How phenotypic plasticity made its way into molecular biology

MICHEL MORANGE
Centre Cavaillès and IHPST, Ecole normale supérieure, 29 rue d'Ulm, 75230 Paris Cedex 05, France
(Fax, 33-144-323941; Email, morange@biologie.ens.fr)

Phenotypic plasticity has been fashionable in recent years. It has never been absent from the studies of evolutionary biologists, although the availability of stable animal models has limited its role. Although opposed by the reductionist and deterministic approach of molecular biology, phenotypic plasticity has nevertheless recently made its way into this discipline, in particular through the limits of the molecular description. Its resurrection has been triggered by a small group of theoreticians, the rise of epigenetic descriptions and the publicized discovery of stem cell plasticity. The notion of phenotypic plasticity remains vague. History shows that too strong a belief in plasticity can be an obstacle to the development of biology. Two important questions are still pending: the link between the different forms of plasticity present at different levels of organization, and the relation, if any, between the modular organization of organisms and phenotypic plasticity. Future research will help to discriminate between possible and actual mechanisms of phenotypic plasticity, and to give phenotypic plasticity its real place in the living world.

[Morange M 2009 How phenotypic plasticity made its way into molecular biology; *J. Biosci.* **34** 495–501]

1. Introduction

A rapid exploration in Medline shows that phenotypic plasticity became a fashionable expression quite recently, in the last five years. Obviously, there is currently a tendency to favour increasing use of the expressions phenotypic plasticity and developmental plasticity. My objective in this contribution is to disentangle the different transformations that have occurred within biology and are able to explain this trend.

A provisional definition is needed. I will adopt that proposed by Mary Jane West-Eberhard: phenotypic plasticity is "the ability of an organism to react to an environmental input with a change in form, state, movement, or rate of activity" (West-Eberhard 2003). Such a definition has been designed to cover many different phenomena, and it is therefore required for the sake of clarity to introduce distinctions in the nature of the changes designated by phenotypic plasticity. These changes can be passive or active, directly resulting from the action of the environment or due to a reaction of the organism to this variation. They can be adaptive or non-adaptive, continuous or discontinuous. The reactions of the organisms to variations in the environment can be, roughly speaking, of two diametrically opposed natures. They may represent an accommodation of the organism to these variations, and consist in the buffering of the internal variations resulting from the external ones. This buffering capacity has been interpreted by Claude Bernard as the maintenance of a "milieu intérieur", and by Walter Cannon as the result of a general capacity of organisms to maintain homeostasis. The resulting properties of organisms are stability and robustness. Gene inactivation (knock out) experiments have shown in the last decade that organisms are not only resistant to variations in the environment, but also to internal variations such as those resulting from gene mutations (Morange 2001). On the other hand, phenotypic plasticity can generate a huge change in the properties of an organism in response to moderate changes in the environment. In the latter case, it can generate alternative states, a phenomenon described by zoologists by the term polyphenism (Nijhout 2003). Changes can be reversible or not: some authors have proposed to reserve the word flexibility for reversible changes, but this rule has not been unanimously adopted.

Finally, it is useful to remember that phenotypic plasticity can concern the organism or the population.

Keywords. Cyclogenic theories; modules; models; multistability; stem cells

In the former, the notion will designate the ability of an organism to successively adopt different phenotypes, while in the second diversity will reveal itself when examining populations, whereas organisms exhibit stable phenotypes. The expression phenotypic plasticity is also used in some cases to designate the aptitude of an organism to alter its phenotype as a response to a change in its environment, not immediately but after a limited number of generations. In this case, phenotypic plasticity is the result of a particular genetic constitution. There are no reasons to exclude one or other of the meanings of the expression phenotypic plasticity, but it is necessary to distinguish them carefully in order to avoid confusion in discussions.

2. Roots of phenotypic plasticity in evolutionary biology

My main concern will be to explain how phenotypic plasticity "made its way" into molecular biology. But it is first necessary to recall that there is a long tradition of discussions on phenotypic plasticity in evolutionary biology, and that recent transformations in biology have only facilitated the rediscovery of this tradition.

