The systems physiology of exercise

Professor Graham Kemp

Department of Musculoskeletal Biology, Institute of Ageing & Chronic Disease

Magnetic Resonance & Image Analysis Research Centre

University of Liverpool

ASE Annual Conference

Biology in the Real World: A Sporting Chance

6 January 2012

Plan

- ‘System physiology’
- Exercise & ‘the human machine’
- Methods: VO_2, MRS and others
- Interpreting ^{31}P MRS data
- Integrating the methods
- Simulation
- Key concepts & implications for interventions

‘System physiology’

UNIVERSITY OF LIVERPOOL

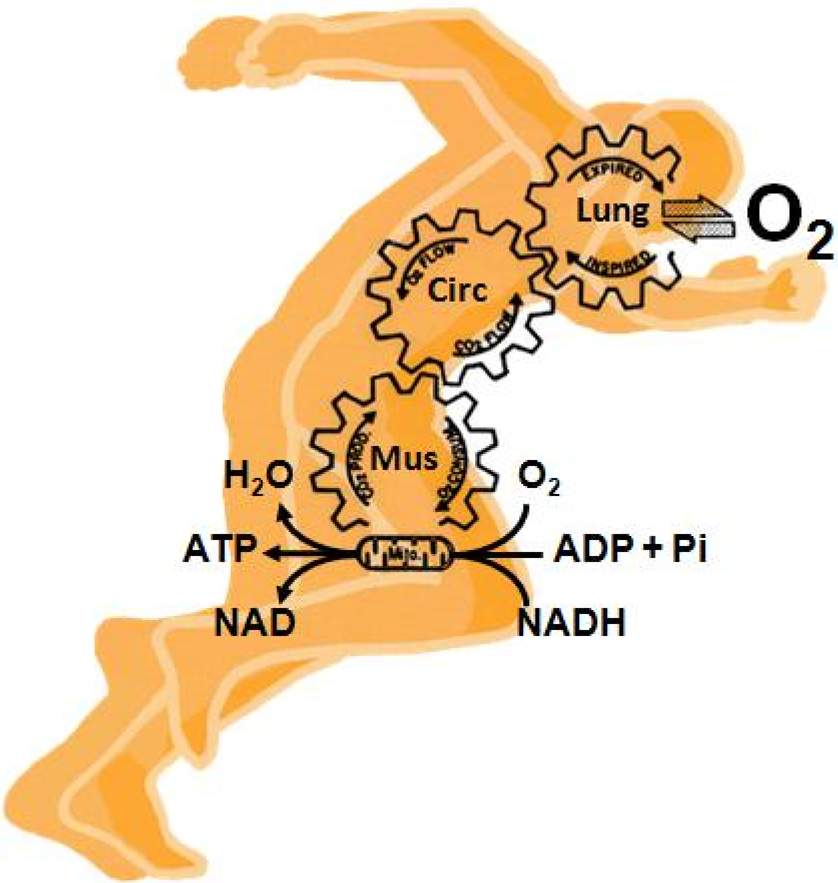
- Just physiology?
- The parts (‘modules’) and the whole
- Interactions & causation
- Quantification, analysis & simulation
- Levels of explanation: scale, time, mechanism
- Methods of study: *ex vivo, in vivo, in silico*
- Manipulation
- Disease (pathophysiology): often complicated

Exercise

UNIVERSITY OF LIVERPOOL

- Physiological challenge
- Inherently multisystem
- Quantitative endpoints
- Relationships to age & health
  - ‘Ability to sustain exercise is a key determinant of cardiovascular health, quality of life and mortality’
- Interventions
  - Training, ‘exercise prescription’, nutrition

'The human machine'



Rossiter, adapted from Wasserman et al, *J Appl Physiol* **22**:71-85, 1967

Exercise tolerance depends on the integration of the pulmonary, circulatory and muscular systems to transport and use O_2.

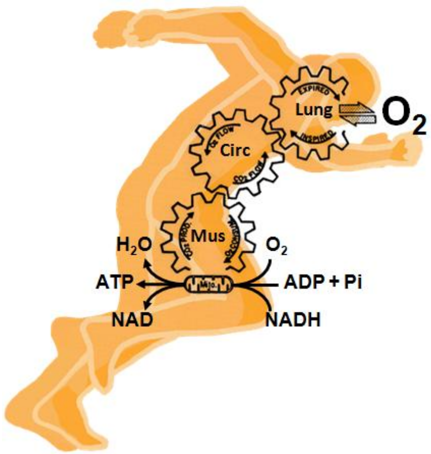
The effective integration of these systems' dynamics remains poorly understood.

… not forgetting:

- skeleton, joints & tendons
- central, peripheral & autonomic nervous system
- gut, liver & adipose tissue

Measuring aspects of the system

- *Ex vivo* measurements
  - Muscle biopsy – metabolites, gene expression, enzymes, histology
  - Blood sampling – metabolites, enzymes, gases
- *In vivo* measurements
  - Magnetic resonance imaging (MRI), ultrasound, DEXA
  - Exercise techniques
    - Muscle magnetic resonance spectroscopy (MRS)
    - Whole body VO_2 – kinetics, VO_{2max}
    - Arteriovenous difference (AVD) studies
    - Near-infrared spectroscopy (NIRS)
    - Electromyography (EMG), force & motion analysis



