ISIS Lecture

How Development Directs Evolution Epigenetics & Generative Dynamics

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Abstract and Introduction

In a paper published 30 years ago, Ho and Saunders (1979) proposed the then outrageous non-Darwinian idea that the intrinsic dynamics of developmental processes is the source of non-random variations that *directs* evolutionary change in the face of new environmental challenges; and the resulting evolutionary novelties are reinforced in successive generations through epigenetic mechanisms, *independently of natural selection*.

Our proposal has held up well against subsequent research findings, and is all the more relevant in view of the numerous molecular mechanisms discovered in epigenetic inheritance (Ho, 2009a,b) that could transmit developmental novelties to subsequent generations.

We have demonstrated how the nonlinear dynamics of living processes predicts the major features of macroevolution such as ‘punctuated equilibria’ (long period of stasis interrupted by abrupt changes); large changes from small critical disturbances, and discontinuous changes from continuously varying parameters; and why macroevolution of form and function is decoupled from the microevolution of gene sequences. We showed that the same (non-random) developmental changes are repeatedly produced by specific environmental stimuli. Furthermore, we demonstrated how general mathematical models can account for all the developmental transformations experimentally produced, which can make strong evolutionary predictions, and offer a natural taxonomy based on the predicted transformations.

However, neither the epigenetic mechanisms nor the dynamics of developmental processes are taken into account in the recent studies on evolution and development.

The totality of research findings gives no support to the neo-Darwinian theory of evolution by the natural selection of random genetic mutations, nor to any theory ascribing putative differences in human attributes to genes. The overwhelming determinants of health and behaviour are social and environmental. Heredity is not in the genes, it is distributed over the entire web of nested organism-environment interrelationships extending from the social and ecological to the genetic and epigenetic. Consequently, there is no separation between development and evolution, and the organism actively participates in shaping its own development as well as the evolutionary future of the entire ecological community of which it is part.

‘Epigenetic’ then and now

The term ‘epigenetic’ as used to-day in epigenetic inheritance refers to effects that do not involve DNA base sequence changes, but only the chemical modifications of DNA or histone proteins in chromatin (complex of DNA and protein that make up chromosomes in the nucleus of cells), which alter gene expression states. Epigenetic inheritance has been defined (Bird, 2007, p. 398) as “the structural adaptation of chromosomal regions so as to register signal or perpetuate altered activity states.” But these definitions are rapidly becoming obsolete (Ho, 2009a-g). In reality, epigenetic modifications encompass a great variety of mechanisms. They act during and after transcription, and at translation of genetic messages; they can even rewrite genomic DNA (see Ho, 2009a). Hence the distinction between genetic and epigenetic is increasingly blurred.

‘Epigenetic’ as originally used, was derived from *epigenesis*, the theory that organisms are not *preformed* in the germ cells, but comes into being through a process of development in which the environment plays a formative role. Most evolutionists have used ‘epigenetic’ to mean hereditary influences arising from environmental effects in the course of development.

Evolution Lamarck *vs* Darwin

Evolution refers to the natural (as opposed to supernatural) origin and transformation of organisms on earth throughout geological history to the present day. The first comprehensive *general* theory of evolution – that evolution has occurred - was proposed by Jean Baptiste de Lamarck in his book published 200 years ago (1809) (see Burkhardt, 1977; Barthelemy-Madaule, 1982; Ho, 1983). (So it is fitting to celebrate the bicentenary of Lamarck’s theory at the same time that we celebrate the bicentenary of Darwin’s birth.) It was an *uniformitarian* theory in that causes proposed to be operating in the past are the same as those that can be observed at present. The theory postulated the spontaneous generation of the living from the nonliving and unlimited transformation over time, which gave rise to whole kingdoms of organisms beginning from a single origin of life. In addition, Lamarck proposed special mechanisms whereby new species could evolve through changes in how the organism relates to its environment in *pursuing its basic needs*, which produce new characteristics that become inherited after many generations. These special mechanisms are ‘use and disuse’, use enhances and reinforces the development of the organs or tissues while disuse results in atrophy; and the ‘inheritance of acquired characters’, the transmission to subsequent generations the tendency to develop certain new characteristics that the organism has acquired in its own development.

Thus, Lamarck was also responsible for the first epigenetic theory of evolution, in which development plays a key role in initiating the evolutionary change while specific epigenetic mechanisms transmit the change and reinforce it in subsequent generations (see Ho, 1983, 1984a,b).

Darwin’s (1859) special theory of evolution by natural selection states that, given the organisms’ capability to reproduce more of their numbers than the environment can support, and there are heritable variations, then, within a population, individuals with the more favourable variations would survive to reproduce their kind at the expense of those with less favourable variations. The ensuing competition and “struggle for life” results in the “survival of the fittest”, so the species will become better adapted to its environment. And if the environment changes in time there will be a gradual but definite “transmutation” of species. Thus, nature effectively ‘selects’ the fittest in the same way that artificial selection by plant and animal breeders ensures that the best or the most desirable characters are bred and preserved. In both cases, new varieties are created after some generations.

In *addition* to natural selection, Darwin invoked the effects of use and disuse, and the inheritance of acquired characters in the transmutation of species. However, those Lamarckian ideas do not fit into the theory of natural selection, and Darwin's followers all regard the lack of a theory of heredity and variation as the weakest link in the argument for natural selection (Ho, 1986).

In my book, *Genetic Engineering Dream or Nightmare? The Brave New World of Bad Science and Big Business* (Ho, 1997, 1998, 2000, 2007), I have described in detail how Darwin's followers created the 'neo-Darwinian synthesis' by expurgated Darwin's Lamarckian tendencies, including his theory of pangenesis. Darwin's theory of pangenesis had actually received a great deal of support (see Ho, 2009h). The rediscovery of Mendel at the turn of the last century provided evidence that particulate genes controlling the characteristics of organisms are passed on unchanged, except for rare random mutations. This fitted in perfectly with August Weismann (1834-1914) 's discovery of the material basis of heredity as the 'germplasm' in germ cells that become separate from the rest of the animal's body early in development to ensure it would be protected from environmental influences. Development is therefore irrelevant to evolution. We now know that Weissman's theory is wrong and there are numerous exceptions to Mendelian inheritance. Nevertheless, Darwinism was promptly reinterpreted according to the gene theory in the 'neo-Darwinian synthesis' from the 1930s up to the 1950s and 60s.