The fact that phenotypes are dependent upon the environment was not unknown to the first geneticists. The following statement by Herbert Spencer Jennings in 1924 clearly demonstrates this: "What happens in any object… depends on the one hand upon the material of which it is composed; on the other hand upon the conditions in which it is found… Organisms are like other objects in this respect; what they do or become depends both on what they are made of, and on the conditions surrounding them. The dependence on what they are originally made of we call heredity. But no single thing that the organism does depends alone on heredity or alone on environment; always both have to be taken into account" (Jennings 1924). But there is a difference between admitting that the characteristics of organisms depend upon their environment, and accepting that the reactions of these organisms to variations in the environment are an active process participating in the adaptation of the organisms to this new environment. Some population geneticists and evolutionary biologists nevertheless recognized the importance of phenotypic plasticity, in particular, but not uniquely, in plants (Schlichting 1986; Stearns *et al.* 1991). A further step is to admit that this initial phenotypic adaptation will pave the way to the subsequent adaptation of organisms by a modification of their genotype. I want to briefly mention here the line of research running from J Mark Baldwin (1896) to Conrad Waddington (1942) and Ivan Ivanovich Schmalhausen (1949), which aimed to explain how a phenotypic adaptation can foster a genetic one. The more recent and better molecularly documented work of Susan Lindquist (Sangster *et al.* 2007) goes in the same direction. There is a long and rich tradition, which has simply been rediscovered recently.

These observations and models have been partially neglected during the past century by a constant process of selection of data and systems, eliminating as much as possible any sign of phenotypic plasticity. This has already been amply discussed by Scott Gilbert (Gilbert 2008). The first experiments of genetics, those of Mendel, are emblematic of this selection process. Mendel selected one particular plant, one species and seven characters, always using the same criterion – stability of the phenotype (Mendel 1966). As is well known, Mendel also selected data that fitted his laws, and discarded the plants that did not produce enough seeds. To generate "laws of heredity" it was necessary to eliminate all sources of perturbation, and in particular the phenotypic plasticity of organisms. This process of selection was repeated throughout the 20th century (Davis 2003). From *Drosophila* to nematodes through *Escherichia coli* and bacteriophages, all these models were selected because of the constancy in their phenotypes, with the risk that the conclusions reached with them could not be extended to other organisms even of a closely related species: the rigid developmental programme of *Caenorhabditis elegans* is the exception rather than the rule! Some geneticists, such as Richard Woltereck, opposed this trend, and devoted their efforts to this plasticity, characterising the "norms of reaction" of organisms. Their efforts did not attract much attention from other geneticists.

But this situation is changing, in part because of the new possibilities raised by technological developments. More and more genome sequences are being generated from organisms that were not selected for their phenotypic stability. And new animal models today are chosen because precisely they exhibit a particularly interesting form of phenotypic plasticity.

It is also necessary to mention other lines of research which (indirectly) favoured the recognition of the importance of phenotypic plasticity. The first is the study of "life histories", a field of research located at the boundary between ecology and evolutionary biology (Stearns 1992). The diversity of life histories, the dramatic differences in ageing and reproductive processes that can occur between close species are interpreted as the result of a complex trade-off between the costs and benefits provided by alternative life strategies. Such a vision is a legacy of the application of the game theory of Von Neumann and Morgenstern (2004) to evolutionary sciences developed in particular by John Maynard Smith (1982). The phenotypic plasticity revealed by careful study of life histories is genetically based. Nevertheless, a limited number of genetic variations are sufficient to generate very different life histories. As we have seen earlier, phenotypic plasticity includes the capacity

of organisms to drastically alter their phenotype through a limited variation in their genotype.

The study of animal and human behaviours is also an appropriate field of research to acknowledge the place of phenotypic plasticity. Probably, it is on human behaviours that the effect of the environment is most visible. Insect societies are also a rich source of examples.

