Spring 2019 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 15 and 16 (April 16 & 23)

Epigenetics and Evolution

- Darwinian Evolution
- Lamarck's Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Hopeful Monsters and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading


Books (Reserve in Library)


Literature


Boomsma JJ, Gawne R. Superorganismality and caste differentiation as points of no return: how the major evolutionary transitions were lost in translation. Biol Rev Camb Philos Soc. 2018 Feb;93(1):28-54.


Lamarck on use and disuse. http://www.ucl.ac.uk/taxome/jim/Mim/lamarck6.html


Waddington CH. Selection of the Genetic Basis for an Acquired Character. 1952 Nature 169: 278

Waddington CH. The Epigenotype. 1942 Endeavour (18-20).


Jollos V. Inherited Changes Produced by Heat-Treatment in Drosophila Melanogaster. 1934 (477-494).


Does evolutionary theory need a rethink?

Researchers are divided over what processes should be considered fundamental.

POINT
Yes, urgently

Without an extended evolutionary framework, the theory neglects key processes, say Kevin Laland and colleagues.

C
Charles Darwin conceived of evolution by natural selection without knowing that genes exist. Now mainstream evolutionary theory has come to focus almost exclusively on genetic inheritance and processes that change gene frequencies.

Yet new data pouring out of adjacent fields are starting to undermine this narrow stance. An alternative vision of evolution is beginning to crystallize, in which the processes by which organisms grow and develop are recognized as causes of evolution.

Some of us first met to discuss these advances six years ago. In the time since, as members of an interdisciplinary team, we have worked intensively to develop a broader framework, termed the extended evolutionary synthesis (EES), and to flesh out its structure, assumptions and predictions. In essence, this synthesis maintains that important drivers of evolution, ones that cannot be reduced to genes, must be woven into the very fabric of evolutionary theory.

We believe that the EES will shed new light on how... PAGE 162

COUNTERPOINT
No, all is well

Theory accommodates evidence through relentless synthesis, say Gregory A. Wray, Hopi E. Hoekstra and colleagues.

I
In October 1881, just six months before he died, Charles Darwin published his final book. The Formation of Vegetable Mould, Through the Actions of Worms sold briskly: Darwin's earlier publications had secured his reputation. He devoted an entire book to these humble creatures in part because they exemplify an interesting feedback process: earthworms are adapted to thrive in an environment that they modify through their own activities.

Darwin learned about earthworms from conversations with gardeners and his own simple experiments. He had a genius for distilling penetrating insights about evolutionary processes — often after amassing years of observational and experimental data — and he drew on such disparate topics as agriculture, geology, embryology and behaviour. Evolutionary thinking ever since has followed Darwin's lead in its emphasis on evidence and in synthesizing information from other fields.

A profound shift in evolutionary thinking began... PAGE 163
The number of biologists calling for change in how evolution is conceptualized is growing rapidly. Strong support comes from allied disciplines, particularly developmental biology, but also genomics, epigenetics, ecology and social science. We contend that evolutionary biology needs revision if it is to benefit fully from these other disciplines. The data supporting our position gets stronger every day.

Yet the mere mention of the EES often evokes an emotional, even hostile, reaction among evolutionary biologists. Too often, vital discussions descend into acrimony, with accusations of muddle or misrepresentation. Perhaps haunted by the spectre of intelligent design, evolutionary biologists wish to show a united front to those hostile to science. Some might fear that they will receive less funding and recognition if outsiders — such as physiologists or developmental biologists — flood into their field.

However, another factor is more important: many conventional evolutionary biologists study the processes that we claim are neglected, but they comprehend them very differently (see ‘No, all is well’). This is no storm in an academic teaream; it is a struggle for the very soul of the discipline.

Here we articulate the logic of the EES in the hope of taking some heat out of this debate and encouraging open discussion of the fundamental causes of evolutionary change (see Supplementary Information; go.nature.com/boffk7).

**CORE VALUES**

The core of current evolutionary theory was forged in the 1930s and 1940s. It combined natural selection, genetics and other fields into a consensus about how evolution occurs. This ‘modern synthesis’ allowed the evolutionary process to be described mathematically as frequencies of genetic variants in a population change over time — as, for instance, in the spread of genetic resistance to the myxoma virus in rabbits.

In the decades since, evolutionary biology has incorporated developments consistent with the tenets of the modern synthesis. One such is ‘neutral theory’, which emphasizes random events in evolution. However, standard evolutionary theory (SET) largely retains the same assumptions as the original modern synthesis, which continues to channel how people think about evolution.

The story that SET tells is simple: new variation arises through random genetic mutation; inheritance occurs through DNA; and natural selection is the sole cause of adaptation, the process by which organisms become well-suited to their environments. In this view, the complexity of biological development — the changes that occur as an organism grows and ages — are of secondary, even minor, importance.

In our view, this ‘gene-centric’ focus fails to capture the full gamut of processes that direct evolution. Missing pieces include how physical development influences the generation of variation (developmental bias); how the environment directly shapes organisms’ traits (plasticity); how organisms modify environments (niche construction); and how organisms transmit more than genes across generations (extra-genetic inheritance). For SET, these phenomena are just outcomes of evolution. For the EES, they are also causes.

Valuable insight into the causes of adaptation and the appearance of new traits comes from the field of evolutionary developmental biology (‘evo-devo’). Some of its experimental findings are proving tricky to assimilate into SET. Particularly thorny is the observation that much variation is not random because developmental processes generate certain forms more readily than others. For example, among one group of centipedes, each of the more than 1,000 species has an odd number of leg-bearing segments, because of the mechanisms of segment development.

In our view, this concept — developmental bias — helps to explain how organisms adapt to their environments and diversify into many different species. For example, cichlid fishes in Lake Malawi are more closely related to other cichlids in Lake Malawi than to those in Lake Tanganyika, but species in both lakes have strikingly similar body shapes. In each case, some fish have large fleshy lips, others protruding foreheads, and still others short, robust lower jaws.

SET explains such parallels as convergent evolution: similar environmental conditions select for random genetic variation with equivalent results. This account requires extraordinary coincidence to explain the multiple parallel forms that evolved independently in each lake. A more succinct hypothesis is that developmental bias and natural selection work together. Rather than selection being free to traverse across any physical possibility, it is guided along specific routes opened up by the processes of development.

Another kind of developmental bias occurs when individuals respond to their environment by changing their form — a phenomenon called plasticity. For instance, leaf shape changes with soil water and chemistry. SET views this plasticity as merely fine-tuning, or even noise. The EES sees it as a plausible first step in adaptive evolution. The key finding here is that plasticity not only allows organisms to cope in new environmental conditions but to generate traits that are well-suited to them. If selection preserves genetic variants that respond effectively when conditions change, then adaptation largely occurs by accumulation of genetic variations that stabilize a trait after its first appearance. In other words, often it is the trait that comes first; genes that cement it follow, sometimes several generations later.

Studies of fish, birds, amphibians and insects suggest that adaptations that were, initially, environmentally induced may promote colonization of new environments and facilitate speciation. Some of the best-studied examples of this are in fishes, such as sticklebacks and Arctic char. Differences in the diets and conditions of fish living at the bottom and in open water have induced distinct body forms, which seem to be evolving reproductively isolation, a stage in forming new species. The number of species in a lineage does not depend solely on how random genetic variation is winnowed through different environmental sieves. It also hangs on developmental properties that contribute to the lineage’s ‘evolvability’.

In essence, SET treats the environment as a ‘background condition’, which may trigger or modify selection, but is not itself part of the evolutionary process. It does not differentiate between how termites become adapted to mounds that they construct and, say, how organisms adapt to volcanic eruptions. We view these cases as fundamentally different.

Volcanic eruptions are idiosyncratic events, independent of organisms’ actions. By contrast, termites construct and regulate their homes in a repeatable, directional manner that is shaped by past selection and that instigates future selection. Similarly, mammals, birds and insects defend, maintain and improve their nests — adaptive responses to nest building that have evolved again and again. This ‘niche construction’, like developmental bias, means that organisms co-direct their own evolution by systematically changing environments and thereby biasing selection.

