Applying the Entelos Metabolism PhysioLab to Pharmaceutical R&D

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Beyond Genome: Systems Biology *June 19, 2003*

Project Background

- Examine a specific antidiabetic target in the J&J pipeline

- J&J PRD/Entelos Collaboration
  - Diabetes Research Forum
  - Entelos/ADA Alliance

- Use Entelos Metabolism PhysioLab platform
  - assess the efficacy of the target for the treatment of type 2 diabetes.

Project Objectives

- Represent the biology of the target
  - Quantitatively model the physiology affected by the specified target so that the metabolic behavior agrees with the literature
- Create virtual patients
  - Model a population of relevant type 2 diabetes patients with variations in disease physiology and variations in target metabolism so that their behaviors agree with clinical data
- Optimize trial designs
  - Simulate a variety of target interventions on the virtual patients

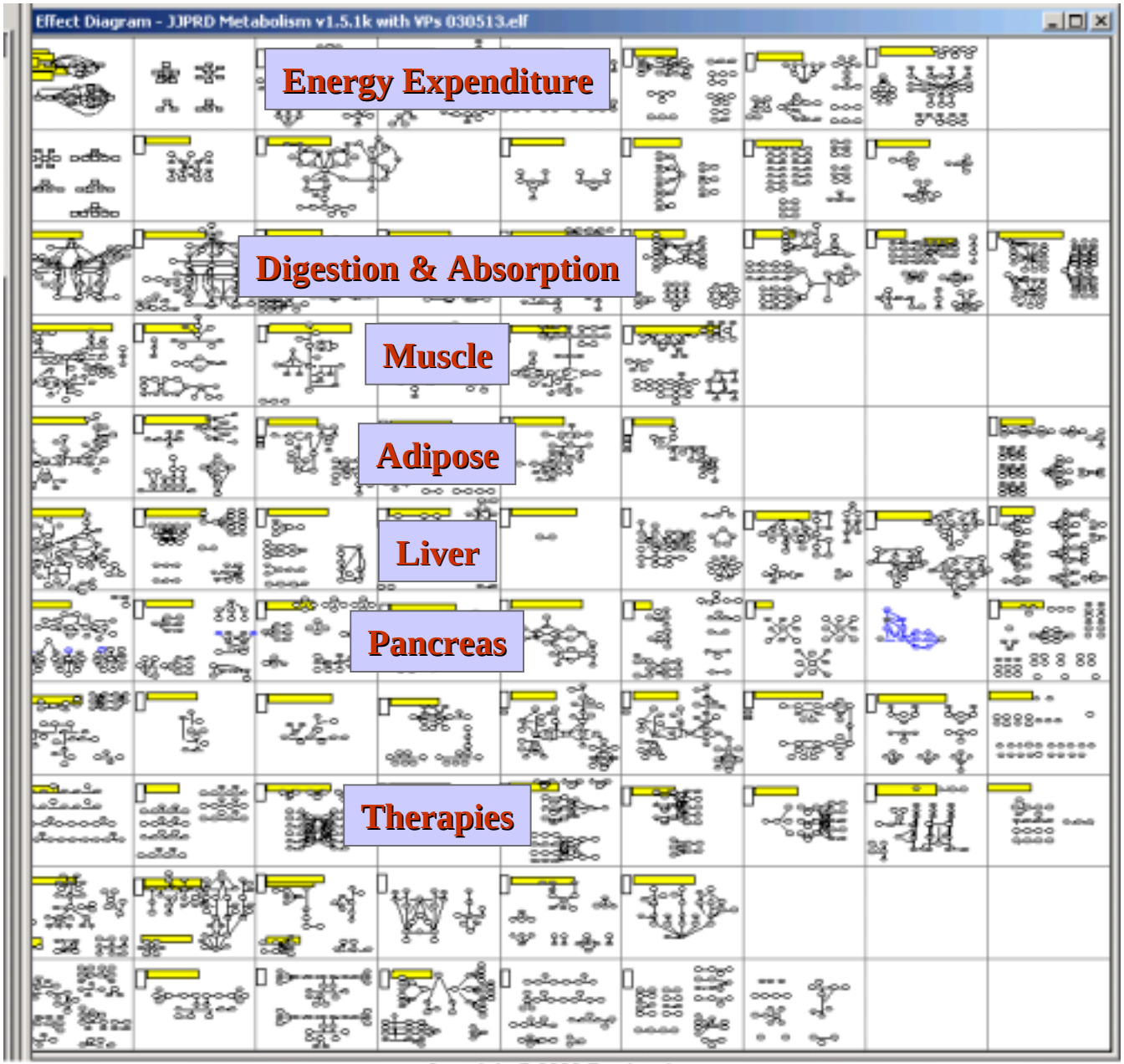
Type 2 Diabetes – Unmet Needs

- 6.2% of the population in US have diabetes.
- Prevalence is increasing in the US and worldwide.
- 90-95% of people with diabetes have type 2 diabetes.
- In most patients, maintaining tight glycemic control is still difficult with current products.

Overview of
Entelos Metabolism PhysioLab
and Virtual Patients

Entelos Approach to Modeling Disease

- Identify questions/hypotheses model should address
- Identify behaviors model should be able to simulate
- Identify *key* physiological processes responsible for behavior
- Represent these processes, use data to determine parameters
  - Ability to represent multiple hypotheses
  - Ability to represent multiple patient types
- First represent normal individual, then diseased individuals
- Iterate!


Effect Diagram - JJPRD Metabolism v1.5.1k with VPs 030513.elf
Energy Expenditure
Digestion & Absorption
Muscle
Adipose
Liver
Pancreas
Therapies
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Virtual Diabetic Patients: Static Behaviors

Output/Behavior	*Value for Virtual Diabetic*
Plasma lactate	> 8 mg/dl, <12 mg/dl
Plasma glycerol	>0.5 mg/dl
Plasma amino acids	30-35 mg/dl
Plasma triglycerides	>75 mg/dl
Plasma free fatty acids	>600 µM
Plasma glucagon	>70 pg/ml
Hepatic glucose output	>140 mg/min
Liver glucose 6-phosphate	90-120 mg/dl
Liver glycogen	>30 g, <75 g
VLDL-TG Production rate	>17.5 mg/min, <30 mg/min
Liver triglycerides	>2000mg/dl, <3000 mg/dl
Lipolysis rate	>89 µmol glycerol/min
Fractional adipose chylo-TG extraction	Peak: <45%
Fractional adipose VLDL-TG extraction	Peak: <5%
Muscle glucose uptake rate	Post-prandial: >3, <6 mg/kg muscle/min
Muscle glycogen	≤14.5 g/kg muscle
Muscle glucose 6-phosphate	>2.0 mg/dl
Muscle pyruvate	>1.5 mg/dl
Muscle intracellular fatty acids	>2.5 mg/dl
Fractional muscle chylo-TG extraction	Peak: <25%
Fractional muscle VLDL-TG extraction	Peak: <5%
1st phase pancreatic insulin pool	= 2500 mU
2nd phase pancreatic insulin pool	= 10000 mU

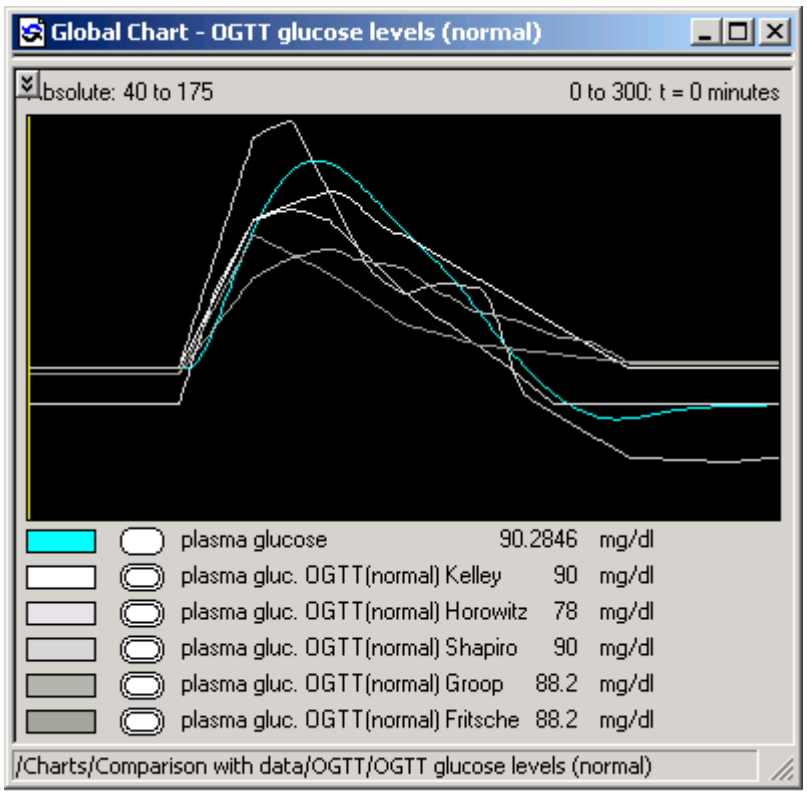
Virtual Diabetic Patients: Dynamic Behaviors