As the result of the neo-Darwinian synthesis, evolution occur strictly by the natural selection of *random* gene mutations, or changes in base sequence of DNA; those that happen to increase reproductive fitness are selected at the expense of the others that do not.

Evolution, development and heredity

The theories of evolution, development and heredity are closely intertwined. Just as evolutionists needed a theory of heredity, so plant breeders in the eighteenth century who inspired Mendel's discovery of genetics were motivated by the question as to whether new species could evolve from existing ones. In accounting for change or transformation, it is also necessary to locate where constancy or stability resides, which constitutes heredity. In order to explain the evolution of form and function, development (epigenesis) is central, as Lamarck clearly grasped. In contrast, Darwin, and neo-Darwinists see new variations arising at *random* in the sense that they bear no direct relationship to the environment, those that happen to be adaptive are selected, while the rest are eliminated. The theory of natural selection is essentially preformist, development playing little or no role in determining evolutionary change (Ho, 1984a, b, 1987)

There are a number of different epigenetic theories of evolution since Lamarck; some predating the neo-Darwinian synthesis. A common starting point for all epigenetic theories is the developmental flexibility of all organisms. In particular, it has been observed that artificially induced developmental modifications often resemble (*phenocopy*) those existing naturally in related geographical races or species that appear to be genetically determined. Thus, it seemed reasonable to assume that evolutionary novelties first arose as developmental modifications, which somehow became stably inherited (or not, as the case may be) in subsequent generations.

Early proponents of epigenetic theory included James Mark Baldwin (1896), who suggested that modifications arising in organisms developing in a new environment produce 'organic selection' forces internal to the organism, which stabilize the modification in subsequent generations. Another notable figure was Richard Goldschmidt (1940) who proposed that evolutionary novelties arise through *macromutations* producing 'hopeful monsters' that can initiate new species. In his defence, he pointed out that monsters could be hopeful because of the inherent *organization* of the biological system that tends to 'make sense' of the mutation. Following Goldschmidt, Søren Løvtrup (1974) advocated a similar theory of macromutations for the origin of major taxonomic groups of organisms such as phyla.

But random mutations - changes in the DNA - that generate hopeful monsters must be hopelessly rare, and to make things worse, major taxonomic groups tend to appear suddenly in clusters, ‘adaptive radiations’, rather than isolated at different geological times

The extraordinarily rich fossil finds of the Cambrian ‘explosion’ responsible for most of the major animal phyla is a prime example of evolution occurring in bursts of ‘adaptive radiation’ followed by relatively long periods of stasis, or ‘punctuated equilibria’ (Gould and Eldredge, 1972). Furthermore, evolution does seem to proceed top-down, from phyla, to subphyla, classes, orders and so on (Valentine, 2004), rather than the converse, as predicted by Darwin and neo-Darwinian natural selection of small random mutations. And crucially, all the evidence indicates that macroevolution is decoupled from molecular or microevolution (more below).

These considerations suggest that ‘adaptive radiations’ involve major novelties arising from epigenetic reorganisation provoked by large environmental changes, which also seem to coincide with adaptive radiations. For example, oxygen is very important for the evolution of complex organisms, and the Cambrian ‘explosion’ is believed to have been triggered by the rapid increase in atmospheric O_2 levels from a low of ~15 % to the current level of ~20 % between 1 billion to 0.5 billion years ago (see Ho, 2009i).

“Evo-devo” still blinded by “genetic programme” of development

In a sense, there is nothing new about the current revival of “evo-devo” (Gilbert, 2003; Carroll, 2005; Brakefield, 2006; Blumberg, 2009; Coyne, 2009). It is still dominated by the idea going back at least 20 years that genes control development in a ‘genetic programme’ of gene regulation and interaction (Coyne, 2009); and that large evolutionary changes in body pattern are the result of changes in gene regulation due to natural selection. There is still no recognition that the *patterns* themselves, and biological *form* need to be explained in their own right, independently of whether natural selection operates or not, and independently of the action of specific genes (Ho, 1986; Ho and Saunders, 1979; Saunders, 1984). Not surprisingly, there is also little or no recognition that epigenetic and non-genetic environmental influences can give rise to large alterations in form and function.

In a brilliant critique of the genetic determinist approach to behaviour, Gottlieb (1998) also deconstructed the idea that genes determine body pattern by pointing to the very different expression patterns of the same *Hox* genes in the fruitfly, the centipede, and the Onychophora. *Hox* (homeotic) genes are supposed to control segmental patterning during development; instead, the same genes appear to be simply responding to different patterning processes in the different animals. There is decidedly no homology of genes corresponding to homology of biological structures.

This same theme emerged in a comprehensive review of segmentation in arthropods by Peel, Chipman and Akam (2005), which showed that different groups have distinct modes of segmentation and divergent genetic mechanisms.

One important motivation for focussing on development for evolutionary change is that developmental changes are far from random or arbitrary (Ho and Saunders, 1979, 1982, 1984; Webster and Goodwin, 1982); but are determined by dynamical structures, independently of the action of specific genes.

Waddington's theory of canalization and genetic assimilation

The most influential figure among the ‘epigenetic evolutionists’ was Conrad H. Waddington (1905-1975), who attempted to accommodate ‘pseudo-Lamarckian’ phenomena within neo-Darwinism in his theory of genetic assimilation. Like all Darwinian and neo-Darwinian evolutionists, he wanted to explain the origin of *adaptive* characters, i.e., characters that seem to fit the functions they serve.