**INHERITANCE BEYOND GENES**

SET has long regarded inheritance mechanisms outside genes as special cases; human culture being the prime example. The EES explicitly recognizes that parent–offspring similarities result in part from parents reconstructing their own developmental environments for their offspring. ‘Extra-genetic inheritance’ includes...
A worm cast pictured in Charles Darwin’s final book.
POINT: YES, URGENTLY ▶ the transmission of epigenetic marks (chemical changes that alter DNA expression but not the underlying sequence) that influence fertility, longevity and disease resistance across taxa. In addition, extra-genetic inheritance includes socially transmitted behaviour in animals, such as nut cracking in chimpanzees or the migratory patterns of reef fishes8,9. It also encompasses those structures and altered conditions that organisms leave to their descendants through their niche construction — from beavers’ dams to worm-processed soils3,4. Research over the past decade has established such inheritance to be so widespread that it should be part of general theory.

Mathematical models of evolutionary dynamics that incorporate extra-genetic inheritance make different predictions from those that do not4–9. Inclusive models help to explain a wide range of puzzling phenomena, such as the rapid colonization of North America by the house finch, the adaptive potential of invasive plants with low genetic diversity, and how reproductive isolation is established.

Such legacies can even generate macro-evolutionary patterns. For instance, evidence suggests that sponges oxygenated the ocean and by doing so created opportunities for other organisms to live on the seabed8. Accumulating fossil data indicate that inherited modifications of the environment by species has repeatedly facilitated, sometimes after millions of years, the evolution of new species and ecosystems10.

“There is more to inheritance than genes.”

BETTER TOGETHER

The above insights derive from different fields, but fit together with surprising coherence. They show that variation is not random, that there is more to inheritance than genes, and that there are multiple routes to the fit between organisms and environments. Importantly, they demonstrate that development is a direct cause of why and how adaptation and speciation occur, and of the rates and patterns of evolutionary change.

SET consistently frames these phenomena in a way that undermines their significance. For instance, developmental bias is generally taken to impose ‘constraints’ on what selection can achieve — a hindrance that explains only the absence of adaptation. By contrast, the EES recognizes developmental processes as a creative element, demarcating which forms and features evolve, and hence accounting for why organisms possess the characters that they do.

Researchers in fields from physiology and ecology to anthropology are running up against the limiting assumptions of the standard evolutionary framework without realizing that others are doing the same. We believe that a plurality of perspectives in science encourages the heritable differences in traits, especially those that bestow some selective advantage. Likewise, there is little evidence for the role of inherited epigenetic modification (part of what was termed ‘inclusive inheritance’) in adaptation: we know of no case in which a new trait has been shown to have a strictly epigenetic basis divorced from gene sequence. On both topics, further research will be valuable.

All four phenomena that Laland and colleagues promote are ‘add-ons’ to the basic processes that produce evolutionary change: natural selection, drift, mutation, recombination and gene flow. None of these additions is essential for evolution, but they can alter the process under certain circumstances. For this reason they are eminently worthy of study.

We invite Laland and colleagues to join us in a more expansive extension, rather than imagining divisions that do not exist.

We appreciate their ideas as an important part of what evolutionary theory might become in the future. We, too, want an extended evolutionary synthesis, but for us, these words are lowercase because this is how our field has always advanced16.

The best way to elevate the prominence of genuinely interesting phenomena such as phenotypic plasticity, inclusive inheritance, niche construction and developmental bias (and many, many others) is to strengthen the evidence for their importance.

Before claiming that earthworms “have played a more important part in the history of the world than most persons would at first suppose”11, Darwin collected more than 40 years of data. Even then, he published only for fear that he would soon be “joining them”12.

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COUNTERPOINT: NO, ALL IS WELL ▶ is genetic variation in the response14. This role for plasticity in evolutionary change is so well documented that there is no need for special advocacy.

Much less clear is whether plasticity can ‘lead’ genetic variation during adaptation. More than half a century ago, developmental biologist Conrad Waddington described a process that he called genetic assimilation15. Here, new mutations can sometimes convert a plastic trait into one that develops even without the specific environmental condition that originally induced it. Few cases have been documented outside of the laboratory, however. Whether this is owing to a lack of serious attention or whether it reflects a genuine rarity in nature can be answered only by further study.

Lack of evidence also makes it difficult to evaluate the role that developmental bias may have in the evolution (or lack of evolution) of adaptive traits. Developmental processes, based on features of the genome that may be specific to a particular group of organisms, certainly can influence the range of traits that natural selection can act on. However, what matters ultimately is not the extent of trait variation, nor even its precise mechanistic causes. What matters is the heritable differences in traits, especially those that bestow some selective advantage. Likewise, there is little evidence for the role of inherited epigenetic modification (part of what was termed ‘inclusive inheritance’) in adaptation: we know of no case in which a new trait has been shown to have a strictly epigenetic basis divorced from gene sequence. On both topics, further research will be valuable.

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Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution

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Abstract

Environment has a critical role in the natural selection process for Darwinian evolution. The primary molecular component currently considered for neo-Darwinian evolution involves genetic alterations and random mutations that generate the phenotypic variation required for natural selection to act. The vast majority of environmental factors cannot directly alter DNA sequence. Epigenetic mechanisms directly regulate genetic processes and can be dramatically altered by environmental factors. Therefore, environmental epigenetics provides a molecular mechanism to directly alter phenotypic variation generationally. Lamarck proposed in 1802 the concept that environment can directly alter phenotype in a heritable manner. Environmental epigenetics and epigenetic transgenerational inheritance provide molecular mechanisms for this process. Therefore, environment can on a molecular level influence the phenotypic variation directly. The ability of environmental epigenetics to alter phenotypic and genotypic variation directly can significantly impact natural selection. Neo-Lamarckian concept can facilitate neo-Darwinian evolution. A unified theory of evolution is presented to describe the integration of environmental epigenetic and genetic aspects of evolution.

Key words: epigenetics, Lamarck, Darwin, natural selection, environment, review.

Introduction

Charles Darwin’s concept of evolution by natural selection is the unifying theme for much of modern biology (Darwin 1859). Remarkably, Darwin had no understanding of the molecular mechanisms involved in this process. Integration of Darwin’s thinking with advances in genetic and molecular sciences over the past century facilitated the development of a well-supported neo-Darwinian theory of evolution (Olson-Manning et al. 2012). The current primary concept for the molecular basis of evolution involves genetics and mutations, such that random DNA sequence and chromosomal alterations create a genetic variation that directly impacts phenotype and phenotypic variation. The majority of models in evolutionary biology involves DNA sequence mutations as the primary molecular mechanism underlying heritable phenotypic variation (Laland et al. 2014). A conundrum in evolutionary theory is that the frequency of potentially advantageous genetic mutations is extremely low (Jablonka and Raz 2009; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Nei and Nozawa 2011; Laland et al. 2014). Although recent studies with organisms such as microbes demonstrate genotypic variation are sufficient (Levy and Siegal 2008; Avelar et al. 2013; Ho and Zhang 2014) and additional mechanisms such as random genetic drift, genetic assimilation, directed mutations and epistasis also play important roles, genetic theory alone has difficulty explaining some aspects of evolution (Laland et al. 2014). For example, phenotypic mutation rates and genotypic mutation rates are dramatically different and genetics has been the primary molecular mechanism considered (Burger et al. 2006), but the inclusion of an additional mechanism such as epigenetics can help explain this discordance. Understanding the origins of genotypic variation and rapid evolutionary phenomenon under environmental pressure is difficult to explain with only classic genetics considered. Opposing groups of evolutionary biologists are now debating the need to “rethink” the theory (Laland et al. 2014). Genetics is the primary molecular mechanism considered in classic neo-Darwinian evolution theory (Olson-Manning et al. 2012) (table 1 and fig. 1).