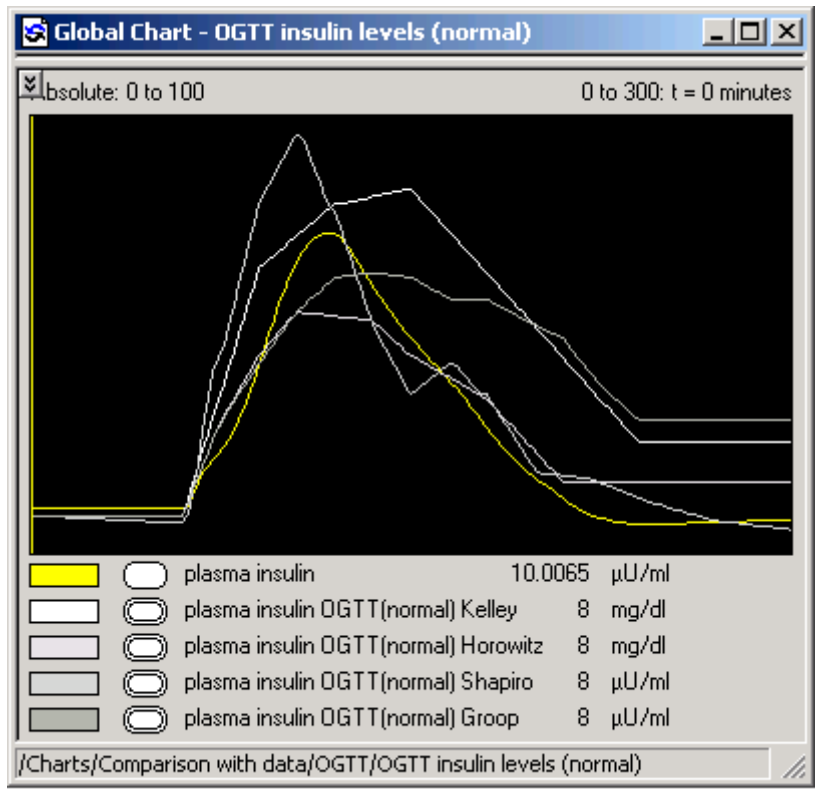
- Overnight-fasted concentrations and fluxes
- Post-prandial concentrations and fluxes
- Metabolic response to a 24 hour fast
- Oral glucose tolerance test (OGTT)
- Intravenous glucose tolerance test (IVGTT)
- Euglycemic-hyperinsulinemic clamp
- Hyperglycemic clamp

Represent the Biology of the Target

Validation Experiment for Specific Target Biology

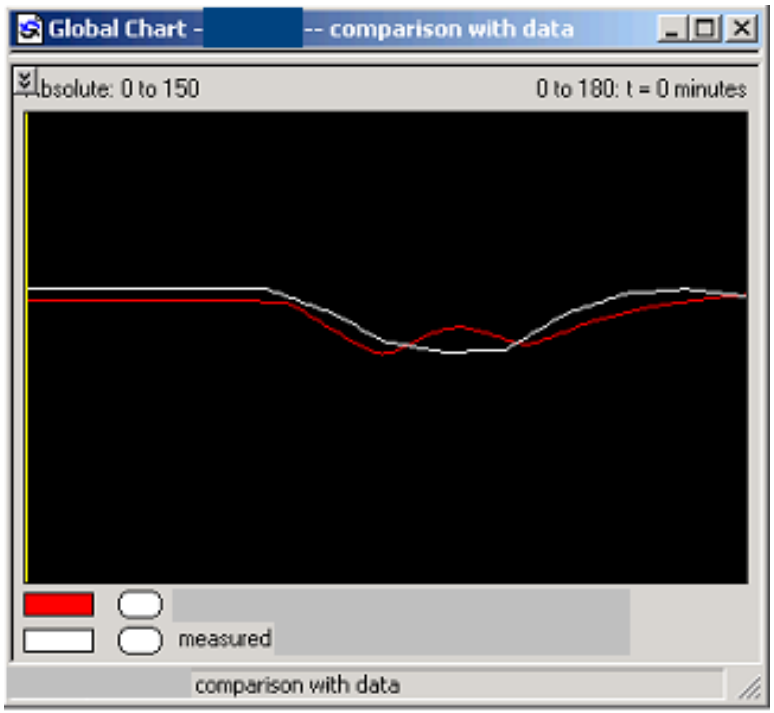
Oral glucose tolerance test (OGTT)