Waddington (1957) conceptualized the flexibility and plasticity of development, as well as its capacity for regulating against disturbances, in his famous ‘epigenetic landscape’, a general metaphor for the non-linear dynamics of the developmental process (Saunders, 1990). The developmental paths of tissues and cells are constrained or *canalized* to ‘flow’ along certain valleys due to the ‘pull’ or force exerted on the landscape by the various gene products that define the fluid topography of the landscape (Fig. 1). Thus, certain paths along valley floors will branch off from one another to be separated by hills (thresholds) so that different developmental results (alternative attractors) can be reached from the same starting point. However, some branches may rejoin further on, so that different paths will nevertheless lead to the same developmental result. Genetic or environmental disturbances tend to ‘push’ development from its normal pathway across the threshold to another pathway. Alternatively, other valleys (developmental pathways) or hills (thresholds) may be formed due to changes in the topography of the epigenetic landscape itself.

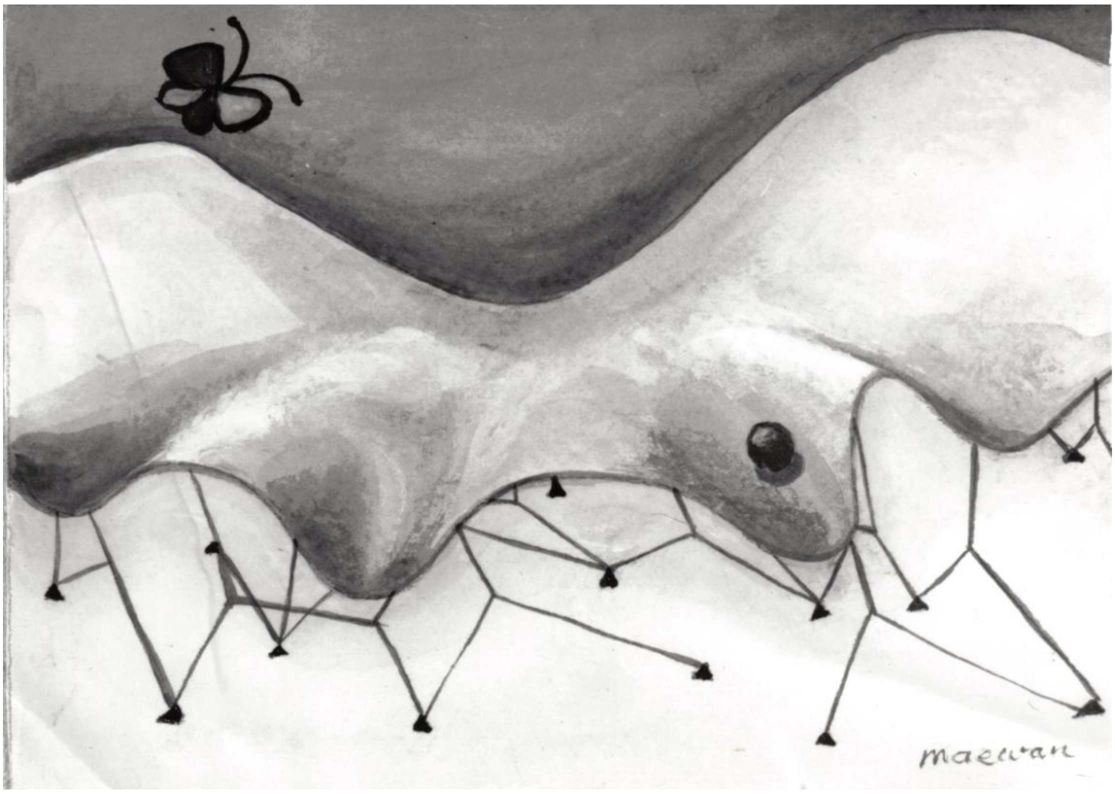


Figure 1 Waddington’s epigenetic landscape

The significance of the conceptual epigenetic landscape is that its topography is determined by *all* of the genes whose actions are inextricably interlinked, and is not immediately dependent on specific alleles of particular genes (Ho and Saunders, 1979). This is in accord with what we know about metabolism and the epigenetic system, particularly as revealed by the new genetics (see later). It also effectively decouples the evolution of the organism, of form and function, from alleles of specific genes, and explains the notable lack of correlation between morphological and genetic differences between species (Lowenstein, 1986).

Waddington proposed that a new phenotype arises when the environment changes so that development proceeds to a new pathway in the epigenetic landscape, or else a remodelling of the epigenetic landscape itself takes place (both of which are possible from what we now know about epigenetic processes at the molecular level). Thereafter, the new phenotype becomes reinforced or ‘canalized’ through natural selection for modifier genes so that a more or less uniform phenotype results from a range of environmental stimulus, and later, the phenotype is ‘genetically assimilated’, so it occurs in the absence of the original environmental stimulus.

Waddington and colleagues carried out experiments showing that artificial selection for the bithorax phenocopy in *Drosophila* induced by ether exposure during early embryogenesis resulted in canalization and genetic assimilation.

Ho and Saunders’ epigenetic theory of evolution

The first distinctive feature of our epigenetic theory of evolution (Ho and Saunders, 1979; 1982, 1984) is that neo-Darwinian natural selection plays little or no role, based on evidence suggesting on the one hand that most genetic changes are irrelevant to the evolution of organisms, and on the other, that a relative *lack* of natural selection may be the prerequisite for major evolutionary change.

The second feature is that the intrinsic dynamics of the epigenetic system is determined not so much by gene interactions as by *physical and chemical forces* of nonlinear complex systems in general, which are amenable to mathematical description (Saunders 1984; 1992). That is why, contrary to the neo-Darwinian view, variations of the phenotype that arise during development in response to new environments are *non-random* and *repeatable*.