In addition to evolution considerations, a large number of biological phenomena have been observed that cannot be
easily explained by genetics alone. These include the fact that identical twins with similar genetics generally have discordant disease (Zwijnenburg et al. 2010; Kratz et al. 2014; Tan et al. 2015), or the fact that generally only a small percentage of a disease population has been found to have a correlated genetic mutation, or the fact that many diseases have increased in frequency an order of magnitude in only a couple decades, or the fact that hundreds of environmental contaminants not able to alter DNA sequence have been shown to alter disease or phenotype later in life (Skinner 2014a). Many biological observations do not follow normal Mendelian genetic rules and are difficult to explain with classic genetic processes or mechanisms (McClintock 1984). An example in evolution is that the rates of molecular and morphological evolution are largely decoupled and these patterns of phenotypic divergence are regulatory and not classic genetic mutations (Janecka et al. 2012). Epigenetic resolution of the “curse of complexity” in adaptive evolution of complex traits has been suggested (Badyaev 2014).

Recently documented molecular mechanisms that can dramatically influence genome activity and contribute to phenotypic variation involve epigenetics (Skinner et al. 2010). Many of the above phenomenon when epigenetics is considered as an additional molecular mechanism can be more easily understood, such as the discordance of identical twins (Zwijnenburg et al. 2010; Kratz et al. 2014; Tan et al. 2015). Waddington (1953) coined the term epigenetics and the classic epigenetic definitions of Waddington (1953) and others (Skinner 2011) are descriptive, without an understanding of the molecular elements (Skinner 2011). Considering our current molecular understanding, epigenetics is defined as “molecular processes around DNA that regulate genome activity independent of DNA sequence and are mitotically stable” (Skinner et al. 2010). These epigenetic mechanisms include DNA methylation, histone modifications, chromatin structure, and selected noncoding RNA (ncRNA) (Skinner 2014a). Epigenetic processes such as DNA methylation can become programmed (e.g., imprinted) and be inherited over generations (Skinner 2014a). Environmental factors have been shown to promote the epigenetic transgenerational inheritance of phenotypic variation. Several examples of environmentally induced epigenetic transgenerational inheritance of phenotypic change have been shown to be inherited for hundreds of generations (Cubas et al. 1999). Therefore, like genetic changes, epigenetic changes can have an important role in short-term microevolution (Day and Bonduriansky 2011) and contribute to macroevolutionary (i.e., at or above the level of species) processes, such as speciation and adaptive radiation (Rebollo et al. 2010; Flatscher et al. 2012). A number of insightful reviews have proposed a role for epigenetics in evolution, primarily as a responsive molecular mechanism in natural selection (Jablonka et al. 1998; Pigliucci 2007; Laland et al. 2014).

**Environment and Evolution**

A variety of environmental factors can influence evolution and general biology. These range from ecological parameters such as temperature and light to nutritional parameters such as caloric restriction or high fat diets. A host of environmental chemicals from phytochemicals to toxicants can also influence...
phenotype and health (Skinner 2014a). Environment has a critical role in natural selection and Darwinian evolution (Darwin 1859). Natural selection is a process in which environmental factors influence the survival or reproductive success of individuals bearing different phenotypes. The current paradigm in evolutionary biology holds that changes in DNA sequence underlie the variation that can evolve in response to natural selection (Laland et al. 2014) (table 1). Although James Baldwin in 1896 suggested environment through sociobiology type mechanisms (i.e., behavior) could alter phenotypic variation, these are thought to be due to genetic changes and considered a neo-Darwinian process (Baldwin 1896; Paenke et al. 2007). Therefore, in neo-Darwinian evolution the primary link between the environment and evolution is to mediate the natural selection process (Olson-Manning et al. 2012; Laland et al. 2014).

In contrast, Lamarck proposed one of the early evolutionary theories in 1802 in that environment promotes the phenotypic alterations associated with evolution (Lamarck 1802; Calabi 2001). This is distinct to the role of environment providing selective pressure in natural selection, such that environment directly alters the phenotype to influence evolution. This theory was seen as conflicting with Darwin’s natural selection evolutionary theory and so was discounted and today is not seriously considered in modern evolutionary theory or neo-Darwinian evolution (Day and Bonduriansky 2011). However, if there was a molecular mechanism that generationally could facilitate the ability of the environment to alter genotypic and phenotypic variation, such a neo-Lamarckian concept may facilitate evolution (table 1 and fig. 1).

Interestingly, Darwin (1868) himself was a strong proponent of the inheritance of acquired characteristics. The blending of inheritance and evolution by natural selection appeared to be a fundamentally flawed concept that would require an untenably high mutation rate in order to maintain the trait variation required for selection (Jenkins 1867). To address this, Darwin (1868) proposed pangensins, a complex theory of environmentally responsive somatic cell transmittance to offspring. Therefore, Darwin conceptually supported Lamarck’s theory of the inheritance of acquired characteristics, but until the last 30 years the potential molecular mechanism was unclear.

Environmental Epigenetics

Epigenetics provides molecular mechanisms for the environment to directly alter phenotypic variation and its subsequent inheritance (Crews et al. 2007; Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A variety of epigenetic mechanisms have been identified including DNA methylation, histone modifications, chromatin structure, and selected ncRNA. All these mechanisms have the ability to program and alter gene expression and have been shown to have a critical role in normal development and biological processes (Skinner et al. 2010; Skinner 2014a). For example, the ability to generate an embryonic stem cell requires the erasure of DNA methylation such that the cell becomes pluripotent (Seisenberger et al. 2013). Although the vast majority of environmental factors cannot alter DNA sequence, epigenetic processes can be dramatically altered in response to environmental factors from nutrition to temperature (Skinner 2014a). All organisms that have been investigated contain highly conserved epigenetic processes (e.g., DNA methylation) that can be environmentally modified (Skinner 2014a). Epigenetics provides an additional molecular mechanism, integrated with genetics, to regulate biology.

The ability of environment to directly alter the development and function of cells and tissues is critical for the health and phenotype of the individual. This direct environmental epigenetic effect on the individual would likely have a limited impact on evolution, unless the epigenetic changes could be transmitted between generations. A large number of environmental factors from nutrition to toxicants have been shown to induce the epigenetic transgenerational inheritance of disease and phenotypic variation (Skinner 2014a). Epigenetic transgenerational inheritance is defined as the germline transmission of epigenetic information between generations in the absence of direct exposure (Skinner et al. 2010). Environmental exposures during a critical period of germline development, fetal gonadal sex determination or gametogenesis, have been shown to permanently program epigenetic marks such as DNA methylation (Skinner 2014a). Nutrition (Pembrey et al. 2006; Burdge et al. 2011), temperature (Song et al. 2013), stress (Skinner 2014b), and toxicants (Anway et al. 2005; Skinner 2014a) have all been shown to promote the epigenetic transgenerational inheritance of phenotypic variation (Skinner 2014a). The phenomenon has been observed in plants, insects, fish, rodents, pigs, and humans (Skinner 2014a). In mammals the altered transgenerational phenotypes have been observed for generations (Skinner 2014a), with environmentally induced epigenetic transgenerational inheritance of phenotypic variation in plants being transmitted for hundreds of generations (Cubas et al. 1999). Therefore, environment can promote the epigenetic transgenerational inheritance of phenotypic variation. The ability of environment to alter phenotype and alter phenotypic variation, independent of genetics, through this epigenetic mechanism is proposed to be important for evolution (Anway et al. 2005; Jablonka and Raz 2009; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Skinner 2014a).

Darwin proposed that one of the critical determinants of evolution was sexual selection (Darwin 1859). A previous study investigated the ability of an environmental factor (toxicant) to promote the epigenetic transgenerational inheritance of an alteration in mate preference associated with sexual selection (Crews et al. 2007). An F0 generation gestating female rat was exposed to the agricultural fungicide vinclozolin transiently and then the F3 generation animals...
Environmental Epigenetics and a Neo-Lamarckian Concept that Facilitates Neo-Darwinian Natural Selection and Evolution

Unified Theory
Environmental epigenetics and epigenetic transgenerational inheritance provide a molecular mechanism for the neo-Lamarckian concept that environmental factors directly alter phenotype (table 1). The ability of environmental epigenetics to alter phenotypic variation provides an initial element for evolution where environment can directly establish the variation and phenotype in a population (fig. 1). Although aspects of the original Lamarckian evolution theory were not accurate (Lamarck 1802), such as having “directed” phenotypes within a generation (Koonin and Wolf 2009; Koonin 2014), the concept that environment can directly impact phenotype and this neo-Lamarckian concept that environment can directly influence phenotype and this neo-Lamarckian concept facilitates neo-Darwinian evolution (fig. 1). This unified theory provides an expanded understanding of the molecular aspects of evolution and solutions for issues such as the mechanisms for rapid evolutionary phenomenon. The mechanisms that environment can impact evolution are also expanded. An integration of epigenetics and genetics will be essential to consider in our future understanding of the molecular aspects of evolution (Jablonka and Raz 2009; Day and Bonduriansky 2011; Laland et al. 2014; Skinner 2014a).

