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EDITORIAL

Evolution evolves: physiology returns to centre stage

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Introduction

This issue of *The Journal of Physiology* is devoted to the integration of evolutionary biology with physiological science. The immediate trigger was a very successful symposium on this theme held during the IUPS Congress in Birmingham in July 2013. The symposium followed an opening plenary lecture based on an article that had recently been published by one of us in the sister journal *Experimental Physiology* (Noble, 2013) and previously in *The Journal of Physiology* (Noble, 2011). The title of that article was ambitious, describing physiology as 'rocking the foundations' of biology. Strong language, perhaps? Yes, but that title was merely reflecting a rising tide of recently published articles in major scientific journals, including *Nature Reviews Genetics* (Müller, 2007), *Proceedings of the National Academy of Sciences of the USA* (Mattick, 2012), *Nature* (Ball, 2013), *Biological Journal of the Linnean Society* (Bateson, 2014) and *Science* (Rosenberg & Queitsch, 2014). It was also prompted by important books that have appeared recently (Margulis & Sagan, 2003; Jablonka & Lamb, 2014; Noble, 2006; Beurton *et al.* 2008; Pigliucci & Müller, 2010; Bateson & Gluckman, 2011; Gissis & Jablonka, 2011; Shapiro, 2011). Those books also propose either significant extensions of existing evolutionary theory or the replacement of the Modern Synthesis by a new synthesis. Despite the radical presentation of the *Experimental Physiology* article, therefore, it contains little that was not already known to those biologists who have been keeping abreast of recent literature. It is becoming increasingly difficult to keep up with this literature because it is widely spread amongst very many scientific journals. A focused issue of a journal, like this one, can therefore be very valuable. We intend that this should be a seminal resource for future research and teaching.

The questions addressed in the papers published here include the following.

- What are the major new developments in evolutionary biology and how do they challenge the Modern Synthesis?
- Which of these developments have implications for how the physiological sciences should further their understanding of health and disease?
- If the Modern Synthesis is to be extended or replaced by a new explanatory structure, what is the role of physiology in the development of this structure?

Function

Why have these questions become important? One answer is that they change the way in which physiological function is relevant to evolutionary biology. We define function here as the role that a part, a process or a mechanism plays within an encompassing system, a role that contributes to the goal-directed behaviour of that system. This definition covers different notions, such as those presented by Wright (1973), Cummins (1975) and Kitcher (1993). There is a possible confusion in discussing function in the context of evolution because current utility is not necessarily how the trait evolved. Further reading on these issues can be found in the articles by Tinbergen (1963), Bateson & Laland (2013) and the one in this issue by Roux (2014).

We are also using a broad definition of physiology as a discipline at the intersection of ecology, behavioural biology, developmental biology and molecular biology. As will be evident in the articles of this focused issue, the new developments encompass all these fields, often in combination.

In standard selection theory, usually called the Modern Synthesis (MS) and sometimes called Neo-Darwinism, function is relevant only to postgenomic change in populations through determining which individuals are successful in reproducing. One of the dogmas of the Modern Synthesis is the impossibility of the inheritance of acquired developmental dispositions. Genomic change, which is seen within the MS framework as a synonym to hereditary change, is assumed to be random with respect to function. Function therefore plays a role only in so far as it determines the fitness of the individual organism in its reproductive success after genomic mutations have created the possibility of an advantage. In contrast, the inheritance of some acquired epigenetic characteristics and other forms of non-DNA inheritance enables function to be involved in pre-genomic change by influencing hereditary change more directly before selection could play a role. Furthermore, mechanisms of genomic change have been identified that were not envisaged by the founders of the Modern Synthesis, including symbiogenesis and natural genetic engineering.

Making a categorical prohibition a central part of a theory can be useful for a time. The Modern Synthesis served an important function in the mid-20th century in stimulating much mathematical work in population genetics, for example. But we have to recognize that by encouraging a dogmatic use of the theory it may also have inhibited many lines of research that have now been found to be important. Theories with categorical prohibitions court their own demise, requiring either fundamental extensions or even complete replacement when contrary experimental evidence emerges. The articles in this issue demonstrate that evidence. The mechanism of random change followed by selection becomes only one of many possible mechanisms of evolutionary change. Moreover, all those mechanisms can interact. We have entered a period of a systems approach to evolution science that contrasts markedly with the parsimonious reductionism of the Modern Synthesis. In this respect, it echoes the move towards a systems approach in many other areas of biology (Melham *et al.* 2013).

