EDITORIAL

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Physiology: alone at the bottom, alone at the top

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To physiologists the term 'systems biology' seems redundant because biology is fundamentally integrative and about systems. Entire fields within biology like ecology and evolutionary biology are about large scale interactions within, between and among living organisms. Perhaps, one step down the biological food chain sits physiology, which in the broadest sense attempts to understand life at the level of the individual organism and how the internal environment of the organism is 'managed' and how the organism interacts with the outside world. Over the years, physiologists have used a collection of tools in an effort to understand these big issues. Biochemical, pharmacological and molecular tools have been applied using reductionist approaches to physiological problems. This has led to the development of organ- or systems-specific sub-disciplines within physiology that contribute to the understanding of regulation, control, or adaptation of some part or parts of the organism. At the opposite end of the spectrum, physiology also informs epidemiology, population health and even public policy. Examples include things like how carbohydrate metabolism and glucose transport intersect with population-based guidelines for body weight, physical activity and diabetes prevention. Another example is how the physiology of thermoregulation has been used to generate guidelines related to athletic competitions held in warm environments and the occupational demands associated with heavy physical labour in harsh environments.

Into this mix has recently been added what might be described as a spontaneous generation of something called 'systems biology'. To physiologists, this term is problematic. First, physiologists have been interested in systems for a long time and how various 'parts' interact to create organs, systems and organisms. Second, at some level one is tempted to speculate that the 'new' systems biology has emerged because of the inability of the molecular reductionists to get satisfying and applicable large scale insights from their work. A third major concern (and point of irony) is that many physiologists remember that in the 1980s and 1990s the molecular reductionists scoffed at the integrative nature of physiology as anachronistic; some of these same individuals now appear to be trying to create a new 'systems' approach that does not make full use of, or seek to integrate itself with, existing systems based knowledge and approaches. A fourth concern is that many versions of systems biology have not really developed beyond the cell and this seems like a contradiction in terms. Perhaps the final concern of physiology about systems biology is the idea that it is acceptable to generate large volumes of reductionist molecular and/or genetic data with no pre-existing hypothesis and then to use modelling tools to evaluate relationships and see what hypotheses might or might not emerge. This contrasts with physiology that has been informed by big ideas like homeostasis, set-points, regulation, feedback control and redundancy to explain and model the interactions between cells, organs, systems and organisms.

In this edition of *The Journal of Physiology*, we take these issues head on in a series of six critical reviews of systems biology by physiologists. Denis Noble highlights the limitations of gene-centred thinking about evolution and physiology and points out that there is much more to phenotype than the digital genome (Noble, 2011). Joyner and Pedersen remind us that biology is a big field and question a number of the parochial assertions made by leading exponents of systems biology and how reductionism might or might not translate to more disease cures or better health outcomes (Joyner & Pedersen, 2011). The metabolic responses to exercise are among the most complex integrated biological responses known, and Greenhaff & Hargreaves (2011) provide a constructive critique of just how new reductionist techniques might or might not contribute to improved understanding of metabolic regulation in response to exercise. Duncker and Colleagues, use the problem of cardiac remodelling to describe how new molecular and 'omic' tools may be incorporated and exploited in a physiological context to generate 'integrative physiology 2.0' (Kuster *et al.* 2011). Two papers on modelling are also included, because modelling complex biological interactions is nothing new to physiologists who have been modelling for ∼400 years. This modelling has been both hypothesis driven and also generated new questions. Secomb & Pries (2011) briefly review how engineering and mathematical principles have been and are being used to understand the microcirculation. Hester and colleagues highlight the current state of the art multi-element of model of human physiology (Hester *et al.* 2011). Both discuss top down and bottom up approaches and perhaps the microcirculation is the middle out.

It has been said that physiology causes nothing but explains everything, and when viewed via its unparalleled ability to weave coherent stories from reductionist data and at the same time explain epidemiological observations, perhaps it is safe to say that as a biological discipline physiology is both alone at the bottom and alone at the top. The review articles in this edition of *The Journal* make these points and suggest a way forward from depths of reductionism. Progress in biology requires integrative as well as reductionist approaches; both have long been encompassed by the discipline of physiology.

References

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