An additional important consideration involves the ability of epigenetic processes to promote genetic mutations (table 1). In cancer biology, altered epigenetics has been shown to promote genome instability and formation of genetic mutations (Feinberg 2004). Nearly all genetic mutations can be directly influenced by epigenetic processes. The most frequent point mutation (single nucleotide polymorphism) is a C to T conversion that is facilitated by CpG DNA methylation (Jones et al. 1992). Repeat elements in the genome when expanded create copy number variations (CNV) that are controlled by hypermethylation of DNA (Liu et al. 2012). Transposable elements are also silenced by hypermethylation of DNA (Yagi et al. 2012). Translocation events and inversions are also influenced by histone modifications, DNA methylation, and ncRNA (Solary et al. 2014). Therefore, epigenetics can directly influence genetic mutations and the origin of genotypic variation is influenced by environmental epigenetic alterations (table 1). In contrast, genetic mutations have been shown to influence epigenetics (Furey and Sethupathy 2013). Recently, we have found that environmentally induced epigenetic transgenerational inheritance of disease and phenotypic variation can promote genetic mutations (i.e., CNV) in later generations (Skinner MK, Guerrero-Bosagna C, Haque MM, unpublished data). Therefore, environmental epigenetics may not only promote increased phenotypic variation, but epigenetics can also drive genetic change and increase genotypic variation. This also needs to be considered in the unified evolution theory (fig. 1).

Discussion
Environmental epigenetics and epigenetic transgenerational inheritance alter phenotypic variation which can be acted on by natural selection. Therefore, environmental epigenetics can directly influence phenotype and this neo-Lamarckian concept can facilitate natural selection and neo-Darwinian evolution. These different aspects of evolution should not be seen as conflicting, but instead can form a unified theory for evolution (fig. 1). This expanded understanding of the molecular aspects of evolution provides novel insights into the mechanism for...
rapid evolutionary events. An expanded understanding of how environment impacts evolution is also provided. The unified theory provides novel considerations that environment can both act to directly influence phenotypic variation and directly facilitate natural selection (fig. 1). Previous evolutionary models have primarily considered genetics and mutations as the primary molecular driver for evolution (Nei and Nozawa 2011; Olson-Manning et al. 2012; Laland et al. 2014). More recently, a number of models have started to consider epigenetics in these evolution models as well (Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badayev 2014; Jablonka and Lamb 2014; Jaeger and Monk 2014). For example, consideration of epigenetics as an additional molecular mechanism has assisted in the understanding of genetic drift (Gordon et al. 2012), genetic assimilation (Zuckerkandl and Cavalli 2007), and directed mutation (Jablonka and Lamb 2007; Kryazhimskiy et al. 2014). The consideration of epigenetics can also be used to better understand neutral evolution (Kimura 1989) through mechanisms, such as robustness (Ohta 2011). The unified theory suggests additional variables that should be considered are the multiple roles of environment and the integration of epigenetics into future evolution models.

Epigenetic transgenerational inheritance of phenotypic variation will have an important role in microevolutionary and macroevolutionary changes, including speciation. A recent study was designed to investigate the epigenetic changes associated with phylogenetic distance in Darwin’s finches (Skinner, Gurerrero-Bosagna, Haque, et al. 2014), a well-known example of adaptive radiation (Darwin 1859; Lack 1947; Burns et al. 2002; Grant and Grant 2008; Huber et al. 2010; Donohue 2011). Erythrocyte DNA was obtained from five species of sympatric Darwin’s finches that vary in phylogenetic relatedness. Genome-wide alterations in genetic mutations, using CNV, were compared with epigenetic alterations associated with differential DNA methylation regions (epimutations) (Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A greater number of epimutations than genetic mutations were observed among the different species, with the number of epimutations increasing with phylogenetic distance. The number, chromosomal locations, regional clustering, and overlap of epimutations suggest that epigenetic change has likely had a role in the speciation and evolution of Darwin’s finches (Skinner, Gurerrero-Bosagna, Haque, et al. 2014). A number of additional observations also support a role of epigenetics and speciation. Using Drosophila and maternally inherited ncRNA silencing of transposons a role for epigenetics and speciation was discussed (Brennecke et al. 2008). The role of epigenetics and a punctuated equilibrium in the mobilization of transposable elements was also suggested (Zeh et al. 2009). An interesting study comparing Neanderthal and human DNA methylation maps also supports a role for epigenetics in speciation (Gokhman et al. 2014) and evolution.

Although the causal role of epimutations was not established in the Darwin’s finch adaptive radiation (Skinner, Gurerrero-Bosagna, Haque, et al. 2014) or other models (Brennecke et al. 2008; Zeh et al. 2009; Gokhman et al. 2014), the causal role of genome-wide genetic mutations has also not been established (Laland et al. 2011). Future studies need to focus on the causal relationship of epigenetic alterations in relation to phenotypic variation that is acted on by natural selection. Genetics and genetic mutations are critical for evolution, but they are not the only molecular factors to consider. Although the major paradigm in the biological sciences is genetic determinism, this paradigm is limited in its ability to explain biological phenomenon ranging from the molecular basis of disease etiology (Skinner 2014a) to certain aspects of evolution by natural selection (Skinner et al. 2010; Day and Bonduriansky 2011; Longo et al. 2012). As Thomas Kuhn suggested during a scientific revolution when the current paradigm reveals anomalies then new science needs to be considered (Kuhn 1962). This type of challenge to current paradigms is also supported by other scientific philosophy, such as Popper (Rieppel 2008) and Macintyre (Macintyre 1977). A paradigm shift is required to explain how genetics and epigenetics integrate to regulate genome activity and evolution, and these advances will need to be incorporated into future evolutionary biology modeling (Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badayev 2014; Jablonka and Lamb 2014; Jaeger and Monk 2014; Skinner 2014a) and theory.

**Summary**

The integration of environmental epigenetics into the molecular aspects of evolution theory suggests a neo-Lamarckian concept that facilitates neo-Darwinian evolution. Several of the novel factors to be considered are summarized below. In regards to the neo-Lamarckian concept:

1. Environmental epigenetics provides a molecular mechanism for Lamarck’s proposal that environment can directly alter phenotype in a heritable manner.
2. Environmental exposures at critical developmental windows promote the epigenetic transgenerational inheritance of germline (e.g., sperm) epimutations that alter phenotypic variation.
3. Direct environmental exposures of developing somatic tissue can alter somatic epigenomes and phenotype in the individual exposed, but this will not be heritable and the phenotypes will often be distinct to transgenerational phenotypes.
4. In regards to novel aspects of neo-Darwinian evolution:
5. Transgenerational germline epimutations after genome stability to promote genetic mutations and genotypic variation in subsequent generations.
6. Phenotypic variation is derived from a combination of integrated genetic and epigenetic processes on which natural selection acts.

7. Environment has a critical role in natural selection, as well as in the induction of heritable adaptive phenotypic variation.

As shown in figure 1, these concepts and components contribute to a unified theory that integrates environmental epigenetics into the molecular aspects of evolution. It is important to note that there is not a dominance of genetics or epigenetics, but the two molecular processes integrate to regulate biology.