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The genotype–phenotype relation

The genotype–phenotype relation, which is at the heart of our view of heredity and development, has turned out to be much more subtle than what the Modern Synthesis made room for, and it is increasingly acknowledged that a better understanding of this relation is key to understanding a range of evolutionary phenomena beyond the explanatory reach of the Modern Synthesis. Considering that the disciplinary goals of physiology are 'the study of the functions and activities of living matter (as of organs, tissues, or cells) as such and of the physical and chemical phenomena involved' (*Webster's Third New International Dictionary*), it is clear that the mechanistic aspects of the genotype–phenotype relation lie within the explanatory domain of physiology. Hence, physiology must of necessity become the backbone of any mature evolutionary theory pretending to merge the proximate and ultimate explanatory domains. The consequence is that we will have to go back to a broader, more inclusive view of heredity, which was captured by William Bateson's original definition of genetics as 'The Physiology of Descent' (Bateson, 1906; see Olby, 2000). A physiological view of heredity enables the integration of the extended evolutionary synthesis view of evolution with the physiological sciences.

More specifically, the genotype–phenotype concept that is currently in wide use within evolutionary theory conceals the facts that it is an abstraction of a relation that is the outcome of very complex dynamics that in many cases are intimately connected to the environment (Gjuvsland *et al.* 2013), and that DNA does not have the privileged place in the chain of causality many attribute to it. As described in more detail by Omholt (2013), if one tries to interpret the function of DNA in systemic terms one finds that DNA allows a system to induce perturbations of its own dynamics as a function of the system's own state (its phenome). In this systems view, the causality flows from the system state through a change in use of DNA that results in a change in the production of RNA and protein, which in turn perturbs the system's dynamics. In those cases where variations in DNA cause changes in the perturbation regimen, it may lead to different system dynamics and thus physiological variation. Thus, the genotype–phenotype relation cannot be understood outside a systems-physiology framework, whatever causes variations in DNA. And any evolutionary theory aiming to explain the manifestation of biological form across time and space needs to be highly articulate about this relation.

Physiology in a broad sense, therefore, now moves to centre stage in evolutionary biology as we are finally in a position to step conceptually and technologically out of the narrow frames of the Modern Synthesis and take explanatory responsibility for a much wider set of evolutionary phenomena and patterns across time and space. Some of the articles in this issue address the consequences that this new intellectual spotlight has for the discipline of physiology itself, including possible consequences for health and disease; it is noteworthy that some of the new mechanisms manifest themselves in the inheritance of the chances of acquired disease states.

The ways in which a systems approach can be applied to the complex dynamics and evolution of organisms are addressed in this issue by Badyaev (2014), who explores 'whether epigenetic effects facilitate adaptive modulation of complex phenotypes by effectively reducing the dimensionality of their deterministic networks'; Baverstock & Rönkkö (2014), who regard the cell 'as a complex dissipative natural process' that 'minimizes the free energy of their ecosystems', a process where genetic variation is largely irrelevant; Jaeger & Monk (2014) showing 'how dynamical systems theory can provide a unifying conceptual framework for evolution of biological regulatory systems'; Lamm (2014), who 'applies the conceptual toolkit of Evolutionary Developmental Biology (evo–devo) to the evolution of the genome and the role of the genome in organism development'; Levin (2014), who analyses 'the control of anatomy by bioelectricity and the evolutionary implications of its top-down causal efficacy'; and Danchin & Pocheville (2014), who discuss the ways in which 'non-genetic inheritance shatters the frontier between physiology and evolution'.

Mechanisms of inheritance

The molecular mechanisms by which non-standard inheritance can occur are diverse.

Natural genetic engineering refers to reorganization of genomes. The mechanisms discovered since McClintock (1950, 1984) first demonstrated mobile genetic elements in plants are many. As Beurton *et al.* (2008) write, 'it seems that a cell's enzymes are capable of actively manipulating DNA to do this or that. A genome consists largely of semi-stable genetic elements that may be rearranged or even moved around in the genome thus modifying the information content of DNA.' In this issue, Shapiro (2014) shows that 'the genome is best modelled as a read–write (RW) data storage system rather than a read-only memory (ROM)'.