Finally, one must not forget the progressive discovery of the plasticity of synaptic connections in the central nervous system. This plasticity forms a bridge between the plasticity of behaviours and the plasticity of developmental processes.

Therefore, phenotypic plasticity was never absent from the minds of evolutionary biologists, but was neglected in the choice of particularly stable animal models. Recent studies on life histories and animal behaviours have permitted its resurrection. The end of the dominant bottom-up reductionist approach of molecular biology and the reappraisal of the significance of the top-down approaches of living phenomena were also favourable.

3. Roots of phenotypic plasticity in functional biology

The notions of phenotypic plasticity and variability do not have a natural niche in functional biology. It seems that they have been excluded by the deterministic and reductionist vision proposed by Erwin Schrödinger (Schrödinger 1944) and supported by the rise of molecular biology. For the eminent molecular biologist Monod, "his interest in cultures of *E. coli* originated in the similarity with the study of ideal gases. Morphological differences among bacteria, in their appearance, in their mobility, are without interest. What is important is what generates mathematical laws, differential equations, affinity constants" (reported by Patrice Debré [1996]). Monod also thought that if the microscope had been prohibited, biology would have made a leap of sixty years: the reason was that the microscope revealed this variability that molecular biologists tried to eliminate. Molecular biology was a desperate and transiently successful attempt to chase variability from organisms and to replace it by the existence of universal principles and laws. In the "classical" vision of molecular biology, the formation of structures as complex as viruses or ribosomes was the result of simple, perfectly organized processes of self-assembly. In the same way, the complex development of an organism was the result of a perfectly determined programme of development.

There is no doubt that this vision represented an epistemological obstacle, in the sense given to this expression by Gaston Bachelard: "an epistemological obstacle is any concept or method that prevents an epistemological break. Obstacles are residues from previous ways of thinking that, whatever value they may have had in the past, have begun to block the path of enquiry. Common sense is, of course, a major source of epistemological obstacles" (Gutting 1990).

But the obstacles were not as great as one may imagine, because very rapidly the models of molecular biology showed their limits, and permitted the reintroduction of a certain form of phenotypic plasticity. Consider for instance the regulatory genetic models, in particular the so-called operon model. This was the source of the notion of a genetic programme. Very rapidly, however, these regulatory systems were shown to be able to generate multistable states from the existence of positive feedback loops: fully active and fully inactive in the case of the lactose system, lysogeny and infection in the case of the λ bacteriophage. Phenotypic plasticity spontaneously re-emerged from the perfectly deterministic models of molecular biology. In addition, in the case of the lactose system, genetic expression of the organism is dependent on variations in the environment (concentrations of lactose). The construction of the operon model was simultaneously the last brilliant achievement of classical molecular biology and the backdoor to the reintroduction of the environment and of phenotypic plasticity, much more than the model of Britten and Davidson proposed ten years later (Britten and Davidson 1969).

The notion of a genetic programme, simultaneously proposed by Ernst Mayr (Mayr 1961) and Monod and Jacob (Jacob and Monod 1961), did not have the utterly negative impact too frequently underlined by philosophers of biology. While some molecular biologists, such as Sydney Brenner, considered it seriously enough to spend two years learning computer programming, others, like Jacob, rapidly abandoned it as a direct guide to their experimental work. Turning to the study of mouse early embryogenesis—using teratocarcinoma cells as a model system—Jacob developed a complex model of early embryogenesis in which membrane proteins and cell-to-cell contacts played a major role, not regulatory genes and proteins (Morange 2000). The notion of programme was still present in his writings, but only meant the succession of steps required for a correct development. Experiments performed by molecular biologists also progressively reintroduced phenotypic plasticity. The generation of multiple stable states by simple systems like the lactose system was similar to the multiple transdifferentiation states revealed by the careful study of Ernst Hadorn on the role of imaginal disks in the development of *Drosophila*. The "Notch system" involved in the control of lateral differentiation, used in different organisms for different purposes, is a wonderful example of the way fluctuations in gene expression and a positive feedback loop can generate bistable states of function (Wilkinson *et al.* 1994).