Previously, an environmental exposure was found to promote the epigenetic transgenerational inheritance of phenotypic traits such as mate preference, which can play an important role in evolution (Crews et al. 2007; Skinner 2014a). Several reviews have subsequently suggested a role for epigenetics in evolution (Jablonka and Raz 2009; Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012) and experimental models have shown the importance of epigenetic associated genes (Mihola et al. 2009) and molecular elements (Long et al. 2013; Skinner, Guerrero-Bosagna, Haque, et al. 2014) in evolution. The current report extends these studies to present a unified theory that combines both neo-Lamarckian and neo-Darwinian aspects and expands our understanding of how environment impacts evolution. The integration of epigenetics and genetics will be critical for all areas of biology including evolution.

Acknowledgments

The authors acknowledge the advice and critical reviews of Dr Richard Gomulkiewicz and Eric Nilsson (Washington State University), and Dr Carlos Guerrero-Bosagna (Linköping University, Sweden). The helpful comments of the reviewers of this article are also very much appreciated. They thank Ms Heather Johnson for assistance in preparation of the manuscript. The research was supported by a John Templeton Foundation grant to M.K.S. The author declares no competing financial interests.

Literature Cited


Avelar AT, Perfeito L, Gordo I, Ferreira MG. 2013. Genome architecture is a selectable trait that can be maintained by antagonistic pleiotropy. Nat Commun. 4:2235.


Darwin C. 1868. The variation of animals and plants under domestication. London: John Murray.


Epigenetics and Evolution

- Darwinian Evolution
- Lamarck’s Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Hopeful Monsters and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading


Books (Available in Library)

Classical Darwinism: Natural selection

Classical Darwinian emphasis on natural selection can be summarized in a few sentences:

1. There is variation among the individual organisms that make up a population of a species.
2. There is an enormous amount of death, and most individuals will not survive to reproduce.
3. Death is selective. Those individuals that best fit into the environment they encounter are more likely to survive; those that do not fit the environment well are usually eliminated.
4. When those individuals that survive reproduce, their progeny have a high likelihood of inheriting the variations that allowed their parents to survive. If individuals who carry those variations continue to be favored (selected), over time this natural selection will alter the overall characteristics of the population.
5. When populations of a species become reproductively isolated (i.e., separated in such a way that members of one population cannot mate with members of another), each population can randomly acquire a distinct and separate suite of variations. If the environmental conditions faced by the isolated populations are different, different variations will be selected. Anatomical and physiological
3
In recent years, biologists have increasingly recognized that evolutionary change can occur rapidly when natural selection is strong; thus, real-time studies of evolution can be used to test classic evolutionary hypotheses directly. One such hypothesis is that negative interactions between closely related species can drive phenotypic divergence. Such divergence is thought to be ubiquitous, though well-documented cases are surprisingly rare. On small islands in Florida, we found that the lizard Anolis carolinensis moved to higher perches following invasion by Anolis sagrei and, in response, adaptively evolved larger toepads after only 20 generations. These results illustrate that interspecific interactions between closely related species can drive evolutionary change on observable time scales.
Lamarck’s Environment and Evolutionary Biology

Lamarckian inheritance was based on physiology, behavior, and phenotypic plasticity: if you used your muscles, they grew bigger. Moreover, such muscular changes would be passed on to subsequent generations, so that the offspring of run-

Lamarck concludes:

Nature has produced all the species of animals in succession, beginning with the most imperfect or simplest, and ending her work with the most perfect, so as to create a gradually increasing complexity in their organisation; these animals have spread at large throughout all the habitable regions of the globe, and every species has derived from its environment the habits that we find in it and the structural modifications which observation shows us.
It is not really helpful to consider modern environmental epigenetics as neo-Lamarckian; and there is no evidence that Lamarck considered the idea original to himself. We must all keep learning about inheritance, but attributing modern ideas to early researchers is not helpful, and can be misleading.

Scientists are not always remembered for the ideas they cherished most. In the case of the French biologist Jean-Baptiste Lamarck, his name since the end of the nineteenth century has been tightly linked to the idea of the inheritance of acquired characters. This was indeed an idea that he endorsed, but he did not claim it as his own nor did he give it much thought. He took pride instead in advancing the ideas that (1) nature produced successively all the different forms of life on earth, and (2) environmentally induced behavioral changes lead the way in species change. This article surveys Lamarck's ideas about organic change, identifies several ironies with respect to how his name is commonly remembered, and suggests that some historical justice might be done by using the adjective "Lamarckian" to denote something more (or other) than a belief in the inheritance of acquired characters.

BACKGROUND: 200 years have now passed since Darwin was born and scientists around the world are celebrating this important anniversary of the birth of an evolutionary visionary. However, the theories of his colleague Lamarck are treated with considerably less acclaim. These theories centre on the tendency for complexity to increase in organisms over time and the direct transmission of phenotypic traits from parents to offspring.

DISCUSSION: Lamarckian concepts, long thought of no relevance to modern evolutionary theory, are enjoying a quiet resurgence with the increasing complexity of epigenetic theories of inheritance. There is evidence that epigenetic alterations, including DNA methylation and histone modifications, are transmitted transgenerationally, thus providing a potential mechanism for environmental influences to be passed from parents to offspring: Lamarckian evolution. Furthermore, evidence is accumulating that epigenetics plays an important role in many common medical conditions.

SUMMARY: Epigenetics allows the peaceful co-existence of Darwinian and Lamarckian evolution. Further efforts should be exerted on studying the mechanisms by which this occurs so that public health measures can be undertaken to reverse or prevent epigenetic changes important in disease susceptibility. Perhaps in 2059 we will be celebrating the anniversary of both Darwin and Lamarck.
Epigenetics as a source of variation in comparative animal physiology - or - Lamarck is lookin' pretty good these days.
Burggren WW.

Conceptual diagram of the various time courses for development and/or loss of phenotypic characteristics in response to environmental stressors. (A) In this scheme, which is over-simplified by mainly depicting responses as ‘on–off’ rather than graded, an environmental stressor intermittently appears in a non-graded fashion over multiple successive generations (indicated by dashed vertical lines). (B) Epigenetically conveyed phenotypic adjustment appears within a generation of the onset of the environmental stressor (at 1), and conveys additional fitness upon the animal. However, when the environmental stressor declines, the epigenetically maintained phenotype begins to disappear, to return once again when the environmental stressor returns (3). In contrast, a phenotypic modification arising by mutation (C) or by natural selection (D) persists in the population even with the disappearance of the environmental stressor at 2.

In the 16th-17th centuries the central question was how a fully integrated multicellular organism develops from a single cell (the fertilized egg). Preformationism believed that adult features were present fully formed in the egg and simply unfolded during growth. Epigenesis held that traits emerge as a consequence of the progressive interaction of the constituent parts of the zygote.
Doctoral thesis (1922) under Hans Przibram on the responses of butterflies to light and gravity. Became Assistant Director of the Vivarium. Studied cell differentiation and the transplanting and reforming of connections in the nerves of limbs; used newts and frogs. Emphasized concept emergence and the idea of “plastic reactions” or the ability to change as a result of experience. Moved to the USA in 1931, published *Principles of Development* in 1939, and in 1954 he became one of the founding professors at the Rockefeller University; awarded the National Medal of Science in 1979.

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**NEO-DARWINIAN EVOLUTION**

Molecular and Genetic Aspects of Evolutionary Biology

Frequency of microdeletions (1–10 bp) (left) and microinsertions (right) during eutherian evolution. Indel rates for the branches shown with dashed lines cannot be accurately estimated. Estimates are based on a set of regions totaling about 280 kb, for which sequence data is available for all 19 mammals.