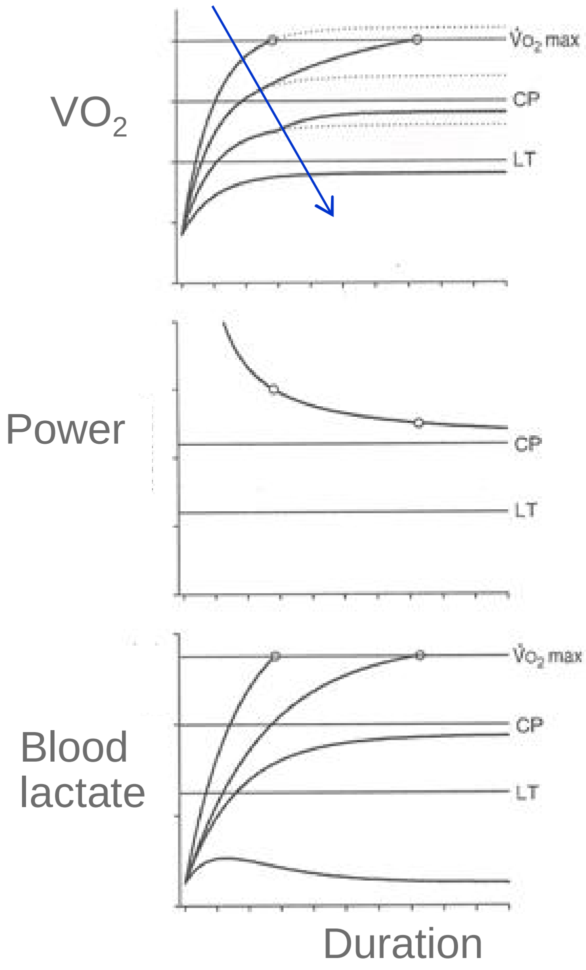
Cardiopulmonary exercise testing

UNIVERSITY OF LIVERPOOL

Human Bioenergetics Research Lab

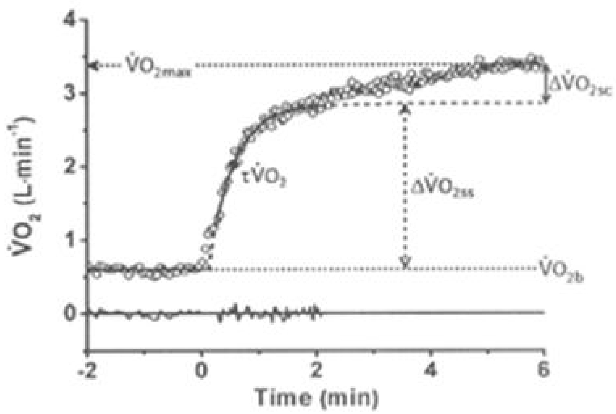
UNIVERSITY OF LEEDS

VO_2 response to exercise



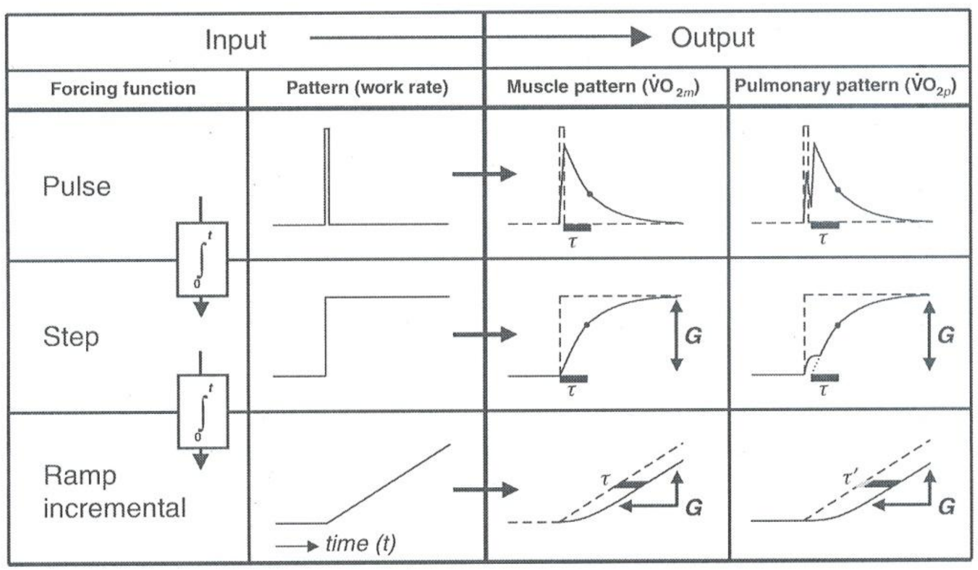
Severe
Very heavy
Heavy
Moderate

Rossiter. *Comprehensive Physiology* **1**: 203-244, 2011

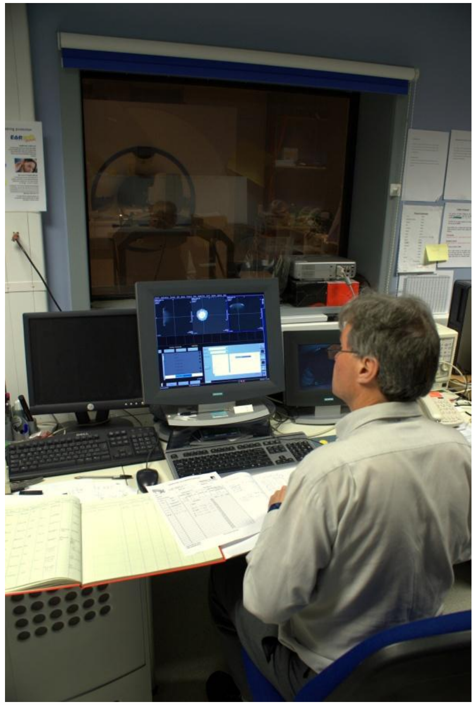


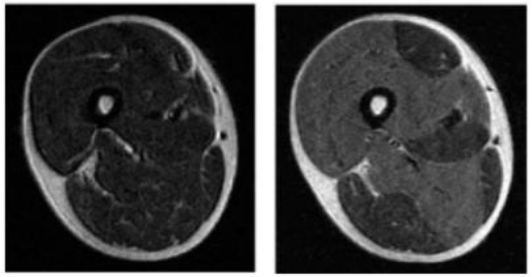
Human Bioenergetics Research Lab
UNIVERSITY OF LEEDS

Murgatroyd et al. *J Appl Physiol* **110:**1598-1606, 2011

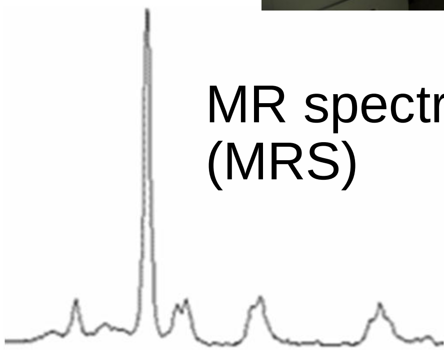


Magnetic resonance methods

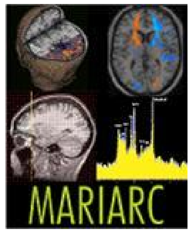




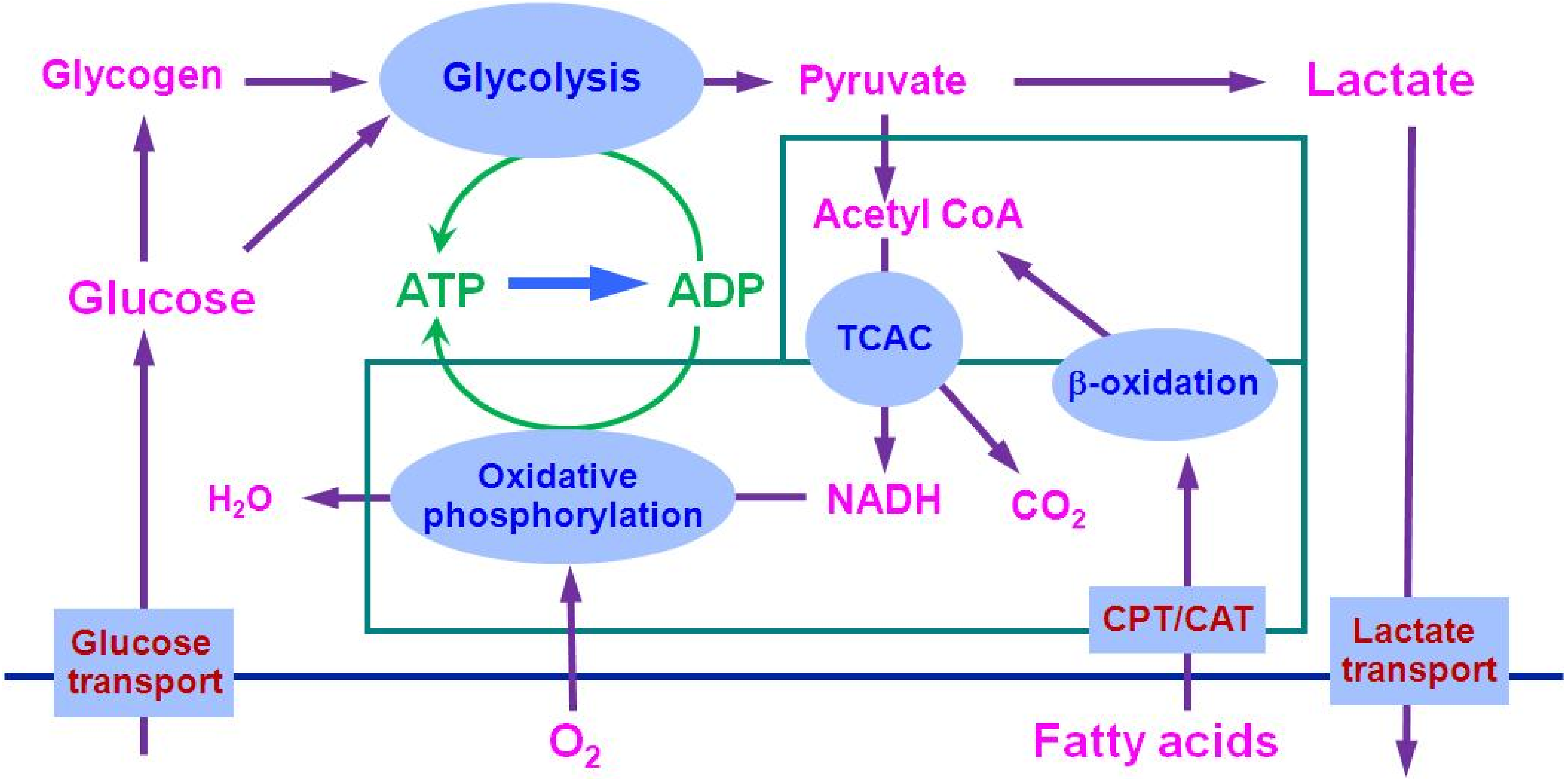
MR imaging
(MRI)



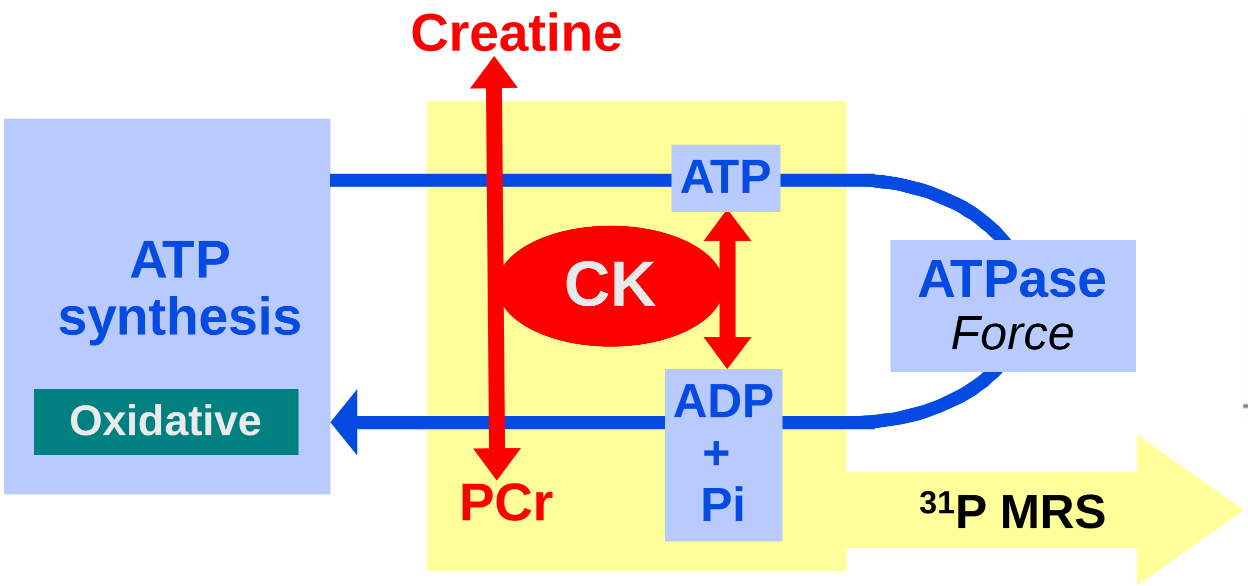
MR spectroscopy
(MRS)