We proposed, therefore, that the intrinsic dynamical structure of the epigenetic system is the source of non-random variations that *direct* evolutionary change in the face of new environmental challenges. These evolutionary novelties are reinforced (canalized) in subsequent generations through cytoplasmic/epigenetic mechanisms, *independently of natural selection*.

When a population of organisms experience a new environment, *or adopt a new behaviour*, the following sequence of events is envisaged.

a. A novel response arises during development in *a large proportion, if not all of* the organisms in a population experiencing a new environment, due to the intrinsic dynamics of the epigenetic system. In the case of a new behaviour initiated by a single individual in a social group, the behaviour can also spread quite rapidly. For example, Kawai (1962) found that the new habit of washing sweet potatoes in the sea initiated by a young female had spread to the entire troop of wild monkeys on Koshima Island in Japan within 9 years. Doubtlessly, this behaviour may also have triggered developmental changes in the monkey’s brain.

b. This response is ‘canalized’ in successive generations through epigenetic mechanisms *independent of natural selection*, and this has been demonstrated in experiments in our laboratory subsequently (see later).

c. After some generations, the response *may* become ‘genetically assimilated’, in that it arises even in the absence of the stimulus. As in Waddington’s epigenetic landscape, this could entail a change in the topography to bias the original branch point in favour of the new pathway, so that the new phenotype will persist in the absence of the environmental stimulus. Random genetic mutations could be also be involved.

Corroborations of Ho Saunders' epigenetic theory

Since our theory was proposed, we have obtained important empirical and theoretical corroboration. We questioned Waddington's assumption that selection of (modifier) genes is necessary for canalization and genetic assimilation, and in a series of experiments, Ho *et al* (1983) demonstrated that canalization occurred in the *absence* of selection *for* the new character. We showed that successive generations of ether treatment during early embryonic development in *Drosophila* increased the frequency of the bithorax phenocopy in the adults, without selecting *for* the phenocopy. If anything, the phenocopy was almost certainly selected *against*, as it obviously interfered with flight and other normal functions. We had identified a case of 'epigenetic inheritance' of a maladaptive character, consistent with recent findings in 'epigenetic toxicology', in which toxic effects of exposure to environmental pollutants are transmitted to grandchildren (Ho, 2009e).

At least one study of the fossil record (Palmer, 2004) provided evidence that left-right asymmetry in animals and plants may have originated as phenotypic novelties that became genetically assimilated subsequently.

We stipulated that genetic assimilation is not a necessary part of the response to change (Ho and Saunders, 1979), as it would preserve the important property of developmental flexibility or 'adaptability'. In retrospect, this has proved correct. We now know that maternal behaviour, long regarded as genetically inherited and instinctive, is actually associated with epigenetic gene markings that are erased at every generation, yet perpetuated indefinitely from mother to daughter (Ho, 2009c).

The complex nonlinear dynamics of the developmental process has been explored mathematically in greater detail (Saunders, 1984, 1989, 1990, 1992), and its evolutionary consequences made explicit. For example, it accounts for 'punctuated equilibria' (Eldrege and Gould, 1972). It also shows how large organized changes can occur with a relatively small disturbance, and how continuously varying environmental parameters can nevertheless precipitate discontinuous phenotypic change (see Saunders, 1990, especially).

The physical and chemical forces that organize living systems were the subject of my book, *The Rainbow and the Worm, the Physics of Organisms* (Ho, 1993, 1998, 2008), now in its 3rd enlarged edition. The book presents evidence that cells and organisms are liquid crystalline, with water the most important constituent of the liquid crystalline matrix. I pointed out that electrical polarities determine the alignment of the liquid crystals and hence the major body axes. Furthermore, electro-dynamical forces acting on liquid crystal mesophases may play a key role in pattern formation and morphogenesis. As consistent with this hypothesis, we demonstrated dramatic effects with brief exposures of early *Drosophila* embryos to very weak static magnetic fields; the segmental body pattern of the larva that emerged 24 hours later were transformed into helices (Ho *et al*, 1992).

In contrast, developmental geneticists generally assume that diffusion gradients of special "morphogens" determine body pattern by providing 'positional information' for particular genes to 'interpret'. For example, in *Drosophila*, where the most complete genetic analysis of development has been carried out (Nusslein-Volhard, 2006, the maternal gene product Bicoid is identified as the morphogen; its antero-posterior gradient serving to initiate the cascade of 'combinatorial regulation' of genes that eventually gives rise to the complete body pattern. The difficulty is that very few molecules diffuse freely in the liquid crystalline matrix, and Bicoid protein is no exception. If anything, it now appears that a gradient of transcription/translation and degradation is actively maintained in the embryo during several cycles of synchronous nuclear divisions (Gregor *et al*, 2007; Gibson, 2007), by an as yet unknown patterning process.

Natural selection plays little or no role in Ho-Saunders' epigenetic theory

In our theory, natural selection plays little or no role in evolution (except in the negative sense of deliminating deleterious mutations with large effects) for the following reasons:

1. The epigenetic (developmental and non-genetic) novelties produced in response to new environments are common to most, if not all, individuals in a population, and would swamp out residual effects due to genetic variation.
2. The fluidity of the genome - the constant interaction between genome and environment, the epigenetic markings of genes, and the blurring between genetic and epigenetic - makes clear that organism and environment are inseparable; hence there can be no selection of any static, preformed variant that's independent, or random, with respect to the selective environment..
3. The physical and chemical forces and flows that *generate* biological patterns and forms are independent of natural selection, and require their own explanations.

Neo-Darwinists seem unable to recognize the logical incoherence of applying natural selection to organisms that are changed and changing in non-random ways under the selective regime. Nor do they accept that the generative dynamical forces, which both create and constrain biological patterns and forms, are *independent* of natural selection, relegating natural selection to a negative role of eliminating the unfit. .