Table 9.1 Example of the Rearrangement Operations That Can Affect (a) the Gene Order or (b) the Gene Content of a Genome

<table>
<thead>
<tr>
<th>Operation</th>
<th>Original</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Operations affecting gene orders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversal</td>
<td>1 2 3 4 5</td>
<td>1 3 2 4 5</td>
</tr>
<tr>
<td>Translocation</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Fusion</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Fixation</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Transposition</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Block interchange (special)</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Block interchange (general)</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>(b) Operations affecting gene contents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duplication</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Insertion</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Deletion</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

FIGURE 9.16 Heterozygosity (change in the amount of a gene product expressed) can help drive evolution. (A) Regions of variability in the expression of the gene for interferon-γ (IFNγ) among primates. Several regions are highly conserved, or invariant, indicating that any change (i.e., mutation) in these nucleotide sequences usually results in decreased fitness. These regions include the enhancers for the 5′ A genes. (B) At position -1248 in the middle of highly conserved enhancer sequences, a mutation in the human population has resulted in a newly formed site for the interferon regulatory factor, enabling IFNγ to be transcribed in greater amounts. Although this has negative effects on fitness, it is likely beneficial in terms of providing the survival of individuals living in places where viral infections are common. Heterozygosity is caused by mutation in the enhancer site of the 6′ A gene. (After Rockman et al. 2003.)
**FIGURE 9.17** Changes in Ubx protein associated with the insect clade in the evolution of arthropods. Of all arthropods, only the insects have Ubx protein that is able to repress Distal-less gene expression and thereby inhibit abdominal legs. This ability to repress Distal-less is due to a mutation wherein a stretch of polypeptide residues is encoded in the carboxyl terminus of the Ubx protein. This mutation is seen only in the insect Ubx gene. (After Galen and Carroll 2002 and Ranalaguen et al. 2002.)

**FIGURE 9.2** Postulated ancestry of the Hox genes from a hypothetical ancestor of both preses warners and deoswarners. The deoswarners, Amphiphrax, has only one set of Hox genes, just like the preseswarners. Vertebrates, derived from an Amphiphrax-like organism, have four Hox clusters, none of which is complete. (After Hall and Garcia-Fernandez 1996.)

**FIGURE 9.3** Expression of regulatory transcription factors in Drosophila and vertebrate embryos along the anterior-posterior axis. The Hox genes specify the anterior-posterior axis and are expressed in similar patterns from the head region posteriorly through the spinal cord. The head regions are defined by homologues of the same three genes in both vertebrates and flies. (After Hirsh and Kocher 1993.)
The dual nature of recombination.

1. Consider two ecologically important genes, D and E, segregating for alleles that are adapted to different environments. Alleles D and E are best suited to environment 1, and alleles e and d are best in environment 2. Finally, genes X and Y are neutral loci. Mating between DE and de can produce maladaptive haplotypes De and dE. An inversion on the DE haplotype will repress recombination between these loci and increase fitness of these alleles in their favoured environment.

2. If alleles f and g are maladapted, then recombination between them will produce the high fitness FG haplotype. In this case, recombination aids in the emergence of adaptive haplotype FG.

3. The inland, annual ecotype of Mimulus guttatus occurs in seasonally dry habitats and flowers early in the spring, whereas the sympatric coastal, perennial form is found in wetter areas and is dormant in the early spring and flowers later. Hybridization between these ecotypes would produce offspring that are less fit in either habitat. Traits that confer local adaptation to these distinct environments are located on an inversion (shown as a long rectangle) that preserves these phenotypic combinations. Photographic images in panels d and e were provided by David Lowry (University of Texas at Austin, USA) and Mathieu Joron (Muséum National d’Histoire Naturelle, Paris, France), respectively.


Importance of network effects for adaptation. A gene’s position in a regulatory network influences its effects on a target phenotype and on other traits. Circular node size is proportional to the gene’s effect on the selected phenotype; the intensity of red colouration is proportional to effects on other traits (where no colour indicates no effect). Nodes that are not connected may be influenced by large-effect, adaptive alleles. Genes encoding upstream proteins (A) often have large effects because they control many downstream genes influencing a trait, although pleiotropy mediated by other connections may weaken net selection on these ‘hub’ genes. Genes encoding protein B have fewer pleiotropic connections but also less control over the target phenotype. Protein C has lower pleiotropic constraint than protein B and integrates more upstream signals — including environmental inputs — resulting in higher evolvability. Proteins at central or ‘bottleneck’ positions (D) often have large effects, even if they have few direct connections with other proteins. Proteins at central or ‘bottleneck’ positions (D) often have large effects, even if they have few direct connections with other proteins. Proteins at central or ‘bottleneck’ positions (D) often have large effects, even if they have few direct connections with other proteins.
The evolutionary significance of ancient genome duplications.

Van de Peer Y, Maere S, Meyer A.

The proper place of hopeful monsters in evolutionary biology.

Theissen G.
Crustaceans such as *Artemia* have 11 pairs of legs (left), whereas *Drosophila* has three pairs of legs. A change in a phosphorylation site of *Artemia* Ubx appears to alter the protein such that development is not repressed in the *Artemia* abdominal segments. See text for further details.

"If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down." (Darwin 1859, p. 189)

Hopeful monsters and morphogens at the beach.

Niswander L, Anderson KV.

Waddington

Environment and Evolutionary Biology

FIGURE 1 - Diagrammatic drawings of sections of the developing wing in the fruit-fly Drosophila. Notice how the wing is at first quite solidly constructed. (Figure 1b is of about the same age as figure 2b.) Then it becomes hollow (figures 2, which corresponds to figure 2b), contracts again (figures 2c, 1, g), and finally becomes folded (figures 3a, b).

FIGURE 2 - Some experimentally controlled alterations in the unfolding of the wing of Drosophila. Figures A, B, and C show the stages of the unfolding that occur in a normal fly. Figures D and E show the stages of the unfolding that occur in a fly in which the formation of the vein in the outer edge has been prevented. Figures F and G show the stages of the unfolding that occur in a fly in which the formation of the vein in the inner edge has been prevented.
(A) Waddington's epigenetic landscape. The development of a cellular state is represented by a ball rolling down a landscape of bifurcating valleys, each representing different cell types. (B) Dynamical-systems representation of cellular states. Each axis represents the expression of a protein whose time development is depicted as a trajectory in space. Final states are attractors and correspond to distinct cell types.
Dynamical-systems view on the differentiation dynamics of a stem cell. (A) By adding self-activation (top, red arrows) to a toggle-switch network, i.e., two mutually repressing genes (9), (bottom) an attractor (red) with balanced expression of the two genes is added between A-activated and B-activated attractors (green and blue, respectively). Differentiation from the balanced expression to either of the biased attractors is triggered by noise. (B) Oscillatory gene expression dynamics (upper right: circulating trajectory shown by an orange arrow) are generated by negative feedback in the regulation network (left, red and black arrows). Cell differentiation is driven by cell-cell communication (green arrow) and fixed through positive feedback in the network (11, 12). An increase in cell number results in some cells leaving the original attractor (stem cell state) to differentiate, whereas those that remain proliferate (lower: orange trajectory bifurcates owing to cell-cell interactions). Orange and blue arrows on the landscape represent the trajectory of cellular state and the gradient of the landscape that affect the movement of the ball, respectively.


Building of the genome regulatory networks. Colored symbols represent retrotransposon insertions that provide a variety of DNA recognition sites (i.e., transcription- or hormone-binding sequences, promoters, enhancers, splicing sites, insulators etc) required for the assembly of functional regulatory networks and also contribute to expand the copy number of miRNA and tRNA coding sequences. Insertions are represented as specifically targeted within the profile of new canalizations. Non-colored symbols represent the insertions of functionally inactivated branches.

Epigenetics and Evolutionary Biology

Mendizabal I, Keller TE, Zeng J, Yi SV. Levels of DNA methylation of 12,063 orthologous promoters in three humans and three chimpanzees analyzed by Zeng et al. (2012). Hierarchical clustering both within and between species was performed using the average methylation of promoters to generate a heatmap. The column to the left of the heatmap designates promoters as similarly methylated (green) or as highly diverged between species (orange).


The epigenomic landscape of African rainforest hunter-gatherers and farmers.

Detection of human adaptation during the past 2000 years.
Field Y, Boyle EA, Telis N, et al.

DNA Methylation: Insights into Human Evolution.
Hernando-Herraez I, Garcia-Perez R, Sharp AJ, Marques-Bonet T

A) Methylated cytosines tend to deaminate over evolutionary time and, thus, the methylation state of cytosines in different species influences the evolution of the underlying genome sequence. B) Species-specific nucleotide changes that disrupt transcription factor (TF) binding sites can alter the methylation state of nearby CpG dinucleotides and, as a consequence, establish species-specific differentially methylated regions (DMRs). C) The insertion of transposable elements in a particular lineage, along with the accumulation of nucleotide changes, can lead to the emergence of novel CpG dinucleotides, creating species-specific regulatory regions.