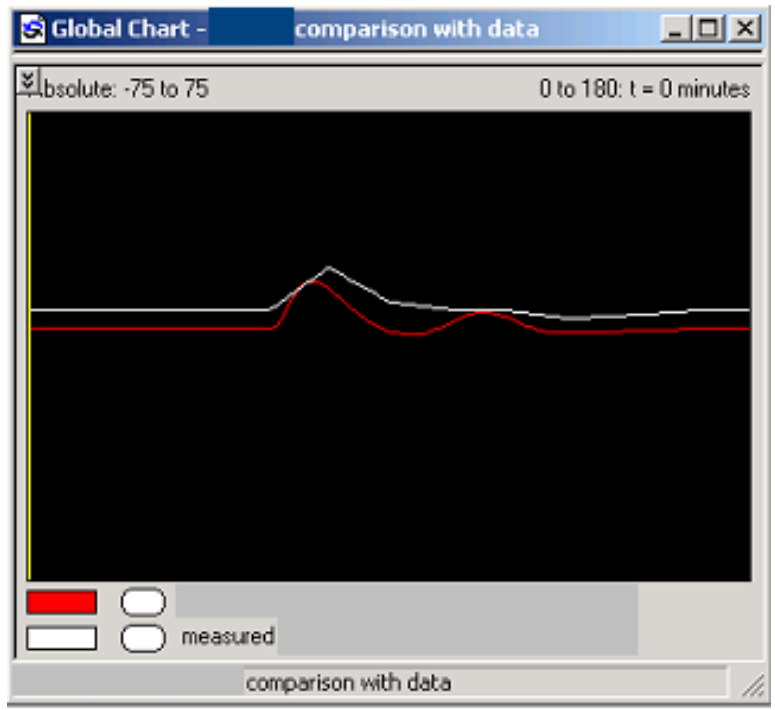




Validation Experiment for Specific Target Biology

In response to drug under fasting conditions

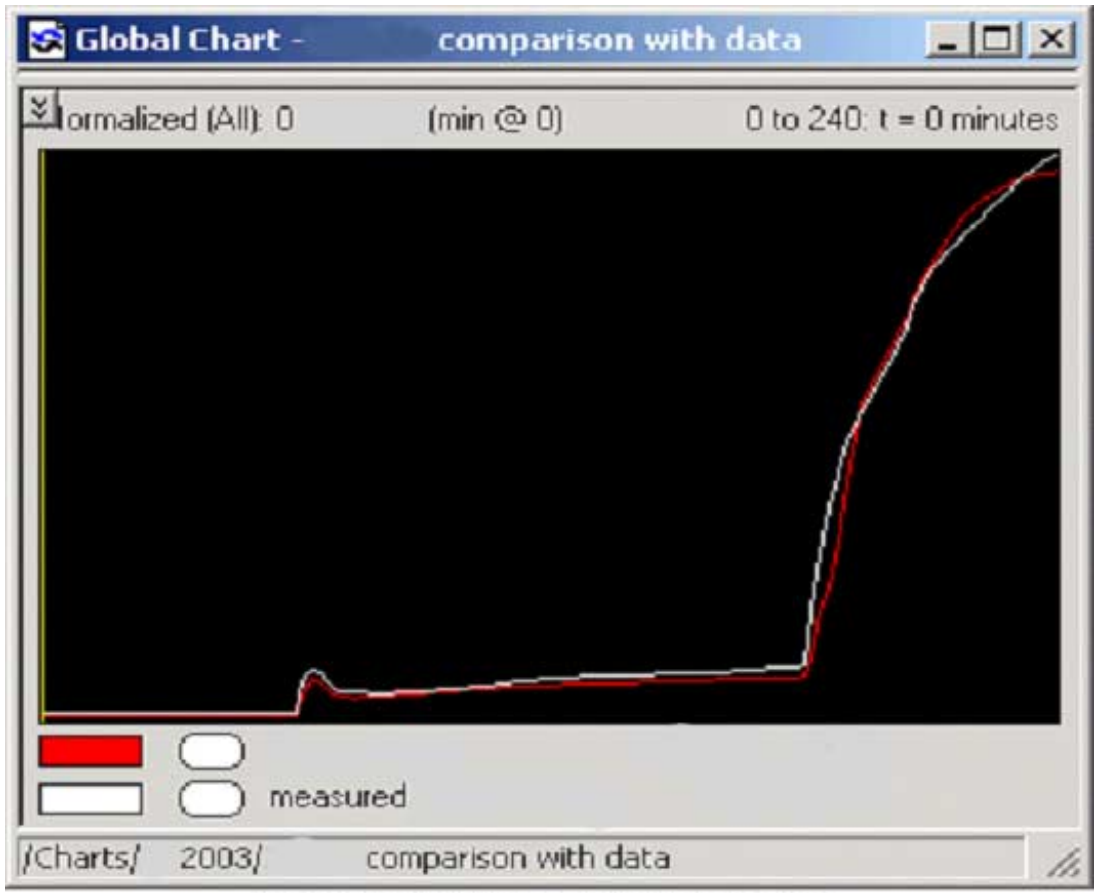




Represent the biology: tune the model

test infusion + drug : ***drug begun prior to start of test infusion***

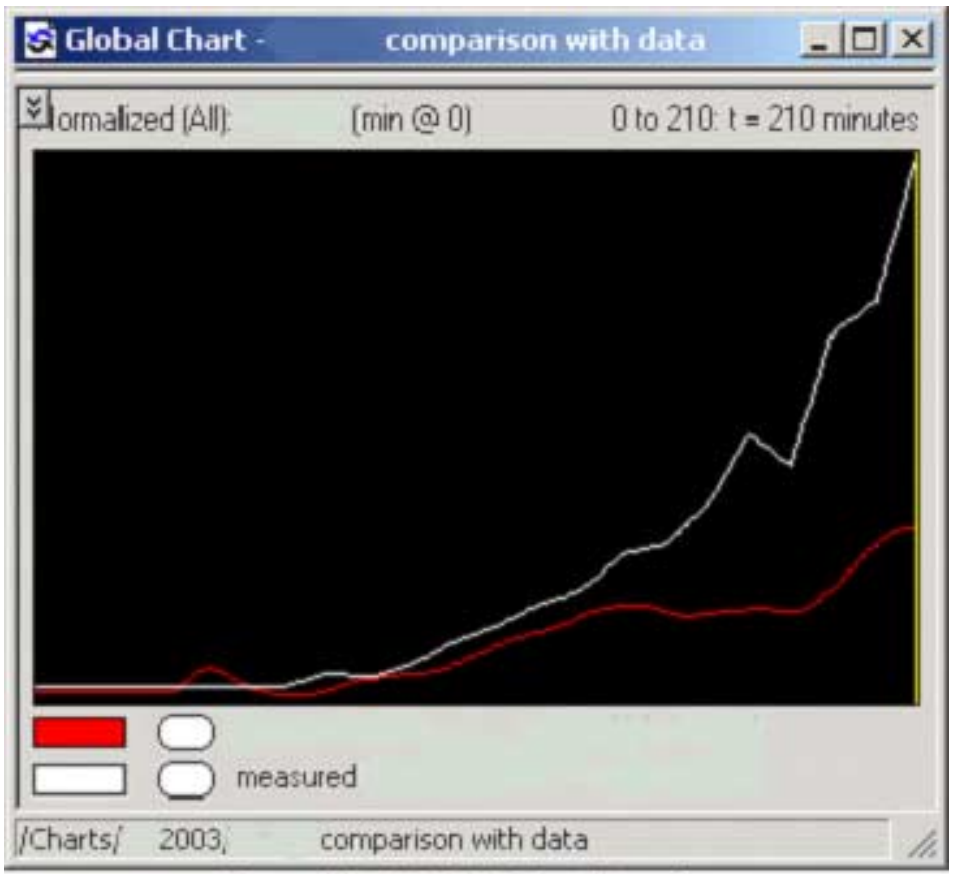
PhysioLab simulation results fitted to Study 1 data



