

EDUCATION

From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans

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It is a popular belief that exercise performance is limited by metabolic changes in the exercising muscles, so called peripheral fatigue. Exercise terminates when there is a catastrophic failure of homeostasis in the exercising muscles. A revolutionary theory is presented that proposes that exercise performance is regulated by the central nervous system specifically to ensure that catastrophic physiological failure does not occur during normal exercise in humans.

of electrons from carbohydrate and fats is tightly coupled to the synthesis of ATP in the mitochondria. During muscle contraction, the resulting increase in ADP concentrations causes an increase in the rate of oxidative phosphorylation, resulting in the resynthesis of ATP, and preventing a dramatic decrease in ATP concentrations in the muscle.

Yet some of the traditional explanations of how fatigue develops during both maximal and more prolonged exercise in humans seemingly disregard this reality. For the popular theories posit that fatigue develops, and exercise terminates, whenever the rate of ATP use by the exercising muscles exceeds the maximum available rate of oxidative ATP production of those muscles. Thus it is believed that, during high intensity exercise, the shortfall in oxidative ATP production is supplemented by the less sustainable “anaerobic” ATP production, leading to fatigue when the rate of ATP production becomes less than its rate of ATP use. During more prolonged exercise, it is proposed that the shortfall in oxidative ATP production cannot be remedied.⁶ Rather the muscles “fatigue” so that either the exercise must be terminated or it can continue only at lower intensities.

These concepts are based on the “limitations” or “catastrophe”⁷ models of exercise physiology, which conjecture that fatigue develops only after one or more bodily systems are stressed beyond their capacity, leading rapidly to the complete system failure that we recognise as exhaustion. The most long standing example, perhaps the earliest source of this intellectual mindset, is the theory that a limiting oxygen delivery to muscle, leading to skeletal muscle hypoxia or anaerobiosis, is the cause of fatigue during high intensity exercise of short duration, the so called cardiovascular/anaerobic/catastrophic model of exercise physiology.⁸

However, the overlooked flaw in this explanation is that fatigue cannot be the immediate consequence of an imbalance in the rates of muscle ATP production and ATP use. For, if that were true, as soon as the rate of ATP production lags behind its rate of use, muscle ATP concentrations must fall inexorably, leading ultimately to muscle rigor.³ But, if muscle rigor does not develop during any form of exercise in vertebrates, then some other control mechanism must exist to terminate exercise even though the rates of skeletal muscle ATP production and use are in balance and skeletal muscle ATP concentrations are sufficiently high to prevent the development of rigor.

Certain truths are self evident; others are more deeply hidden. Perhaps the most interesting question in exercise physiology is the one that is not often asked: why do muscles not develop rigor during exercise of high intensity and short duration (seconds to minutes) or when their fuel reserves are depleted during more prolonged exercise lasting two or more hours? Consider for example, the following. Human skeletal muscle can increase its peak rate of ATP utilisation to about 3 $\mu\text{mol/s/kg}$ wet weight within seconds of beginning intensive exercise.¹ Yet skeletal muscle ATP concentrations are 5–7 $\mu\text{mol/kg}$ wet weight.² Thus as little as seven seconds of peak exercise would deplete the muscle ATP stores and induce rigor as a catastrophic event if the peak rate of muscle ATP production was less than 80% of demand. Indeed, Newsholme and Start² have calculated that total ATP stores in the flight muscles of the fly, *Lucilia sericata*, would sustain about 0.1 second of flight, and the white leg muscles of the rabbit about 1.0 second of running respectively if other mechanisms for instantaneous rephosphorylation of ADP did not exist.

As muscle rigor has yet to be described during exercise in any vertebrate, the rates of ATP use and production must be perfectly matched, even during maximum exercise in all members of the animal kingdom. As a result, ATP concentrations in maximally exercising muscles fall relatively little during exercise,³ even in muscles that are deficient in certain key metabolic enzymes which would impair their capacity to generate ATP, especially the group of conditions collectively termed McArdle’s syndrome.^{4,5} Thus it appears that muscle ATP concentrations during exercise are homeostatically regulated with exquisite accuracy, as they are at rest. This has to be so because, under physiological conditions, the flow



This paper forms part of a symposium series. Each of the four accompanying papers will be published in the journal over the next few issues, and the full series will be accessible at <http://bjism.bmjournals.com/supplemental>

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In a symposium at the 2001 American College of Sports Medicine Annual Conference in Baltimore, three presentations, reproduced here in an updated format, were delivered that, together, presented a different solution to this historical dilemma.