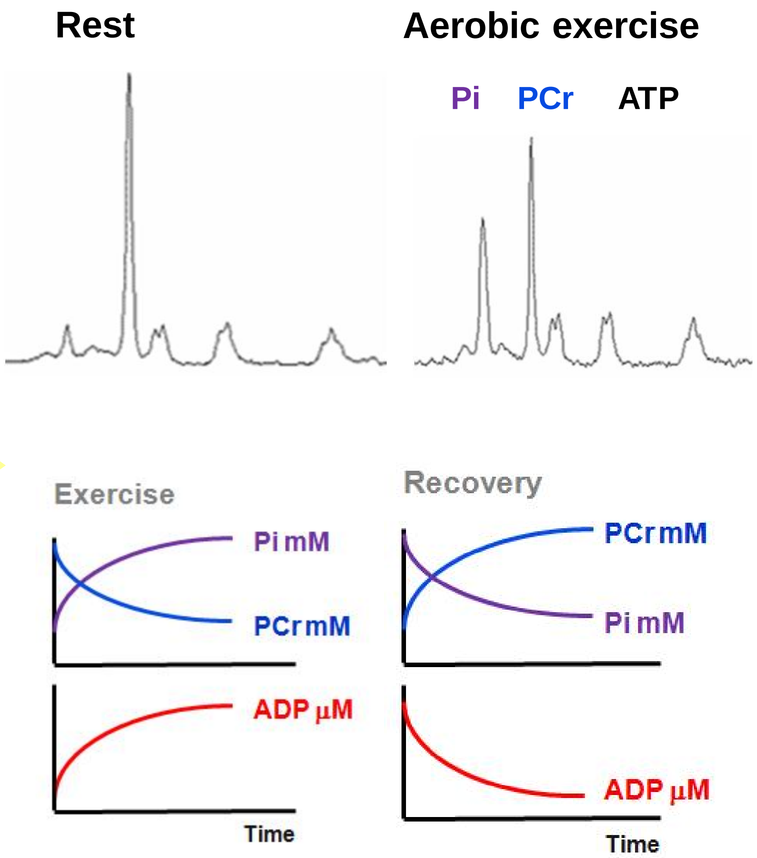


Muscle metabolism in outline



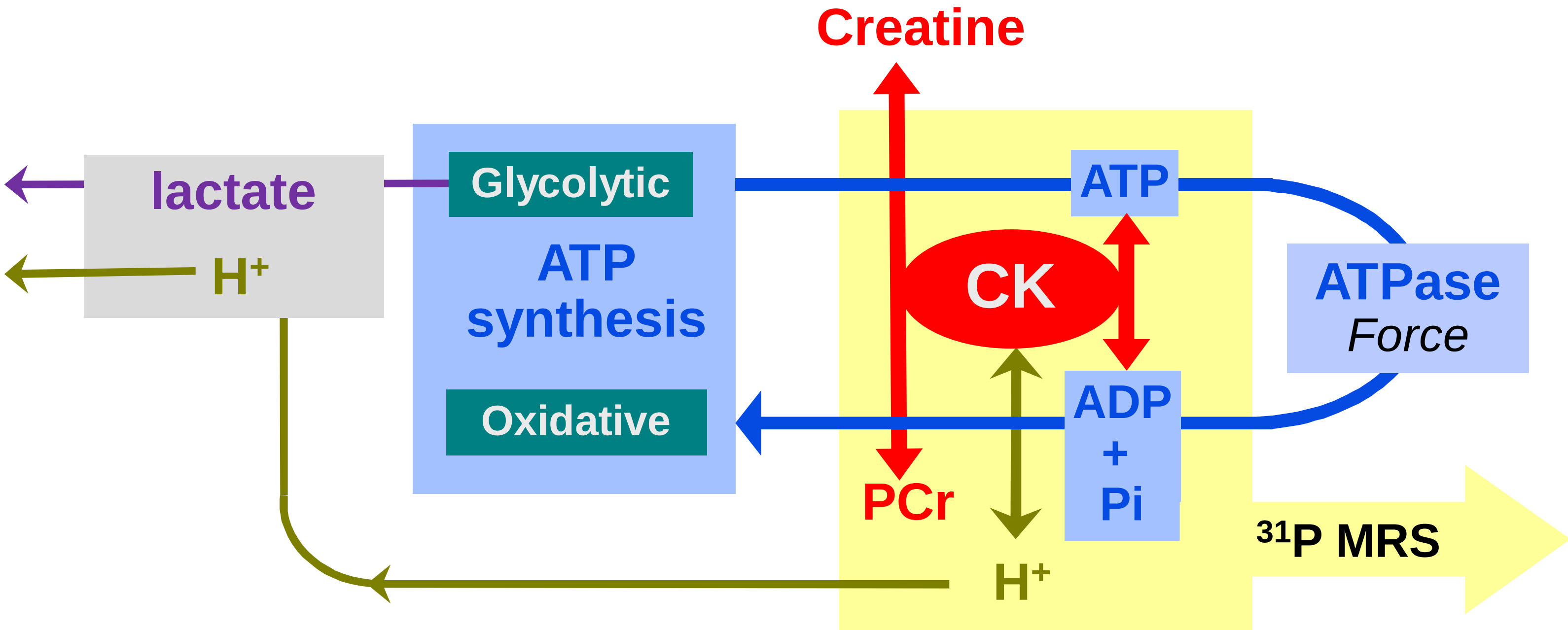
The ^{31}P MRS 'window'

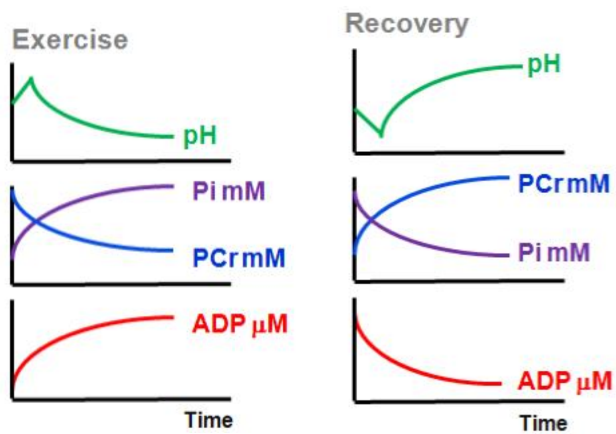




- ATP supply & demand system
- Large dynamic range
- Creatine kinase equilibrium buffers [ATP]

