Rainbow Babies
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The Metabolome Component of the Digital Astronaut

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Multiscale Model of Metabolism

- Develop multiscale computational model of skeletal muscle metabolism which integrates
  - Cellular biochemical processes to muscle fibers
  - Skeletal muscle and other organs/tissues metabolism to whole body metabolic function

- Predict the metabolic response of skeletal muscle and whole body to acute exercise after a period of space travel or training.

Dynamic Physiological Responses

- Investigate mechanisms of metabolic regulation in tissues/organs and entire organism during conditions that challenge ATP homeostasis:
  - Ischemia
  - Hypoxia
  - Exercise
    - Rest-work Transition
    - Exercise-Recovery Transition
    - High intensity exercise

Time Course of Adaptations

- Exercise training is recommended to:
  - Maintain or loose weight
  - Prevent/slow down chronic disease development
  - Improve insulin sensitivity
  - Reduce blood pressure and/or cholesterol levels
  - Improve aerobic capacity or performance
  - Minimize medical problems associated with military operations in mountainous terrains
  - Counteract the deleterious effects of long-duration space travel

Effects of Chronic Unloading

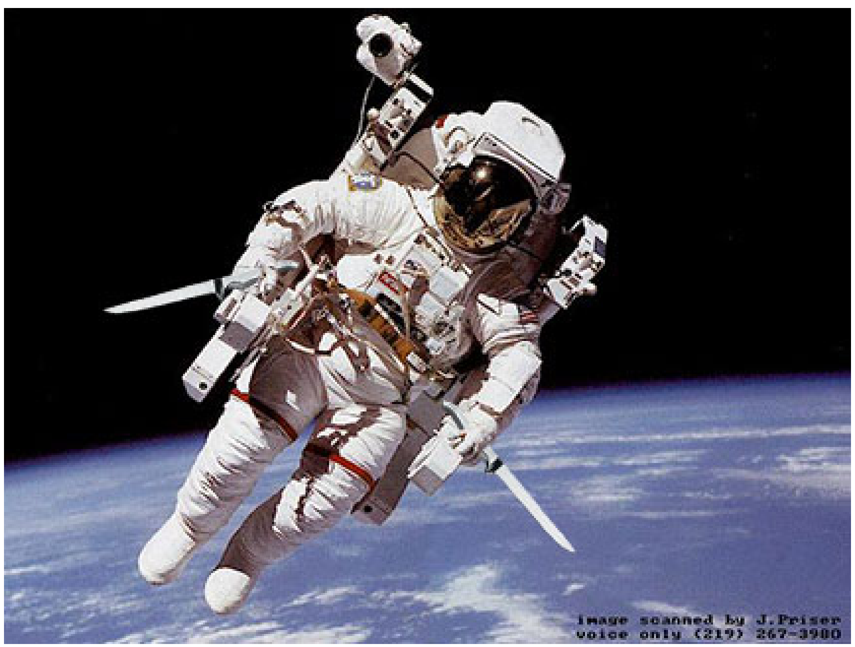
- Chronic unloading (e.g., space travel, physical inactivity, bed rest, limb immobilization) induces alterations in skeletal muscle structure, metabolism, and function.

- Endurance and/or resistance training programs may compensate for the loss of muscle mass and function and overall reduced work capacity consequence of long duration spacetravel.

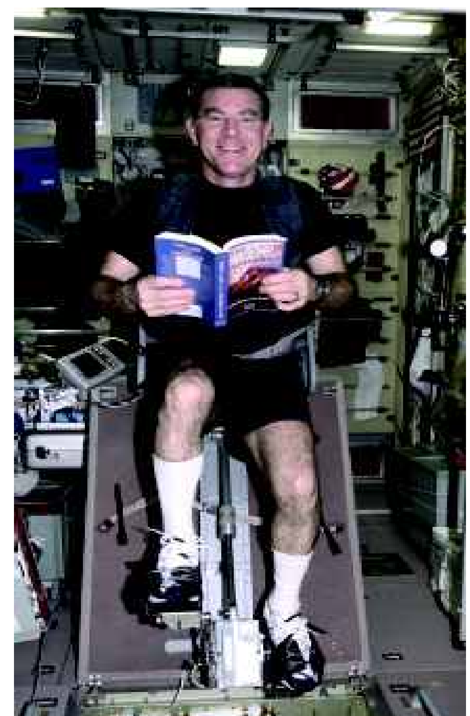
Long-term Goals

1) Predict astronaut's skeletal muscle and whole-body **metabolism and function** during altered loading states

- Prolonged space travel

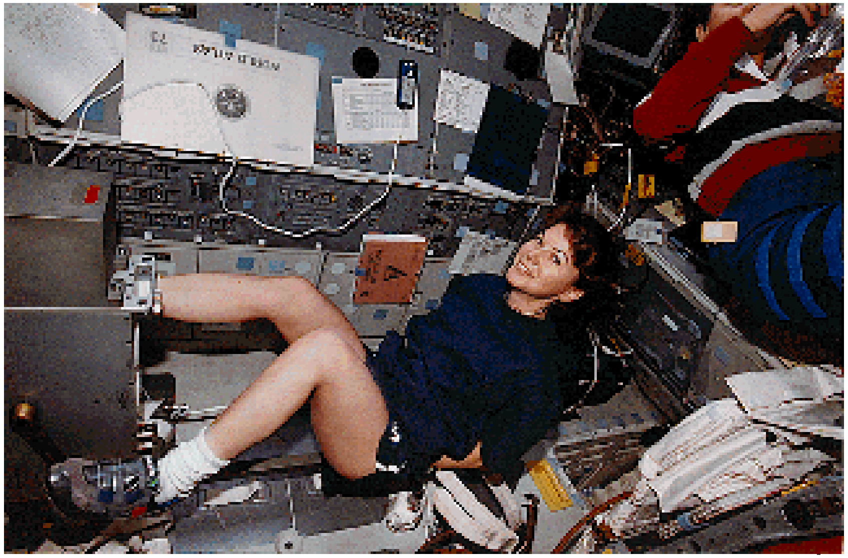


- Exercise training



Long-term Goals

2. Develop countermeasures that take into account the time course of muscle atrophy and its metabolic correlates



$$V_{c,j}\frac{dC_{c,j}}{dt}=\sum_{p}\beta_{c,j,p}\phi_{c,p}-\sum_{u}\beta_{c,j,u}\phi_{c,u}+J_{b\leftrightarrow c,j}$$