Symbiogenesis has been involved in the most dramatic examples of genome re-organization, i.e. the acquisition of DNA from other organisms through lateral gene transfer. As is now well known, this is thought to explain the origin of mitochondria, chloroplasts and other organelles.

Lateral gene transfer is now recognized to be much more extensive and widespread than it was previously assumed to be; occurring in most orders and often among them. Recent examples include mechanisms of transfer from prokaryotes to eukaryotes generally (Redrejo-Rodríguez *et al.* 2012) and transfer from bacteria to insects (Acuña *et al.* 2012).

Epigenetic mechanisms that lead to persistent developmentally induced changes in gene activity include diverse processes and factors. One type of system, the chromatin marking system, includes methylation of cytosines and histone modifications, which interact with each other and with other epigenetic control factors (such as small RNAs). Chromatin marks were originally thought to be wiped clean during transmission between generations. It is now clear that this is not always true. Moreover, recent work has shown 'heritable epigenetic changes [that] persisted for multiple generations and were fully reversed after consecutive crosses through the alternative germ-lineage' (Nelson *et al.* 2012). For example, induced epigenetic (methylation) changes affecting a wide range of characteristics were transmitted for three generations following ancestral exposure to fungicides (e.g. Anway *et al.* 2006), and conditioned fear to an odorant was transmitted for two generations in mice (Dias & Ressler, 2014). Transmission of epigenetic variations through the germ line is, however, not necessary for inheritance between generations. Chromatin marks can be transmitted across generations

by epigenetically marking the genome in the newborn, leading, through their physiological and behavioural effects, to the reconstruction of developmental conditions in the offspring (Weaver, 2009). Such genomic marking may also underlie inherited maternal (Gluckman *et al.* 2007) and nutritional effects (Kaati *et al.* 2007). Another non-standard inheritance system, the RNAi-mediated inheritance system, which interacts with the chromatin marking mechanisms, underlies the transmission of many important characteristics in both plants and animals. An example of RNA-transmitted resistance to viruses has been shown to be transmitted stably for 100 generations in nematodes (Rechavi *et al.* 2011). In this issue, Stern *et al.* (2014) demonstrate that 'exposure to [antibiotic] stress reduces the maternal levels of *Polycomb* in the offspring embryos and [that] this reduction contributes to the inheritance of induced expression'. Also in this issue, Bateson *et al.* (2014) discuss a form of developmental plasticity, the predictive adaptive response (PAR), 'in which cues received in early life influence the development of a phenotype that is normally adapted to the environmental conditions of later life'. Sela *et al.* (2014) suggest 'that non-coding RNAs synchronize the different transgenerational epigenetic effects by interacting with and therefore surveying both the transcriptome and the genome'.

The physiological adjustment of organisms to changes in conditions within and between generations involves corresponding epigenetic changes. Selection for the stabilization of the physiological adjustments can lead both to the selection of epigenetic changes that are inherited between generations and/or to the selection of genetic changes that further stabilize, expand or otherwise improve the physiological adjustments. This process, genetic assimilation, was first demonstrated by Waddington (1957), who also introduced the term 'epigenetics', though not with its current usage. A more inclusive term, 'genetic accommodation', was suggested by Mary-Jane West-Eberhard (2003). This process can lead to the stabilization and canalization of previous developmentally induced changes, to an increase in plasticity and to the buffering of potentially deleterious side-effects. In all cases, the processes are usually initiated by developmental changes that induce new patterns of gene activity in alleles that already exist in the population (but not in that combination in any individual) and expose the new allelic combination to natural selection. No new mutations are required in this process, although a new mutation can contribute to it. Given that it is gene combinations and developmental networks that are the targets of selection, genetic accommodation is yet another process showing the advantages of focusing on networks of interactions rather than on individual 'genes' (we return to the definition of 'gene' later). Thinking through the process of genetic accommodation requires consideration of the interactions between different developmental mechanisms at different levels of biological organization. Following genetic accommodation, the inheritance becomes standard DNA inheritance; therefore, it would be difficult to determine from genomic sequencing whether this process had occurred. However, comparisons of chromatin marking and small RNA profiles in populations that are at the initial stages of evolutionary divergence can uncover the epigenetic correlates of the physiological adjustments that drive genetic assimilation and can point to epigenetic factors that are inherited and contribute to the stabilization of the new adjustments. Further valuable insights on these questions can be found in the article in this issue by Bateson *et al.* (2014).

