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Introducing the epigenetic landscape into middle-years biology teaching

Neil R. Ingram

Abstract Conrad Hal Waddington's epigenetic landscape is now a central paradigm in evolutionary developmental biology. This article proposes that it should be adopted into middle-years (ages 11–16) biology curricula as a way of visualising the interactions of the genome with the environment. The epigenetic landscape is explained, with some biographical detail of Waddington's achievements. Two narratives are then presented for middle-years biology classes: the differentiation of human stem cells and the formation of leaf shape in the water crowfoot, *Ranunculus aquatilis*. The benefits of including epigenetic landscape in middle-years biology curricula are considered.

Across the world, many middle-years (ages 11–16) biology curricula consider the life processes of organisms and the inheritance of genetic material. Only a few curricula, such as the Living Environment Core Curriculum from the United States, integrate these ideas into a coherent narrative to explain the development of living cells:

Genes are inherited, but their expression can be modified by interactions with the environment... The many body cells in an individual can be very different from one another, even though they are all descended from a single cell and thus have essentially identical genetic instructions. This is because different parts of these instructions are used in different types of cells, and are influenced by the cell's environment and past history. (The State Education Department, 2008: 11–12)

In some biology curricula, the teaching of stem cells is inferred. Scotland's National 4 Cell Biology Unit Specification (ages 15–16) refers to the 'therapeutic use of cells' (Scottish Qualifications Association, 2018: 1), while the National Curriculum in England for key stage 4 (ages 14–16) (Department for Education, 2014:7) explicitly refers to 'stem cells in animals and meristems in plants'. The trend towards the inclusion of stem cells in the curriculum is, perhaps, partly motivated by their future potential benefits in medical interventions. It also reflects the renaissance of evolutionary developmental biology (informally, 'evo-devo'), utilising powerful new techniques for analysing how changes in the activity of genomes impact on the development of organisms.

Evo-devo biologists have rediscovered the explanatory power of the 'epigenetic landscape', a paradigm proposed by Conrad Hal Waddington in the 1940s, the significance of which had been overlooked in the quest to understand the molecular basis of the gene. This article proposes introducing the concept of the epigenetic landscape into middle-years biology curricula as a model for

explaining interactions between genomes and their environments, and for providing a contemporary context for understanding the differentiation of stem cells.

This article has four sections. The epigenetic landscape will be explained together with some biographical details for Waddington. Two narratives of the epigenetic landscape will be presented in forms suitable for middle-years biology students. The epigenetic landscape will be used to explain the differentiation of human stem cells and also the formation of leaf shapes in water crowfoot (*Ranunculus aquatilis*).

R. aquatilis can be obtained easily and safely cultivated in school ponds or laboratories and can offer students first-hand experiences of the interaction of genomes and their environments. It has the potential to be a model organism for demonstrating these ideas in schools. The article concludes with some general recommendations.

Conrad Hal Waddington and the epigenetic landscape

Conrad Hal Waddington was an English biologist who carried out most of his innovative research during the 1940s and 1950s. He was the son of tea planter in South India and, as a boy, spent much of his time at boarding school in Clifton College, Bristol, England. One summer holiday, his chemistry teacher, E. J. Holmyard, introduced the young Waddington to several ancient alchemy texts in Arabic and Greek, which he claimed were the origins of modern chemistry (Robertson, 1977; Ingram, 2003, 2019).

Waddington's fascination with alchemy grew into a typed 97-page essay, which he completed in his final sixth-form year at Clifton College in 1923. Two ideas in particular had a lifetime's influence on Waddington's thinking: the 'philosophers' egg' and the 'ouroboros'. The philosophers' egg was 'used to designate the fecundity of the

earth and in particular the alchemists' work of engendering gold' (Waddington, 1923). The ouroboros is a symbol of a snake eating its tail and he drew a representation of it in the essay (Figure 1).

The ouroboros is associated with the Ancient Greek epigraph, ἕν τὸ πᾶν (*hen to pān* or 'the all is one'), equating to the idea that 'any one entity incorporates into itself in some sense all other entities in the universe' (Waddington, 1969). Waddington eventually associated ouroboros with ideas of homeostasis and regulation. Ingram (2019) discusses in detail how the alchemical ideas of the philosophers' egg and the ouroboros lie at the core of Waddington's greatest theoretical contribution, the epigenetic landscape.