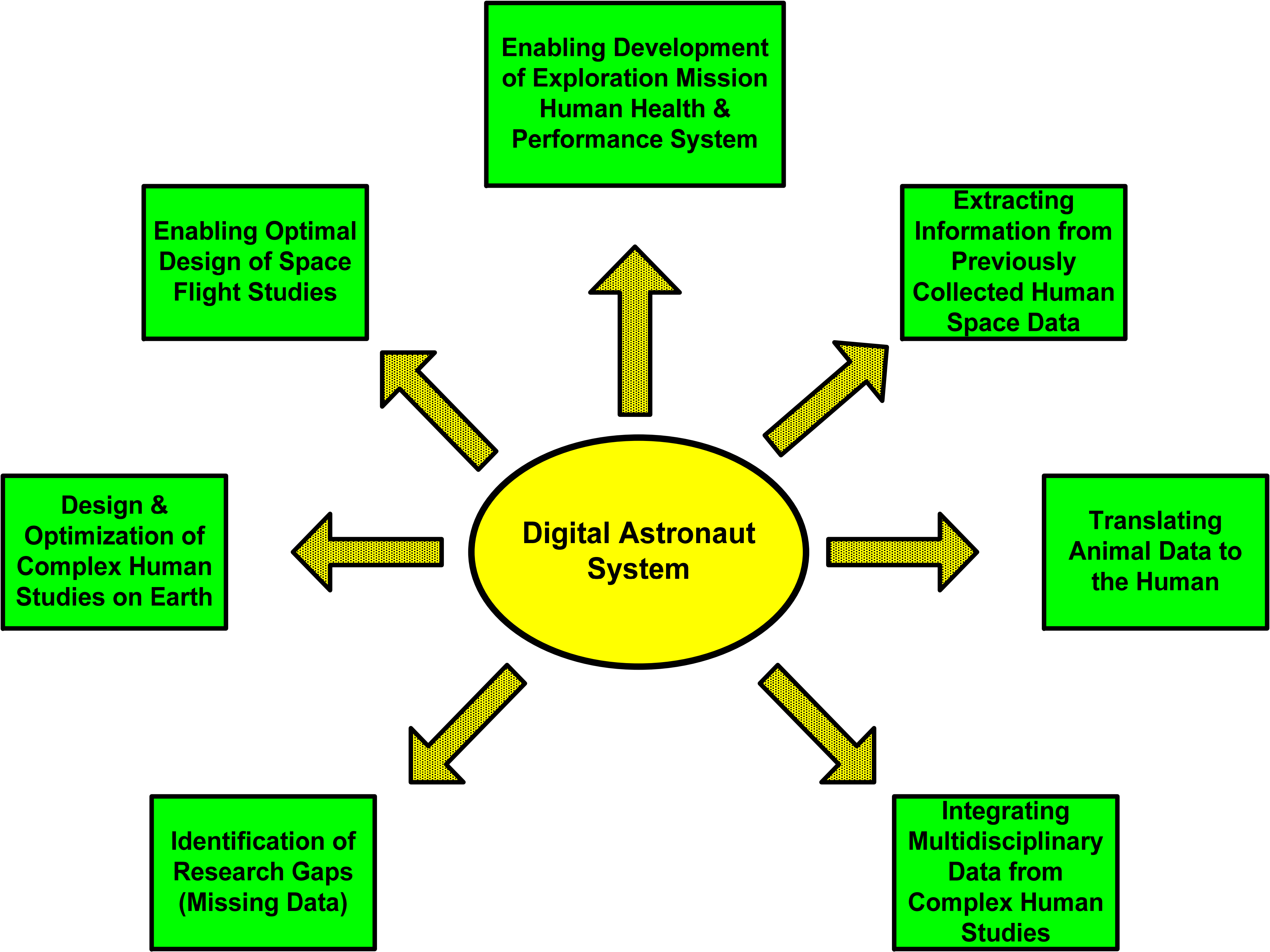
	Control	Trained	Space
Vmax, GLY-G6P	1.72	1.72	2.08
Vmax, G6P-GAP	1.63	1.45	1.91
Vmax, PYR-LAC	8.81	6.86	8.81
Vmax, FAC-ACA	0.95	1.2	0.77
Vmax, ACA-CIT	6.84	9.54	5.71
Vmax, SUC-OXA	5.87	8.8	4.89
Vmax, O_2-H_2O	24.6	35.2	20.3