Instead, they insist that the generative dynamics only provides 'developmental constraints' that limit the action of natural selection to some extent, but natural selection still plays the 'creative' role in evolution (see Bonner, 1982).

I shall show why the dynamics that generate patterns and forms are much more than weak 'developmental constraints' to natural selection; and then address the 'neutral mutation hypothesis', the proposal that most, if not all, DNA base changes during evolution are due to random genetic drift decoupled from the evolution of organisms

Rational taxonomy based on the generative dynamics of biological form

The dynamics of developmental (epigenetic) processes, being amenable to mathematical description, provides a powerful perspective for understanding the development and the evolution of form. That is the basis of 'structuralism in biology' (Webster and Goodwin, 1982, Goodwin et al, 1989); or more accurately in our view, 'process structuralism' (Ho and Saunders, 1984; Saunders, 1984, 1989; 1992, 1993; Ho, 1984a, 1988a).

The developmental dynamics define a set of possible transformations that is highly constrained, so that particular transformations may be *predictably* linked to specific environmental stimuli. The fundamental importance of development for evolution is that evolutionary transformations can ultimately be understood in terms of developmental transformations that can be empirically investigated and that this in turn provides us with the criteria for a rational taxonomy, a natural system of classification based on the generative dynamics of form. I shall describe two examples, the segmentation defects in *Drosophila* larva produced by exposing early embryos to ether vapour, and phyllotaxis, the arrangement of leaves around the stem.

The segmentation pattern of the first instar *Drosophila* larva is determined during early embryogenesis. In the course of our studies on the bithorax phenocopy, we discovered that brief exposures to ether vapour also produced characteristic defects in the segmental pattern reflecting a dynamic process arrested at different stages (Ho *et al*, 1987). These defects phenocopy *all* the major genetic mutants identified. And the most general model of successive bifurcation could produce all the observed defects, giving a rational taxonomy of both the observed yet to be observed forms (Ho, 1990, Ho and Saunders, 1993). This rational taxonomy based on generative dynamics differs from one based on genealogy or similarity of DNA, and interestingly, also differs significantly from one based on cladistic analysis (Ho, 1990). Saunders and Ho (1995) subsequently produced a mathematical model of reliable segmentation based on successive bifurcation.

Figure 2 (Ho 1990, Ho and Saunders 1993) is a transformational 'tree' of the range of segmental patterns obtained *during development*. The main sequence, going up the trunk of the tree, is the normal transformational pathway, which progressively divides up the body into domains, ending up with 16 body segments of the normal larva. All the rest (with solid outlines) are transformations in which the process of dividing up the body has been arrested at different positions in the body. The patterns with dotted outlines are hypothetical forms, not yet observed, connecting actual transformations.

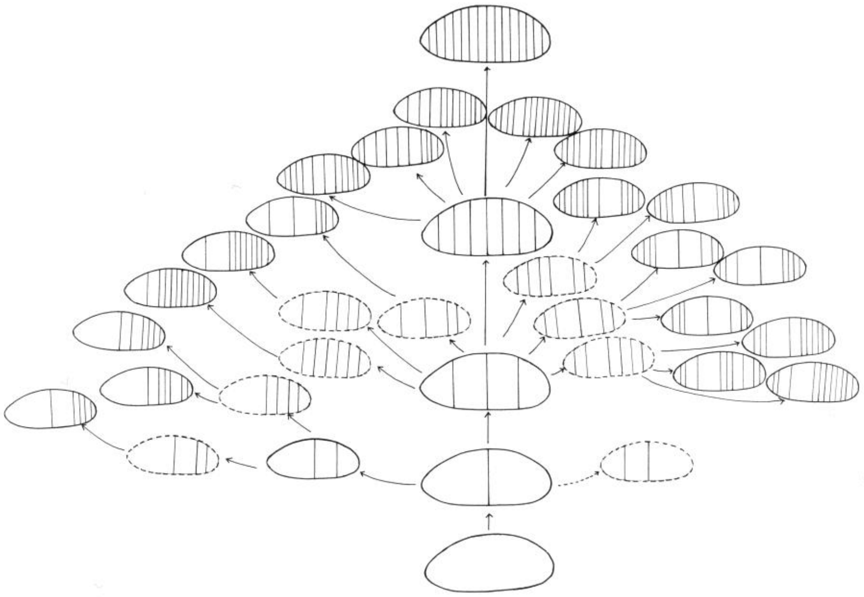


Figure 2. Transformation tree of body patterns in fruit fly larvae based on a model of successive bifurcation

This transformational tree reveals how different forms are related to one another; how superficially similar forms are far apart on the tree, while forms that look most different are neighbours. It is the most parsimonious tree relating all the forms.

More importantly, the ontogenetic transformation tree predicts the possible forms that can be obtained in evolution (phylogeny), mostly likely by going up the sequence of successive bifurcations, but occasional reversals to simpler forms could also take place. This is why phylogeny appears to recapitulate ontogeny (Gould, 1977). Though actually *it does not*; ontogeny and phylogeny are simply related through the dynamics of the generic processes generating form.

A *natural* system of classification results from the tree. The twenty-four actual forms or species are classified hierarchically into one 'Family' with two 'Orders', the first Order containing three Genera, and the second Order, eight Genera. The forms not yet found (depicted in dotted lines in Fig. 2), would also fit neatly in the natural system of classification should they be discovered in future. There are 676 possible forms according to the dynamic model of successive bifurcation. If all the body segments were free to vary independently, the number of possible forms would have been 2^{16}, or more than 60 000. This demonstrates how highly the generative dynamics can constrain the possible forms, and why, incidentally parallelisms are rife in evolution (Ho and Saunders, 1982, Ho, 1984b).