Later, at Cambridge University, Waddington discovered the philosophy of A.N. Whitehead, who was interested in the processes through which the world develops. Waddington developed a strong interest in the theoretical ideas underpinning biology as well as becoming an outstanding practical experimental scientist (Peterson, 2016; Slack, 2002).

Waddington's research into the development of wing shape in *Drosophila* is considered to be the first demonstration of the intermediate steps between genotype and phenotype. He is credited for the first modern use of the term 'epigenetics' and is regarded by some as the 'father' of epigenetics. His 'epigenetic landscape' is a powerful expression of the various ways in which genomes interact with their environments.

Waddington was also passionate about painting and sculpture, especially the modernist art being produced in the 1920s and 1930s. The first appearance of the epigenetic landscape in print was in the form of a painting by the celebrated artist John Piper. The representations in Figure 2 are a later reworking of the model.

Figure 2a presents the epigenetic landscape as it is usually drawn, as a gently undulating valley that slopes down towards the observer. A ball, which could represent a stem cell in the process of differentiation, is presented

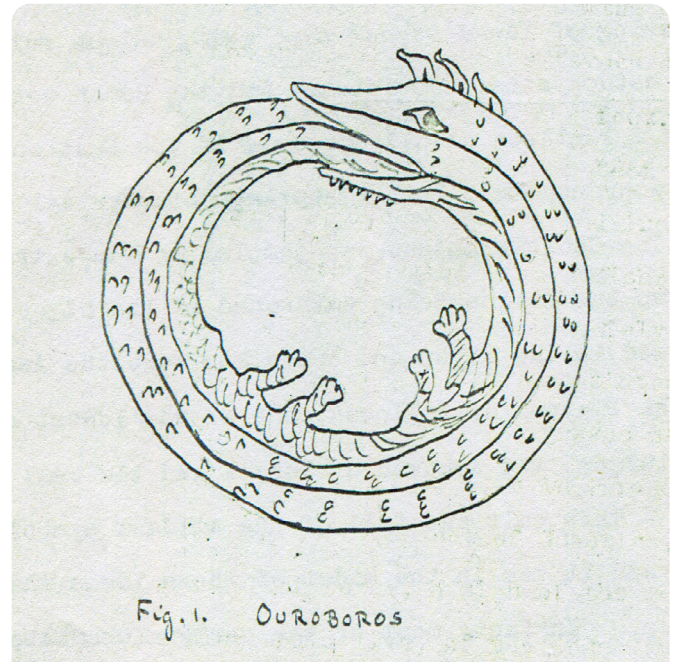


Figure 1 The ouroboros, drawn by Waddington in his school essay of 1923 (by permission of the Centre for Research Collections, University of Edinburgh. Coll-41/2/1/1)

with a series of distinctive alternative pathways represented by the valleys. Some of the valleys are deeper than others. As the cell progresses through the landscape it will change and develop into one of the final resting states that represent mature cell types (such as a blood cell, brain cell or muscle cell). The valley represents all the physical and chemical factors in the environment surrounding the cell, including the flow of energy and nutrients, hormones and 'signal' chemicals. These are the factors that initiate changes with the cell that cause it to develop into its mature form.

The undulating landscape is also shaped by the totality of the organism's genome, represented by the network of tent pegs underpinning the landscape in Figure 2b. This is a key point: it is not one or two genes working in isolation, rather it is the whole of the genome that works to shape the landscape. In this regard, Waddington

