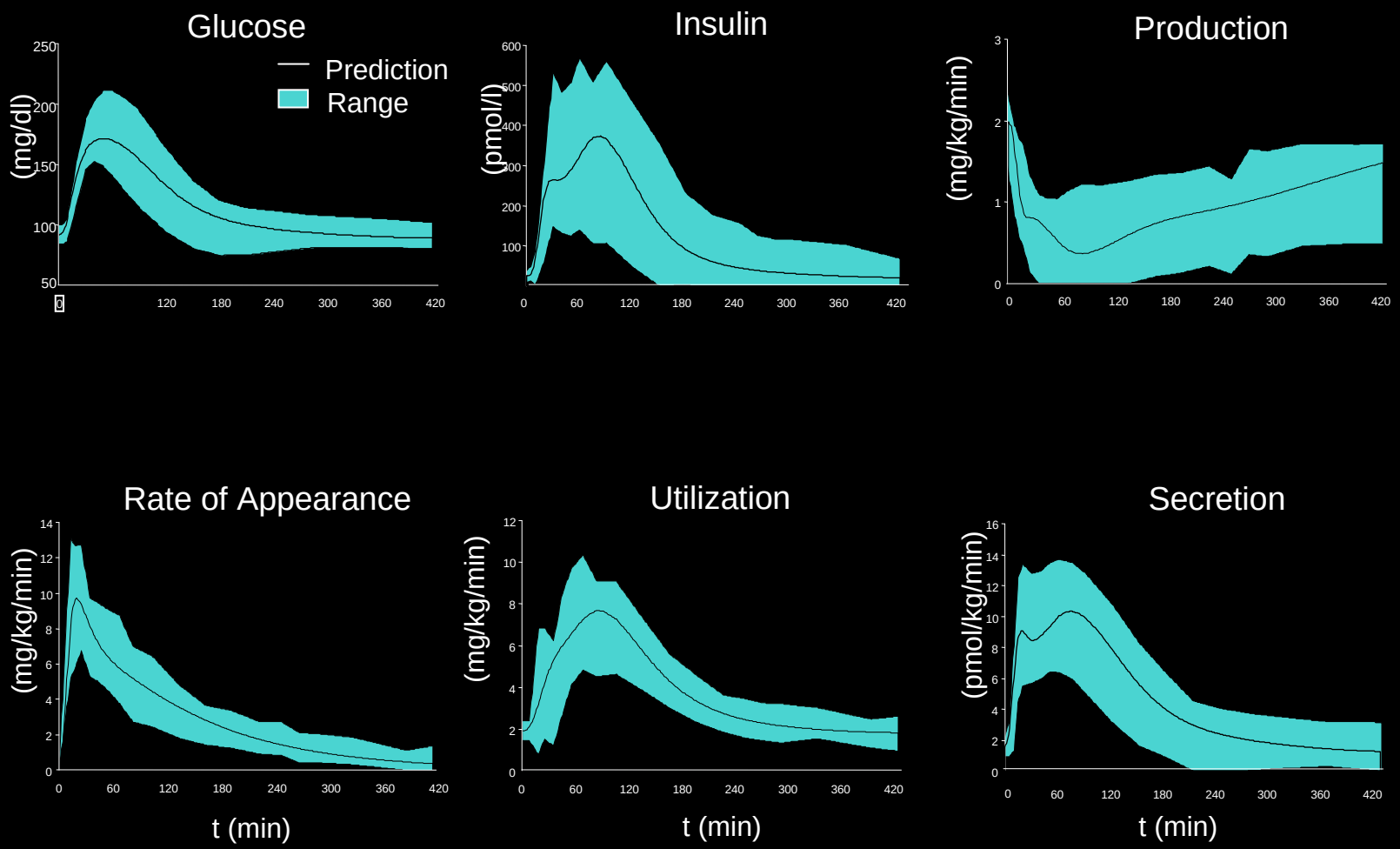


Identification: System Decomposition & Forcing Function Strategy

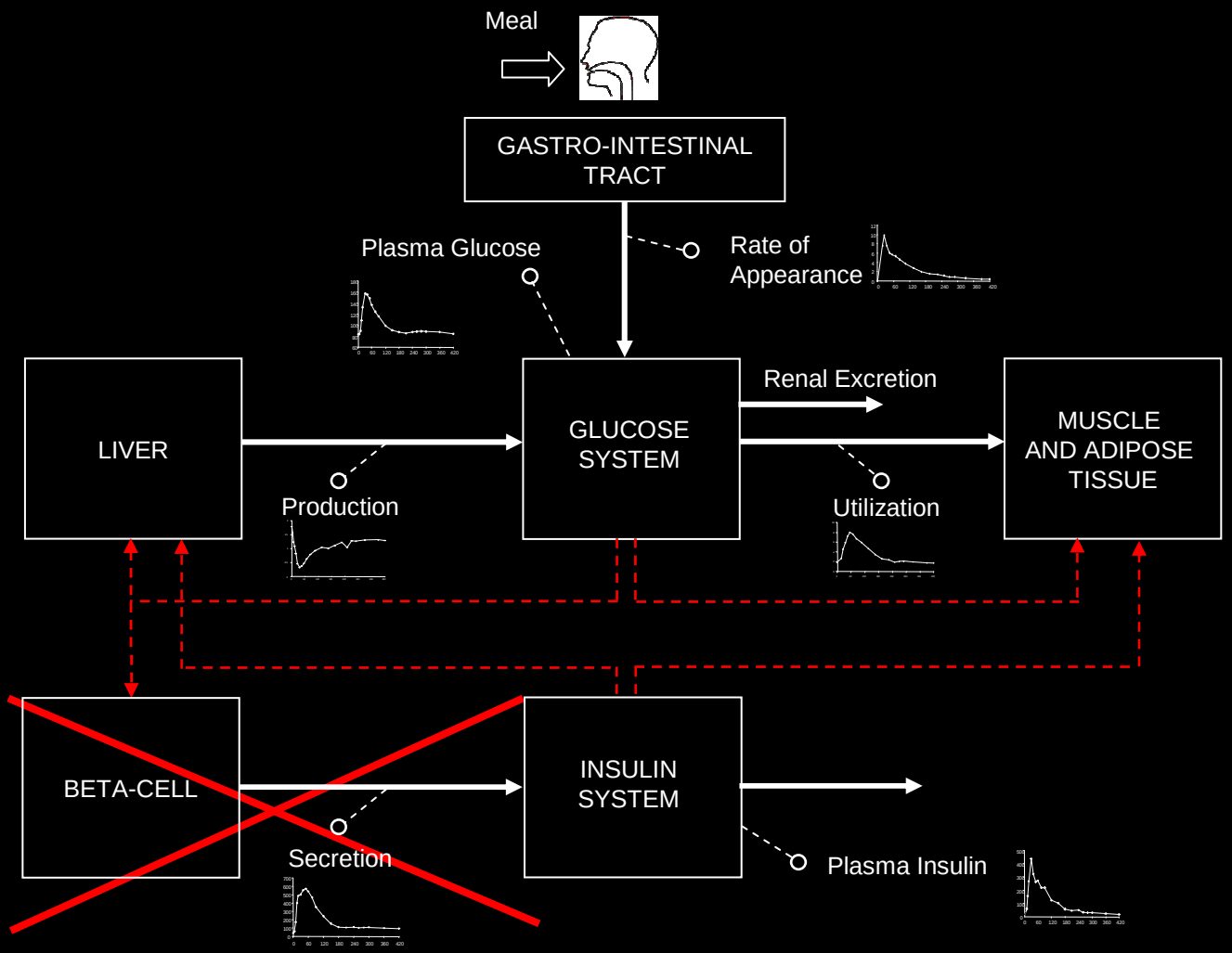


Model Performance

Mean Subject

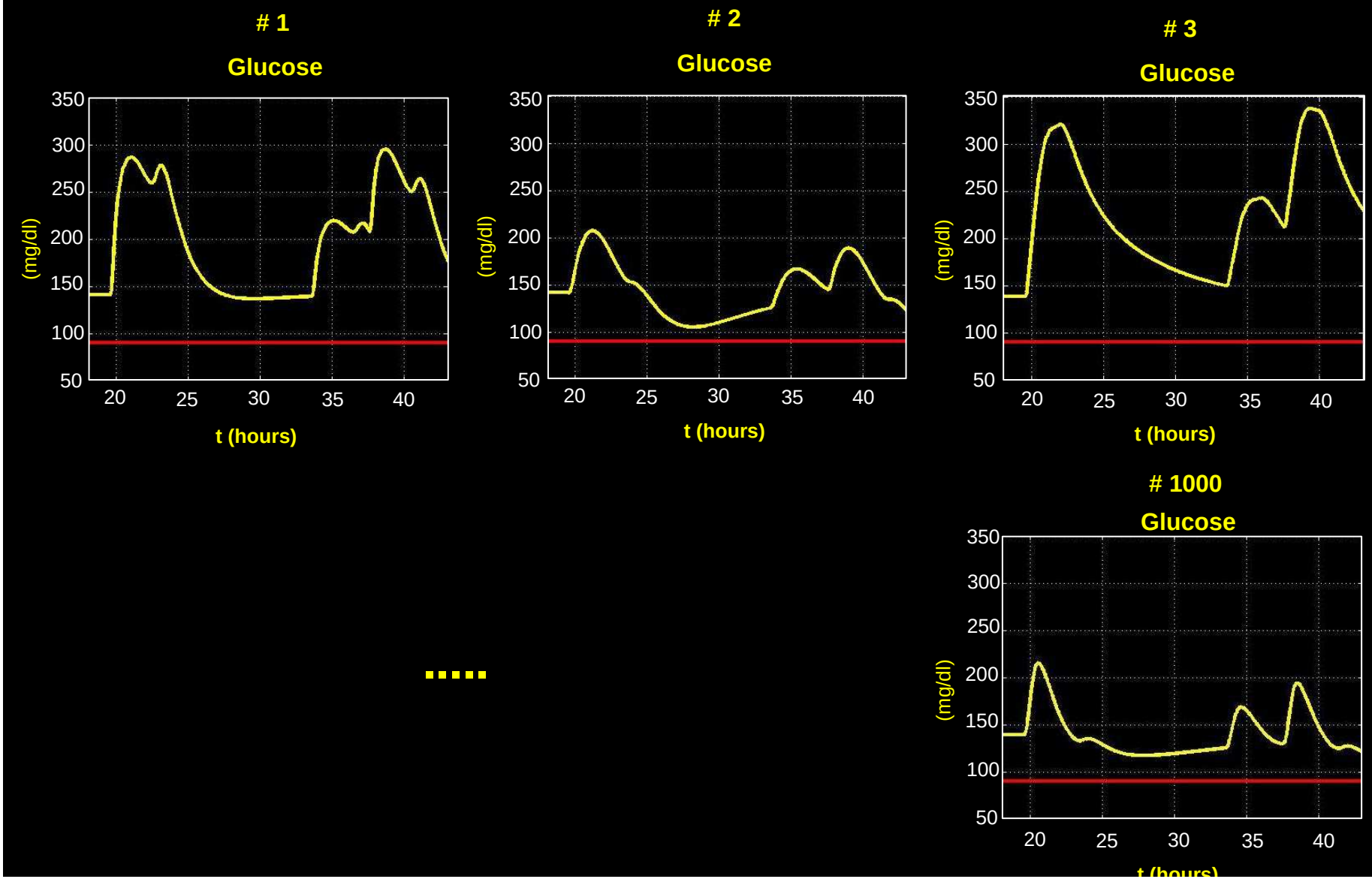