The Digital Astronaut

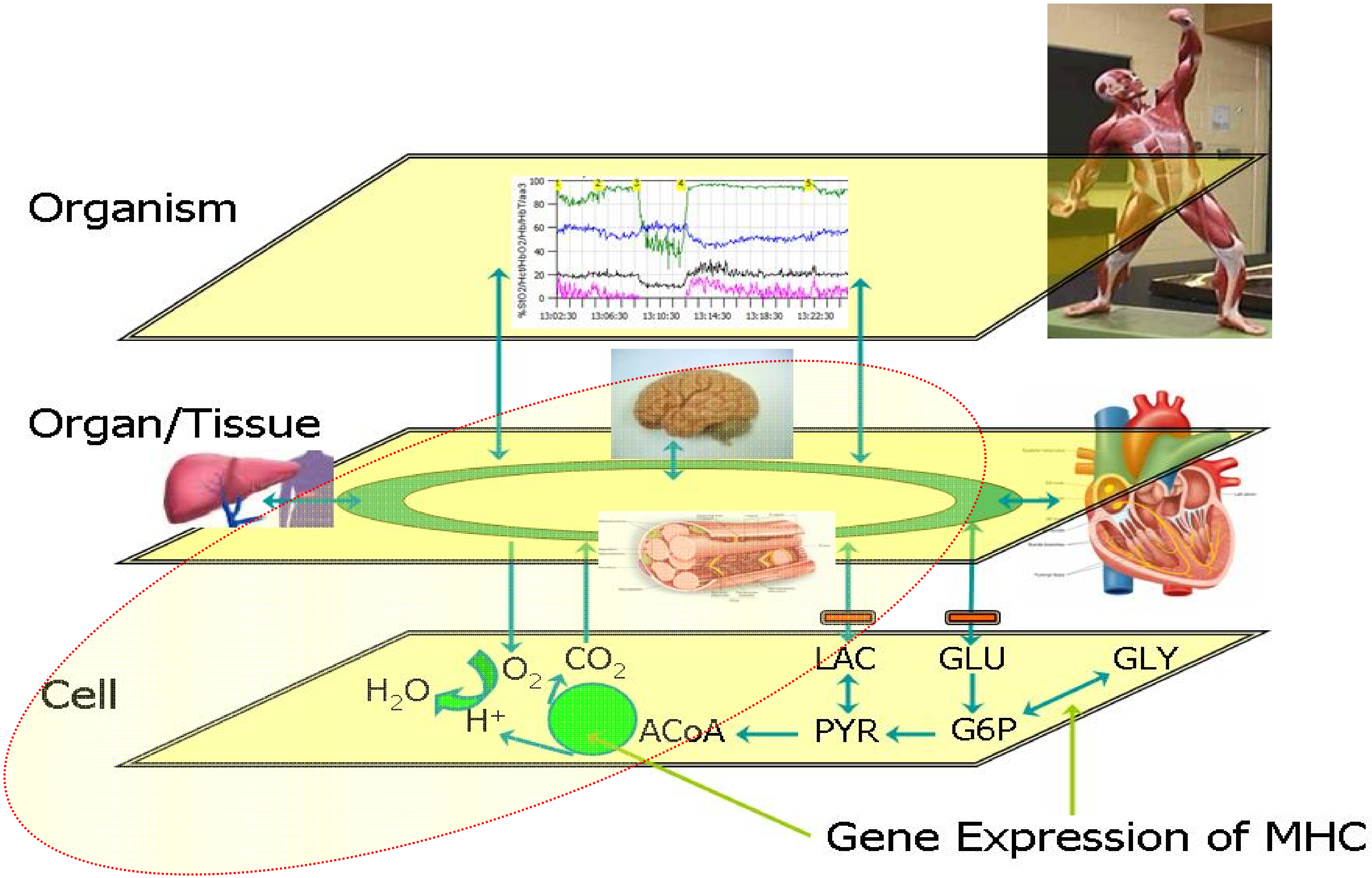
The Digital Astronaut

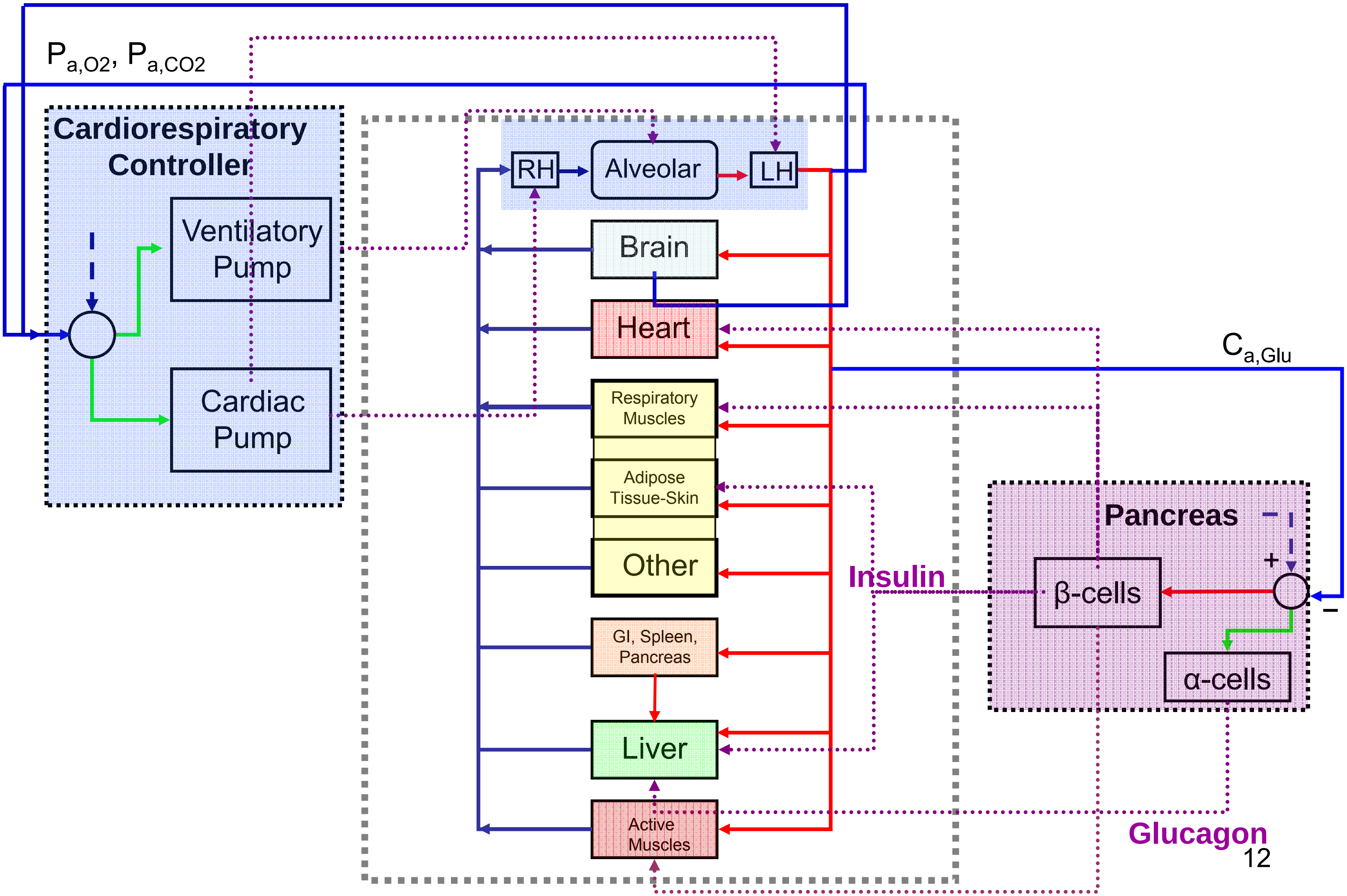
- It provides a modern, general, multi-disciplinary **simulation infrastructure** that can utilize the **data** from human physiological research for **predictive** purposes:
  - *Need for countermeasures*
  - *Consequence of countermeasure activity in space*

White RJ and McPhee JC. Acta Astronautica 2007


Enabling Development of Exploration Mission Human Health & Performance System
Enabling Optimal Design of Space Flight Studies
Extracting Information from Previously Collected Human Space Data
Design & Optimization of Complex Human Studies on Earth
Digital Astronaut System
Translating Animal Data to the Human
Identification of Research Gaps (Missing Data)
Integrating Multidisciplinary Data from Complex Human Studies

Structural Integration - Multiscale



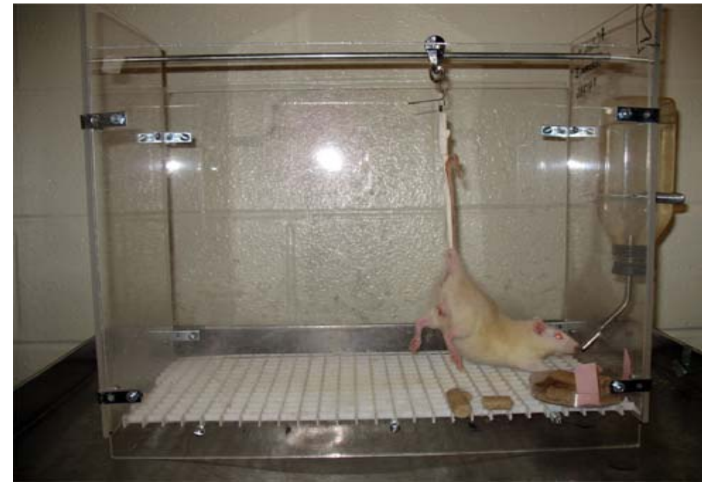


$P_{a,O2}$, $P_{a,CO2}$
Cardiorespiratory Controller
Ventilatory Pump
Cardiac Pump
RH
Alveolar
LH
Brain
Heart
Respiratory Muscles
Adipose Tissue-Skin
Other
GI, Spleen, Pancreas
Liver
Active Muscles
$C_{a,Glu}$
Insulin
Pancreas
β-cells
α-cells
+
–
Glucagon

Sources of Information

- Space flight
  - Skylab and Spacelab missions
  - International Space Station Research
- Earth-based Analogue Studies (Humans)
  - Bed rest; Unilateral Lower Limb Suspension
- Earth-based Analogue Studies (Rats)
  - Hindlimb Suspension
  - Treadmill running

Data on Loading/Unloading



Limitations in the Development & Validation of Multiscale Models

- Scarce *in vivo* data in humans
- Use of *in vitro* data not completely satisfactory when examining regulatory mechanisms in vivo
- Biological samples comprise multiple compartments
- Few data on dynamic responses to stimuli or time course of adaptations
- Simultaneous phenomena not simple to measured in region investigated
- Numerous unknown parameters to be estimated
- Genomic/proteomic information difficult to incorporate in mechanistic or phenomenological models

Alternative Approaches

- Interleaved ^{1}H and ^{31}P NMR spectroscopy and ^{1}H NMR imaging
- Near infrared spectroscopy
  - Ambiguous spatial and molecular origins of re-emitted signal
- Mass spectroscopy
  - Limited to one tracer per experiment
- Constrained large-scale parameter estimation (thermodynamic, energy, physiological constrains)