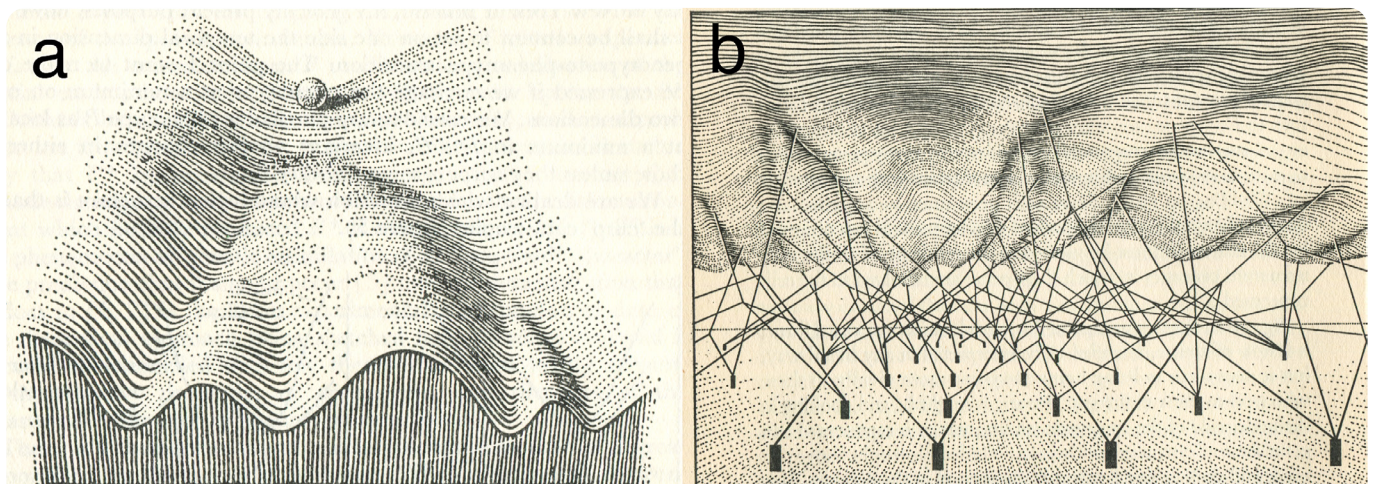


Figure 2 Two views of the epigenetic landscape; reproduced with permission from Waddington (1957)

was decades ahead of other contemporaneous thinkers. Modern genomic analyses support Waddington's claims for the importance of the whole genome (especially as 99% of the genome does not carry DNA codes for proteins), and the epigenetic landscape is now established as a key paradigm in contemporary biology.

The cell travels down a channel that Waddington visualised as a canal. It is difficult for a cell to escape the sides of the channel to enter another one. This means that final cells produced by the landscape are distinctive types (e.g. red blood cells or nerve cells) and intermediate forms are not found.

The final fate of the cell is not irrevocably determined by the conditions at the start of the pathway. Alterations to the physical or chemical environment or genetic mutations might change the shape of the landscape. Some channels are less deep than others and are more easily disrupted. Such a disruption to the landscape could cause the cell to enter a different channel and proceed down a different developmental pathway. Experiments with the fruit fly *Drosophila* showed that the expression of the *crossveinless* phenotype can be suppressed through temperature shocks (Waddington, 1942).

Stem cells

The differentiation of three mature cells (red and white blood cells and a nerve cell) from a single embryonic stem cell is presented as an epigenetic landscape in Figure 3. Differentiation is an extraordinarily complex series of changes that are now being mapped and understood. Our increasing ability to use stem cells as medical therapies depends on this knowledge.

The embryonic stem cell is pluripotent: it can divide by mitosis to produce cells that can develop into any cell type. As these cells mature, certain parts of their genomes are activated and other parts become silent, which means that these cells are only able to give rise to a more restricted

range of cells. These are multipotent stem cells. Blood (haemopoietic) stem cells and nerve stem cells will give rise to different cell types, and these differences are partly due to which parts of their genomes are active and which are silent. These differences are shaped by local differences in the physiochemical environment of the epigenetic landscape. Chemical signals from neighbouring cells are especially important and gradients of chemical signals exist across particular tissues in the body. This creates an orderly formation of cells: nerve cells and blood cells are produced where they are needed and nowhere else.

There is a bustling array of activity in the genome that is initiated and coordinated by the epigenetic landscape. This activity leads to the production of the structural proteins, enzymes, organelles and structures associated with the mature cell types. The whole of the genome is involved in this activity: key genes are activated to produce proteins that, in turn, activate networks of other genes. Those parts of the genome that are active in the early stages of the process might become silent in later stages. Other parts of the genome are tagged by chemical markers so that the genes in that region become permanently inactive.

The genome does not control this process; it is not the brain of the cell. It works as part of a network and control is distributed across the whole network.