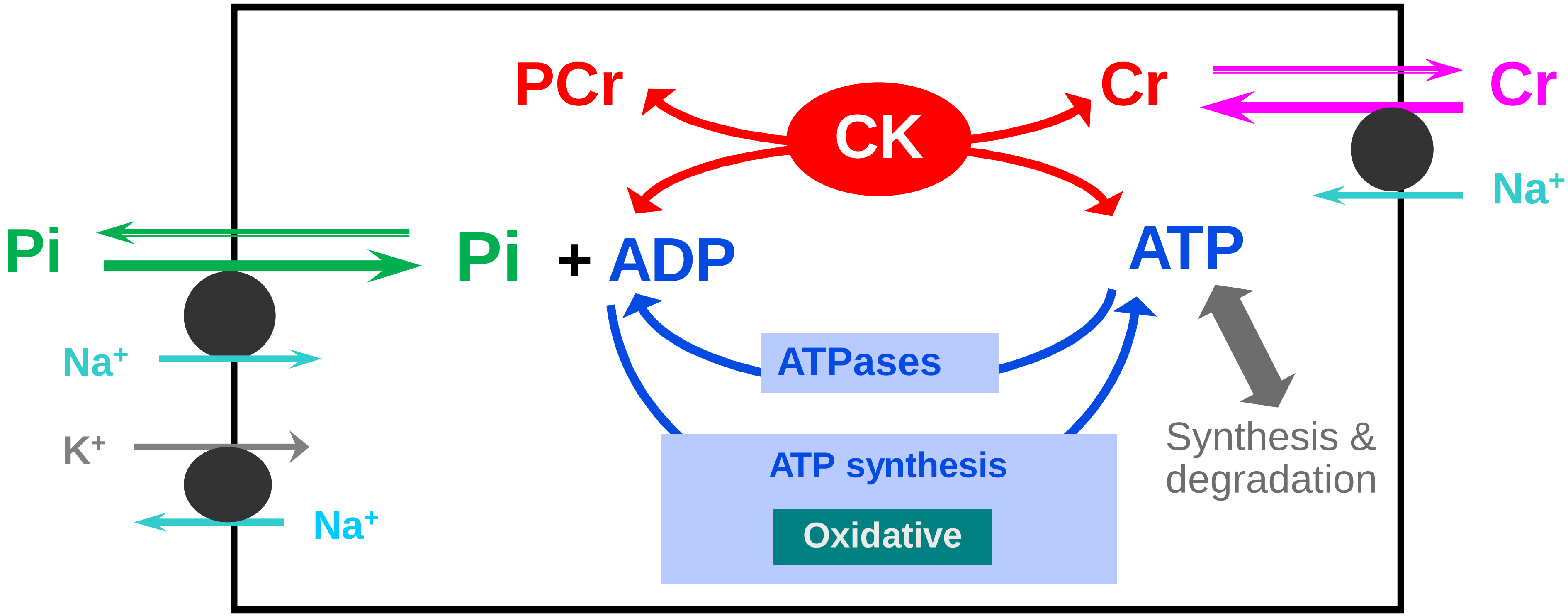
^{31}P MRS & muscle: 'mixed' exercise





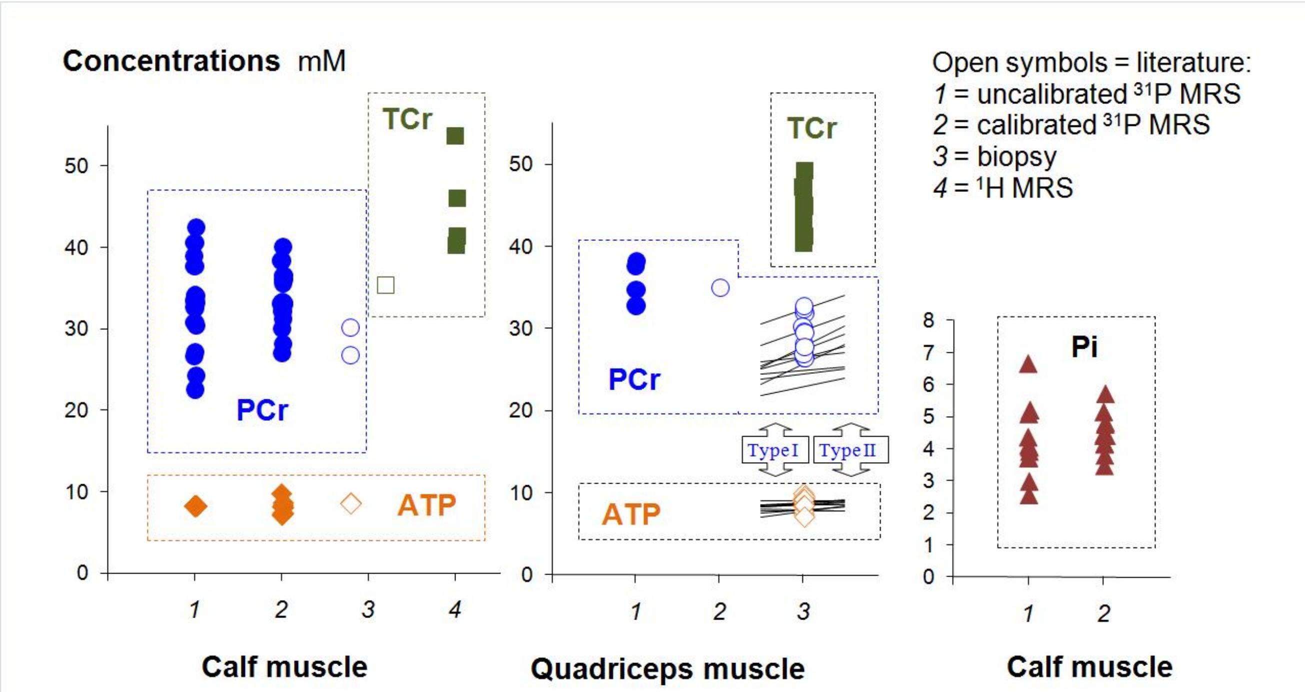
- Glycolytic & oxidative ATP synthesis
- pH change
- H^+ efflux/buffering

Muscle at rest: some physiology

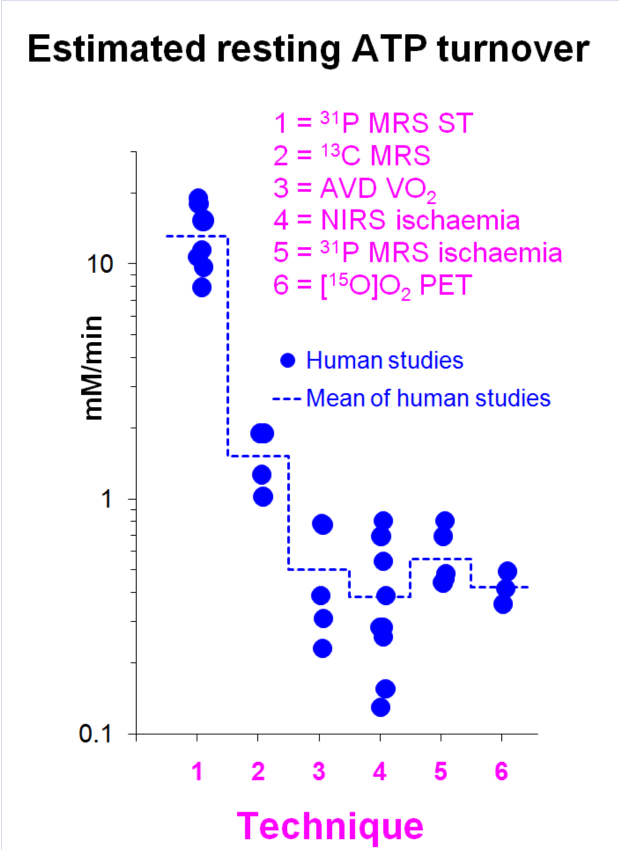


Kemp & Bevington *J Theor Biol* **161:** 77-94, 1993
Kemp *J Theor Biol* **170:** 239-246, 1994

Muscle at rest: some data



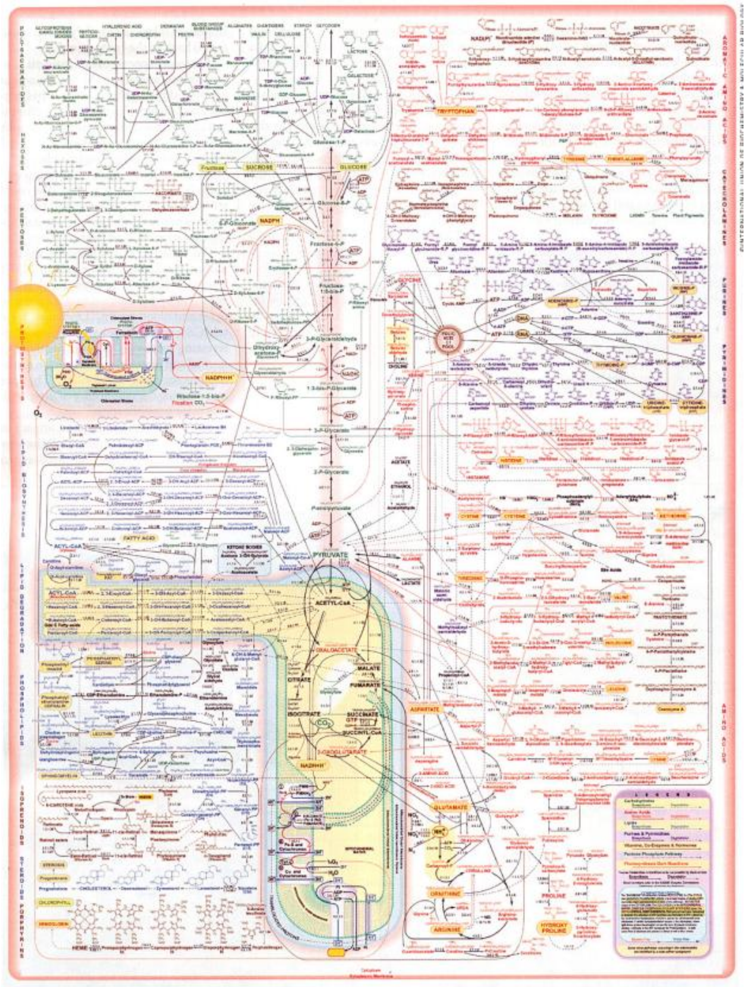
Kemp et al. *NMR in Biomed* **20:** 555–565, 2007

