The systems physiology of exercise

Understanding fitness in health and disease

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Key words
exercise
respiration
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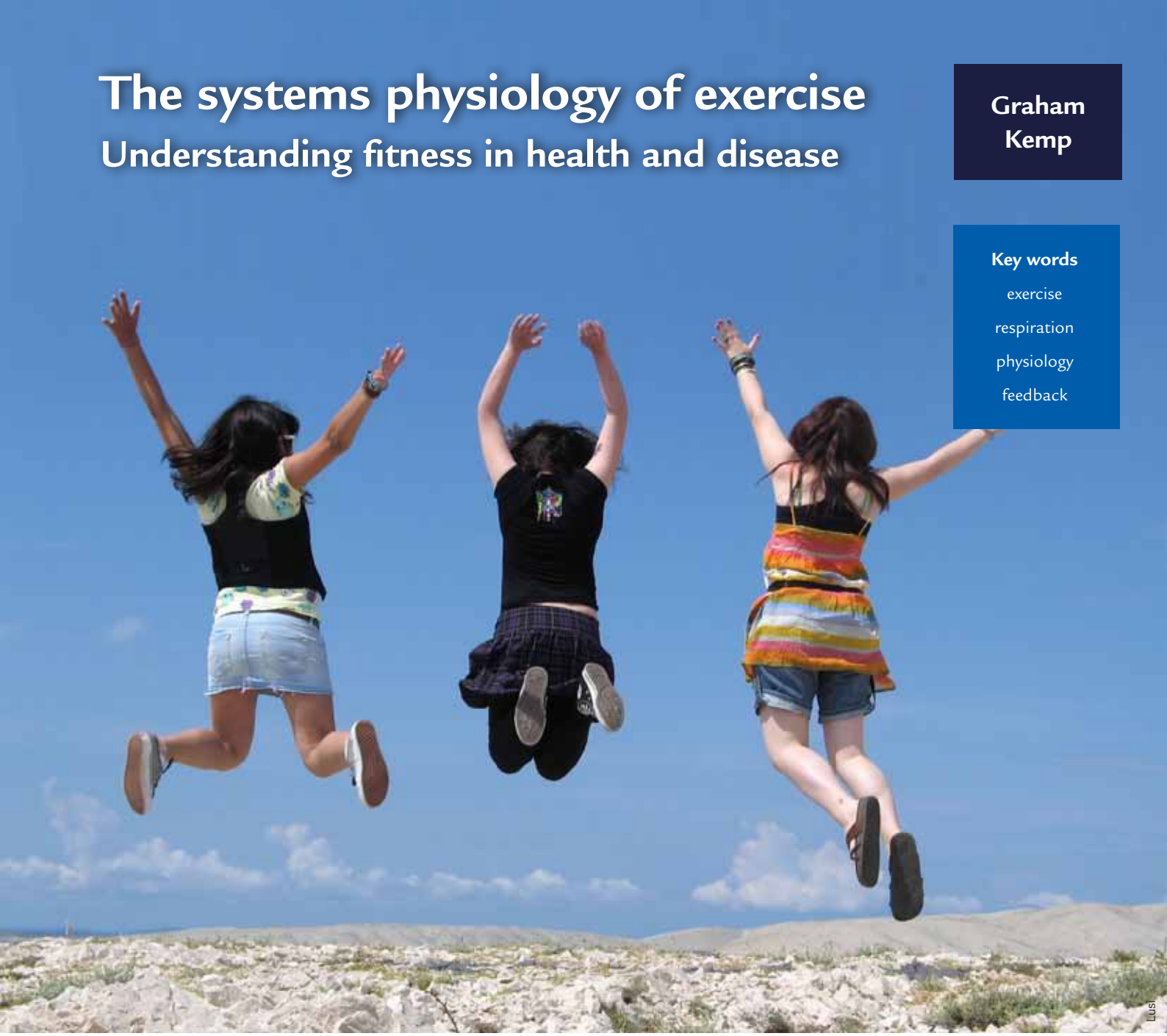
feedback