Represent the biology: locate discrepancies

test infusion + drug: ***drug begun prior to start of test infusion***

PhysioLab simulation results compared to Study 2 data

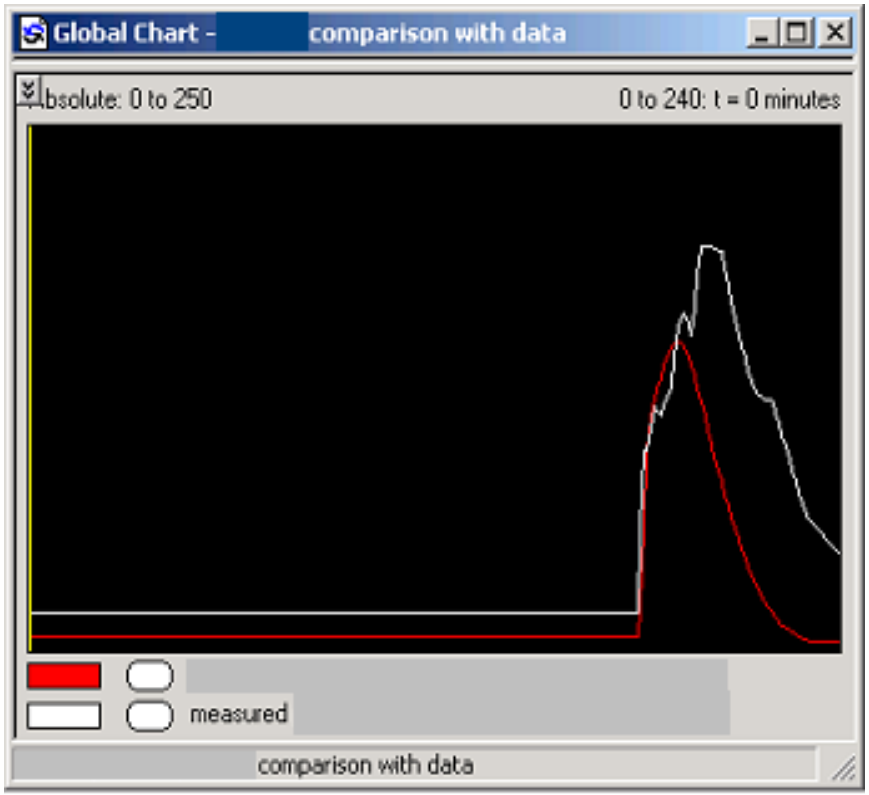


Represent the biology: verify discordant results

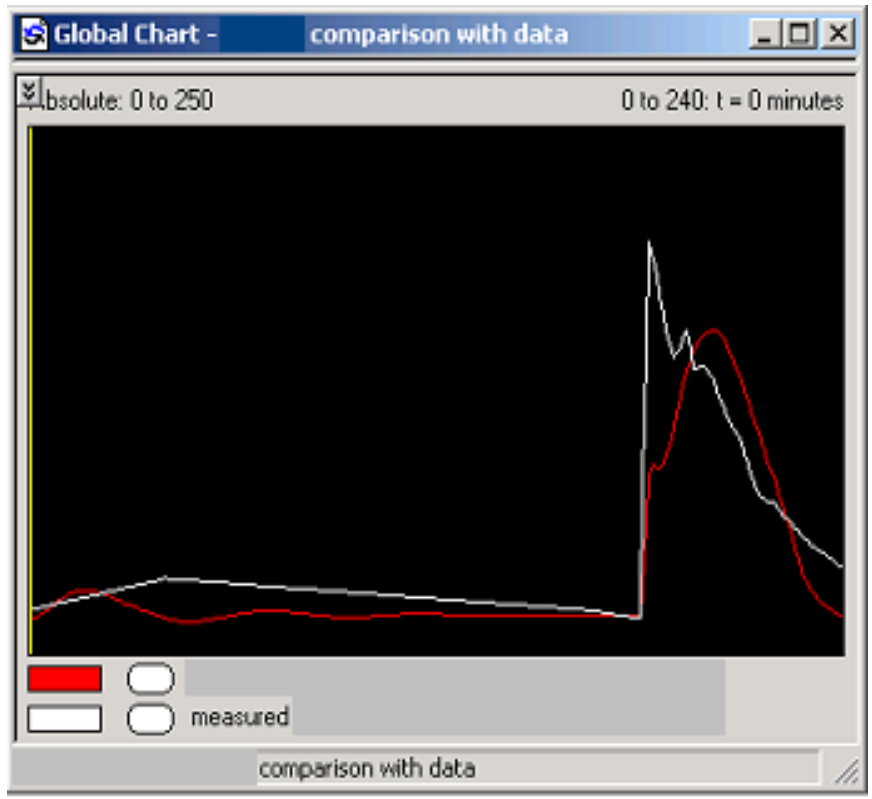
test infusion + drug: ***drug begun at the start of test infusion***

PhysioLab simulation results compared to Study 3 data

acute response

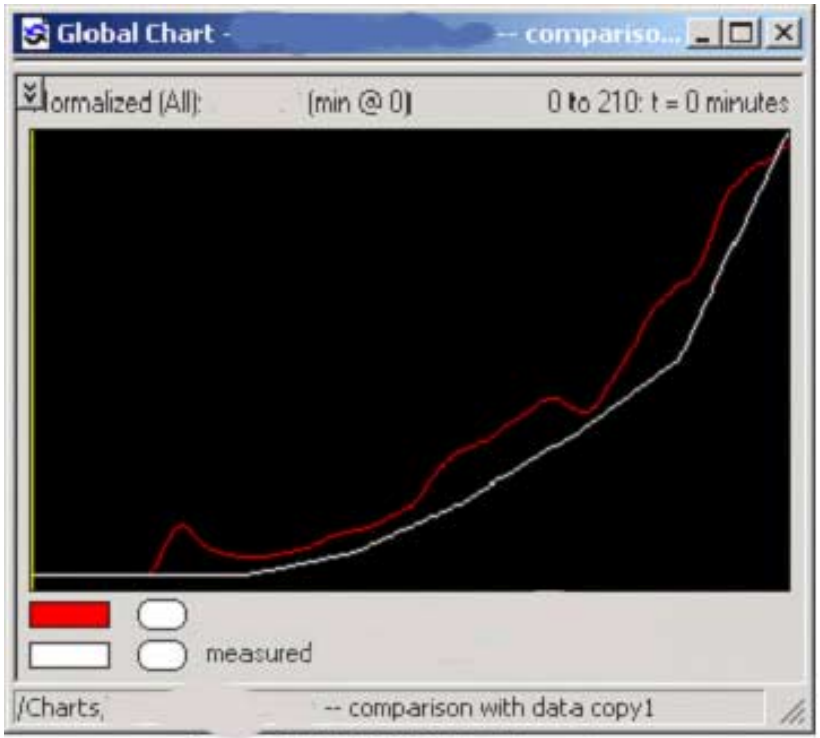


chronic response

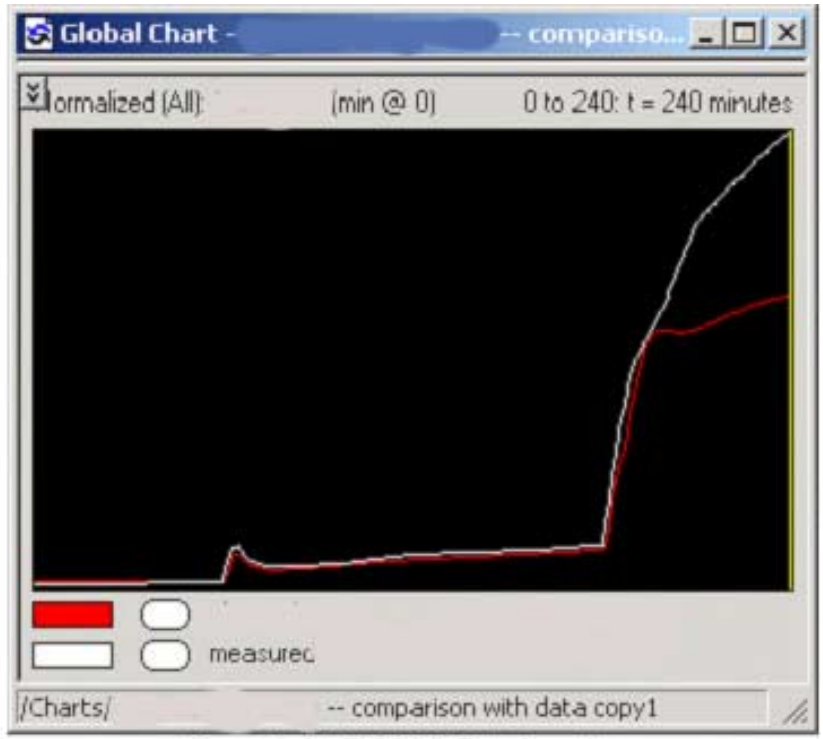


Represent the biology: alternate fittings still inconsistent

Model recalibrated to agree with Study 2



New simulation results for Study 1 protocol still lower than measured data



Is there a difference in the patient populations?

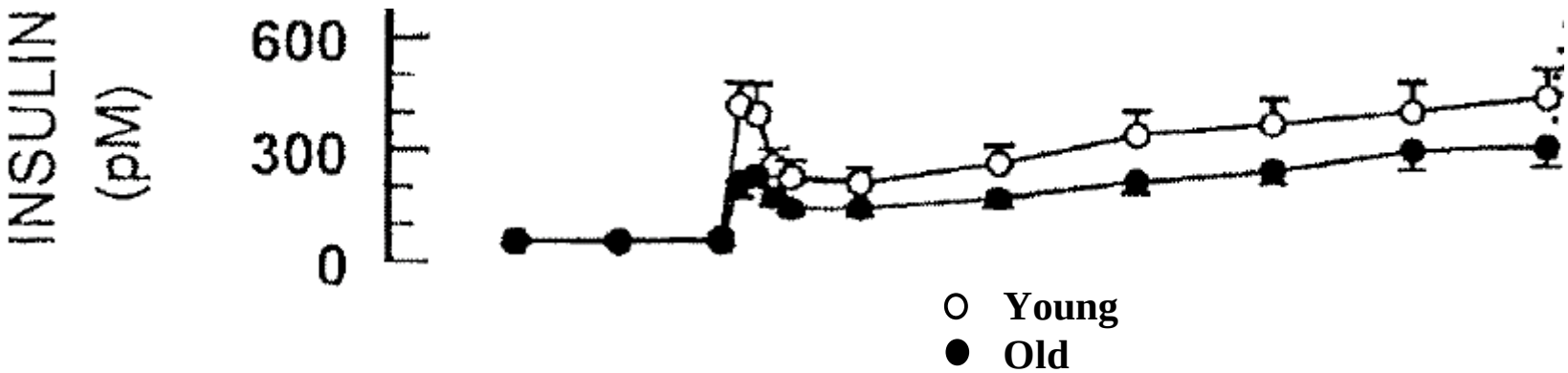
PhysioLab virtual patients

Lean, young

Overweight, old

Study 1 | Study 2 | Study 3

- Aging is associated with insulin resistance and deteriorating beta cell function
- Obesity is associated with insulin resistance and hyperinsulinemia