In the second example, we produced a transformation tree for all possible ways leaves are arranged around the stem in plants (Fig. 3) (Ho and Saunders, 1994), based on the generic and robust dynamics that generate the patterns, discovered by French mathematical physicists Douady and Couder (1992). The discovery caused quite a stir in France, as leaf arrangement, or *phyllotaxis*, has been a long-standing problem in biology, ever since the brilliant mathematician and code-breaker Alan Turing (1912-1954) drew attention to how the spiral patterns of leaves around the stem conform to the Fibonacci sequence (Saunders, 1984, 1989). Many neo-Darwinian ‘just-so stories’ have been invented over the years to account for different leaf arrangements in terms of ‘selective advantage’; all of which have been proven irrelevant in one stroke. The power of dynamics - the syntax of form - is that it predicts the set of possible transformations, *excluding all others*. It also tells us how the possible forms are related by transformation (Ho, 2008a).

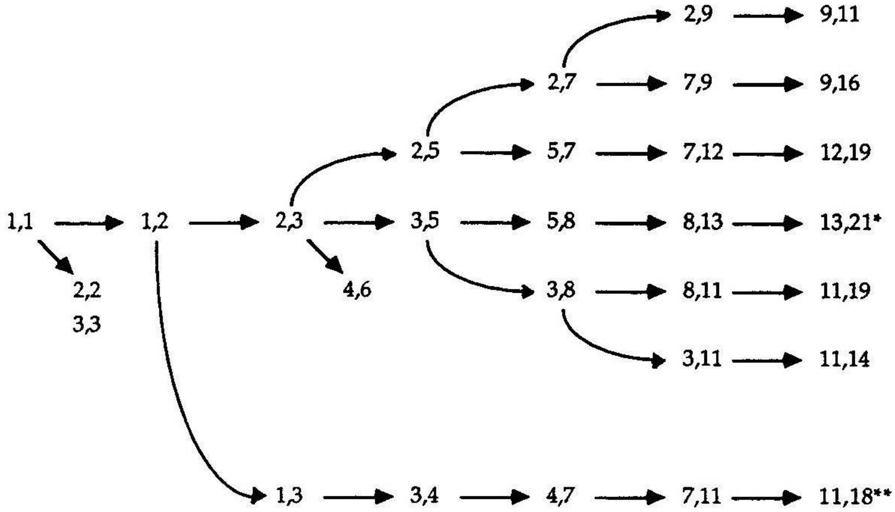


Figure 3. The transformation tree of possible phyllotaxis patterns

It is not known if all the possible forms in Fig. 3 actually exist in nature. The main Fibonacci sequence with divergence angle of 137.5^{o} is in the middle row (marked with *). At the bottom is an alternative Fibonacci sequence with divergence angle of 99.5^{o} (marked with **). Like the transformation tree in Fig. 2, it makes very definite predictions concerning neighbouring transformations. Thus, parastichies 8,11 and 9,11 (secondary spirals, the numbers indicate spirals to the right and left respectively starting from the centre of the flower or top of the cone), despite their apparent similarity, are quite far apart on the tree, whereas the neighbouring parastichies 8,13 and 13,21 appear superficially very different. As the tree is also an ontogenetic tree, it predicts that plants such as the Canadian pine (*Pinus resinosia*) with parastichies 8,13 in the cone, goes through all of the main sequence in development. We do not know if that is true, but we did find that the leaf shoot bearing the cone has 3,5 parastichies.

For the same reasons, we would predict that the decussate arrangement 2,2 is the earliest divergence from the main Fibonacci sequence, followed by the alternative Fibonacci sequence beginning with 1,3. Phylogenetic transformations are strictly predicted. For example, one would not expect an ancestor of a plant with parastichies 8,13 to have had parastichies 7,12, or even 2,5, but most likely, 5,8.

The dynamics of the processes are subject to contingent ‘complexification’ (or simplification) in the course of evolution, by virtue of the lived experience of the organisms themselves. Nevertheless, it is highly constrained, when it comes to pattern formation.

It has become clear that directed genetic changes in given environments are just as non-random as morphological changes, and hence, possibly subject to comparable systemic constraints (Ho, 1987) (see later).

Natural selection and molecular evolution

Molecular evolution, the study of how proteins and nucleic acid sequences in different species evolve, has been dominated by the neutralist/selectionist controversy that continues to the present day.

Motoo Kimura (1924-1994) was best known for his neutral theory of molecular evolution (Kimura, 1968), which proposed that most of the amino acid and base changes in evolution resulted from random genetic drift of neutral mutations, i.e., mutations that did not influence the ‘fitness’ of the organisms. In fact, he did not deny that natural selection could be operating; only that it was not reflected in the evolution of molecules. In effect, molecular evolution appears decoupled from the evolution of organisms, which, at least, is consistent with all other observations indicating the lack of simple translations between genes and phenotype, and is an independent corroboration of Waddington’s (1957) concept of the epigenetic landscape.

The neutral mutation theory was inspired by earlier discoveries that when the amino acid or DNA base sequence of genes in different organisms were compared, they diverged apparently linearly according to the time at which the organisms shared a common ancestor. This gave rise to the ‘molecular clock’ hypothesis (Zuckerkandl and Pauling, 1962; Margoliash, 1963), according to which, the rate of amino acid or nucleotide substitution is approximately constant per year over evolutionary time and among different species (Lowenstein, 1986).

As more data became available, the molecular clock hypothesis ran into trouble. Although there is a correlation between genetic distance and time of divergence, such correlation is not universal, and is often violated.

Numerous studies on extant organisms show that mutation rates are far from constant (Huang, 2009). For example, genetic differences between two subpopulations of medaka fish that had diverged for ~4 million years is 3 times that between two primate species, humans and chimpanzees, that are thought to have split 5-7 million years ago. Genetic distances measured on genealogical timescales of less than one million years are often an order of magnitude *larger* than those on geological timescales of more than a million years.

To illustrate the paradox, four randomly selected genes in different species are compared for their similarity (percent identity). All four genes behave as good clocks in macroevolution from fish *(D. rerio*, zebrafish), to frog (*X. laevis*, African clawed toad), to bird (*G. gallus*, red jungle fowl), to mouse (*M. musculus*), and human (*H. sapiens*).