General classification of eukaryote transposable elements. TEs are abundant and ubiquitous mobile sequences capable of jumping inside the genome. TEs are divided into two major classes on the basis of differences in their transposition mechanisms: Class I Retrotransposons copy and paste through an RNA intermediate, whereas Class II DNA transposons cut and paste their own molecule. Autonomous retrotransposons harbor long terminal repeats in their ends (LTR) or at LUNA-Bal, and can be infected agents (endogenous retroviruses). Non-autonomous retrotransposons, such as SINEs, are dependent on autonomous elements to be copied and pasted in trans. The same dependency is observed among DNA transposons, where MITEs need a full-length transposase coded by autonomous DNA transposons to be cut and pasted in trans. Full-length helitrons, recently identified Class II DNA transposons, play an important role in exon shuffling through their “rolling circle” replication mechanism. For a recent classification of eukaryote TEs, please refer to Wicker et al., 2007. Boxes represent open reading frames, triangles are either inverted repeats (IR) in blue, or long terminal repeats (LTR) in green, and small blue arrows correspond to duplicated insertion site representations. DDE elements: transposases carrying the aspartate (D), aspartate (D), glutamate and (E) motif. MITE: miniature inverted repeated elements; ERV: endogenous retrovirus; LINE: long interspersed nuclear element; SVA: composite element composed of parts of SINE (short interspersed nuclear element), VNTR (variable number of tandem repeats) and Alu repeats—the first box represents CCCTCT hexamer repeats; SINE red boxes indicate a diagnostic feature; Gag, Pol, Env: retroviral-like proteins coded by TE open reading frames.

Conceptualization of the interaction between epigenetics and evolutionary change. A number of population-level processes (left) cause genomic strata, leading to the induction of epigenetic phenomena (right arrow, center). These various phenomena operate in an ecological and evolutionary context to produce novel phenotypes (right center), ranging from molecular to morphological. These new phenotypes are subjected to the filter of natural selection – those surviving may then undergo longer-term evolutionary processes such as retention or loss of initially epigenetically fixed states.

Computational approaches for understanding the evolution of DNA methylation in animals.

Yi SV, Goodisman MA.

DNA Methylation variability among individuals is related to CpGs cluster density and evolutionary signatures.


Reconstructing ancient genomes and epigenomes.
Orlando L, Gilbert MT, Willerslev E.
Nat Rev Genet. 2015 Jul;16(7):395-408

Genomic data reveal high conservation but divergent evolutionary pattern of Polycomb/Trithorax group genes in arthropods.

The evolutionary landscape of PRC1 core components in green lineage.
Chen DH, Huang Y, Ruan Y, Shen WH.


Potential mechanisms for increasing functional genomic complexity. The human brain may have evolved rapidly through a number of mechanisms, including protein innovations, altered epigenetic programs, expansion of regulatory RNAs that direct chromatin modifications, and retrotransposition. Especially relevant for the evolution of higher-order cognition is the dramatic increase in RNA editing of primate-specific Alu sequences and the human-specific isoforms of APOBEC3 that mediate retrotransposition during post-developmental cellular responses.
Plant epigenetic mechanisms include DNA methylation, histone modification, and RNA-directed DNA methylation (RdDM). RdDM involves two plant-specific RNA polymerases (Pol IV and Pol V), an RNA-dependent RNA polymerase (RDR2), an enzyme that cleaves double-stranded RNA (DCL3), and an Argonaute-family RNA-binding protein (AGO4). [Adapted with permission from (19)]


Evolution of Epigenetic Regulation in Vertebrate Genomes.
Lowdon RF, Jang HS, Wang T.

The seahorse genome and the evolution of its specialized morphology.

Spring 2019 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 15 and 16 (April 16 & 23)

Epigenetics and Evolution
- Darwinian Evolution
- Lamarck’s Environment and Evolutionary Biology
- History Environment and Evolutionary Biology
- Waddington Environment and Evolutionary Biology
- Molecular and Genetic Aspects of Evolutionary Biology
- Holistic Models and Evolutionary Biology
- Epigenetics and Evolutionary Biology
- Sociobiology and Evolutionary Biology
- Sexual Selection and Evolutionary Biology
- Epigenetic Transgenerational Inheritance and Evolutionary Biology
- Summary Epigenetics and Evolutionary Biology

Required Reading

Books (Reserve in Library)
Environment and Evolution

Synthesizing the role of epigenetics in the response and adaptation of species to climate change in freshwater ecosystems.

Jeremias G, Barbosa J, Marques SM, Asselman J, Gonçalves FJM, Pereira JL.

Scenario of genetic assimilation, as applied to the evolution of aggression in honey bees. Initially, individual phenotypic plasticity provides an adaptive response to variable environmental stimuli—for example, aggressive response to predation pressure (time 1). Subsequently, with an environmental change (time 2), such as increased predation pressure, the gene expression pattern inducing the aggressive response is more often exhibited compared to the nonaggressive response. This may allow aggressive colonies to move into previously unoccupied niches in the environment (time 3), such as very high predation environments. Over time, environmentally induced responses in gene expression and aggressive phenotype can become fixed differences as a result of the accumulation of accommodating mutations (time 4). The response then becomes canalized, resulting in a loss of plasticity, and individuals are fixed for the aggressive phenotype, and associated gene expression, even in the absence of the high predation environmental stimulus (time 5).
Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences.
Vogt G.

The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish.
Reid NM, Proestou DA, Clark BW, et al.

Genome-Wide DNA Methylation Profiling Reveals Epigenetic Adaptation of Stickleback to Marine and Freshwater Conditions.
Mol Biol Evol. 2017 Sep 1;34(9):2203-2213.
Artemov AV, Mugue NS, Rastorguev SM, et al.
The genetics and epigenetics of animal migration and orientation: birds, butterflies and beyond.
Merlin C, Liedvogel M.

Contribution of epigenetic variation to adaptation in Arabidopsis.

Epigenetics as an answer to Darwin’s “special difficulty,” Part 2: natural selection of metastable epialleles in honeybee castes.
Front Genet. 2015 Feb 24;6:60.

The key role of epigenetics in the persistence of asexual lineages.
Castonguay E, Angers B.

Hypothesis of the epigenetic mechanism underlying the flexibility of a genotype. (a) Phenotypic variation observed in sexual and asexual species. The points represent individual scores of Chrosomus eos, C. neogaeus, and asexual hybrids from two principal component analyses performed on body distance and nondistance measures (modified from [61]). In sexual species, the phenotypic variation among individuals is mostly the result of genetic variation, whereas, in asexual hybrids, it results from differentially expressed alleles of a same genotype. (b) Putative genetic and epigenetic variation at four genes is represented for three individuals per species. Arrows refer to expressed genes, larger arrows to different alleles of an expressed gene (genetic difference), and blocks to silenced genes (epigenetic difference). (c) Under the General Purpose Genotype model, an epigenetically flexible genotype may provide a wide ecological niche for asexual hybrids, where each different epigenetic variant would occupy a narrower niche.
Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior.


Fig. 1. An integrative framework for the analysis of social behavior and its evolution. Themes for studying both the proximate and ultimate mechanisms of social decision-making are presented on the level of the individual (left panel) and the population (right panel).

Evolution

Fig. 2. Challenge and opportunity: a functional framework. Behavioral responses to challenge and opportunities in the social environment are equivalent across animals, although the specific behavioral response may be divergent across lineages due to life history, ecology, and/or evolutionary history.
Fig. 3. Approach and avoidance: a mechanistic framework. Quantitative measures of behavioral responses to challenges and opportunities that are tractable in all species provide an important foundation for analyzing the molecular and neural basis of social behavior and its evolution. Brains are shaded differently by forebrain and midbrain.