Create Virtual Patients

Creating virtual patients: match subjects in clinical studies

- **Control patients**

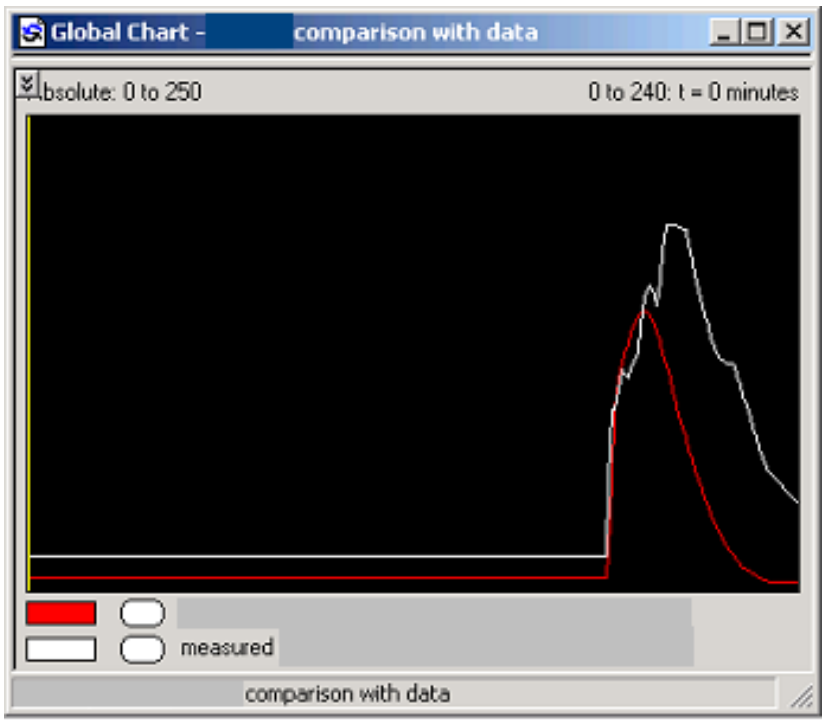
  lean + young vs. overweight + older

- **Diabetic virtual patients**

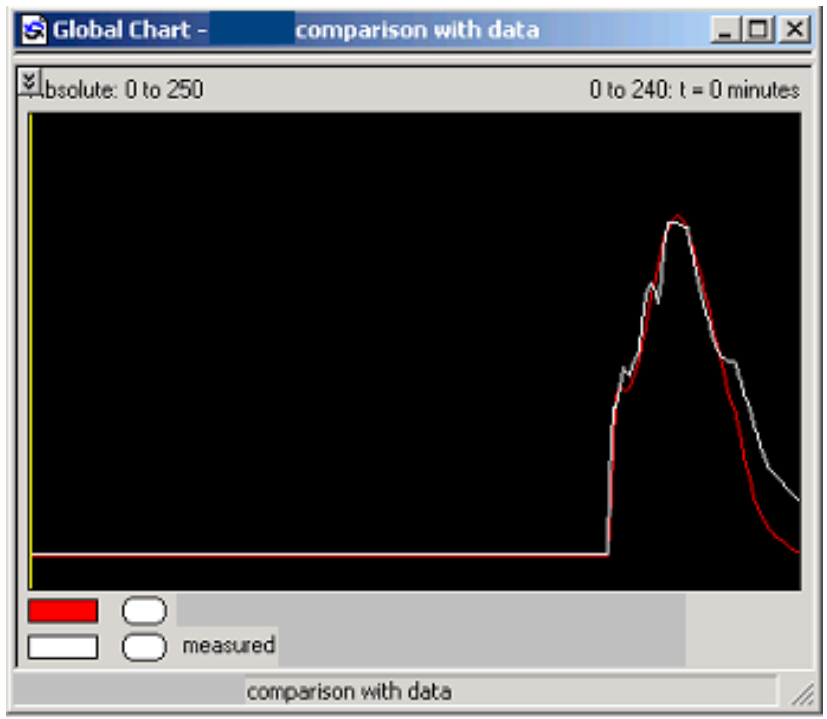
Key Test of Target on Virtual Patients

Acute response to drug in overweight, older patients

Test on lean, young virtual patient



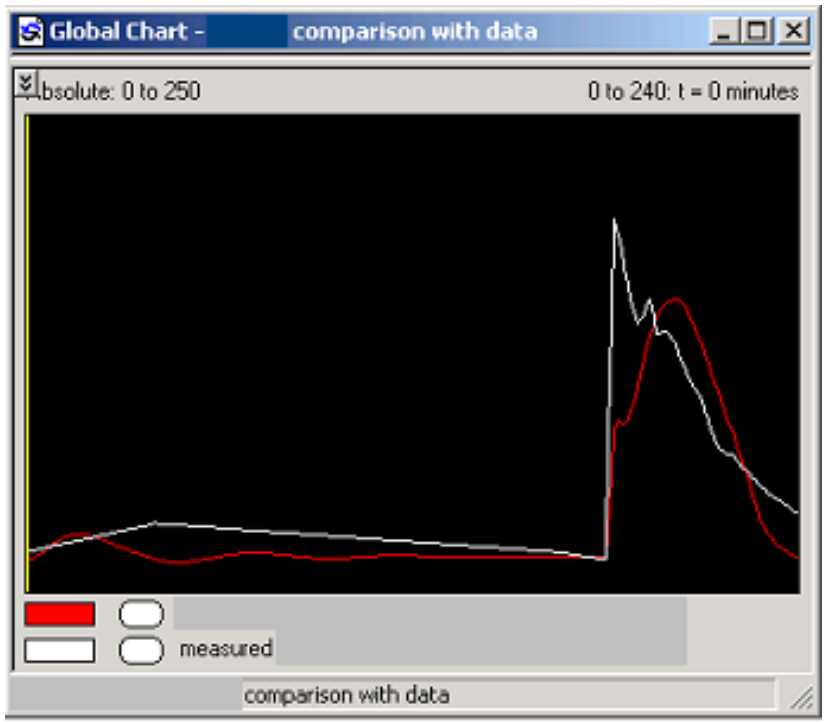
Test on overweight, older virtual patient