However, they give wildly contradictory timing at lower levels (see Table 1).When different species of fish are compared with each other, *F. rubripes* (puffer fish) vs *D. rerio*, divergence time ranged from 91 to 420 myBP.

Table 1 Genetic distance and estimated divergence time (Huang, 2009)

	Percent Identity					
	Prdm2	BTK	CytC	GCA1A		Div. time (MyBP)
H. sapiens vs ***D. rerio***		39	61	80	66	450
H. sapiens vs ***X. laevis***		55	85	75		360
H. sapiens vs ***G. gallus***	71	85	87	81		310
H. sapiens vs ***M. musculus***		91	98	91	91	91
F. rubripes vs ***D. rerio***	45					420
		71				400
			89			200
				91		91

Epigenetic complexity *vs* genetic diversity, macroevolution *vs* microevolution

Huang (2009) proposed that an inverse relationship exists between genetic diversity and epigenetic complexity: multicellular organisms differentiated into tissues and cells are epigenetically complex and can tolerate less genetic variation (germline DNA mutation), whereas single celled organisms, being epigenetically simple, can tolerate more. Consequently, each level of epigenetic complexity will reach its maximum level of variations. This simple theory explains the major features of evolution, including the paradox of an overestimate of divergence times when some gene sequences in lower taxonomic levels are compared (see Table 1).

Humans are undoubtedly the most epigenetically complex species; but in terms of the number of genes, it has only roughly 1.6 times that of a fruit fly and about the same as the mouse or fish. However, the number of certain enzymes responsible for epigenetic gene organisation, such as the PRDM subfamily of histone methyltransferases, increases dramatically during metazoan evolution from 0 in bacteria yeasts and plants, to 2 in worms, 3 in insects, 7 in sea urchins, 15 in fishes, 16 in rodents and 17 in primates. Also, the core histone genes H2A, H2B, H3 and H4 have been duplicated in humans but not chimpanzees, and the number of genes for microRNA (which play key regulatory functions) correlates well with organism complexity. Complex organisms also show complex gene expression patterns: 94 percent of human genes have alternative products or alternative splicing compared to only 10 percent in the nematode *C. elegans*.

For any organism of a certain epigenetic complexity, it can undergo epigenetic changes or genetic mutations in a certain range allowed by the epigenetic complexity. More significantly, epigenetic complexity change is almost by definition, macroevolution, whereas genetic changes due to mutations causing minor variations in phenotypes and do not affect the epigenetic programmes are microevolution. Microevolution, says Huang (2009), is a continuous process of accumulating mutations.

Macroevolution from simple to complex organisms is associated with a punctuational increase in epigenetic complexity and in turn a punctuational loss in genetic diversity. From a common ancestor, the genetic distance between two splitting descendants may gradually increase with time until a maximum is reached and remaining constant thereafter.

The maximum genetic diversity hypothesis predicts that if time is long enough for genetic distance to reach the maximum, then the genetic distance between two genera of the same family should be similar to that between two families, or orders, or phyla. That was demonstrated to be the case for a very old group such as fungi; in contrast, the molecular clock hypothesis predicts that the genetic distance between two fungi genera of the same family should be *smaller* than that between families, and still smaller than that between orders, and so on.

His hypothesis, Huang claims, explains top-down evolution, which is also consistent with the epigenetic origin of evolutionary novelties (see earlier), and the decoupling of macroevolution from the microevolution of genetic distance.

Continuity between epigenetic and genetic changes

Huang's theory does explain a lot and could, in principle, resolve nearly all the major paradoxes in molecular evolution, except perhaps the widely different rates of divergence between different genes within the same organism.

More importantly, I believe Huang's hypothesis that epigenetically complex organisms are less tolerant of genetic or germ line diversity is incomplete, because the level of germ line diversity is actively maintained.

A key feature of epigenetics in complex organisms is that they have become more efficient at generating the sequence diversity required at the precise local somatic level (Ho, 2009f); and incidentally, also more efficient at reducing it at the germ line level through mechanisms such as gene conversion and concerted evolution (Ho 2004a-d), all part of the death of the Central Dogma of molecular biology, that has been happening since the 1980s.

Epigenetic processes such as RNA editing, alternative and trans-splicing, exonisation and somatic hypermutation, can generate huge sequence diversity wherever and whenever required (Ho, 2009f). Some of those processes, coupled with reverse-translation, are powerful mechanisms for generating sequence diversity that can be tested by function within the individual organism, and then used to overwrite the germ line sequence(s). I have reviewed these mechanisms in some detail elsewhere (Ho, 2009a), including a range of evidence indicating that mutations are far from random, with the organism choosing when and how to mutate, or not to mutate at all (Ho, 2004c)

DNA recoding – rewriting genome DNA – appears to be a central feature of both the immune and nervous systems. DNA recoding is involved at the level of establishing neuronal identity and neuronal connectivity during development, learning and brain regeneration. And it appears that the brain, like the immune system, also changes according to experience.

Mattick and Mehler (2008) suggest that the potential recoding of DNA in nerve cells (and similarly in immune cells) might be primarily a mechanism whereby productive or learned changes induced by RNA editing are *rewritten* back to DNA via RNA-directed DNA repair. This effectively fixes the altered genetic message once a particular neural circuitry and epigenetic state has been established (see Ho, 2009f). Steele (2008) has proposed a similar RNA-directed recoding of DNA for the immune system.

Unlike Steele, Mattick and Mehler (2008) fall sort of proposing that the RNA-templated recoding of the genome and the associated structural and functional adaptations could be transmitted to the next generation. This could be crucial for brain evolution in primates leading up to humans, so that the gains made by successive generations could be accumulated (Ho, 2009f).