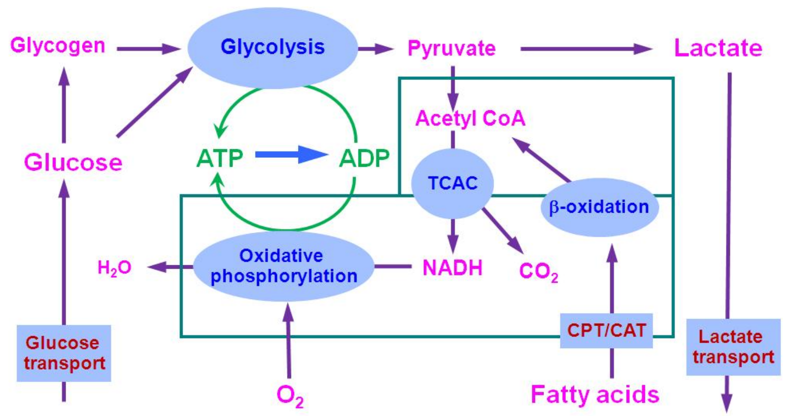


Kemp *Am J Physiol* **294:** 640-642, 2008

1 point = 1 study

Analysing metabolic control





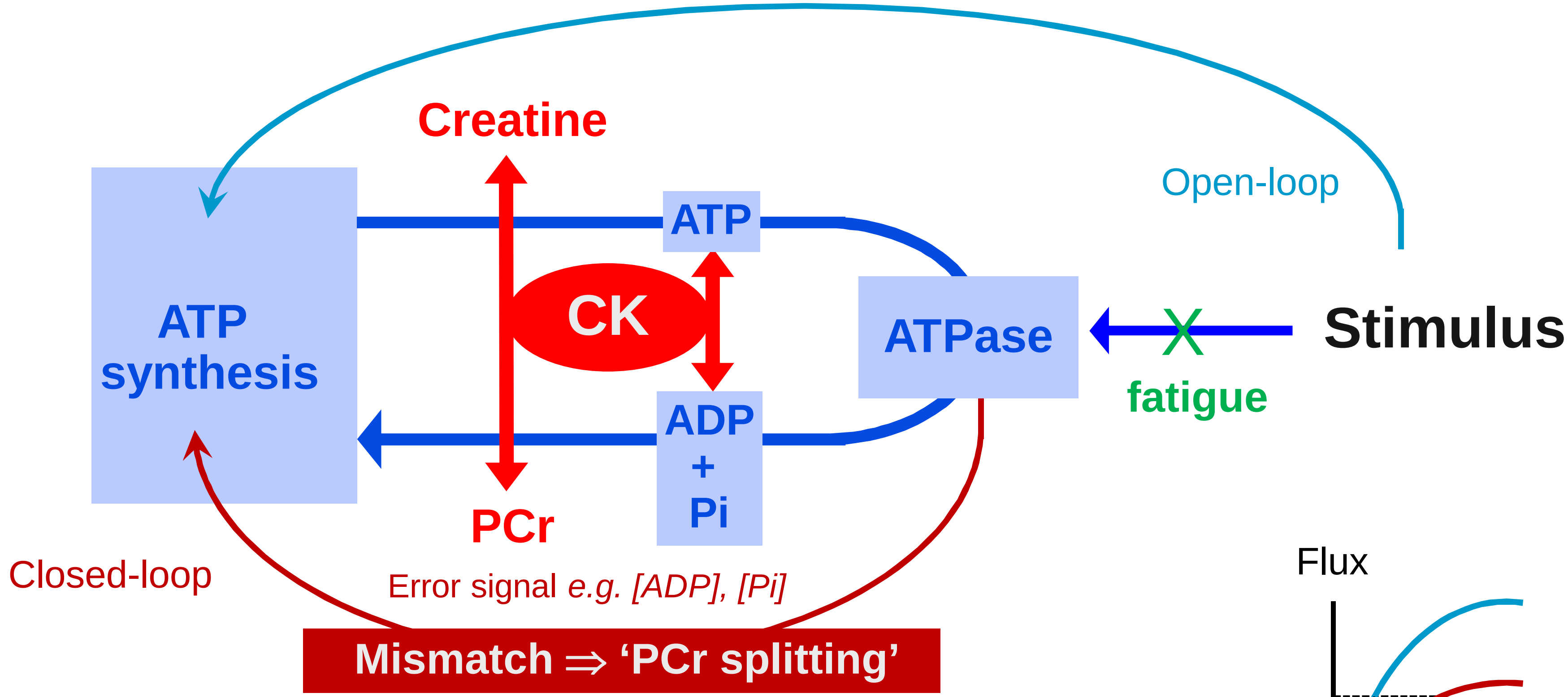
Metabolic control analysis

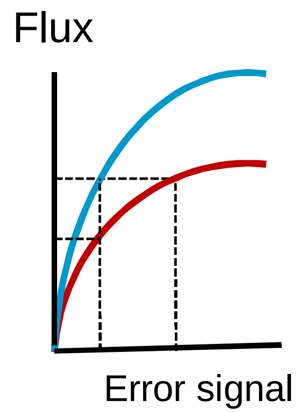
$$X_0 \xrightarrow{E_1} S_1 \xrightarrow{E_2} S_2 \xrightarrow{E_3} X_1$$

- Flux control distributed between many enzymes
- Multiple activations, most unknown
- Importance of control by demand

http://io9.com/metabolism/

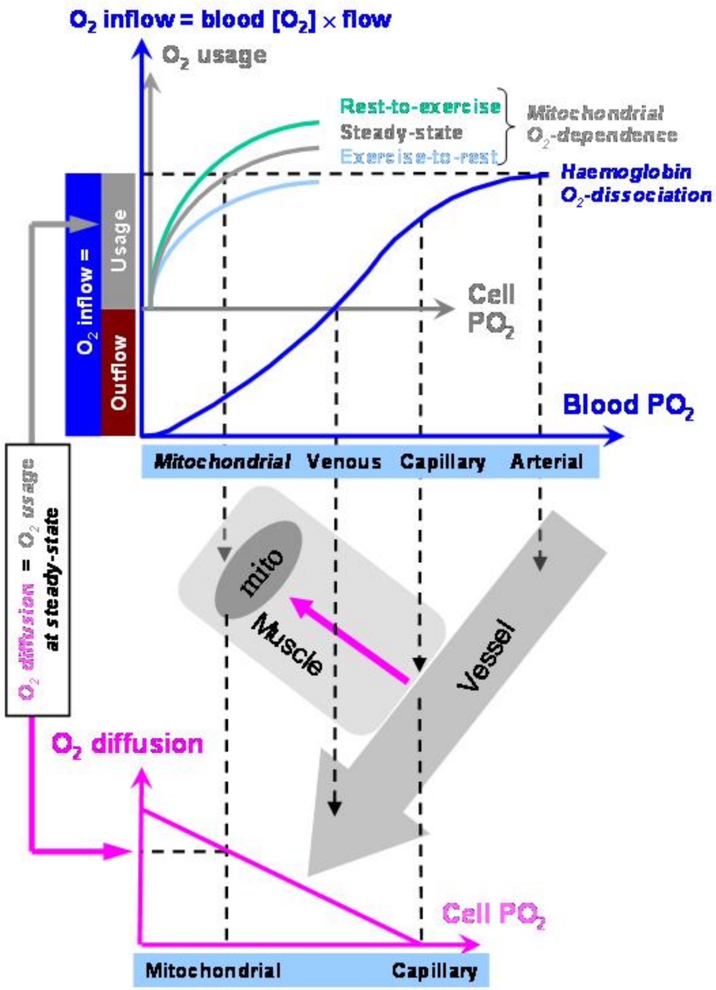
Open- and closed-loop feedback





- ATP turnover is demand-driven, until fatigue
- Closed-loop, integral feedback
- Open-loop, parallel activation?

Aerobic metabolism of muscle



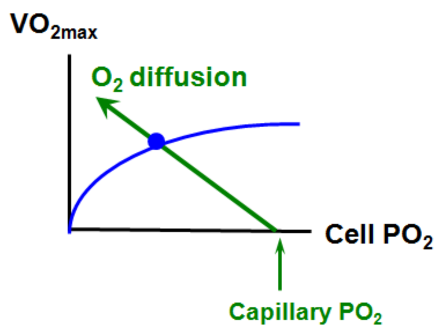
Kemp *Mitochondrion* **4:**629-640, 2004

O_2 delivery to mitochondrion

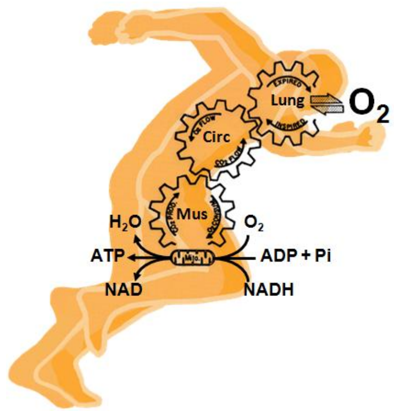
- Net O_2 supply to muscle
  - = flow × (arterial-venous $[O_2]$)
- O_2 flux to mitochondrion
  - = diffusion coefficient ×(capillary-mitochondrial ΔPO_2)

Mitochondrial O_2 consumption

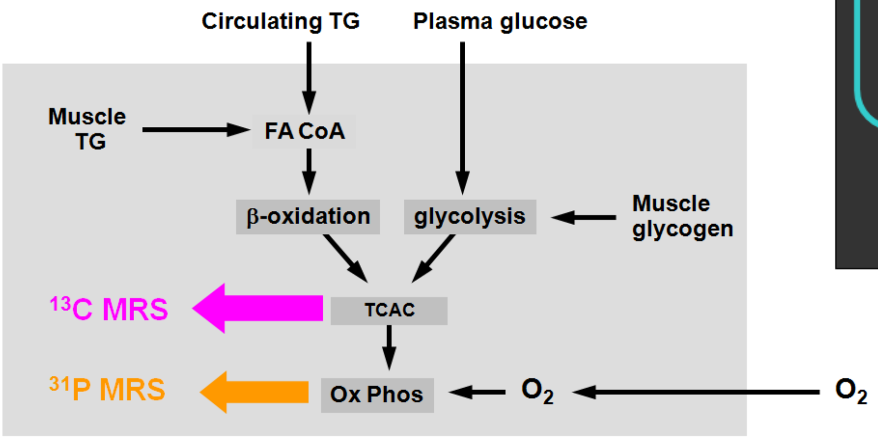
- PO_2-dependence of cytochrome oxidase
- Closed-loop feedback by e.g [ADP]
- Open-loop influences?