The quite recent development of new tools and technologies—fluorescent reporter proteins, dramatic improvements in the treatment of spectroscopic signals of low amplitude—suddenly revealed the variability, at the macromolecular level of organization, that results from

the low number of molecules involved, the weak kinetic constants of some fundamental reactions as transcription, and the spontaneous Brownian motion of macromolecules. This variability, for instance in gene expression, was previously unobservable, due to the absence of appropriate technologies, but also neglected because of this constant search for reproducibility, and for general and stable processes at the core of the functioning of organisms.

Developmental plasticity represents today a large fraction of the studies on phenotypic plasticity, but developmental biology as a discipline was not at the forefront of the work that forced a reappraisal of the importance of phenotypic plasticity. While the Notch system described by developmental biologists was an exquisite example of the kind of mechanisms likely to generate such developmental plasticity, and the discovery of "programmed cell death" proposed a suitable mechanism for permanent remodelling of the organism, the notion of a genetic programme of development still dominates the description and the interpretation of data in this discipline.

4. The recent trigger in favour of phenotypic plasticity

In addition to the transformations that I described earlier, what were the events which acted as triggers for the rapid re-emergence of phenotypic plasticity? The first was clearly the theoretical work performed by biologists and philosophers such as Mary Jane West-Eberhard (2003), Marc Kirschner and John Gerhart (2005), and all the contributors to Developmental Systems Theory, who aimed to rebalance the respective roles of the genetic material and of the environment in inheritance (Oyama *et al.* 2001). This rapid succession of important and original contributions prepared minds for a radically new vision of evolution.

But the rapid development of epigenetics was also important; not the study of the relations between genotype and phenotype as defined by Waddington, but the complex modifications of DNA and chromatin proteins that may alter gene expression (Jablonka and Lamb 2005). An unknown world was suddenly revealed, with a huge and exquisite complexity of mechanisms. Epigenetic modifications have different characteristics, important for biologists interested in phenotypic plasticity. They can simultaneously regulate the activity of numerous genes; they depend upon the environment and/or the functional state of organisms; they can be partially inherited; and, most of all, they are involved in major diseases as cancer (Feinberg 2007). Taking them into account opens the way to new original therapeutic strategies. Epigenetic modifications are well positioned to contribute to an understanding of phenotypic plasticity.

The attention paid to recent work on stem cells, either embryonic or somatic, made a large scientific audience aware of the extraordinary phenotypic plasticity of these cells. This plasticity is simultaneously an opportunity for experimenters, and a risk that has to be narrowly controlled. This plasticity was not a surprise for specialists familiar with work done more than two decades ago on mouse embryonal carcinoma and embryonic stem cells (Morange 2006). Depending upon its proximate environment, its niche, a stem cell may remain undifferentiated or enter into one or another differentiation pathway. Recent results have shown that this plasticity can be transferred to somatic cells—which are then transformed into stem cells—by the transfection of a limited number of controlling genes (Rossant 2007). Cloning also showed the extraordinary plasticity of the nucleus, which by transplantation from a somatic cell to an oocyte can be reprogrammed to generate a fully normal organism. This plasticity depends upon a change in the epigenetic marks, creating an additional link between epigenetics and plasticity.

Plasticity of stem cells created a kind of continuum between plasticity and variability at the molecular level, and the phenotypic plasticity at the level of the organism.

5. Some questions and remarks on phenotypic plasticity

I have described the scientific events and transformations that have built a currently favourable niche for the development of phenotypic plasticity. But the value of a historical study lies not in justification of the present, but in clarifying its true meaning.