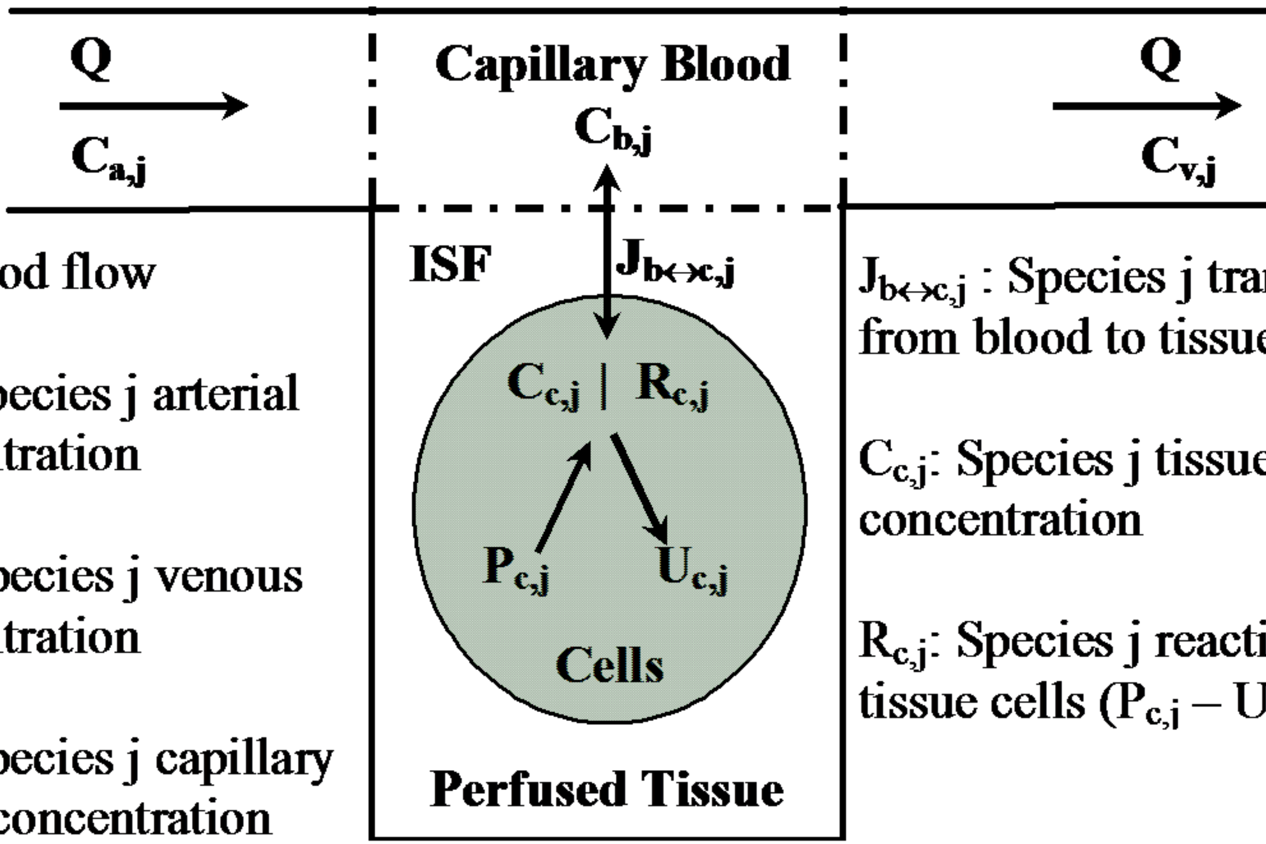
New Initiatives-Collaborations

- France
  - Pierre Carlier
    - Institute of Myology, Pitie-Salpetriere University Hospital, Paris
    - *Understanding the Regulation of Respiration in vivo as a Multiscale Complex System*
- Italy
  - Bruno Grassi
    - Università degli Studi di Udine, Udine, Italia
    - *Central and Peripheral Factors Contributing to the Impaired Oxidative Metabolism in Microgravity: Experimental and theoretical approach*

Multiscale Model Components

- Data on initial values of metabolites + parameters
- Metabolic maps and flux balance analysis
- Flux-metabolites relationships
- Mass and energy balance equations
- Physiological and thermodynamic constraints
- Input functions
- Metabolic control systems
- Modules incorporating human adaptation

Model of Blood-Tissue Unit



Q: Blood flow

$C_{a,j}$: Species j arterial concentration

$C_{v,j}$: Species j venous concentration

$C_{b,j}$: Species j capillary blood concentration

$J_{b\leftrightarrow c,j}$: Species j transport rate from blood to tissue cells

$C_{c,j}$: Species j tissue cells concentration

$R_{c,j}$: Species j reaction rate in tissue cells ($P_{c,j} - U_{c,j}$)

$$P_{c,j} = \sum_p \beta_{c,j,p}\phi_{c,p} \quad \text{and} \quad U_{c,j} = \sum_u \beta_{c,j,u}\phi_{c,u};$$

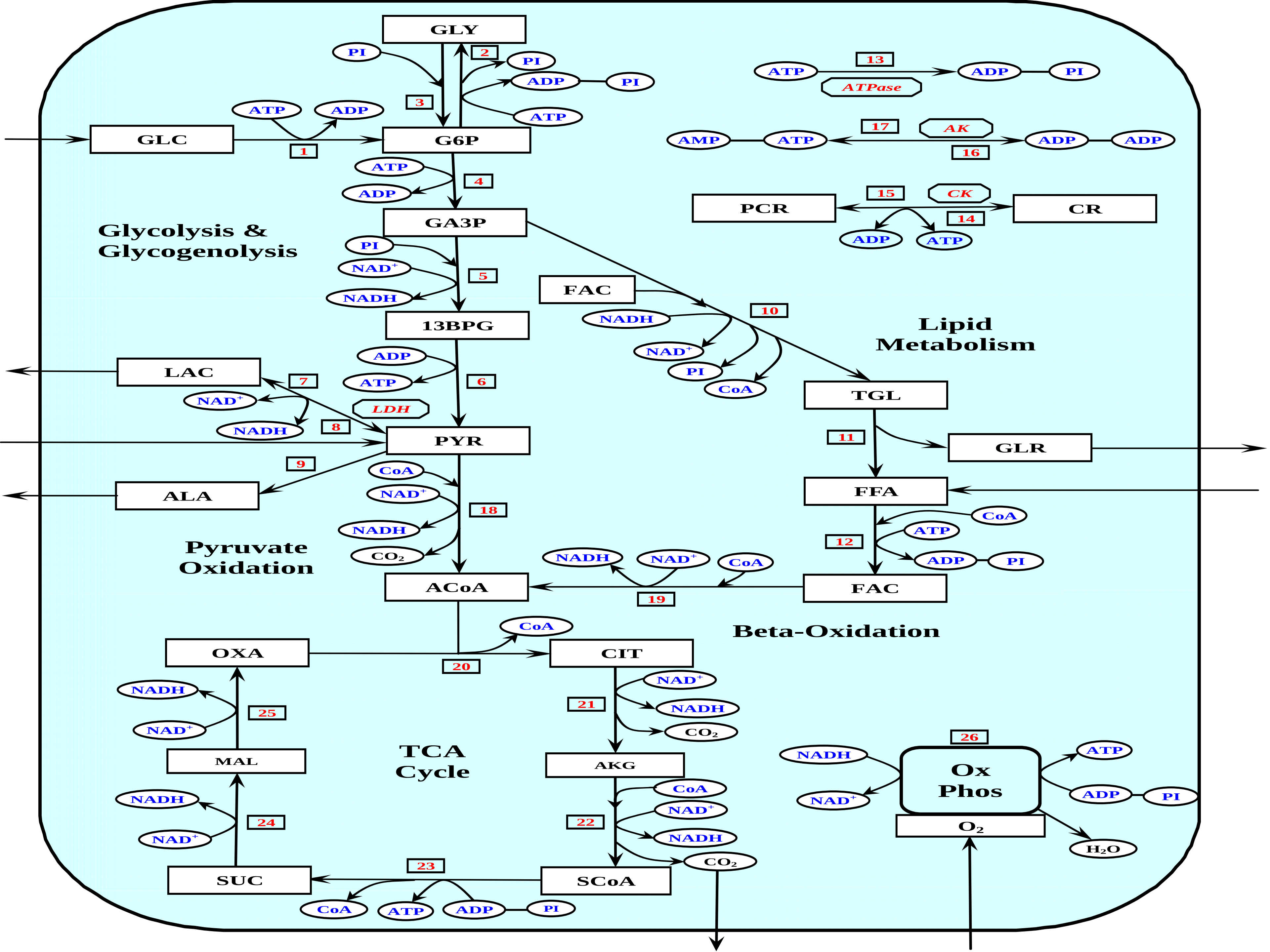
ϕ: reaction fluxes; β: stoichiometric coefficients

Dynamic Mass Balance Equations

Blood: $$\left(V_{b,j}+V_{isf,j}\right)\frac{dC_{b,j}}{dt}=Q\left(C_{a,j}-C_{b,j}\right)-J_{b\leftrightarrow c,j}$$ (8 ODEs)

Cells: $$V_{c,j}\frac{dC_{c,j}}{dt}=\sum_{p}\beta_{c,j,p}\phi_{c,p}-\sum_{u}\beta_{c,j,u}\phi_{c,u}+J_{b\leftrightarrow c,j}$$ (30 ODEs)

- Q: muscle blood flow,
- $J_{b\leftrightarrow c,j}$: net inter-domain transport fluxes,
- $\phi_{c,p}$, $\phi_{c,u}$: metabolic reaction fluxes in cells,
- $\beta_{c,j,p}$, $\beta_{c,j,u}$: stoichiometric coefficients.