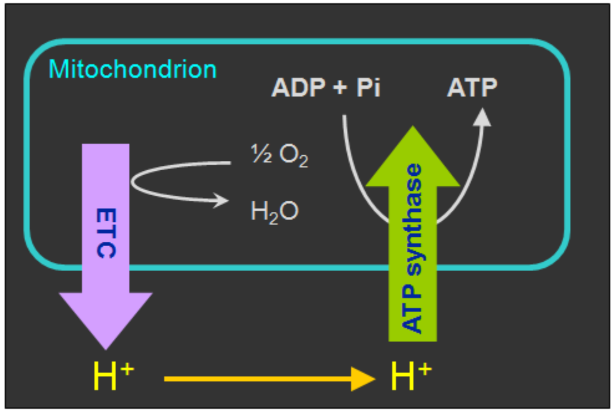


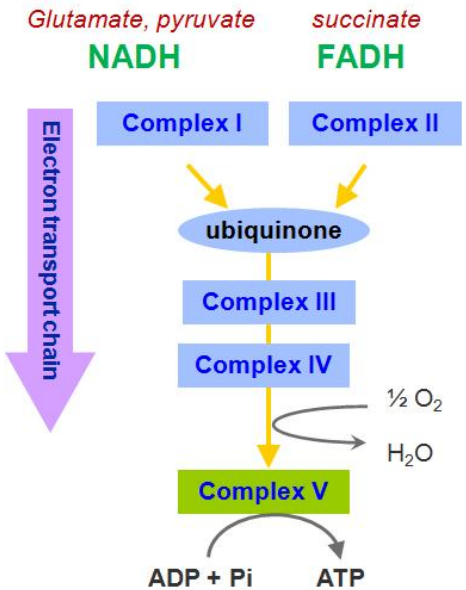
Richardson et al *J Appl Physiol* **87:**325-331,1999



Mitochondrial metabolism





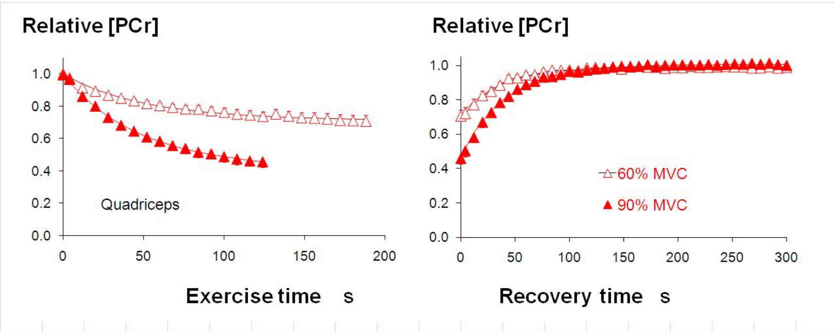


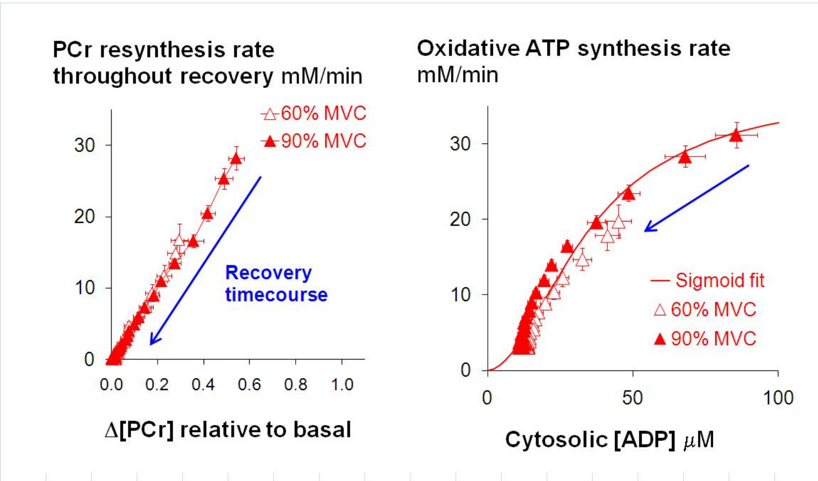
Studying mitochondria ex vivo

- Mitochondrial numbers & volume
- Molecular genetics: mitochondrial DNA copy number; transcription/expression of e.g. proliferator-activated receptor-γ coactivator 1α (PGC-1α) and genes it controls (e.g nuclear respiratory factors (NRFs), mtTFA)
- In extracts: mitochondrial enzymes: citrate synthase, OGDH
- Isolated mitochondria: ATP production and respiration +/- inhibitors

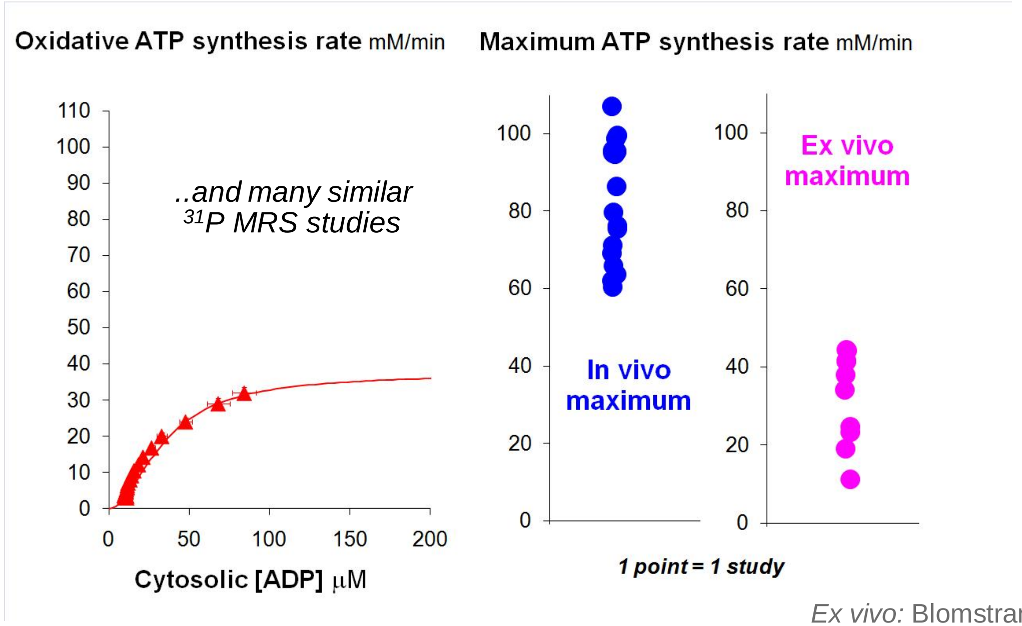
Mitochondrial function by ^{31}P MRS

'Aerobic exercise' at two intensities





Implications for mitochondrial function



Ex vivo: Blomstrand, Rasmussen, Sahlin *In vivo:* Sahlin, Bangsbo, Richardson etc

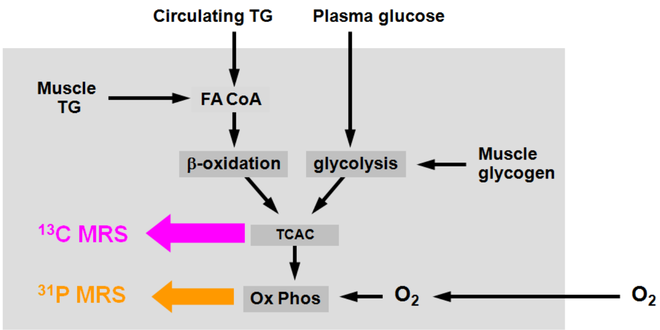
Measures of 'mitochondrial capacity':

- increase with endurance training,
- decrease with age
- correlate appropriately with mitochondrial content & VO_{2max}
- reduced in disease: mitochondrial, vascular, cardiopulmonary

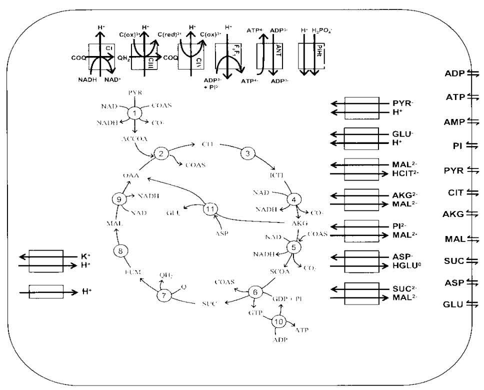
BUT 'maximum' rates are functions of state, assumptions and method

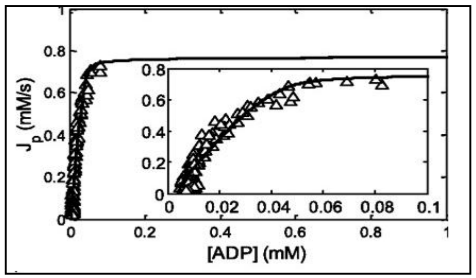
More about muscle mitochondria

Mitochondrial function is a system property



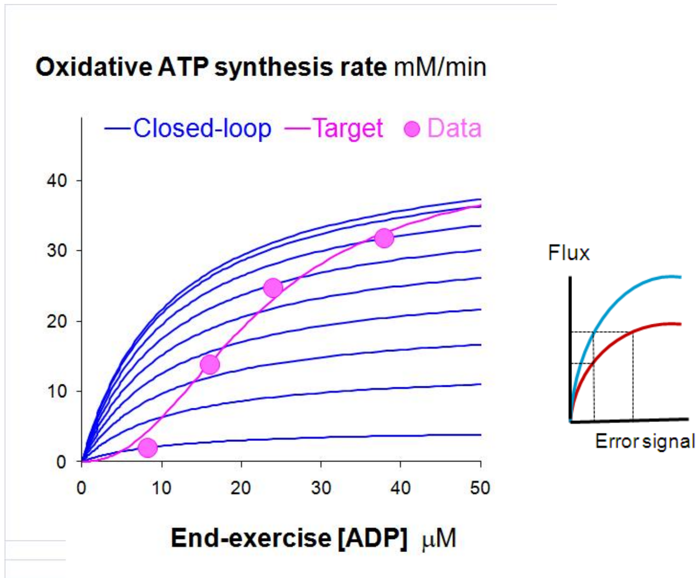
Feedback role of ADP & Pi arises from complexity

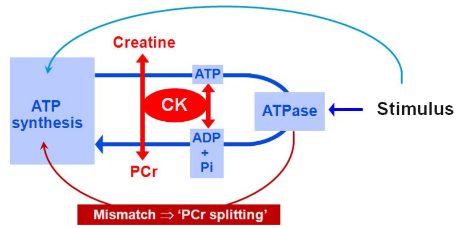




Beard *PLoS Comput Biol* **1:** e36.2005
Wu et al. *Am J Physiol* **292**:115-124, 2007.
Jeneson et al. *Am J Physiol* **297**:774-784, 2009

Open-loop control?