In the first paper, Noakes and St Clair Gibson⁹ present a historical overview of the evolution of the different models used to explain the physiological factors that are currently thought to limit human performance in exercise of either short duration and high intensity or lower intensity and longer duration.^{10–16} They pay special attention to the cardiovascular/anaerobic/catastrophic model because it is this model that has had the greatest influence on teaching and research in the exercise sciences¹⁷ since its first formulation in the early 1920s by AV Hill and his colleagues in London.

As astrophysicist Steven Hawking¹⁸ has written: “A theory is a good... model if it describes a wide class of observations and if it predicts the results of new observations. Beyond that it makes no sense to ask if it corresponds to reality, because we do not know what is reality independent of a theory. How can we know what is real, independent of a theory or model with which to interpret it?” Rather, the value of a model is that it makes predictions, the veracity of which can then be evaluated. If these predictions prove untrue, then the model must be relinquished: “Eventually the theory becomes a creaking and ugly edifice. Then someone suggests a new theory in which all the awkward observations are explained in an elegant and natural manner”

There are at least six hallmark requirements if the cardiovascular/anaerobic model is both plausible and defensible. Under all conditions of maximal exercise, there must be: (a) a “plateau” in oxygen consumption indicating (b) the onset of skeletal muscle anaerobiosis; (c) a maximum (limiting) cardiac output; (d) complete (maximal) recruitment of all available motor units in the muscles that are exercising; (e) identical concentrations of inhibitory metabolites in the maximally recruited muscles at exhaustion regardless of the circumstances of the exercise; and (f) an absolute state of fatigue from which complete recovery occurs only after a defined period of rest. As this model predicts that fatigue results from discrete system failure consequent to the attainment of a limiting cardiovascular function, the seventh prediction of this model is that there must be evidence of homeostatic failure at fatigue, hence the development of a physiological “catastrophe”. However, there is no conclusive evidence that fatigue during maximal exercise fulfils any, let alone all, of these predictions. Therefore the argument is advanced that this traditional model is a “creaking and ugly edifice”¹¹ in need of urgent revision and reformulation.

The paper continues by evaluating the current models used to explain those forms of fatigue that develop during high intensity exercise of very short (less than 60 seconds), intermediate (minutes to hours), and very prolonged (two to eight hours) durations. It proposes that these current models also fail adequately to explain all the published findings. In particular, the model of fatigue during more prolonged exercise, which is believed to be due to muscle glycogen depletion causing “the rate of ATP production to fall below the rate of ATP use”,⁶ cannot be correct. For the ultimate outcome must also be the development of rigor, which, as is the common observation, does not occur during prolonged exercise.

Hence Noakes and St Clair Gibson⁹ conclude that the current models, which posit that fatigue is regulated exclusively by changes that occur in the exercising muscles, do not explain most forms of exercise fatigue. The most telling evidence for their conclusion is the finding that motor unit recruitment in the active muscles is never absolutely maximal^{19–21} during voluntary exercise in humans. Yet the

single absolute requirement of the traditional (peripheral) model of exercise regulation is that all the motor units in the active muscles must be recruited at exhaustion during all forms of exercise. However, there is neither any known nor proposed mechanism by which the accumulation or depletion of metabolites in the active muscles can directly prevent the fresh conscription of additional motor units that are quiescent at exhaustion because they have yet to be recruited by the central nervous system (CNS). For the conscription of additional motor units would allow the exercise to continue past a state of apparently absolute exhaustion but which is nonetheless associated with a less than maximum recruitment of available motor units.

More probable is the theory that such metabolites can more profitably act to regulate skeletal muscle function by influencing the number of motor units that are recruited in the exercising skeletal muscles at any time by the CNS. In essence, they argue that neither ATP nor lactic acid is the most important chemical regulating the function of exercising skeletal muscle, but rather the calcium released from the skeletal muscle sarcoplasmic reticulum in response to neural inputs from the central and peripheral nervous systems, which is also the essential chemical initiator of skeletal muscle contraction.

Accordingly, in the second paper, St Clair Gibson and Noakes²² begin to establish the basis for a new model which they believe is better able to explain all the current observations. They argue that the peripheral model of fatigue is an example of a linear dynamic system in which system failure results from the progressive increase in the quantity of some, perhaps metabolic, variable until an absolute maximal concentration is reached. Once the system has failed catastrophically, causing physical exhaustion, a period of rest is required before exercise can again commence and during which the metabolites responsible for the fatigue are removed. However, they argue that, in humans with an intact CNS, no single metabolite has yet been identified that causes fatigue according to this linear model. More importantly, no example of absolute system failure, such as skeletal muscle rigor, has ever been reported; yet this is the logical prediction of the catastrophe model of Edwards.⁷

They next review the contrasting central neural or central governor model of fatigue, which is based on the evidence that there is always skeletal muscle motor unit “recruitment reserve”^{19–20} in all forms of fatigue, indicating that the CNS regulates and indeed limits the extent of skeletal muscle recruitment, specifically to ensure that homeostasis is maintained and catastrophe averted.