Leaf formation in the water crowfoot

Some plants that live in water develop different kinds of leaves, a phenomenon called heterophylly. The causes of heterophylly in the water crowfoots (e.g. *Ranunculus aquatilis*, *R. trichophyllus*) have fascinated biologists for centuries.

The water crowfoot produces two types of leaves, as shown in Figure 4. The most common leaf is the *divided* leaf phenotype, which is made up of branches of thin circular tube-like segments. They contain many

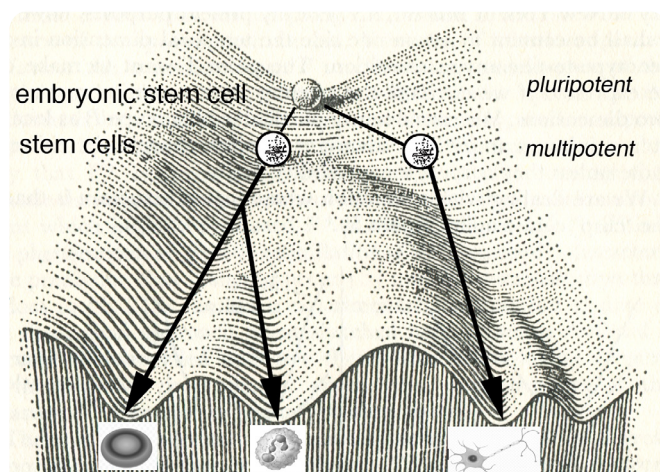


Figure 3 The epigenetic landscape and stem cell differentiation

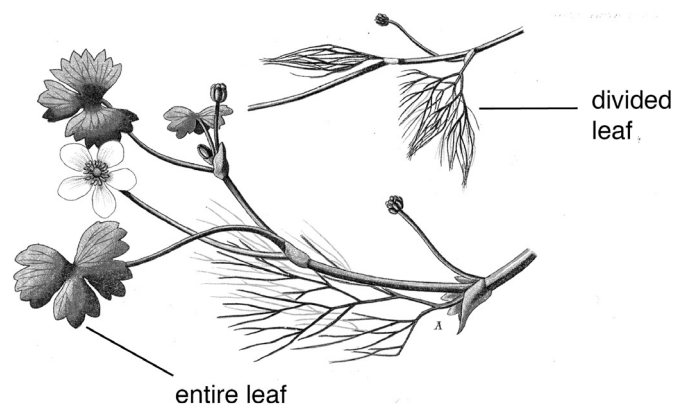


Figure 4 The two types of leaf of the water crowfoot (adapted from Professor Dr Otto Wilhelm Thomé (1885) *Flora von Deutschland, Österreich und der Schweiz*, Gera, Germany; permission granted to use under GFDL by Kurt Stueber)

internal air spaces, and lack stomata. The aquatic plant also forms *entire* leaves. This leaf form only when the bud is submerged in water and, as the leaf expands, it floats with its lower (abaxial) surface below the surface of the water. It also has internal air spaces and functional stomata on the upper surfaces. Entire leaves form after the plant has flowered in May–June.

Modern genomic techniques show that the development of leaf form in the crowfoot fits Waddington's model of the epigenetic landscape, providing a simple and effective demonstration of how the crowfoot genome interacts with its immediate and wider environments. This is illustrated in Figure 5, which shows the environmental triggers for the development processes. Leaf development is dependent on photoperiod (the number of hours of daylight). During short photoperiods (16 hours of daylight or less) only divided leaves form. In water, above 16 hours of daylight, entire leaves can form, although some leaves will continue their developmental pathway towards becoming divided.

The epigenetic pathway that leads to entire leaves forming seems to be a shallow channel, which can be suppressed by changes to the environment. Plants growing in fast-moving water, for example, produce few entire leaves. The epigenetic pathway that leads to divided leaves forming seems to be a deeper channel and is much less sensitive to disruption by the environment. The majority of leaves on an aquatic crowfoot plant are divided.

Recent research in a related species (*R. trichophyllus*) suggests that entire leaves contain higher levels of abscisic acid (ABA), whereas submerged divided leaves contain higher levels of ethylene (Kim *et al.*, 2018). The ABA/ethylene signals cause different patterns of gene activity, with some genes becoming more active and others becoming more silent. These are seen in the different types of leaves. Some technical details are given, for completeness, in Table 1, although this is detail that middle-years students do not need to be given. These genes have a significant impact on leaf development and are major contributors to the epigenetic landscape.