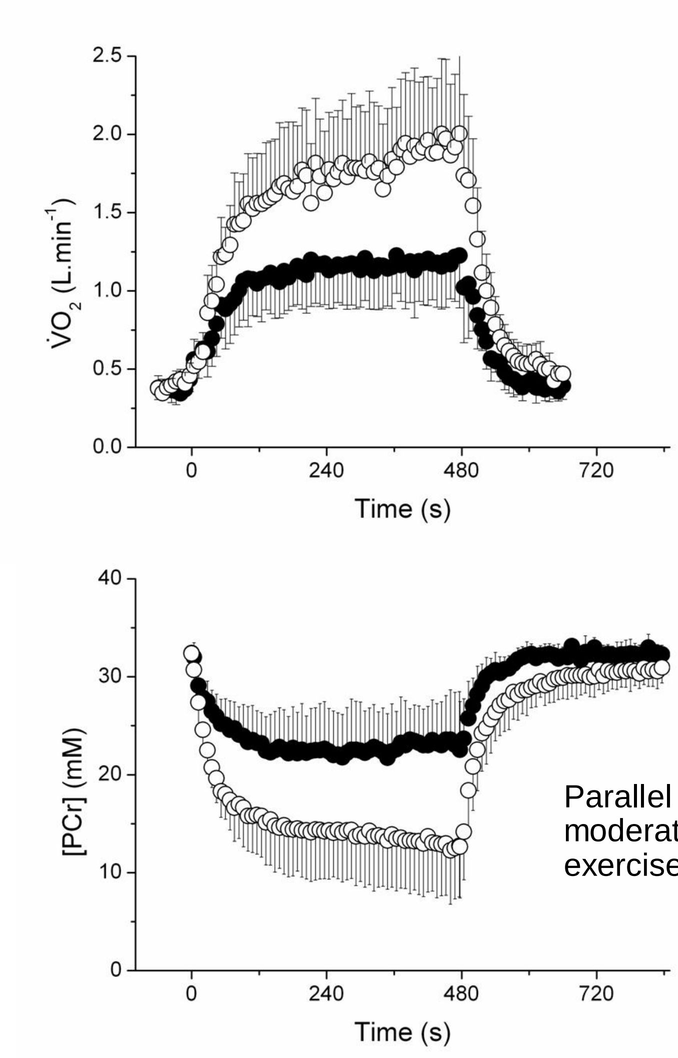


Cf Wüst et al *J Physiol* **589:** 3995-4009, 2011

Integration of methods: VO_2 &^{31}P MRS

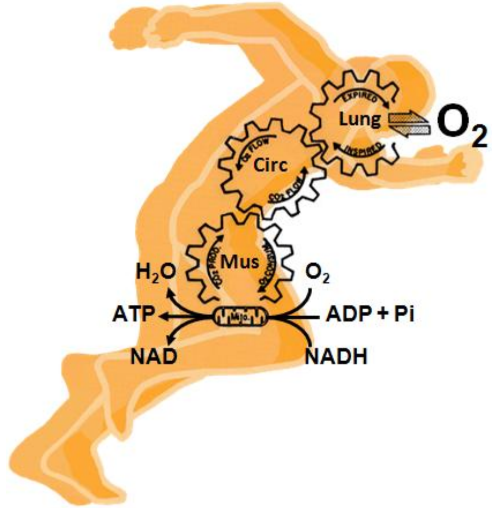
ATP turnover increased between 3 and 8 min of supra-lactate threshold (LT), but not sub-LT, exercise.

Thus reduced work efficiency in heavy exercise is partly wholly due to increased contraction cost, although reductions in P:O may also contribute.



Parallel measurements of VO_2 and [PCr] during moderate (●) and heavy (○) knee extension exercise & recovery. Means with SD bars

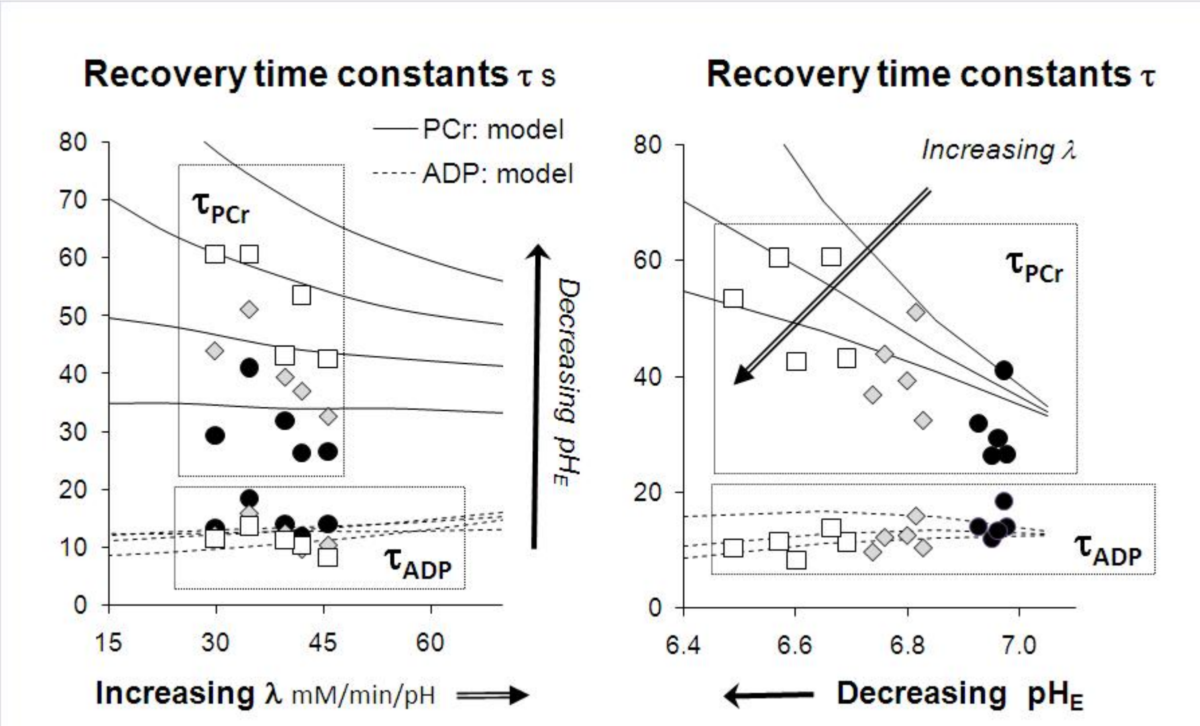
BBSRC bioscience for the future



Human Bioenergetics Research Lab
UNIVERSITY OF LEEDS

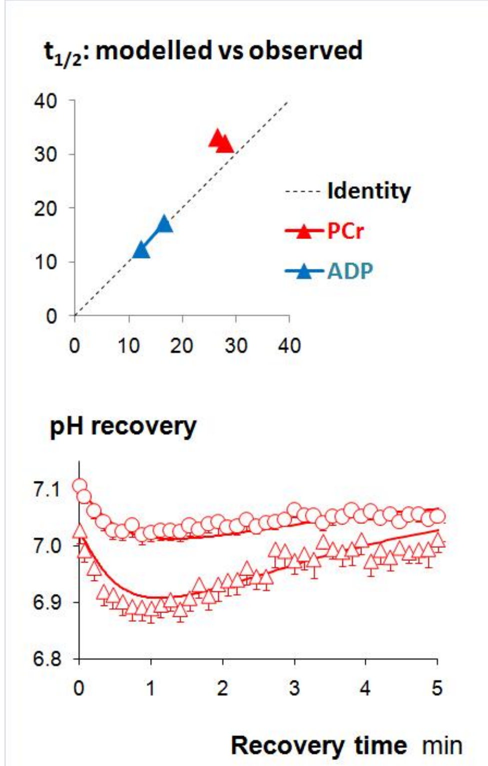
MARIARC

Simulation: ^{31}P MRS recovery data



Data from Van den Broek *Am J Physiol* **293**:228-237, 2007
5 subjects, exercise at a variety of intensities