This system would probably be controlled by either feed forward regulation from higher cortical structures or reflex inhibition of efferent neural command by type III and IV chemoreceptors reacting to changes in peripheral substrate or metabolite concentrations, or even perhaps from the input of skeletal, cardiac, or respiratory muscle mechanoreceptors. On the basis of a number of their own^{23–24} and other^{25–27} recent findings, they next propose an updated and more comprehensive version of their original model, described by Noakes *et al.*²⁸

According to their central governor model, they propose that during self paced exercise, which is the natural, as opposed to laboratory, form of human physical activity, the CNS continuously modifies the pace as part of a complex, non-linear dynamic system. In this model, the power output (work rate) during exercise is continuously adjusted on the basis of metabolic calculations performed at a subconscious CNS level. These calculations take into account prior knowledge acquired during previous exercise bouts, the planned end point of the current exercise bout, and the current metabolic rate, among many other potential variables. These

subconscious calculations create a continuously adjusting power output, and hence pace, during exercise. This model provides the revolutionary insight that fatigue is not a physical event but rather a sensation that is the conscious manifestation of these subconscious CNS processes.^{20 29 30}

Thus the model predicts that the ultimate control of exercise performance resides in the brain's ability to vary the work rate and metabolic demand by altering the number of skeletal muscle motor units recruited during exercise. Thus the key question becomes: what physiological parameters determine the number of motor units recruited by the CNS in actively exercising skeletal muscles?

In the third paper, Lambert, St Clair Gibson, and Noakes³¹ examine peripheral regulation of metabolic activity, and how peripheral processes integrate with the regulatory centres in the CNS. They review the evidence showing that peripheral metabolites can provide information to central (brain) regulatory centres by way of afferent neural pathways and that they are therefore an integral part of the regulatory process. Alterations in efferent neural command generated as a result of peripheral afferent sensory input has a natural time delay, which leads to a continuously adjusting, oscillating power output, or pace, as part of a whole body, complex, non-linear, dynamic system.

Lambert, St Clair Gibson, and Noakes³¹ further argue that these alterations in power output may also be determined partly by regulatory systems that also exist in the periphery. These peripheral systems contribute to a hierarchical system of control with redundant properties, and this redundancy of command processes creates a more robust—that is, a complex—control system capable of maintaining homeostasis more efficiently than would single, isolated control processes that lack a central integration or the presence of redundancies.

Finally, they show that the neural and metabolic responses to exercise may be “reset” by factors such as antecedent exposure to exercise. Even a single bout of exercise before a particular event can alter metabolic activity and the conscious sensation of fatigue during the subsequent exercise bout, indicating that the central governor processes are mutable and can be continuously reset on the basis of continuing and novel experiences.

The ideas presented here are revolutionary as opposed to evolutionary because they make three novel predictions.

- Firstly, as at rest, now also during all forms of exercise, all physiological functions are homeostatically regulated by CNS control mechanisms to ensure that bodily harm does not result.
- Secondly, the conscious sensation of fatigue does not arise directly from the action of metabolites in the periphery, but rather from the regulatory centres in the subconscious parts of the brain, the function of which is to ensure homeostasis during exercise.³⁰ Therefore the distinct sensation of fatigue is not directly related to a physical end point, but is rather an interpretation of the effect of the current level of activity on future exercise capacity and any threats that immediate and future events pose to the maintenance of homeostasis.^{30 32}
- Thirdly, as the sensation of fatigue is an emotion rather than a physical state, pacing strategies and their control during self regulated exercise—the journey and not just the end point—are probably the most important phenomena in exercise physiology.

The authors therefore develop the argument that the “limitations” or “catastrophe” models of exercise physiology fail specifically because they do not explain what is most obvious. That far from being limited by the failure of one or

What is already known

A popular teaching is that exercise performance is limited by metabolic changes in the exercising muscles, so called peripheral fatigue. This model predicts that exercise terminates when there is a catastrophic failure of homeostasis in the exercising muscles.

What this study adds

In a series of five articles introduced here, we present a revolutionary theory that explains the key findings better than the traditional catastrophe model of exercise physiology. The model proposes that exercise performance is regulated by the CNS specifically to ensure that catastrophic physiological failure does not occur during normal exercise in humans.

more physiological systems during exercise, the reality is that all physiological systems in the body, both at rest and during physical activity, are homeostatically regulated in a continuous process, specifically to prevent catastrophic failure, including irreversible physical exhaustion, widespread cell damage, or even death, as the outcome of exercise.

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