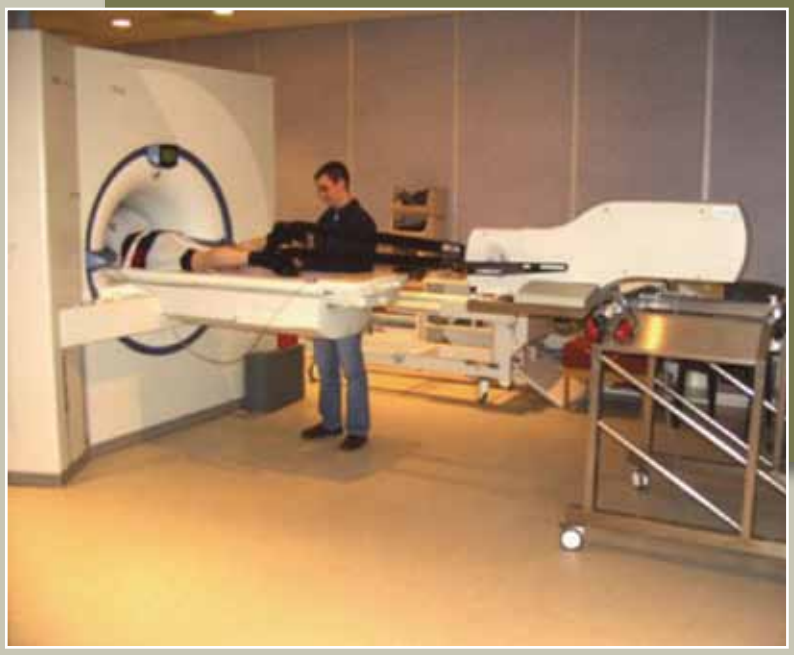
The ability to exercise is fundamental to life. Poor fitness contributes to reduced life expectancy and reduced ability to exercise reduces quality of life in the ill or aged. At the other end of the scale, excellent exercise performance can win Olympic gold. The hope of scientists is that understanding the mechanisms which limit 'exercise tolerance' (Box 1 on page 12) can contribute to enhanced performance for the sportsperson, and to health and to quality and length of life for everyone. How can we best approach this?

How the body works

Systems physiology is about understanding the body at work. We can understand the body in many ways as a machine. When a signal from the brain makes muscles contract, the force is transmitted to, for example, the floor beneath a foot according to the mechanical properties (length, elasticity) of the tendons and bones involved. The force and speed of the muscle depend on the properties of its component fibres, for example, 'slow twitch' muscle fibres have more endurance, and 'fast twitch' fibres have greater speed and power.

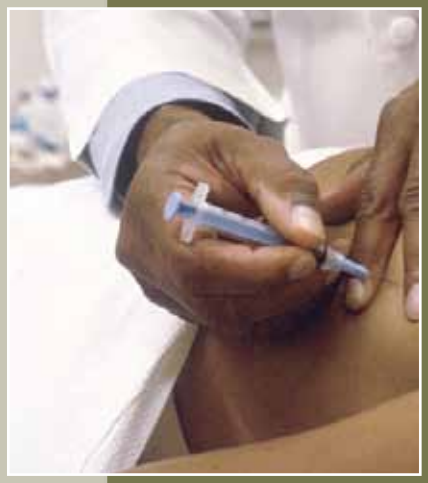
Muscles contain a storage carbohydrate, glycogen, which is the main fuel for the rapid, high-force contractions of fast twitch fibres. As exercise carries on they switch to using glucose and then fatty acids delivered by the blood, which also delivers the oxygen. For sustained exercise this aerobic (oxygen-requiring) energy supply system is crucial (Box 2 on page 13).

The Big Picture on pages 10-11 shows seven different techniques used to measure physiological changes during exercise.