GLY
GLC
G6P
GA3P
13BPG
PYR
LAC
ALA
ACoA
FAC
TGL
GLR
FFA
PCR
CR
OXA
CIT
AKG
SCoA
SUC
MAL
Ox Phos
O_2
H_2O
CO_2
ATP
ADP
AMP
PI
NAD+
NADH
CoA
ATPase
AK
CK
LDH
Glycolysis & Glycogenolysis
Lipid Metabolism
Pyruvate Oxidation
Beta-Oxidation
TCA Cycle
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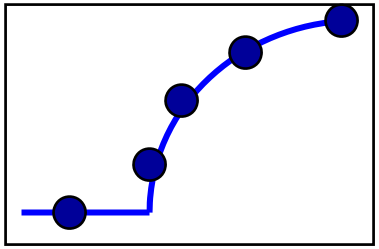
Adaptations and System Response

System

Skeletal Muscle Metabolism



Chronic Stimulus

Adaptation at Cellular Level

Response at Tissue Level

Skeletal Muscle Adaptations

Muscle Characteristic	**Endurance Training (~ 8 wk)**	**Space Travel (~ 3-4 wk)**
Cross sectional area	↔	↓ 8%
Capillary density	↑	↓
Mitochondrial content	↑	↓ 50%
Blood flow	↑	↓ ↔
Glycolytic enzymes	***↓ 5-7 %***	***↑ 15-17 %***
Lipolytic enzymes	***↑ 80-100 %***	***↓ 45-75 %***
Oxidative enzymes	***↑ 60-80 %***	***↓ 20-40 %***
↑ increase; ↓ decrease; ↔ no change		

Maximal Reaction Velocities

	Untrained	Trained	Detrained
$V_{max, GLY-G6P}$	1.72	1.72	2.08
$V_{max, G6P-GAP}$	1.63	1.45	1.91
$V_{max, PYR-LAC}$	8.81	6.86	8.81
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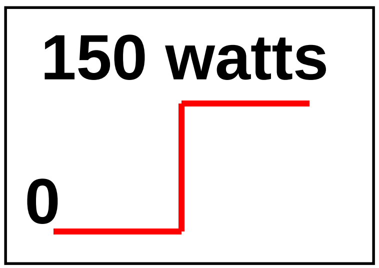
Step Response after Intervention

Input



Computer Model

$$V_m \frac{dC_{m,i}}{dt} = P_i - U_i + Q_m(C_a - \sigma C_{m,i})$$

System of non-linear algebraic and differential equations

	Untrained	Trained	Detrained
Vmax, GLY-G6P	1.72	1.72	2.08
Vmax, G6P-GAP	1.63	1.45	1.91
Vmax, PYR-LAC	8.81	6.86	8.81
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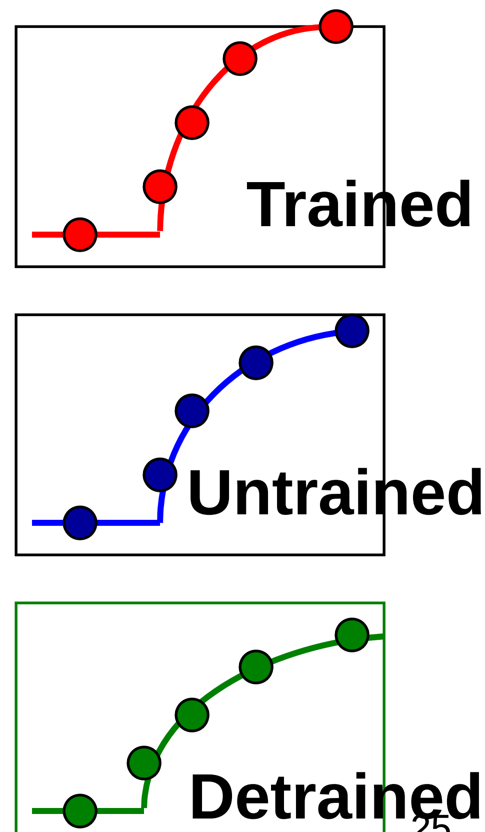
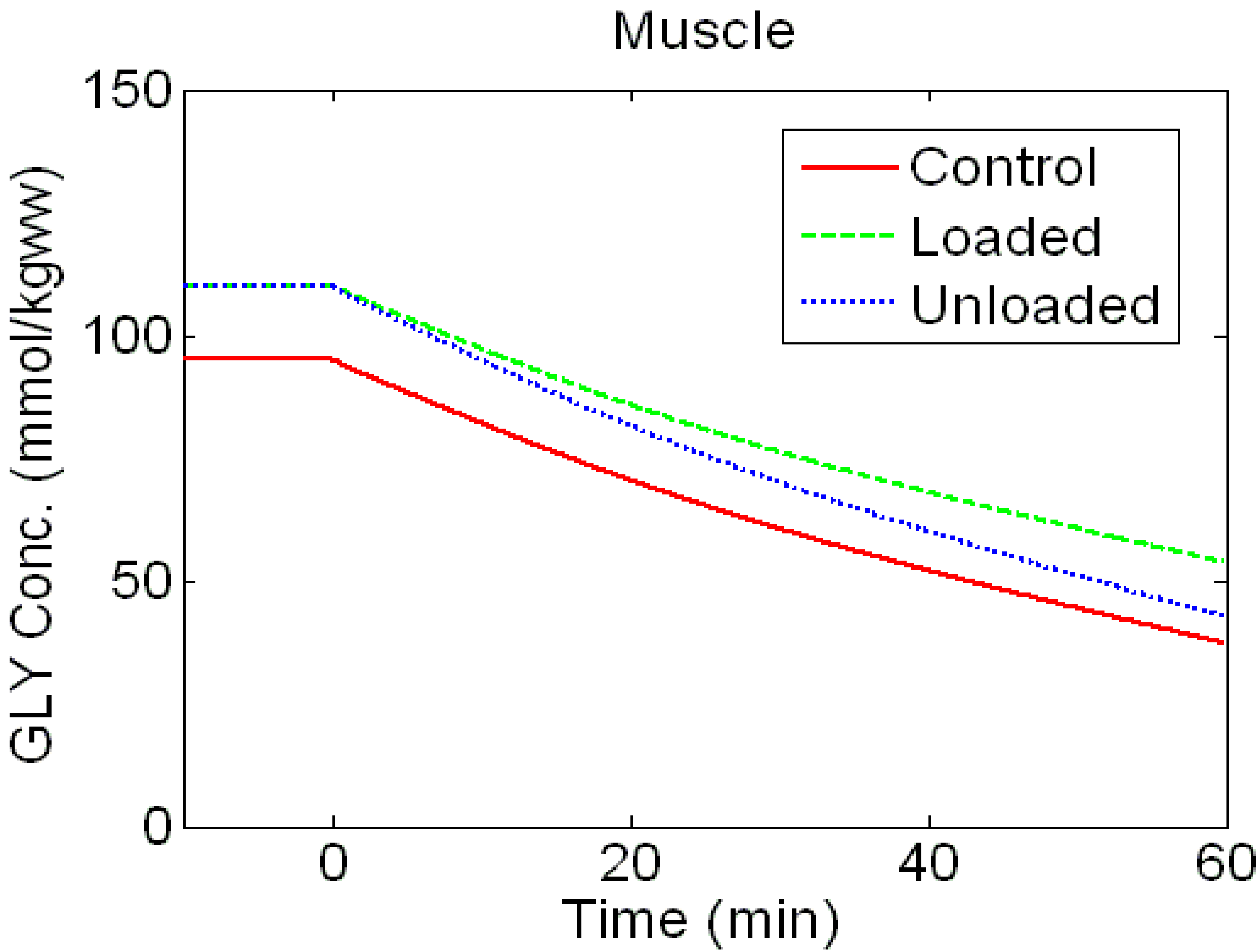
Outputs