Physiological changes can accompany and stabilize cultural changes. Poverty and ethnic conflicts are cultural phenomena that may have long-term, heritable physiological effects. For example, young people living in developing countries in conditions of social and political insecurity, such as ongoing political conflicts, are likely to be exposed to hunger, psychological stress and toxic pollutants, which can alter their epigenetic profiles and adversely affect them and their offspring. This concern is highlighted by data from the 'Dutch Starvation Winter' of 1944–1945, which has shown that a deprived *in utero* environment can have lifelong effects, including the incidence of many chronic non-communicable diseases (Portrait *et al.* 2011; van Abeelen *et al.* 2012). Adverse effects also develop rapidly in the switch from low-calorie to high-calorie environments, as is now happening in China and India, with serious consequences in, for example, the prevalence of type 2 diabetes. The physiology of culture and of cultural inheritance emerges today as a new and urgent concern.

The neglect of physiological responsiveness may also lead to unwarranted, gene-centric, adaptationist interpretations. Organisms adapt to their environment at many levels that challenge a strict genotype-to-phenotype world view. For example, it has been suggested that positive selection pressure led to an increase in the prevalence of the EDARV370A variant of the human ectodysplasin receptor in the Han Chinese. This variant is associated with increased eccrine sweat gland function (Kamberov *et al.* 2013), and the idea is that it facilitated thermoregulation and thus survival in a warm, humid environment. This gene-centric interpretation fails to account for the fact that thermoregulation is highly adaptable in humans and that sweat rate can double with only a few weeks of heat exposure (Robinson *et al.* 1943; Wyndham, 1967).

Sun & Zhu (2014) in this issue show the limitations of the gene-centric view in the study of cross-species clones that provide 'an ideal system to study the relative role and crosstalk between egg cytoplasm and zygotic nucleus in development', emphasizing that 'the developmental process should be interpreted in a systemic way, rather than in a way that solely focuses on the role of nuclear genome.'

The question now, therefore, is not whether developmental plasticity and non-standard forms of inheritance occur but how often they occur and to what extent they contribute to evolutionary change. It is also important to incorporate these changes into mathematical models (Tal *et al.* 2010; Danchin *et al.* 2011) and to define the differences in the regulatory architecture that underlie, for example, broad and narrow sense inheritability (Wang *et al.* 2013). It will be important to assess the contribution these regulatory mechanisms may have made to the speed of evolution and how interactions between the mechanisms, such as genetic assimilation, contribute. These are all open and difficult questions. Nature is even more wondrous than the architects of the Modern Synthesis thought, and involves processes we thought were impossible.

Relevance to health and disease

The Modern Synthesis has also been a driver of biomedical research priorities and experimental diagnostic and therapeutic thinking since at least the US 'War on Cancer', which started in 1971. A

key idea was that discrete genetic and molecular dysfunction led to specific cancer phenotypes. If these could be identified and then targeted with drugs, cancer could be cured. This view is now being abandoned, and cancer is seen as a far more complex problem, involving many pathways, frequently trigged by environmental or behavioural factors, with only limited evidence for marked genetic risk in common cancers (Gatenby & Gillies, 2008; Watson, 2013). Paradoxically, successes in the War on Cancer have largely been through prevention, most notably via tobacco control.

In a similar vein, the human genome project saw a tight linkage between genotype and phenotype, with two major outcomes envisioned. For diseases with known genetic causes, cures based on gene therapy or other forms of genetic engineering would emerge. For more common non-communicable diseases, such as diabetes and heart disease, common gene variants would explain much of the lifetime risk of the disease and lead to pre-emptive medicine. In other words, people could be screened for high-risk genes and then given either lifestyle advice or drugs to prevent disease.