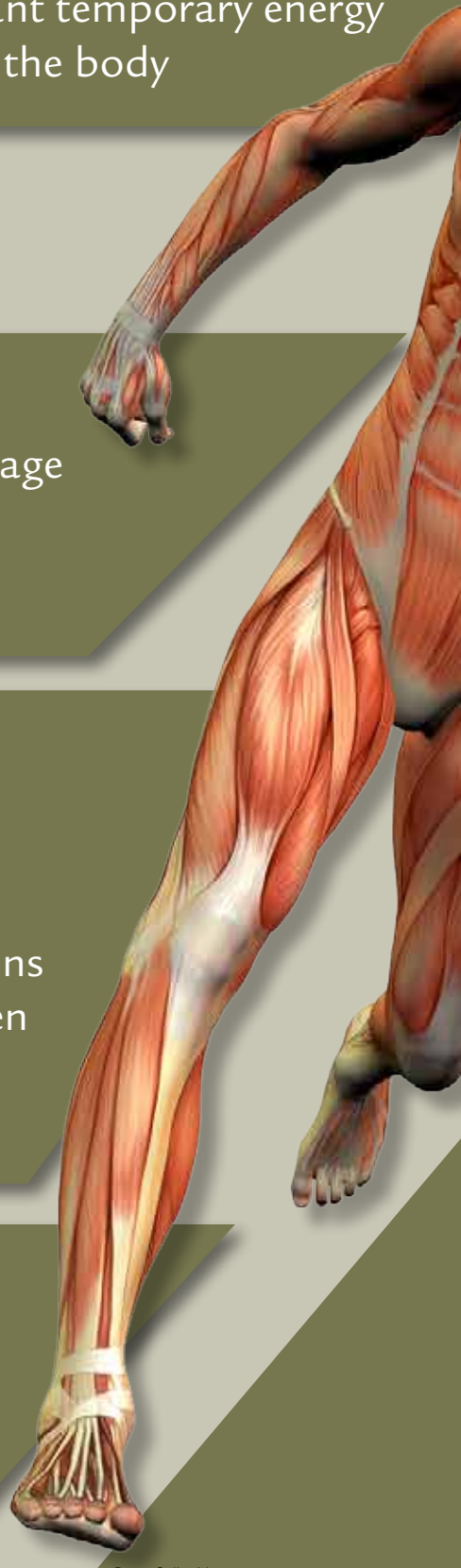
^{31}P MRS (phosphorus magnetic resonance spectroscopy)
measurement of changes in pH and the concentration of phosphocreatine (PCr), an important temporary energy store in the body

Spirometry
measurement of oxygen usage via a simple face mask; a non-invasive technique



Needle biopsy
measurement of enzyme content, gene activation patterns, mitochondrial function and concentrations of chemicals in blood taken from muscle tissue

Arteriovenous sampling
direct measurement of such things as oxygen use



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Catalyst

www.catalyststudent.org.uk

NIRS (near infrared spectroscopy)
measurement of muscle oxygen content

Blood sampling
measurement of concentrations of circulating chemicals (metabolites) including lactate made in anaerobic respiration

Whole Body
measurements of running speeds, power output

Measuring the system

The Big Picture (pages 10-11) shows the major ways in which we can measure physiology in the exercising human. Some difficulties exist with these methods. Subjects, especially if they are patients rather than volunteers, are much more willing to participate with non-invasive techniques such as spirometry. Needle biopsy is especially difficult and, although in theory very good for looking at changes over time, the multiple samples that would be needed pose ethical and practical problems.

In addition, none of these techniques tells us everything we want to know about this system – this would be ethically and practically impossible. However, quantitative analysis of the data (i.e. analysis which pays attention to the actual values of concentrations and rates, and the size of changes) with a knowledge of the underlying physiology and supported by computer modelling, can give us much valuable information.