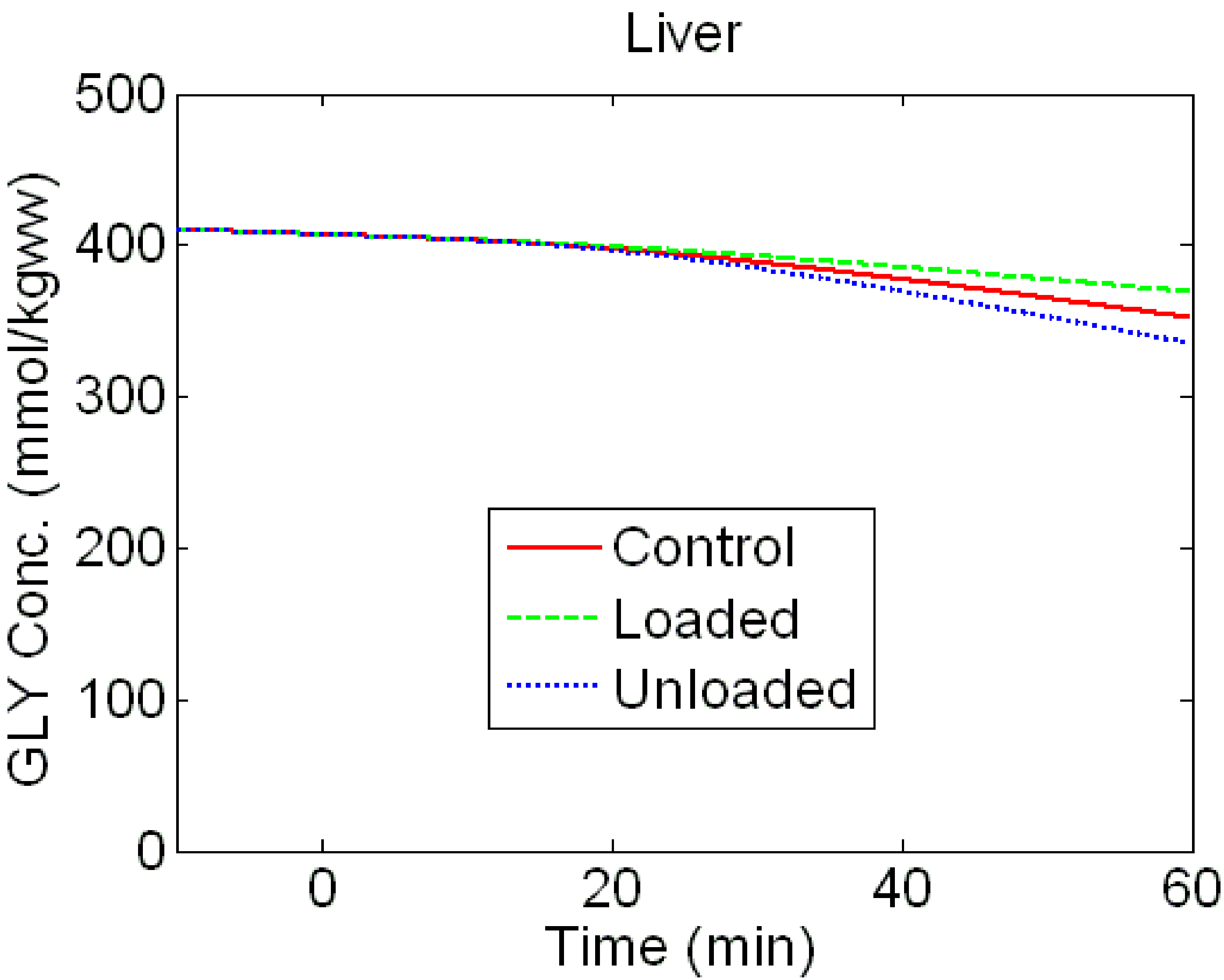
Predicting Integrated Response

- **Input**: Acute exercise bout
- **System**: Skeletal Muscle – Whole Body
  System Adaptations *due to space travel or endurance exercise training*
- **Outputs**
  - Glycogen concentration (muscle – liver)
  - Arterial glucose balance
  - Respiratory quotient and respiratory exchange ratio
  - Glucose and lactate metabolism and exchange
  - Fuel distribution and oxidation patterns