It would be wrong to assume that these few genes represent the only genomic activity occurring. The study showed that nearly 16% of the active genome differed between the two types of developing leaf. This equates to a lot of genomic activity. A comparable study of the pondweed *Potamogeton octandrus* suggested that there were 81103 genes active in the development of

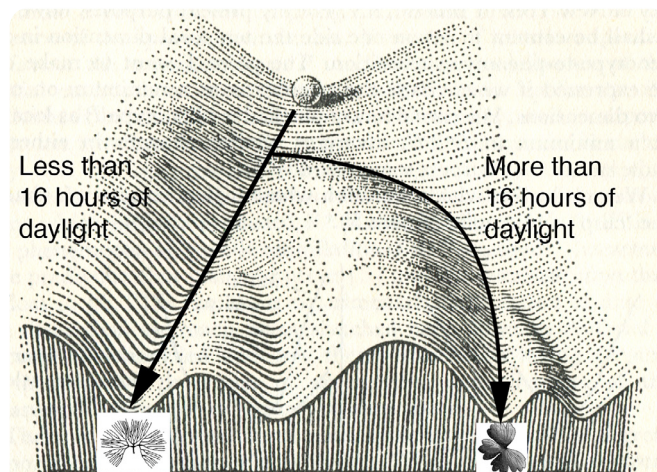


Figure 5 The epigenetic landscape and leaf shape in water crowfoot (adapted from Cook, 1969)

submerged and floating leaves, and 6822 of these were expressed differently in the development of the two forms of leaves (He *et al.*, 2018).

The totality of the genome and its many products play significant and interconnected roles and ably illustrate Waddington's metaphor of the epigenetic landscape, where genes are the 'guy ropes' beneath the undulating landscape (Figure 2b). The epigenetic landscape is a simple way of visualising the complexity of the interrelationships, as Figure 5 shows.

Conclusion

The epigenetic landscape is a powerful visual metaphor that can be applied to any level of biological organisation. It is simple to understand, and any child who has played pinball can appreciate the consequences of interrupting the motion of a ball travelling down a sloping surface. There is, however, more to it than this. In the model, the activities of genes are distributed across the whole genome, which is in constant interaction with the local physiochemical environment. This overcomes the misconceptions that genes 'control' characteristics or that everything is determined by the environment. It exposes the false dichotomy between nature and nurture (Keller, 2010).

Introducing the epigenetic landscape into the teaching of stem cells brings in a new way of thinking about the whole of developmental biology. This will be of value in more advanced studies. For example, it is possible to 'deprogramme' differentiated cells so they function

Table 1 The activity of some key genes in the formation of leaf shape in the crowfoots

Leaf type	Genes activated	Genes silenced	Impact of gene activity
Submerged divided leaf (high ABA)	Abaxial genes, <i>RtKANAD1as</i>	<i>STOMAGEN</i> , <i>VDN7</i>	Narrow shape, lack of stomata, reduced xylem vessel development
Entire leaf (high ethylene)	Adaxial genes, <i>STOMAGEN</i> , <i>VDN7</i> , <i>RtHD-ZIP11s</i>	Abaxial genes, <i>RtKANAD1as</i>	Development of upper and lower surfaces of the leaf, stomata, xylem vessels

as stem cells. The epigenetic landscape provides a way to visualise this process: the ball can be persuaded to move back up its channel to its resting state at the top of the landscape. This will require the manipulation of the epigenetic landscape with energy, nutrients and the appropriate signal chemicals.

Waddington (1942) suggested that Wilhelm Johannsen's classic statement:

genotype + environment → phenotype

be rewritten as:

genotype + environment + epigenotype → phenotype

I propose that schools should accept Waddington's thinking and reinterpret it as:

genome + epigenetic landscape → phenotype

which would provide a balanced mindset for students in their middle-years education to discover post-genomic biology.

The author has developed worksheets with teachers' notes, designed to be used with middle-years students (ages 14–16), that cover the key ideas in this topic. These are in line with current curriculum demands. The resources are available at an epigenetic landscape micro-site: <http://neilingram.co.uk>.

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