Experiments shown earlier



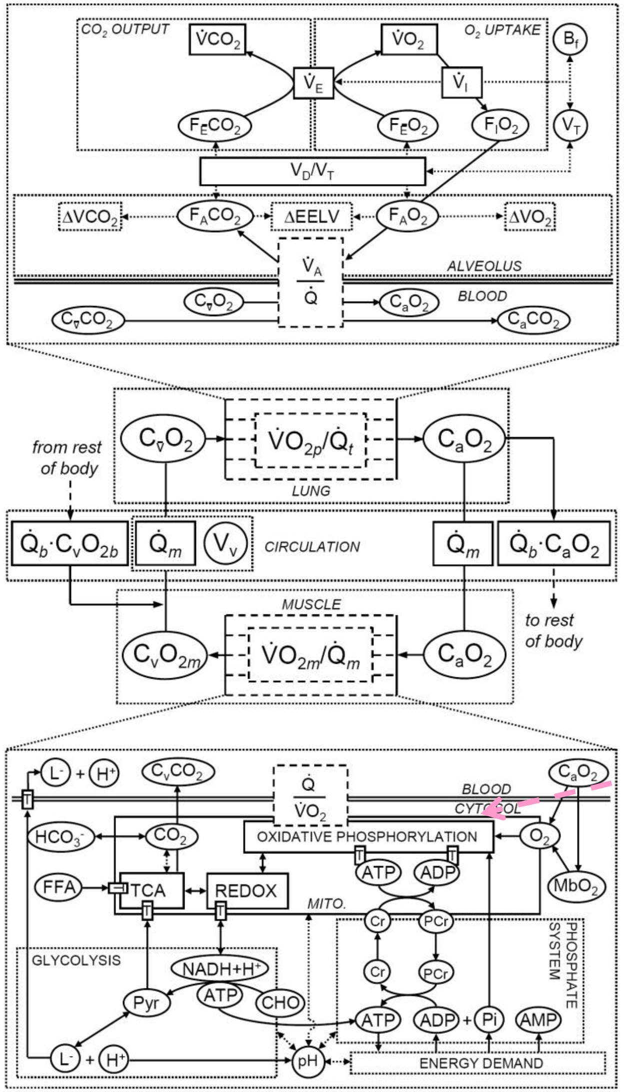
A simple model using (pH-dependent acid efflux and ADP-dependent ATP synthesis) reproduces main features of pH- and efflux-dependence of PCr and ADP recovery

Computational approach to O_2 usage

UNIVERSITY OF LIVERPOOL

Human Bioenergetics Research Lab

UNIVERSITY OF LEEDS

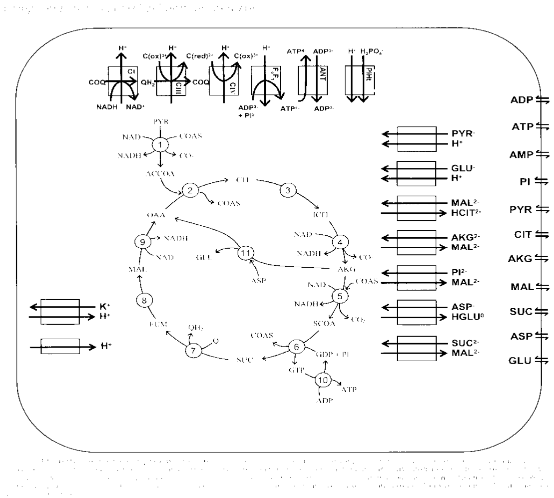


Details of lung

Lungs & muscle linked by circulation

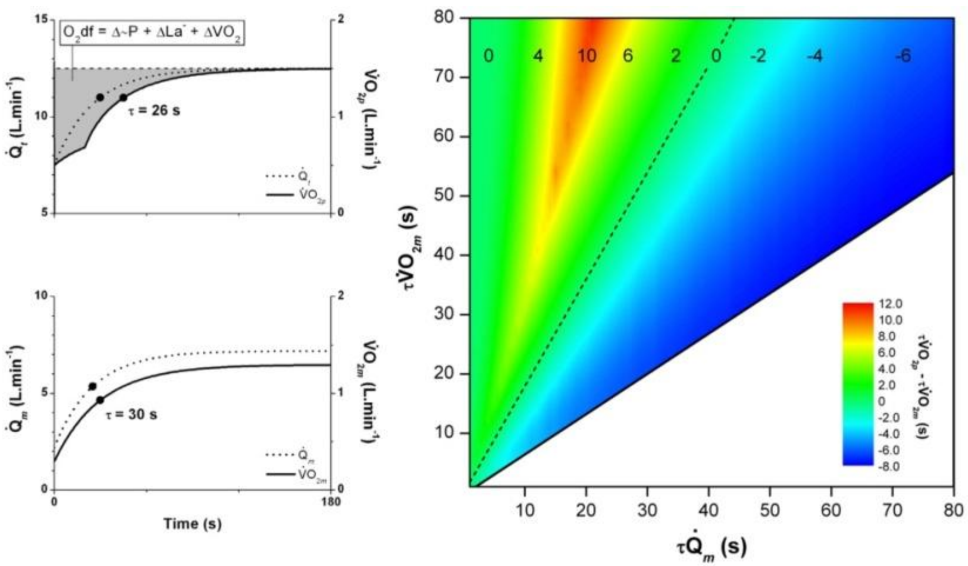
Details of muscle

Rossiter. *Comprehensive Physiology* **1**: 203-244, 2011

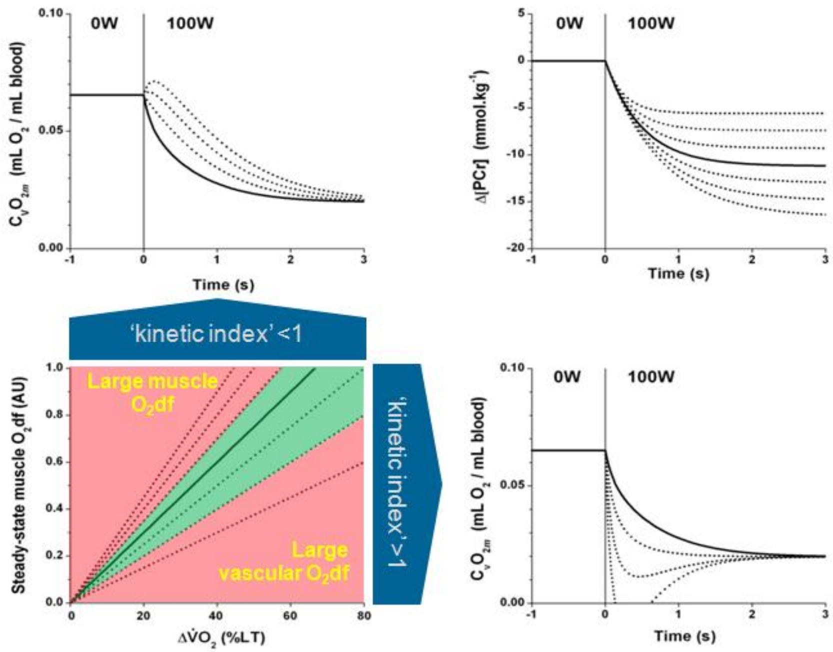


Beard *PLoS Comput Biol* **1:** e36.2005
Jeneson et al. *Am J Physiol* **297**:774-784, 2009

Simulation of VO_2 responses



Effect of muscle blood flow (Q_m) on pulmonary oxygen uptake (VO_2p) kinetics at onset of moderate-intensity exercise



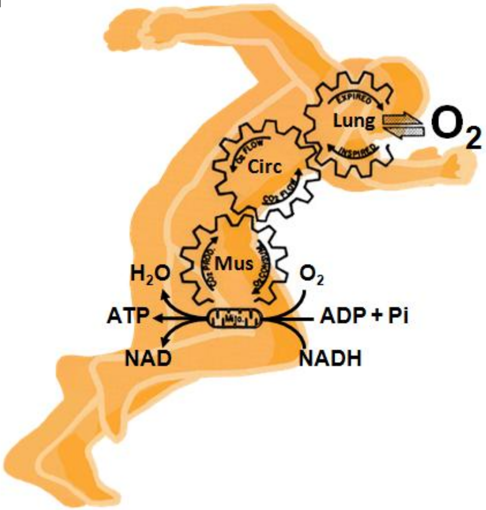
When muscle oxygen consumption (VO_{2m}) lags muscle blood flow (Qm) (upper curves) venous oxygen content (CvO_{2m}) is well maintained in the transient. If vice versa, CvO_{2m} undershoots

Human Bioenergetics Research Lab
UNIVERSITY OF LEEDS

Rossiter. *Comprehensive Physiology* **1**: 203-244, 2011

Key concepts

- Systems & modules; organs, pathways
- Feedback, stability
- Supply & demand, challenge & response
- Steady-state *vs* kinetic responses
- Dynamic range, quantitation
- Control coefficients
- Levels of explanation/causation
  - spatial & temporal
  - mechanisms – metabolic, signalling, genetics & epigenetics, expression



Implications for interventions

- Interventions
  - Training: strength, endurance, daily activity
  - Nutrition
  - Pharmacotherapy
- Issues:
  - ‘control strength’
  - trade-offs
  - understanding vs engineering vs empirics