This latter strategy has been marked by a general failure to identify common gene variants that place large numbers of people at high risk for common non-communicable diseases. Instead, a large number of variants with small effect sizes have been identified. In general, the inclusion of genetic information in risk-prediction algorithms does little to improve risk prediction beyond simple questionnaires and blood tests for conditions such as diabetes and cardiovascular disease (Thanassoulis & Vasan, 2010; Echouffo-Tcheugui *et al.* 2013). The current worldwide rise in obesity seems so driven by the combination of high calories and low physical activity that some have concluded that the search for obesity-risk genes is futile (Veerman, 2011). Finally, even if such predictive information were available, would the average person change their behaviour or would low-risk individuals feel free generally to ignore well-known health guidelines? These issues are dealt with in more detail in the article by Joyner & Prendergast (2014) in this issue.

There is also a parallel story for rare phenotypes. In the case of extreme longevity (>100 years) the search for a clear-cut genotype–phenotype narrative (Sebastiani & Perls, 2012) has been slow to emerge and hard to unravel. For sudden death in young athletes, most commonly caused by hypertrophic cardiomyopathy, multiple causative rare genetic defects have emerged (Landstrom & Ackerman, 2010). However, even within the same family siblings with the potentially lethal gene variant do not always manifest the tragic phenotype.

At some level, biomedical research driven by the Modern Synthesis is being repackaged again. The idea is that certain gene variants might offer new therapeutic targets for common diseases. A notable recent example is the targeting of pathways associated with the *PCSK9* gene (Steinberg & Witztum, 2009) to reduce cholesterol. The extent to which this new strategy is more effective than the earlier focuses on genetic engineering or the common variant common phenotype remains to be seen.

Based on the above overview, it might be argued that the biomedical efforts informed by the Modern Synthesis have stalled or at least underperformed. In contrast, progress in epidemiology and public policy marches on, with ever more evidence showing the powerful effects of behaviour, environment and social circumstances on health (McGinnis *et al.* 2002; Wilkinson & Marmot, 2003; Bortz, 2005; Kuznetsova, 2012).

The extent to which the genome project has not influenced medical practice is striking (Editorial, 2010). For example, several recent clinical trials have shown little or no benefit of genetic testing to improve the dosing of the commonly used anticoagulant warfarin. Additionally, the need to design clinical trials to evaluate personalized therapy objectively, based on individual genetic markers, is critically needed.

The ubiquity and abundance of between-generation epigenetic inheritance has implications for assessing disease risk and the responses to ecological stresses. New methods for identifying and estimating the extent of heritable, epigenetic variation in populations are necessary. One method for doing this has been developed by Tal *et al.* (2010), who have combined a classical quantitative genetics approach with information about the number of opportunities for epigenetic reset between generations and assumptions about environmental induction to estimate the heritable epigenetic variance and epigenetic transmissibility. The application of this or similar methods to epidemiological data can help to uncover the epigenetic correlates and causes of complex metabolic and environmental diseases and help in finding adequate treatments. Further relevant material can be found in the article on the Predictive Adaptive Response (PAR) in this issue (Bateson *et al.* 2014).

Relevance for an extended evolutionary synthesis

It is clear, therefore, that evolutionary theory is undergoing ferment. Advances in the empirical and conceptual approaches to evolution prompt a renewed appreciation of the multiplicity of processes interacting in evolutionary change, leading to an expanded theoretical framework beyond the standard population genetic account (Margulis & Sagan, 2003; Beurton *et al.* 2008; Pigliucci & Müller, 2010; Gissis & Jablonka, 2011; Shapiro, 2011). Physiological science has an important role in this encompassing reform of evolutionary theory, because of three major contributions it can make, namely the reintroduction of function, the addition of higher order organizing principles and an account of organismal systems properties.