Model of the Type 1 Diabetic Subject

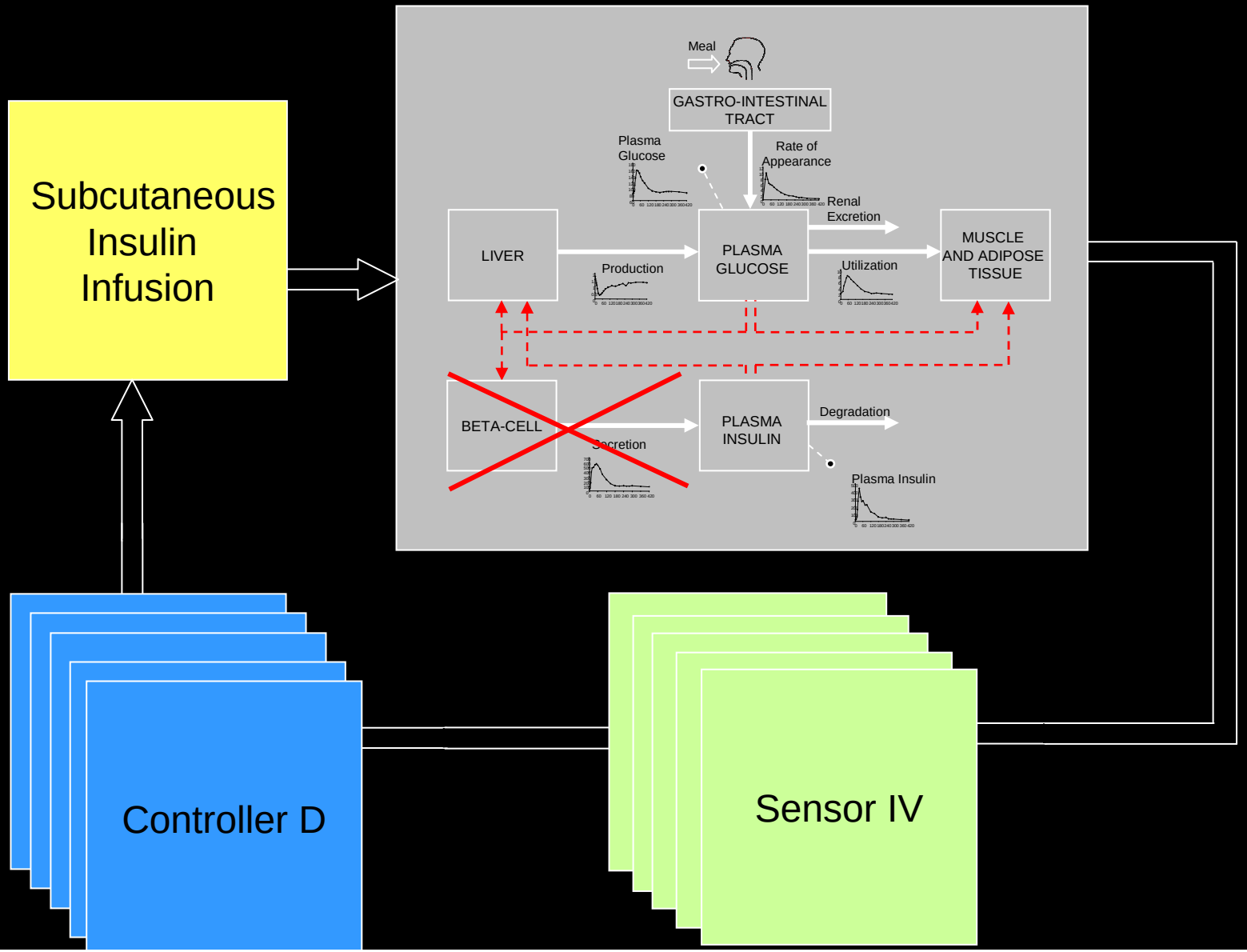


Generation of Type 1 Synthetic Subjects

Exploiting model parameter inter-subject variability



Artificial Pancreas Project (JDRF)



Conclusions

1. Importance of System Models in Diabetes Research

2. Increasing Awareness of Importance of Physiological Protocols, e.g. Meal and OGTT, vs Nonphysiological, e.g. IVGTT and Clamp

3. Models to Measure: Powerful Tool to Understand Pathophysiology of Diabetes from a Physiological Test

4. Models to Simulate: New Generation of Meal Models for in Silico Trials

Thanks

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