The first question which immediately emerges concerns the true novelty of phenotypic plasticity. As we have seen, it is more a re-emergence than a recent birth. To the already cited precursors, I would like to add the philosopher of science Georges Canguilhem, who is not well known internationally, but who had a huge influence on French thought. In 1944, in a book entitled *The normal and the pathological* (Canguilhem 1991), Canguilhem opposed the reductionist view of disease, based on the existence of absolute norms which would allow automatic discrimination between the normal and the pathological. For Canguilhem, disease is something very different, a new state adopted by an organism and a way for it to adapt to an external or internal perturbation, and to redefine its own norms. Although the major concern of Canguilhem was medicine, it is obvious that his conviction that the supposed norms vary from one organism to another, and from one time to another, that disease is a new state resulting from the efforts of the organism to adapt to a new situation, is clearly in harmony with the present importance accorded to phenotypic plasticity.

Maybe the best way to interpret the present interest in phenotypic plasticity is to adopt the vision of Gerald Holton (Holton 1978), according to which scientific conceptions

balance permanently between a limited number of antagonistic notions, what he called *themata*. For instance, physicists have always balanced between considering light and matter as waves or particles. Similarly, biological explanations have always oscillated between emphasizing the permanence and reproducibility of the phenomena occurring in organisms and, conversely, the diversity and plasticity of these organisms. With the domination of molecular biology, the emphasis was placed on determinism and reproducibility. The interest in phenotypic plasticity is the sign that the pendulum has now swung in the opposite direction; the risk being that phenotypic plasticity will be accepted as blindly and dogmatically as molecular biologists viewed determinism and reproducibility.

According phenotypic plasticity a pre-eminent place is not without its risks. The first, probably the major risk, is that of confusion. As we saw, the expression phenotypic plasticity is used to account for observations of a very different nature. Mechanisms likely to generate phenotypic plasticity also have to be carefully distinguished: self-organization and chaotic processes may both contribute to phenotypic plasticity, although they are of a different nature. Fashionable words such as "attractors" have to be used with care. Too many contributions to phenotypic plasticity, including the major opus of West-Eberhard, consist of a disorganized accumulation of data describing phenomena of different natures, which are placed side by side instead of being carefully distinguished and organized (West-Eberhard 2003).

A second risk emerging naturally from this disorganized presentation of data is that of hypothesizing that there is a general theory of biological organization responsible for all observations on phenotypic plasticity (as proposed in Fontana *et al.* 1994). It is impossible at present to discard such a possibility, but nothing in the highly diverse observations made so far points in this direction.

These risks are not purely theoretical. At least one historical example shows that theories that accorded plasticity too large a role acted as brakes on the growth of scientific knowledge: such is the case of the cyclogenic theories of the first decades of the 20th century, in which it was admitted that bacteria permanently changed their morphologies according to a complex cyclic process, up to the point of completely disappearing during certain phases (Amsterdamska 1991). This theory, supported by the existence of rare but well-defined phenomena such as sporulation, delayed the rise of bacterial genetics.

Finally, an emphasis on phenotypic plasticity may be in harmony with certain metaphysical views of life, where the latter is characterized by the power to react, to adapt to its environment, and to evolve. I do not want to accuse biologists interested in phenotypic plasticity of offering a Trojan horse for the reintroduction of an outdated vitalistic metaphysics into the life sciences, but I believe that every biologist has to be aware of this historical, yet not so distant, connection. In a similar way, phenotypic plasticity can be the way to reintroduce Lamarckian models of evolution.

6. Conclusions

I will end with two questions that I consider fundamental for the study of phenotypic plasticity, and which will surely be the topic of lively debate in the future. The first concerns the relations between plasticity at different levels of organization in the living world. Phenotypic plasticity concerns the organism at a higher level of organization. But, as we have seen, plasticity and variability also occur at the cellular and molecular levels. Are these different phenomena linked? Is the existence of plasticity and variability at the lowest levels of organization a prerequisite for the existence of plasticity at the highest levels of organization? The answer appears evident when one considers the books written in support of the importance of phenotypic plasticity: the existence of plasticity at the molecular level is presented as strong support for the importance of phenotypic plasticity (West-Eberhard 2003). But is this conviction rationally founded? Maybe phenotypic plasticity is an emergent phenomenon, which does not exist at the lowest levels of organization, a phenomenon resulting, for instance, from the production of multiple stable states of functioning by highly complex systems. The risk of putting in the same bag phenomena observed on very different scales is that it will confuse rather than explain, and lend too much importance to the observation of exotic phenomena.