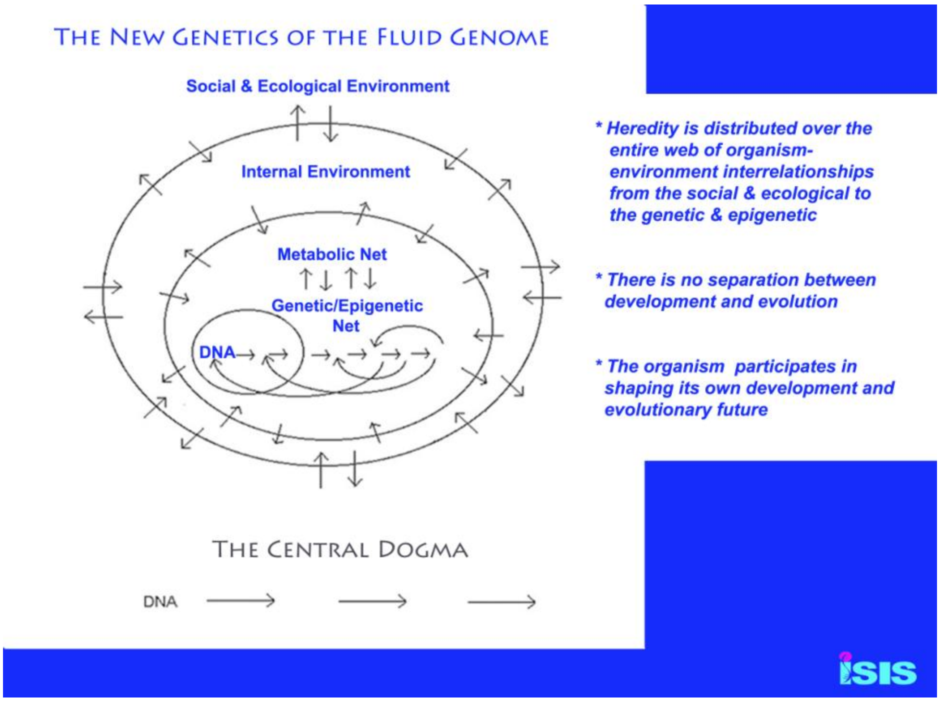
If the analogy with the immune system holds, then as suggested by Steele and colleagues, edited RNA messages or their reverse transcribed DNA counterparts could become inherited via the sperm (Steele, 1981; Ho, 2009g). "Sperm-mediated gene transfer" is well-documented as a process whereby new genetic traits are transmitted to the next generation by the uptake of DNA or RNA by spermatozoa and delivered to the oocytes at fertilization.

Macroevolution therefore involves epigenetic and epigenetically directed genetic changes, and is decoupled from the random microevolutionary accumulation of base sequence changes.

There processes (reviewed in greater detail in Ho, 2009a) are part and parcel of the fluid genome (Ho, 2003), a molecular 'dance of life' that's necessary for survival (see Ho, 2008b, for example).

Heredity and evolution in the light of the new genetics and epigenetics

How should we see heredity in the light of the new genetics and epigenetics? Where does heredity reside if the genome itself is dynamic and fluid? Clearly, heredity does not reside solely in the DNA of the genome. Rather, it resides in an epigenetic state, a dynamic equilibrium between genetic/epiegentic and other cellular processes. But heredity does not end at the boundary of cells or organisms. As organisms engage their environments in a web of mutual feedback interrelationships, they transform and maintain their environments, which are also passed on to subsequent generations as home ranges and other cultural artefacts (Ho and Saunders, 1982; Ho, 1984, 1986; Gray, 1988). Embedded between organisms and their environment are social habits and traditions, an inseparable part of the entire dynamical complex that give rise to the stability of the developmental process, and which we recognize as heredity (Ho, 1984, 1986, 1988b). Heredity is thus distributed over the whole system of organism-environment interrelationships, where changes and adjustments are constantly taking place, propagating through all space-time in the maintenance of the whole, and some of these changes may involve genomic DNA. Thus, the fluidity of the genome is a *necessary* part of the dynamic stability, for genes must also be able to change as appropriate to the system *as a whole* (see Fig. 4).



THE NEW GENETICS OF THE FLUID GENOME

- *Heredity is distributed over the entire web of organism-environment interrelationships from the social & ecological to the genetic & epigenetic*
- *There is no separation between development and evolution*
- *The organism participates in shaping its own development and evolutionary future*

THE CENTRAL DOGMA

Figure 4 Heredity of the fluid genome vs the Central Dogma

While the epigenetic approach fully reaffirms the fundamental holistic nature of life and discredits any theory ascribing putative group differences in human attributes to genes, it also gives no justification to *simplistic mechanistic* ideas on arbitrary effects arising from use and disuse or the inheritance of acquired characters. It does not lead to any kind of determinism, environmental or genetic. Organisms are above all, complex, nonlinear dynamical systems (Saunders, 1992), and as such, they have regions of stability and instability that enable them to maintain homeostasis, or to adapt to change, or not, as the case may be. The appearance of novelties and of mass extinctions alike in evolutionary history are but two sides of the same coin, we cannot be complacent about the capacity of organisms to adapt to any and all environmental insults that are perpetrated, the most pressing of which is anthropogenic global warming. The dynamics of the developmental process ultimately holds the key to heredity and evolution, in determining the sorts of changes that can occur, in its resilience to certain perturbations and susceptibility to others. And our knowledge in this crucial area is urgently required.

What implications are there for evolution? Just as interaction and selection cannot be separated, nor are variation (or mutation) and selection, for the ‘selective’ regime may itself cause specific epigenetic variations or ‘directed’ mutations. The organism experiences its environment in one continuous nested *process*, adjusting and changing, leaving imprints in its epigenetic system, its genome as well as on the environment, all of which are passed on to subsequent generations. Thus, *there is no separation between development and evolution*. In that way, the organism actively participates in shaping its own development as well as the evolution of its ecological and social community. We do hold the future in our hands; it is precious, be careful.

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