In the classical view of the Modern Synthesis, function – in general – was all but excluded from having any role in the generation of selectable variation, the directionality of evolutionary change (which was assumed to be the consequence of selection alone) or the kind of information transmitted from one generation to the next. The contributions to this issue demonstrate that this view is unwarranted on all three accounts. Hence, a representation of functional principles is required in the evolutionary framework. Indeed, while functional and evolutionary explanation were once regarded as distinct (Mayr, 1961), since the 1980s function has been re-appreciated, mostly in terms of constraints acting on the generation of phenotypic variation (Wagner, 1984; Maynard-Smith *et al.* 1985). More recently, functional principles have come to be addressed via evolutionary studies of gene regulation, embryonic development, comparative behaviour, ecological systems and, in particular, physiology. The trigger for this was the desire to achieve a better mechanistic understanding of the genotype–phenotype relation in the evolutionary process. It is hardly surprising that the emphasis has been, and still is, on the molecular analysis of gene

action, through functional genomics, transgenic techniques and genetic engineering. Essentially, this provides a means of experimental testing of the predictions made by statistical genetic inference (Dean & Thornton, 2007), thus adding a new level of analysis to evolutionary science.

While these aspects of function improve our mechanistic understanding of the genotype–phenotype relation, physiology brings function to evolution also in a different way, through the higher order control that physiological systems exert over basic molecular processes. Hormonal activity, metabolic networks or electrolyte regulation, to name but a few, represent physiological systems that are not restricted to specific gene activity, but affect the behaviour of numerous cells, tissues and developmental processes at once. Such functional systems may themselves be a target of selection, but, more importantly, they can also affect the pace and directionality of evolutionary change. In these cases, the phenotypic outcome is not an immediate consequence of natural selection, but a consequence of the functional properties of the given system. For instance, physiological activity during development, such as embryonic movement, when altered through evolution, leads to specific morphological consequences, e.g. the loss or gain of skeletal elements (Müller, 2003). Moreover, the functional properties of proteins already present in unicellular organisms, when mobilized in a multicellular context, may dictate the possible arrangements of primary metazoan body plans (Newman *et al.* 2006).

Functional systems affect evolutionary processes also through their influence on inheritance, e.g. via epigenetic marking or gene silencing. Epigenetic models show that the rate and direction of evolutionary change can differ markedly from that inferred from population genetic models (Day & Bonduriansky, 2011; Geoghegan & Spencer, 2012), and epigenetic inheritance may accelerate genetic accommodation processes (e.g. Klironomos *et al.* 2013). Heritable epigenetic changes may also accompany ecological and genomic shocks and contribute to macroevolutionary change, for example in speciation events (Jablonka & Lamb, 1995, 2014). Furthermore, epigenetic DNA methylation, which leads to tissue-specific gene silencing, can greatly accelerate the rate of fixation of beneficial recessive mutations (Chess, 2012) and adaptive evolution by gene duplication (Rodin *et al.* 2005). These effects strongly modify the standard picture of evolutionary theory and induce further questions about the role and the evolutionary sophistication of epigenetic mechanisms during the major transitions in evolution (Jablonka & Lamb, 2006).

Another way in which functional systems shape evolution is through their multilevel interactions. Biological functions interconnect at many different levels of organization, from molecules to whole organisms, some aspects of which can now be quantified through systems biological approaches, such as the physiome project (Hunter *et al.* 2002; Hunter & Borg, 2003). Hunter & de Bono (2014) in this issue combine 'a multiscale hierarchy of functional tissue units (FTUs) with the corresponding application of physical laws to describe molecular interaction networks and flow processes over continuum fields within these units' to explore the 'biophysical constraints on tissue evolution'. Newman (2014) also discusses how the application of physical laws in biology can show that 'large-scale changes in organismal form now [provide] a scientific basis other than gradualistic natural selection based on adaptive advantage'.

In developmental processes that generate biological form, for instance, cellular architecture, tissue activity, physiological regulation and gene activation play together in intricate functional networks, without any privileged level of control. Evolutionary modification of such multilevel dynamics, be it through mutation, natural selection or environmental induction, will always affect the entire system. By necessity, such multilevel systems exhibit emergent properties (Badyaev, 2011) and produce threshold effects that influence the phenotypic outcome (Lange *et al.* 2013; Čapek *et al.* 2014). On the evolutionary scale, such properties can lead to non-linear dynamics in population change (Jaeger *et al.* 2012). By connecting levels of organization and by defining the effective parameters and boundary conditions for functional interactions among them, the physiological sciences can make a major contribution towards the explanation of non-gradual evolutionary dynamics and macro-evolutionary events.