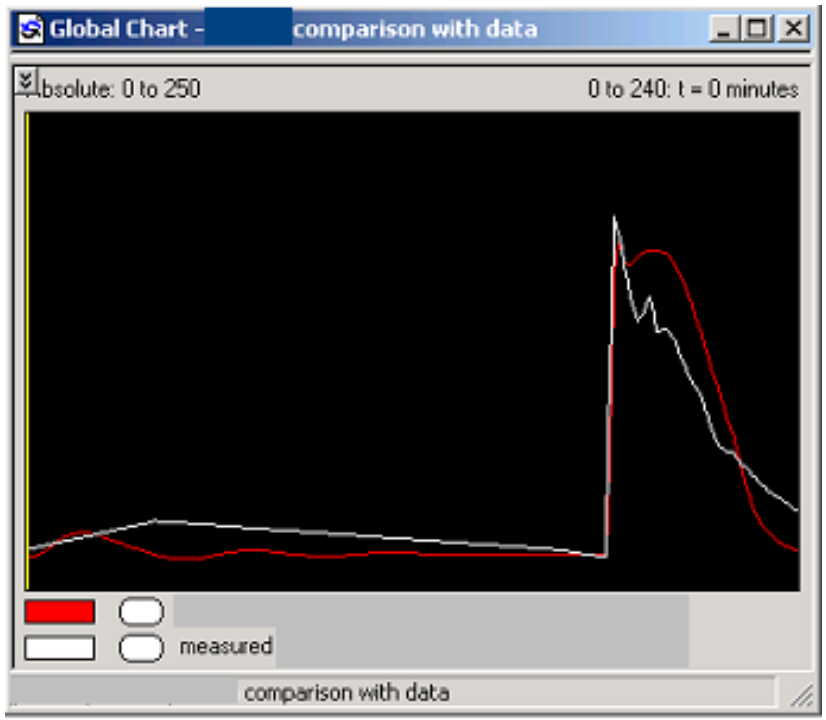
Key Test of Target on Virtual Patients

Chronic response to drug in overweight, older patients

Test on lean, young virtual patient

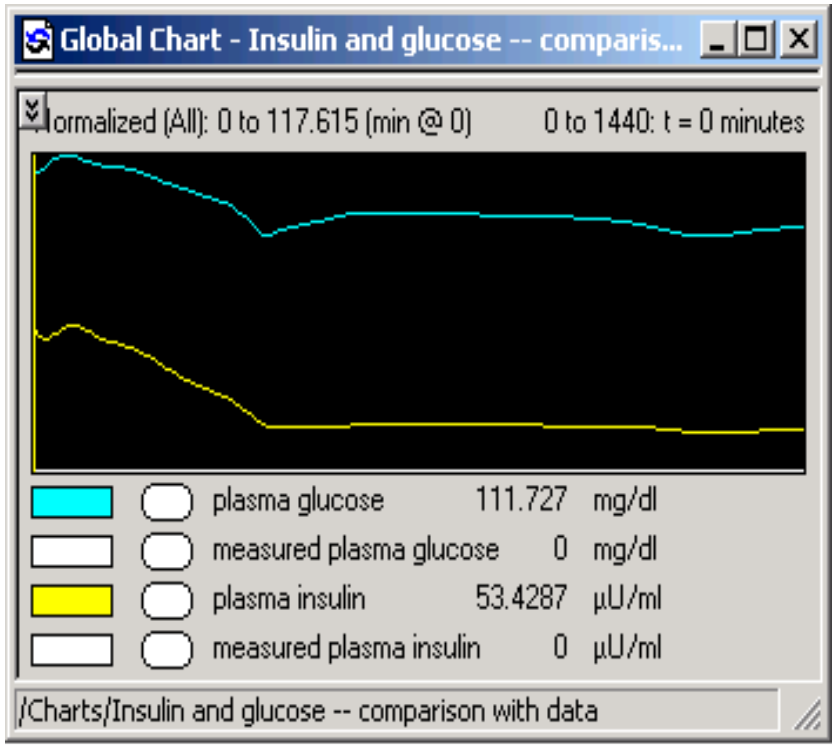


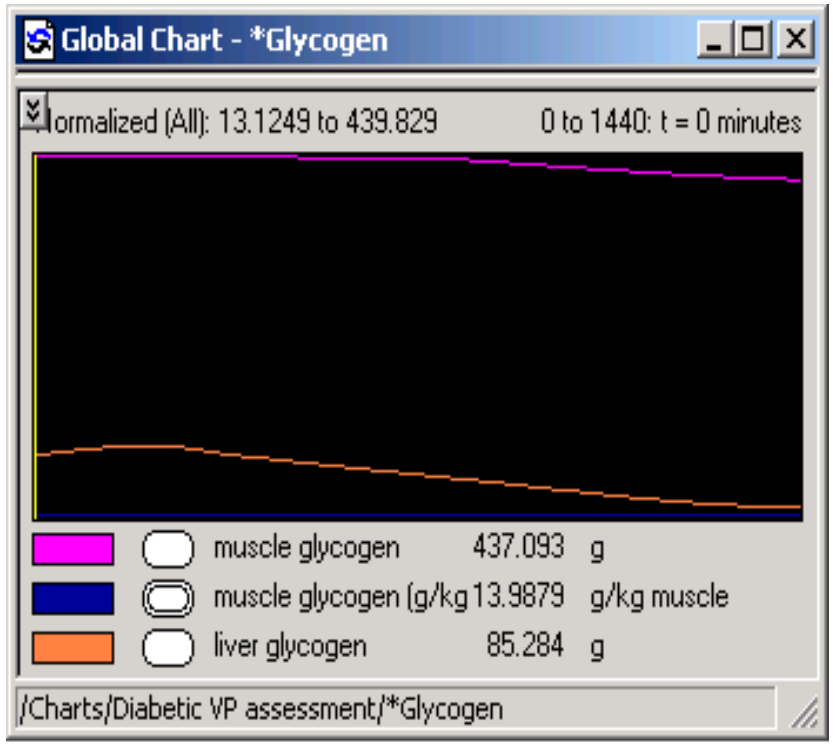
Test on overweight, older virtual patient