Understanding the system

We now know a great deal about the anatomy of this system, the nature of its protein components, and the chemistry of the pathways of synthesis and breakdown of storage compounds, fuel oxidation and energy transformation. During sustained exercise, oxygen must be delivered from the atmosphere and fuel from the stores (liver glycogen, adipose tissue triglyceride) at a sufficient rate.

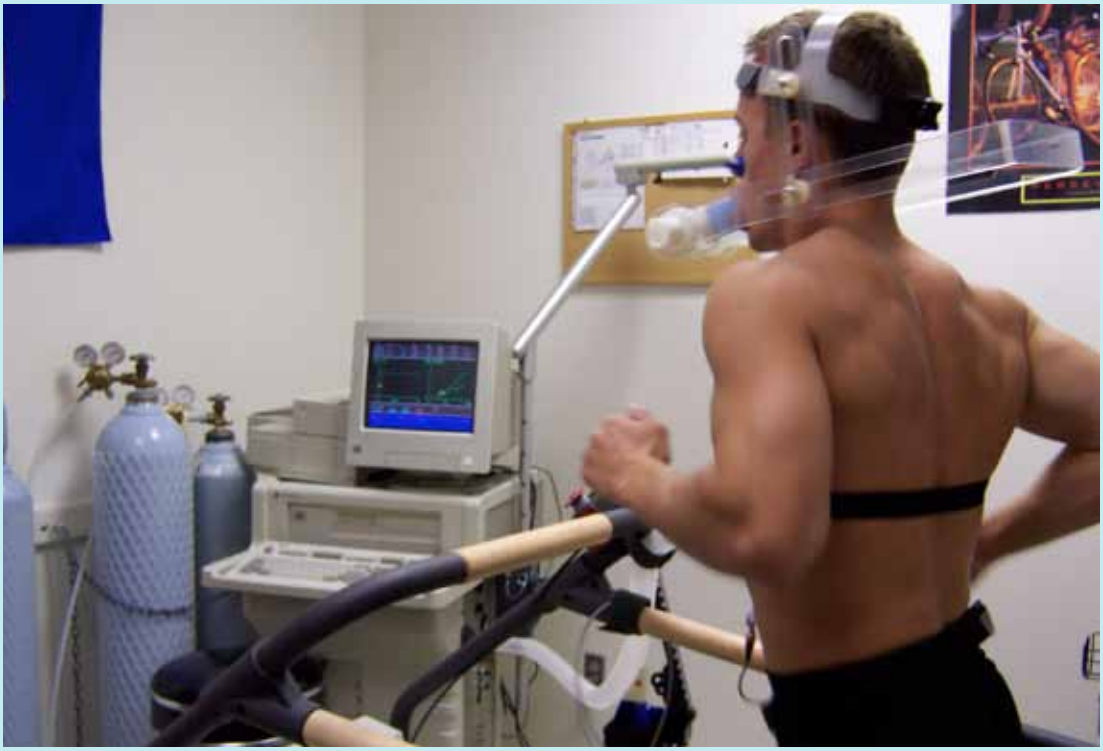
Regulation is very important. In the muscle cell we understand how energy supply is switched on in exercise and then off again. Two important principles are the idea of steady states versus kinetics (time-dependent changes), and the engineering concept of **feedback**.

When a muscle is instructed by the brain to contract, its energy (ATP, see Box 3 opposite) needs to increase rapidly. In the time it takes for processes of ATP production to catch up, the shortfall is met by phosphocreatine (PCr), which can be considered a temporary energy store. PCr stabilises at new steady-state level when ATP production matches ATP demand. When exercise ends the ATP demand falls to its low resting-muscle value, and the temporary excess ATP supply is used to replenish PCr.

Using ^{31}P magnetic resonance spectrometry, we can follow these PCr concentration changes. As PCr falls in response to ATP hydrolysis the concentration of ADP (see BOX 3) rises, stimulating ATP production. ADP is the 'error signal' in the feedback loop, matching ATP supply to demand. This explanation is broadly accepted, but current research is examining several unanswered questions. Is ADP really the key signal? Are there also direct signals activating ATP synthesis ('parallel' or 'feedforward' activation)? How much account must we take (e.g. by mathematical simulation approaches) of the complexity of metabolic reactions within the mitochondrion itself?