Thus, function in general, and physiological function in particular, does affect the generation of selectable variation, the directionality of evolutionary change and the transmission of genetic and non-genetic information. Hence, evolutionary biologists should genuinely be interested in the functional physiological approach. First steps are being made, and a functional synthesis between molecular biology and evolutionary biology has been proposed (Dean & Thornton, 2007). What we advocate here is different; not only does molecular function need to be reconciled with statistical gene variation, but the rules of higher order functional principles need to become part of a major reform of the general evolutionary framework that is currently taking place through the inclusion of new concepts from evo–devo, niche construction [see the article by Laland *et al.* (2014) in this issue], epigenetic inheritance and other areas (Pigliucci & Müller, 2010). Consideration of function permits the integration of this extended synthesis view of evolution with physiology. The hallmark of such a reform is a relinquishment of any privileged levels of causation in the evolutionary process and a replacement of gene reductionism by systems principles (Noble, 2012, 2013). Aware of the fact that many of the relevant processes now have become accessible to empirical research, Morange (2011) noted correctly: 'the obstacles for a merging of functional and evolutionary biology have potentially disappeared'.

Consequences for concepts and definitions

Finally, we note some consequences for the definitions of key elements and concepts, focusing on the concept of the gene. The articles by Keller (2014), Roll-Hansen (2014) and Roux (2014) in this issue should be consulted for important accounts on the history and philosophy of the relevant concepts and for their interpretations of the consequences.

The concept of 'gene' is primary amongst these, because the Modern Synthesis is a gene-centred theory of evolution. There has always been a tension between its original definition as a discrete, inheritable phenotype following Mendelian laws and the modern molecular biological definition of a gene as a template for a specific protein (Keller, 2000; Noble, 2008). The tension was manageable for so long as it was thought that the relations between genotype and phenotype were at least fairly direct, even if people long ago gave up 'the silent assumption [that] was made

almost universally that there is a 1:1 relation between genetic factor (gene) and character' (Mayr, 1982) to acknowledge that many genes are involved in each physiological function. From a physiological viewpoint, even this concession is not enough. Organisms are remarkably well buffered against DNA changes through built in back-up mechanisms. In the heart's pacemaker, multiple back-up mechanisms exist, so that targeting any one protein may result in only small changes in rhythm (Noble *et al.* 1992; Noble & Noble, 2011). In yeast, 80% of single knock-outs are silent in normal physiological conditions (Hillenmeyer *et al.* 2008). The relation between DNA and the phenotype is better represented as being mediated by functional networks, in which not all the components are specified in DNA sequences (Kohl *et al.* 2010). To this problem we need to add that posed by genetic assimilation, which, as we argued earlier, cannot be represented properly in terms of individual genes, but rather as networks of alleles; to which we can add the difficulty, also referred to already, that DNA sequences provide a relatively poor prediction of disease risks.

There has therefore been a new tendency within the Modern Synthesis view to represent this as a problem of 'missing inheritance', 'honorary genes' or 'phantom inheritability' (Zuk *et al.* 2012). This misleading terminology hides the problem in terms that have no role in scientific discourse. The better way forward is to recognize, quite simply, that we need a much better notion of inheritance through a systemic understanding of the genotype–phenotype relation. From such understanding we will, for example, be able to explain how the statistical concepts of broad and narrow senses of heritability are functions of regulatory anatomy and the environment (Wang *et al.* 2013).

It is also important to distinguish between different meanings of 'function' in physiology and in evolutionary biology. They are significantly different but often confused. As Roux (2014) says, '[since selectionist theories] restrict the functional attribution of a trait to its past selective value and not its current properties, these theories are inconsistent with the concept of function in physiology'. Many other terms in the discourse also need rethinking in the light of these considerations, such as 'genetic code', 'genetic programme' and 'book of life'.

Conclusions

The wide-ranging set of articles published in this issue reveal a major challenge both for the physiological sciences and for evolutionary biology. As the integration between the two proceeds, neither can remain unchanged. Evolutionary theory requires extension or even replacement, while physiological science needs to address the exciting possibilities opened up for the future. We hope that our article, and those published here, will enable both disciplines to respond effectively to that challenge.

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