General Tests on Virtual Patients

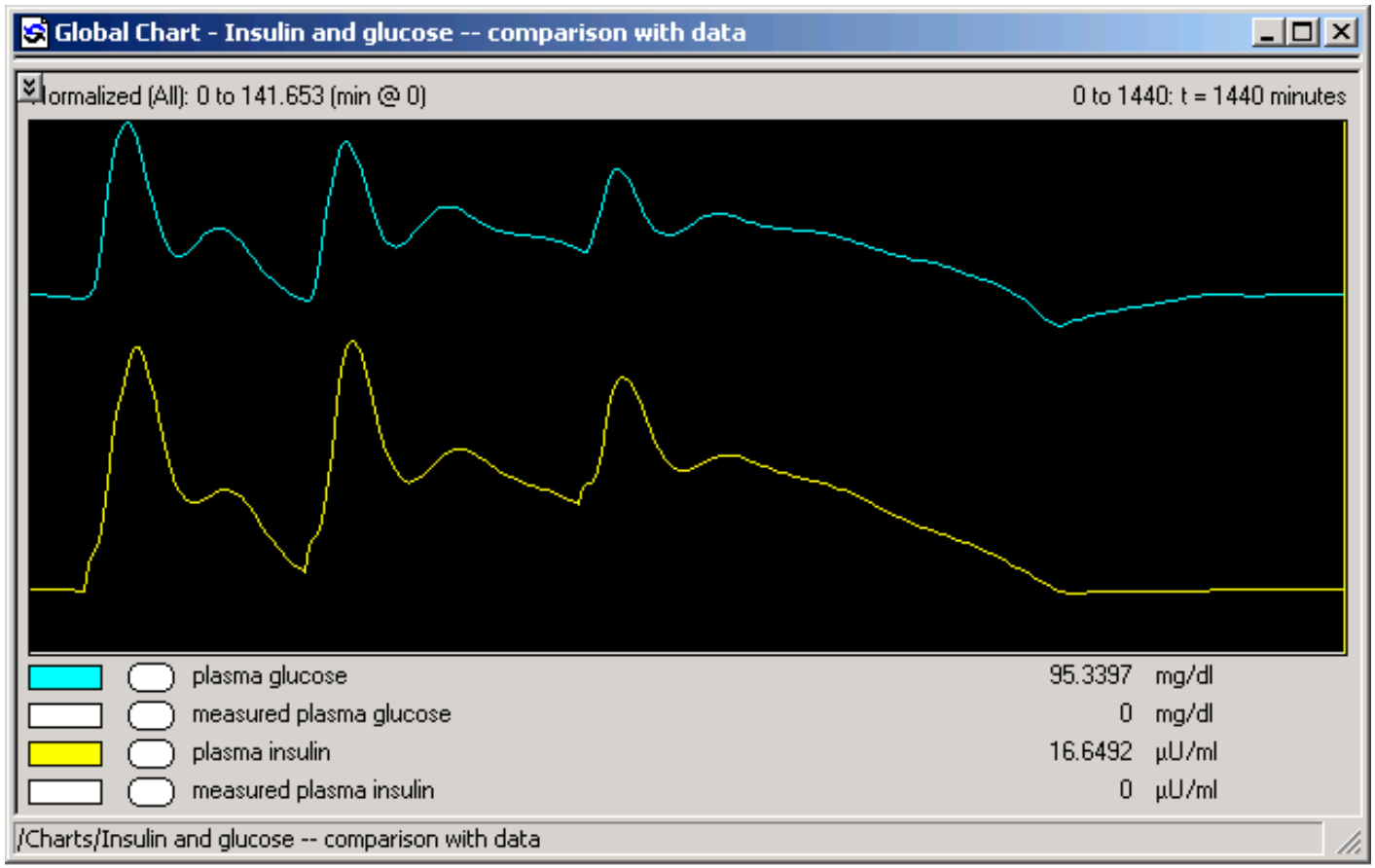
Metabolic response to a 24 hour fast





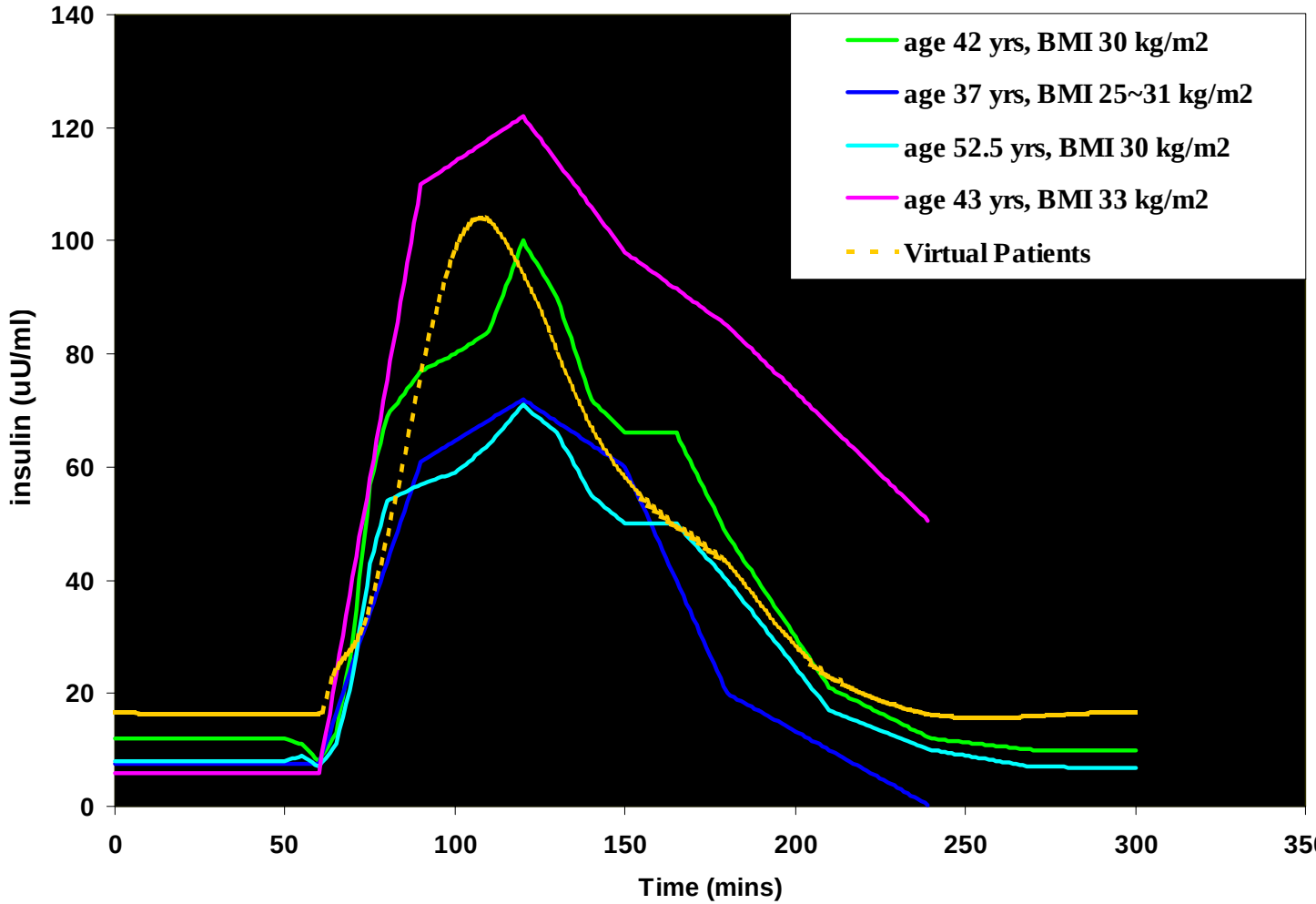
General Tests on Virtual Patients

Post-prandial concentrations and fluxes



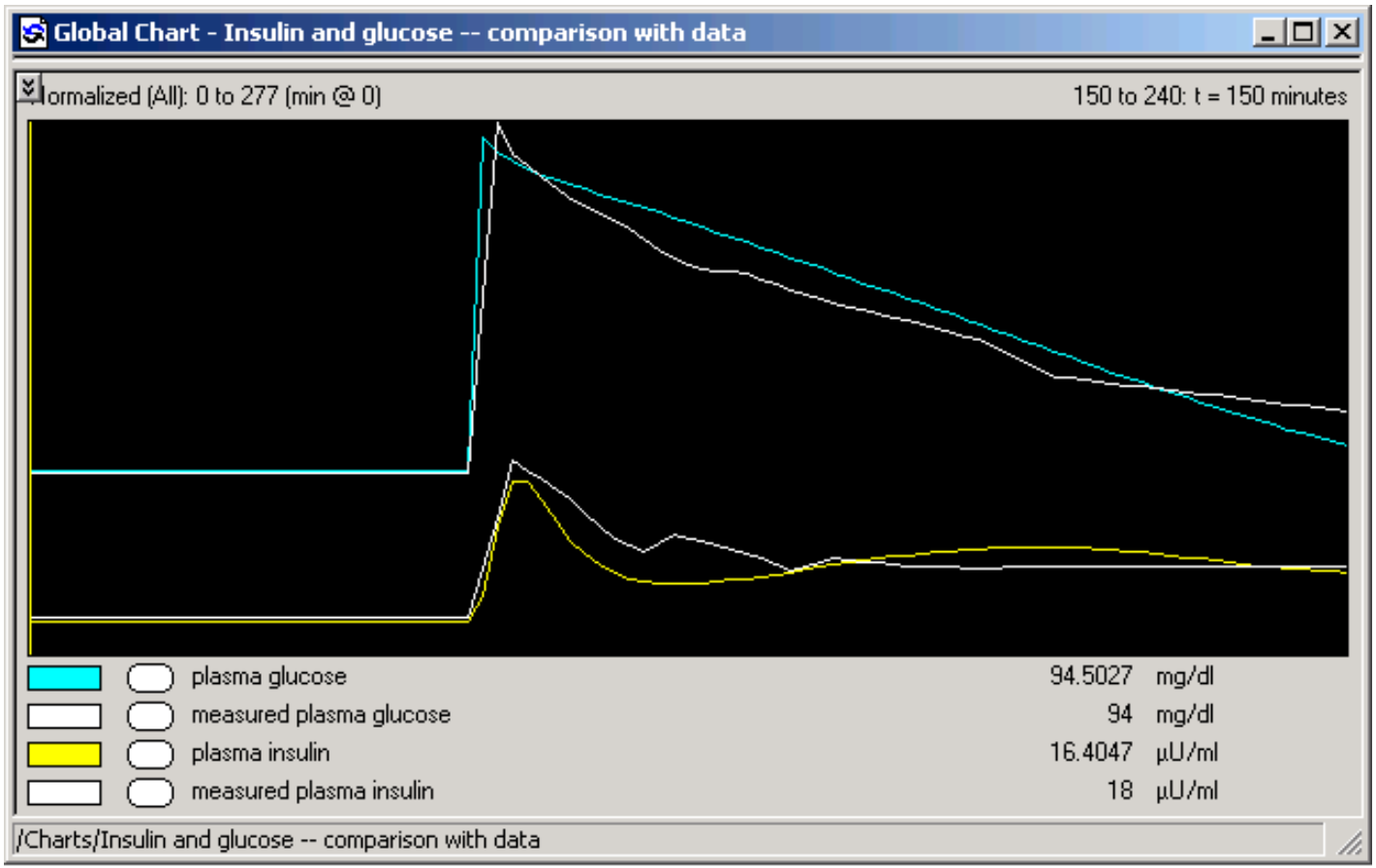
General Tests on Virtual Patients

Oral glucose tolerance test (OGTT)