Box 1

Exercise tolerance is the level of physical exertion an individual may be able to achieve before reaching a state of exhaustion. Exercise tolerance tests are commonly performed on a treadmill under the supervision of a health professional who can stop the test if signs of distress are observed.



The system as a whole

More generally, to understand how the system works, we need to grasp it as a whole; not only to understand how the parts work in isolation but also how they interact. There is nothing magic about this, but there is sometimes extraordinary complexity. At the same time the results can often seem quite simple. For example, physiological processes often behave in a first-order way, typical of systems in which the force which restores a system to its original condition is proportional to the size of the original change which moved it away from steady state. This applies to post-exercise PCr recovery, as described above, where the PCr resynthesis rate is roughly proportional to how much further it has to recover to reach the resting value.

The resulting recovery can be described by a rate constant (inversely proportional to the time taken for 50% recovery). This is related to the mitochondrial capacity of the muscle, the maximum rate at which it can make ATP. The faster PCr recovery is, the larger the recovery rate constant, the larger the estimated mitochondrial capacity.

Mitochondrial capacity is a complex property, depending on the many organs and processes involved; lungs, heart, blood vessels, muscle capillaries, muscle mitochondrial enzymes and other proteins (Box 2). It is generally reduced in diseases that affect any of these, and it is increased by aerobic (endurance) training. This makes it a useful concept in clinical and sports-science research, but we would like to understand how these factors interact, in a model that incorporates all we know of how the parts of the system work, and of the interactions between them.

For example, how much does limitation in cardiac performance affect the performance of several muscle groups (e.g. in bicycle exercise) compared to a single muscle group (e.g. in single knee extension)? How much does reduction in muscle mitochondrial numbers contribute to intolerance to exercise in chronic heart disease?

This knowledge will also help us to decide what to do in a specific case. In a disease, for example, a drug improving muscle metabolism directly is unlikely to be beneficial if the main factor limiting exercise tolerance is cardiac function, however in sport if a 5% increase in muscle mitochondrial function increases overall performance by just 1%, this may be just what it takes to win Olympic gold! Only a quantitative systems understanding can answer these questions.

Box 2
The parts of the machine

The **lungs**, which acquire oxygen from the air and let it diffuse into the pulmonary capillaries.

The **heart**, which pumps blood round the circulatory system.

The muscle **vascular system**, which distributes the blood so that oxygen can diffuse across the capillary wall into the cell, and then through the cytoplasm to the mitochondria.

The **subcellular organelles** where the cellular respiration (the oxidation of fuels) takes place.

The way forward

If we can develop this kind of approach, not only will we understand our measurements better, but we will also be better able to predict what changes may influence overall performance, and by how much. This is the practical goal of a system physiology approach, and it has many applications in health and sports science. While we can only fully understand the whole, we are of course allowed to focus. We may want to concentrate (as I have done here) on muscle use of oxygen and fuel. We may be more interested in timescales of seconds to minutes (as I have been here) rather than the millisecond events of nerve stimulation, the hours-to-days effects of gene activation, or the days-to-months events of growth and development.

Ideally the scientist progresses from experiment through analysis, simulation and prediction to new experiments. This requires the collaboration of scientists with a range of skills: these may be sports scientists, medical doctors, computer scientists, biochemists, biophysicists, physiologists, cell biologists, pharmacologists and neuroscientists. Systems thinking provides a model of how individual contributions sum to a greater whole, which is a key principle of scientific knowledge itself.

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Box 3

Respiration generates adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and phosphate. ATP is the 'energy currency' of the cell, and is hydrolysed (i.e. broken down) to release energy where it is needed – for example, when the highly structured proteins actin and myosin interact to generate force in a contracting muscle. ADP is a by-product of this breakdown.