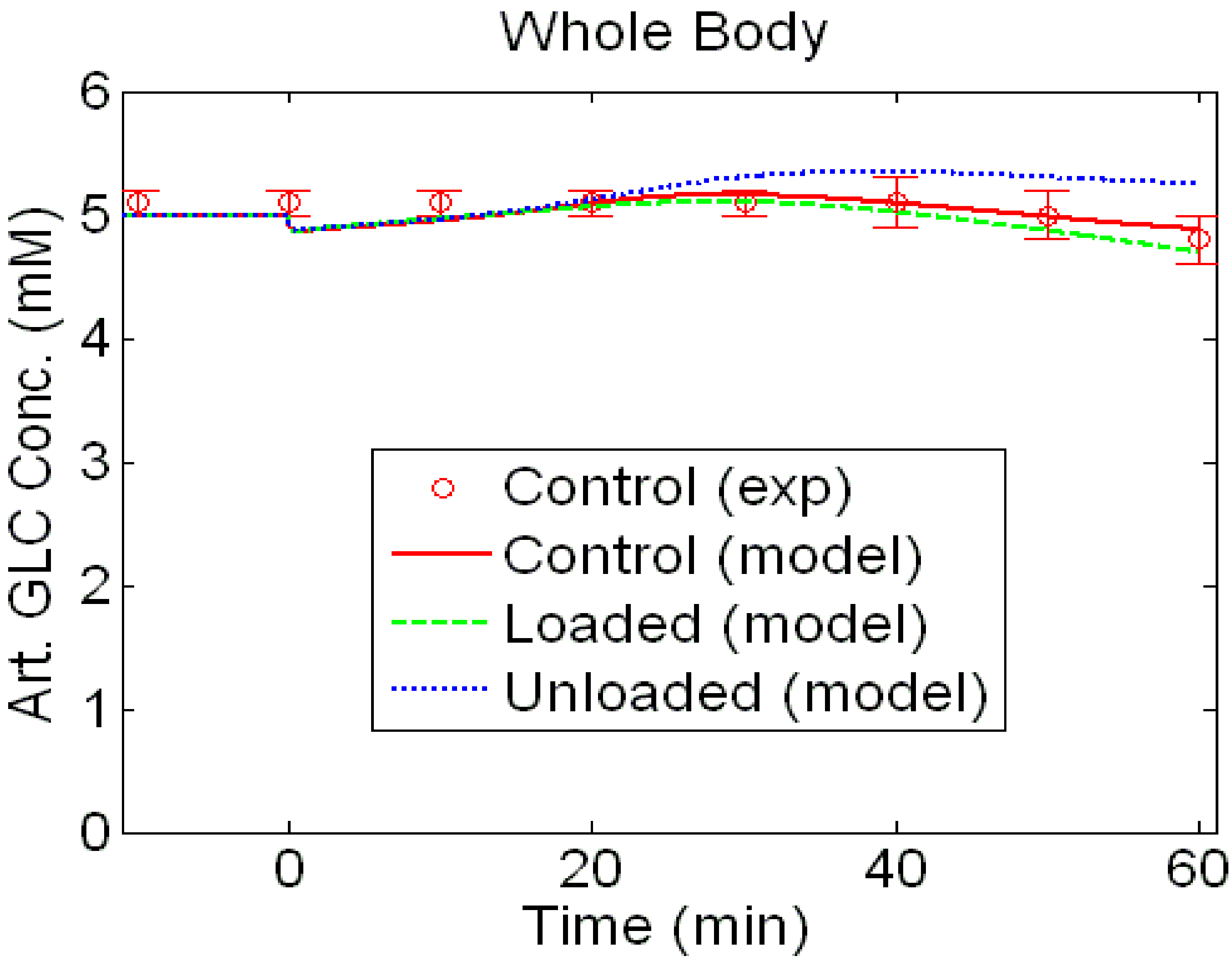
Muscle Glycogen



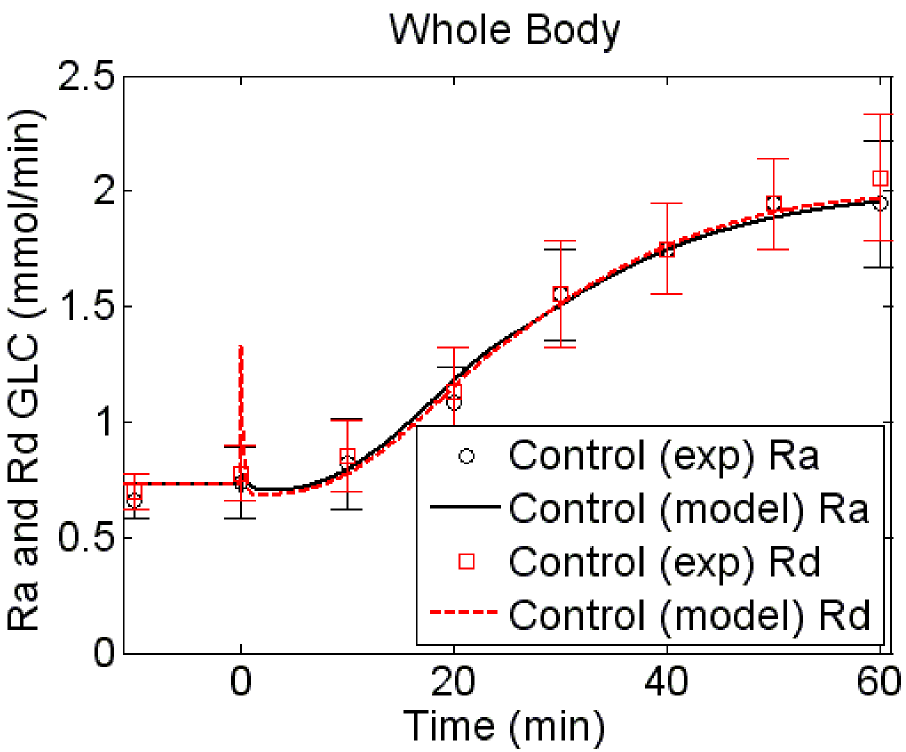
Liver Glycogen

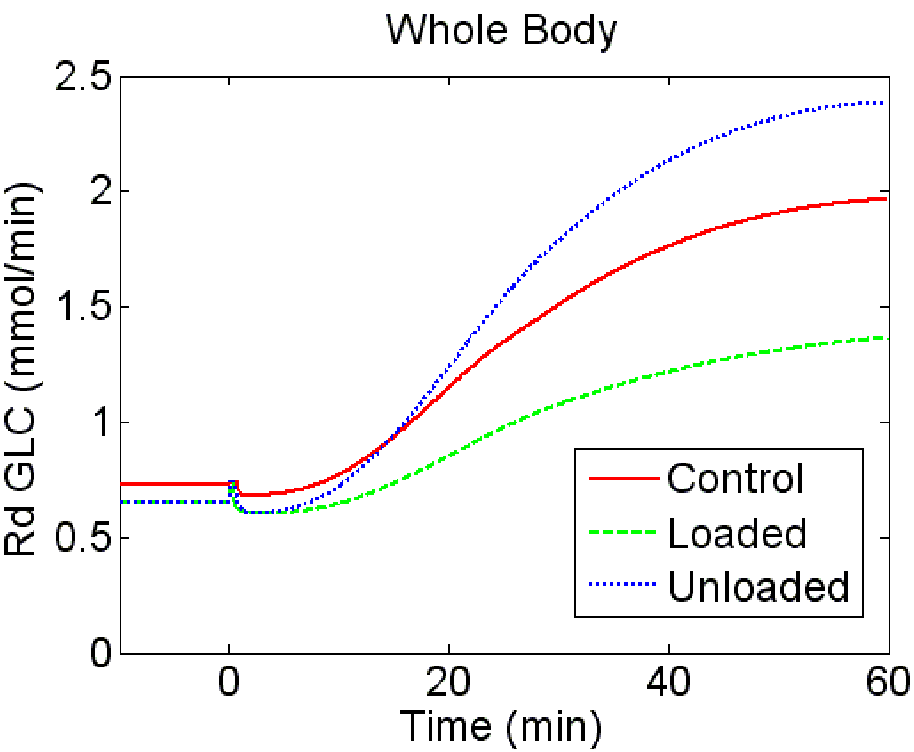


Arterial Blood Glucose

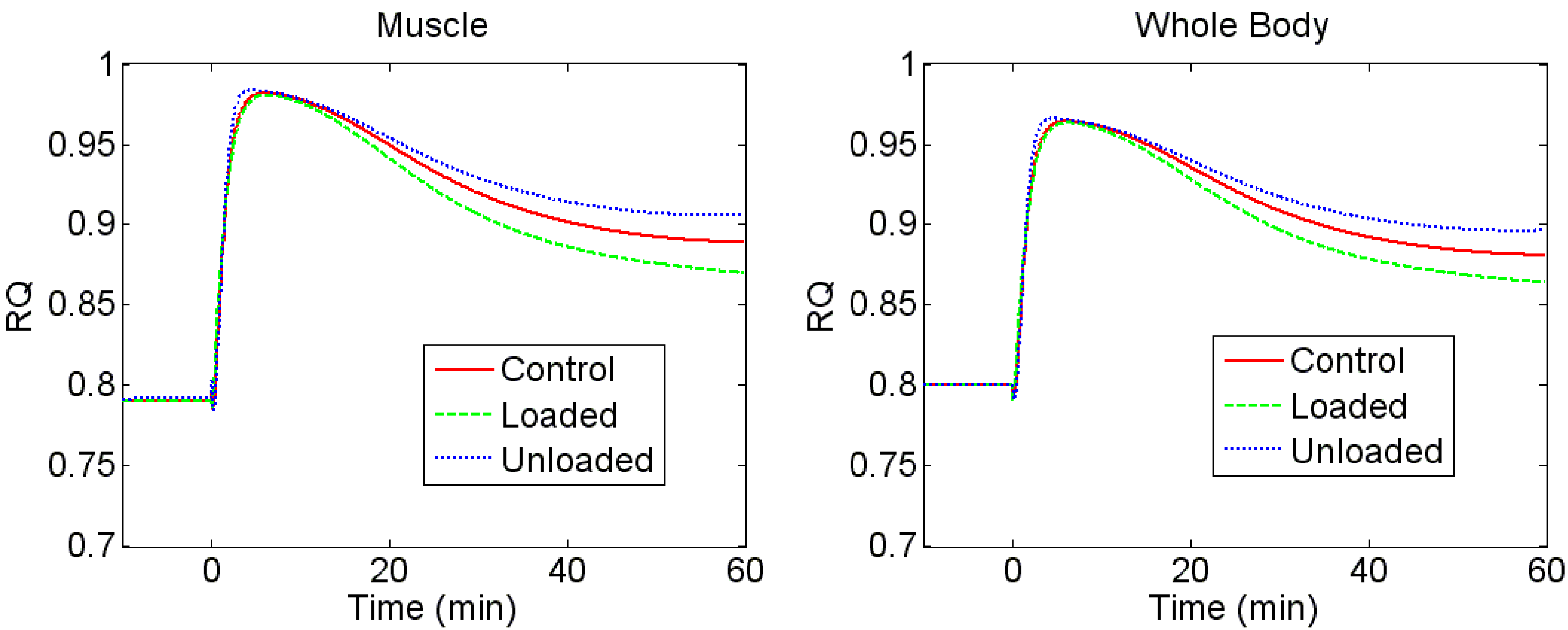


Rate of Glucose Appearance

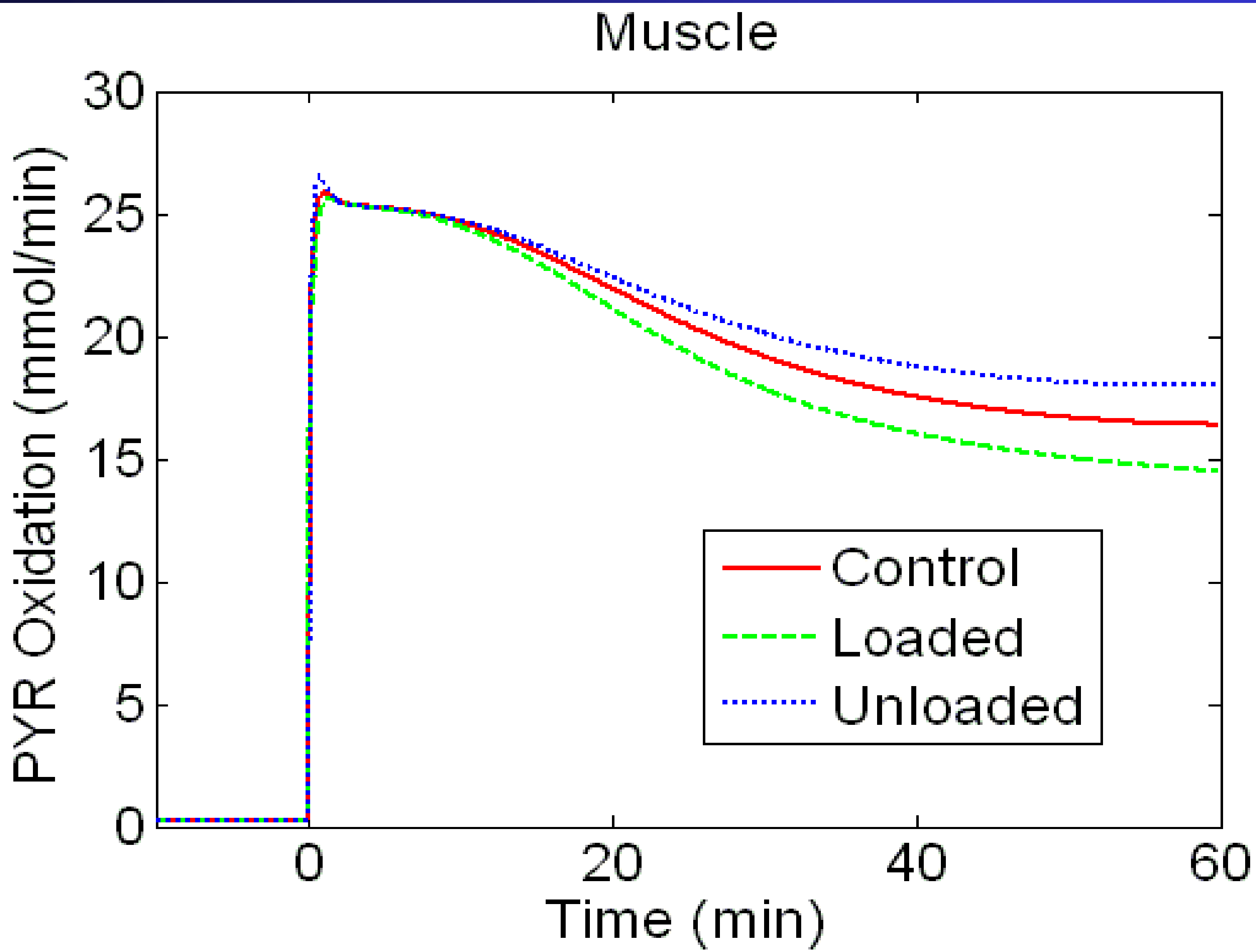




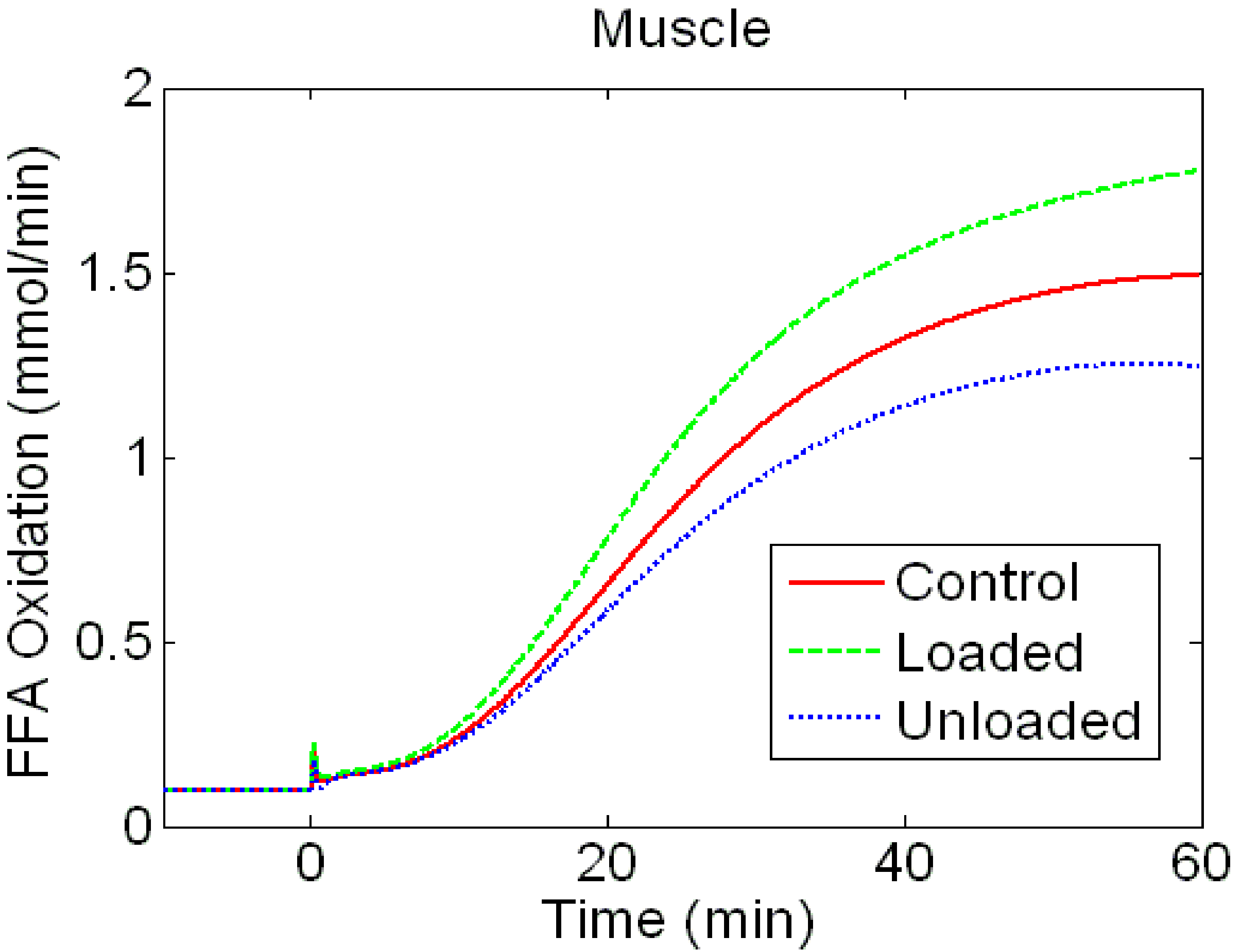
Respiratory Quotient



Pyruvate Oxidation



Fatty Acid Oxidation



Conclusions

- The dynamic responses of skeletal muscle and whole body
  - Glycogen and glucose concentrations
  - Respiratory quotient
  - Rates of pyruvate and fatty acids oxidation

to a step change in work rate can be predicted with the help of physiologically-based computational models.

Conclusions (Cont.)

- Changes in these responses from control values were used to quantify the effect of *Unloading (induced by space travel) and Loading (induced by endurance training)* on skeletal muscle, liver, and whole-body metabolism.

- Computer simulations predict a fuel shift and increased reliance on carbohydrate oxidation during exercise after prolonged space travel from alterations at cellular level

Staff and Students in Multiscale Modeling and Experimental Studies

Kinetic Modeling: Ranjan K. Dash, Ph.D.
Experimental Studies – Unloading: Ilya BVederman, Ph.D.
Experimental Studies – Exercise Training: Fatima F. Silva, Ph.D.
Postdoctoral Fellows: Nicola Lai, Ph.D. (O_2 transport and metabolism)
Marco Camesasca, Ph.D. (Adaptations Model)

Graduate Students:

Russell Valentine – Multiscale model and exercise responses after loading/unloading
Jaeyeon Kim – Whole-body models of glucose homeostasis
Model of adipose tissue
Yanjun Li – Model of skeletal muscle metabolism
Lufang Zhou – Model of cardiac metabolism
Haiying Zhou – Multi-organ model of cardiorespiratory control

***Undergraduate Students:** Leigh Praskac, Jeffrey Shuster, Steven Ewart John DiBella*

***Laboratories:** Computational Physiology Lab; Rodent Exercise and Metabolism Lab; Human Performance and Exercise Physiology Lab*

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