My feeling is that one has to be very cautious. There are some cases where it is possible to relate phenotypic plasticity to variability at the molecular level: the Notch system is a good example. But it is not general, and some phenomena of plasticity at the molecular or cellular level have no consequences at the level of the organism for the simple reason that buffering mechanisms have progressively evolved to neutralize them. Consider, for instance, the micro-vibrations that affect any chemical bond. They do not prevent most proteins from adopting a unique and well-defined 3D state.

Similarly, the structure of the genome is plastic. Retrotransposons may move from one part of the genome to the other, and new DNA sequences can be inserted by horizontal gene transfer (Shapiro 2005). It is far from evident that these phenomena of genomic plasticity are related to the well-demonstrated phenomenon of phenotypic plasticity observed at the level of organisms. It is in most cases an error to try to seek the origin of phenotypic plasticity at the molecular level. The fact that observations of phenotypic plasticity at the molecular level are frequently favoured raises an interesting paradox, since most of those

interested by the study of phenotypic plasticity were more or less active opponents of molecular biology and of its deterministic and reductionist views.

A second important question is the role of modules in phenotypic plasticity. The notion of a modular organization of organisms has gained credence from the numerous studies done in systems biology and synthetic biology (Hartwell *et al.* 1999; Schlosser and Wagner 2004). This modular organization is seen as the basis of phenotypic plasticity. Reassortment and recombination of modules would generate plasticity. However, the genealogical relations between plasticity and modularity are not clear, some authors considering that plasticity can generate modularity as much as modularity favours plasticity. Nevertheless, in both cases the link between modularity and plasticity is considered as firmly established.

Is this so? Like plasticity, the word "modules" is used with as many different meanings as there are people using it! Modules can have an ontological or a methodological value: in the first case, they do exist, and represent a principle of the construction of organisms; in the second, they are only a tool in the analytical approach of science: the simplest way to analyse a complex system is to imagine the existence of subsystems or modules within it (Mitchell 2006). Even if modules were shown to exist, their contribution to phenotypic plasticity would remain to be demonstrated.

The study of phenotypic plasticity has opened new avenues of research. What remains to be done is to distinguish between the possible and the actual (Jacob 1982): the possible is the huge diversity of recently described mechanisms that may generate phenotypic plasticity, and probably many other mechanisms still to be discovered; the actual is those mechanisms that really generate the cases of phenotypic plasticity described thus far, and all the other cases yet to be described.

Acknowledgements

I am indebted to David Marsh for critical reading of the manuscript.

References

Amsterdamska O 1991 Stabilizing instability: The controversy over cyclogenic theories of bacterial variation during the interwar period; *J. Hist. Biol.* **24** 191–222

Baldwin J A M 1896 A new factor in evolution; *Am. Nat.* **30** 441–451

Britten R J and Davidson E H 1969 Gene regulation for higher cells: a theory; *Science* **165** 349–357

Canguilhem G 1991 *The normal and the pathological* (New York: Zone books)

Davis R H 2003 *The microbial models of molecular biology* (Oxford: Oxford University Press)

Debré P 1996 *Jacques Monod* (Paris: Flammarion)

Feinberg A P 2007 Phenotypic plasticity and the epigenetics of human disease; *Nature (London)* **447** 433–440

Fontana W, Wagner G and Buss L 1994 Beyond digital naturalism; *Artificial Life* **1** 211–227

Gilbert S F 2008 The adequacy of model systems for Evo-Devo; in *Mapping the future of biology: evolving concepts and theories* (eds) A Barberousse, M Morange and T Pradeu (in Press)

Gutting G 1990 Continental philosophy and the history of science; in *Companion to the history of modern science* (eds) R C Olby, G N Cantor, J R R Christie and H J S Hodge (London: Routledge) pp 127–147