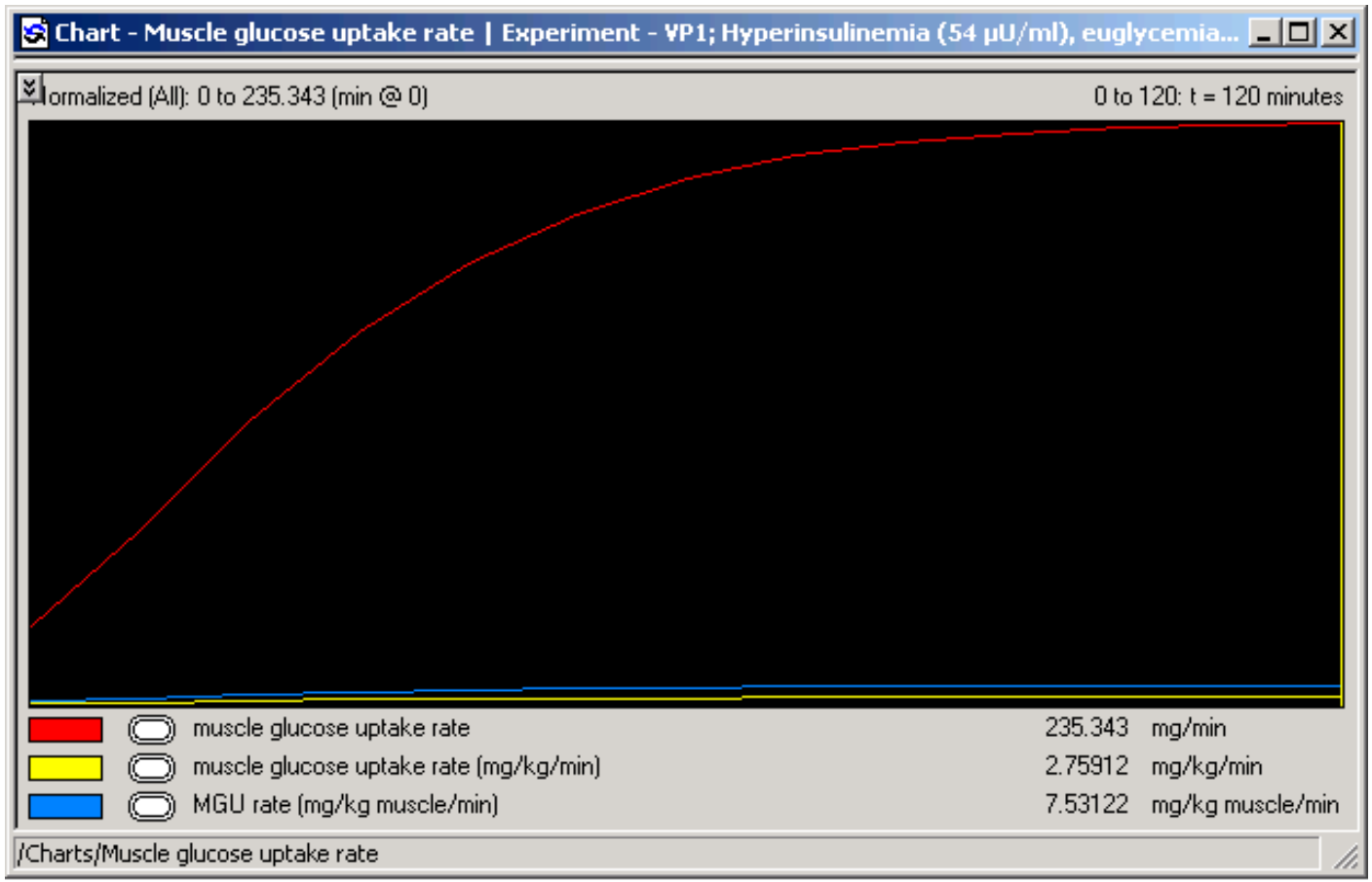
General Tests on Virtual Patients

Intravenous glucose tolerance test (IVGTT)



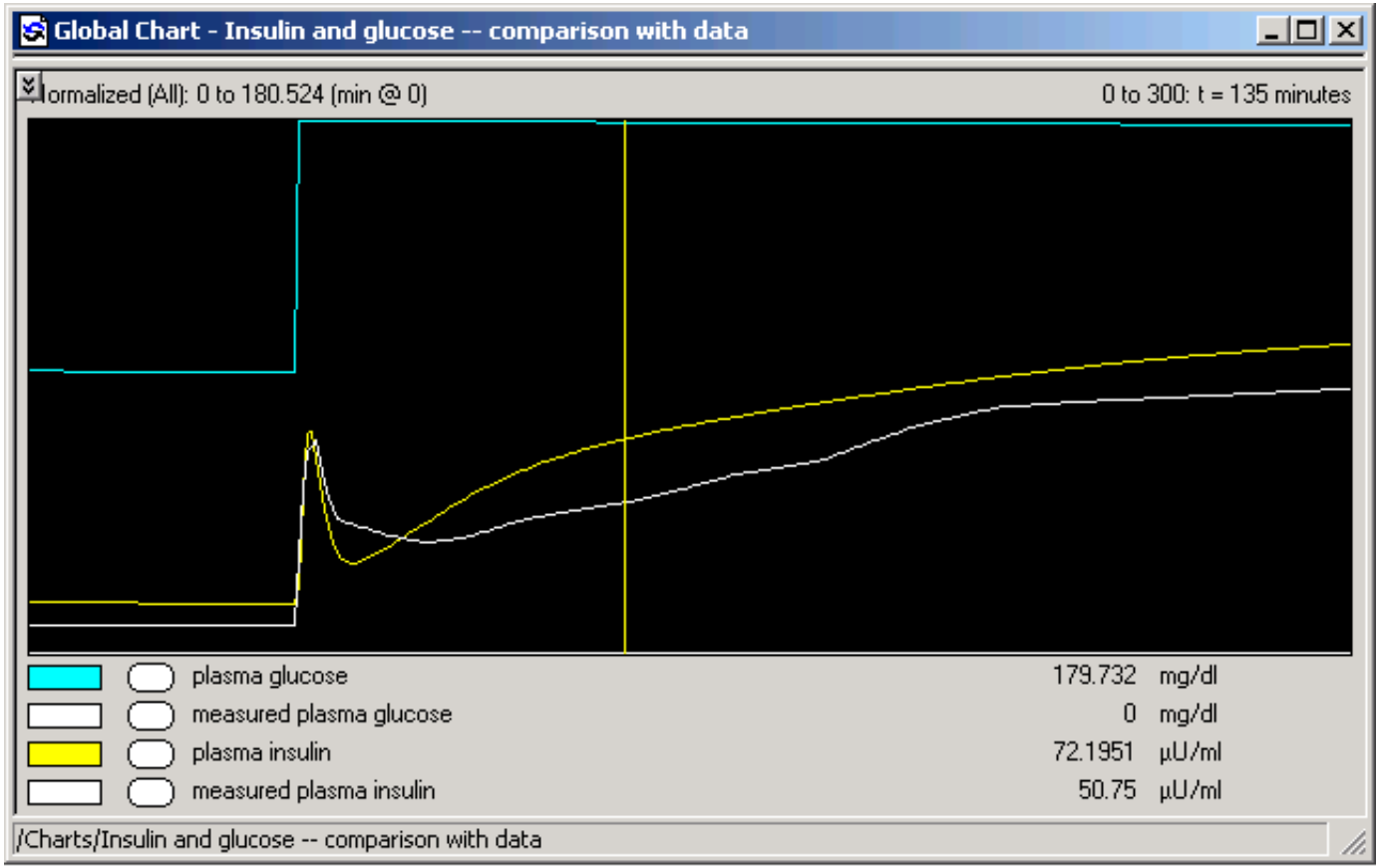
General Tests on Virtual Patients

Euglycemic-hyperinsulinemic clamp



General Tests on Virtual Patients

Hyperglycemic clamp



Summary

- Understand the mechanism of action of the target
- Identify the inconsistencies in experimental data
- Distinguish between subtypes of patients

- ***Next steps – Optimize Trial Designs****: Test the efficacy of the target through simulation on control and diabetic virtual patients*