Hartwell L H, Hopfield J J, Leibler S and Murray A W 1999 From molecular to modular cell biology; *Nature (London)* **402** C47–C52

Holton G N 1978 The *scientific imagination: Case studies* (Cambridge: Cambridge University Press)

Jablonka E and Lamb M J 2005 *Evolution in four dimensions: Genetic, epigenetic, behavioral and symbolic variation in the history of life* (Cambridge: The MIT Press)

Jacob F 1982 *The possible and the actual* (Seattle: University of Washington Press)

Jacob F and Monod M. 1961 Genetic regulatory mechanisms in the synthesis of proteins; *J. Mol. Biol.* **3** 318–356

Jennings H S 1924 Heredity and environment; *Scientific Monthly* **19** 226–238

Kirschner M W and Gerhart J C 2005 *The plausibility of life* (New Haven: Yale University press)

Maynard Smith J 1982 *Evolution and the theory of games* (Cambridge: Cambridge University Press)

Mayr E 1961 Cause and effect in biology; *Science* **134** 1501–1506

Mendel G 1966 (1865) Experiments on plant hybrids in *The origin of genetics: A Mendel source book*, Stern C and Sherwood E R eds. (San Francisco: Freeman)

Mitchell S D 2006 Modularity – more than a buzzword?; *Biol. Theory* **1** 98–101

Morange M 2000 François Jacob's lab in the seventies: The *T*-complex and the mouse developmental genetic program; *Hist. Philos. Life Sci.* **22** 397–411

Morange M 2001 *The misunderstood gene* (Cambridge: Harvard University Press), chapter 5

Morange M 2006 Twenty-five years ago: The production of mouse embryonic stem cells; *J. Biosci.* **31** 537–541

Nijhout H F 2003 Development and evolution of adaptive polyphenisms; *Evol. Dev.* **5** 9–18

Oyama S, Griffiths P and Gray R D 2001 *Cycles of contingency: Developmental systems and evolution* (Cambridge: The MIT Press)

Rossant J 2007 The magic brew; *Nature (London)* **448** 260–262

Sangster T A, Bahrami A, Wilczek A, Watanabe E, Schellenberg K, McLellan C, Kelley A, Kong S W *et al.* . 2007 Phenotypic diversity and altered environmental plasticity in *Arabidopsis thaliana* with reduced Hsp90 levels; *PLoS One* **7** e648

Schlichting C D 1986 The evolution of phenotypic plasticity in plants; *Annu. Rev. Ecol. Syst.* **17** 667–693

Schlosser G and Wagner G P 2004 *Modularity in development and evolution* (Chicago: The University of Chicago Press)

Schmalhausen I I 1949 *Factors in evolution: The theory of stabilizing selection* (Philadelphia: Blakiston University Press)

Schrödinger E 1944 *What is life?* (Cambridge: Cambridge University Press)

Shapiro J A 2005 A 21st century view of evolution: genome system architecture, repetitive DNA, and natural genetic engineering; *Gene* **345** 91–100

Stearns S, de Jong G and Newman B 1991 The effects of phenotypic plasticity on genetic correlations; *TREE* **6** 122–126

Stearns S C 1992 *The evolution of life histories* (Oxford: Oxford University Press)

Von Neumann J and Morgenstern O 2004 *Theory of games and economic behavior: Sixtieth-anniversary edition* (Princeton: Princeton University Press)

Waddington C H 1942 Canalization of development and the inheritane of acquired characters; *Nature (London)* **150** 563–565

West-Eberhard M J 2003 *Developmental plasticity and evolution* (Oxford: Oxford University Press)

Wilkinson H A, Fitzgerald K and Greenwald I 1994 Reciprocal changes in expression of the receptor *lin-12* and its ligand *lag-2* prior to commitment in a *C. elegans* cell fate decision; *Cell* **79** 1187–1198

*e*Publication: 3 August 2009