Fig. 4. A neural circuit framework. Schematic representations of a mammalian brain are shown with brain regions of the mesolimbic reward system (blue; top panel) and social behavior network (yellow; bottom panel). Regions shared by both circuits are labeled in green. Adapted from Ref. [199]. Arrows indicate directionality of functional connections between brain regions. Abbreviations: AH: anterior hypothalamus; blAMY: basolateral amygdala; BNST: bed nucleus of the stria terminalis; HIP: hippocampus; LS: lateral septum; mAmy: medial amygdala; mHCO: nucleus accumbens; PAG/CG: periaquaductal gray/central gray; POA: preoptic area; STR: striatum; VMH: ventromedial hypothalamus; VP: ventral pallidum; VTA: ventral tegmental area.

Fig. 5. Alternative hypotheses for the evolution of neuroethological mechanisms. The phenolog hypothesis predicts that some gene/protein-interaction networks underlying social behavior and other complex phenotypes can be conserved across animals, even if the phenotypes are completely different. The developmental system drift hypothesis states that the molecular mechanisms underlying homologous phenotypes can diverge substantially during the course of evolution. Nodes and edges represent gene networks involved in a phenotype.

The Genome and Methylome of a Subsocial Small Carpenter Bee, Ceratina calcarata.
Rehan SM, Glastad KM, Lawson SP, Hunt BG.
The Genome and Methylome of a Beetle with Complex Social Behavior, \textit{Nicrophorus vespilloides} (Coleoptera: Silphidae).
Cunningham CB, Ji L, Wiberg RA, et al. 

A two-ring pie chart showing results of annotation with BLAST against the complete UniProtKB database. First outer ring (gray) shows the proportion of gene models that could be annotated. Second ring (multicolored) shows the proportion of best BLAST hits of the annotations by order for all species with five or more best hits (97.8%). The best BLAST hits were overwhelmingly from other beetles and other Arthropods.

Adaptation or pathology? The role of prenatal stressor type and intensity in the developmental programming of adult phenotype 
St-Cyr S, McGowan PO.

On the origin of species by natural and sexual selection.
van Doorn GS, Edelaar P, Weissing FJ. 
Speciation and the evolution of gamete recognition genes: pattern and process.

Palumbi SR.

When eggs of the sea urchins *Echinometra oblonga* and *E. mathaei* are given sperm from either species in no choice experiments, interspecific fertilization rate is high. However, when sperm from the two species are mixed in equal proportions, eggs are 2.5–4 times more likely to be fertilized by conspecific sperm, showing that conspecific sperm precedence is strong in these sympatric species (Geyer and Palumbi, 2005).

(a) The Hawaiian sea urchins *Echinometra oblonga* and *E. mathaei* are reciprocally monophyletic at bindin alleles despite a large amount of intraspecific polymorphism at this locus. (b) Allele genealogies at other loci including RNA-deacylase (shown here) show highly polyphyletic allele genealogies. Labels denote *E. mathaei* (M) or *E. oblonga* (O). Trees are from Heuristic searches in PAUP 4.0. (Data from Palumbi, 1999; SR Palumbi and J Alipaz, unpublished.)

Architecture of sperm receptor proteins in abalone and sea urchins typically includes repeated amino-acid motifs. Motifs that bind sperm proteins are circles in the abalone receptor and rectangles for sea urchins. Motifs under positive selection have dark shading. The sea urchin receptor is modeled after *Strongylocentrotus purpuratus*. The congener *S. franciscanus* is reported to have a different arrangement of sperm binding motifs. (Modified from Galindo et al., 2002; Kamei and Glabe, 2003.)

Amino-acid variation in the hyalin-like repeats motifs of the sea urchin sperm receptor within and between species. The top 11 sequences are from different repeats of the EBR1 gene sequenced from *Strongylocentrotus purpuratus* (Kamei and Glabe, 2003), showing variation at six amino-acid positions. Sequences from one individual *Echinometra mathaei* (Em16) and one *E. oblonga* (Eo27) show strong homology to *S. purpuratus* at about half of the amino-acid positions but are highly variable among repeats. Sequences were obtained by amplifying genomic DNA with primers that recognize intron–exon junctions present in each repeat, cloning PCR products into plasmid vectors and sequencing individual clones. (Data from Kamei and Glabe, 2003; SR Palumbi and J Alipaz, unpublished.)
Cyclic and directional modes of gamete adaptation (left and right, respectively) that derive from ecological conditions favoring high sperm and low sperm densities.
Epigenetic Inheritance Systems
The Inheritance of Environmentally Induced Traits

Ecological evolutionary developmental biology, or “eco-evo-devo,” has the data to bring two controversial alternative inheritance systems back into the discussion of evolutionary biology. The first idea concerns the inheritance of environmentally acquired traits, an ancient idea usually associated with Jean-Baptiste Lamarck (1744-1829), but which was also used by Charles Darwin and many other Victorian naturalists. The second controversial idea usually goes by the name “genetic assimilation,” and it concerns the genetic fixation of an adaptive, plastic response into the genome. In this hypothesis, a response that was once part of a phenotypically plastic repertoire is now part of the normative genetic “program.”

Weismann proposed that only the germline counted in heredity, and that the germline was separate from the somatic lineages of cells that formed the body. Therefore, anything that affected the individual could not influence heredity if the germline was not affected. Weismann cut off the tails of mice for nineteen generations and showed that a tailless race did not develop.

The Ghost of Lamarck
Epigenetic inheritance systems recall the specter of a banished ghost—Lamarckian inheritance. The year 2009 is not only the bicentenary of Darwin’s birth and the centenary of the Wolterbeek and the Johanssen papers described in Chapter 1, it is also the bicentenary of Lamarck’s Philosophie Zoologique.
Role of Germ Line in Epigenetic Transgenerational Inheritance

Environmental Factor

Germ Line

F0 Generation

Mechanisms?

Germ Line

Altered DNA Methylation

(Imprint?)

F1 Generation

Germ Line

Germ Line

F2 Generation

Somatic Cell Transcriptional Alteration

Adult Onset Disease

Somatic Cell Transcriptional Alteration

Adult Onset Disease

F3 Generation

Embryo Adult

Embryo Adult

Embryo Adult


Weinhold A.

Transgenerational stress-adaption: an opportunity for ecological epigenetics.

Experimental setup to investigate the epigenetic origin of transgenerational stress-adaption in plants. A pool of near isogenic plants could be divided into control and stress receiving groups, and treated with either biotic or abiotic stresses. The offspring would be analyzed regarding persistence of a stress induced phenotype. Candidate genes can be selected based on gene expression differences and analyzed for their epigenetic marks (e.g., cytosine methylation).

Epigenetic Transgenerational Sexual Selection Effect

Collaboration- David Crews UTA

PNAS 2007
Fig. 7. Third-generation female rats whose progenitors were exposed to vinclozolin, a common-use fungicide with endocrine-disrupting (EDC) properties, and hence epigenetically altered, prefer males from the unexposed Control-lineage. Males do not show this preference. See Fig. 6 for further details. Both females and males from Control- and EDC-lineages were tested with pairs of Control- and EDC-lineage stimulus partners. Presented are the mean (+1 standard error) differences in the time spent in each behavior. Left panel: Behaviors exhibited by females from Control- and EDC-lineages towards males from Control-lineage (positive, right side) and EDC-lineage (negative, left side). Right panel: Behaviors exhibited by males from Control- and EDC-lineages towards females from Control-lineage (positive, right side) and EDC-lineage (negative, left side). The various behavioral measures and test are described in Crews et al. (2007). Reprinted by permission from Crews et al. [24].

Epigenetic inheritance: a contributor to species differentiation?

Boffelli D, Martin DI.

Model for the gain of an active state in somatic tissues following a change of epigenetic state in the germline. We assume that the germline state of certain transcriptional regulatory elements constrains the range of somatic cell types in which those elements will be active (the open elements, representing the ancestral state of an element, are active in a restricted set of cell types). A change in the germline epigenetic state of such an element (e.g., loss of methylation) will result in a broader range of somatic activity, so that the element is now active in cell types where it was silent in the ancestral species (the closed elements are active in more cell types). If germline epigenetic states can be faithfully transmitted between generations, such a change may create a heritable phenotypic difference. This model predicts that CpG islands whose methylation state has been found to deviate from the ancestral state will have activity in a broader range of somatic cell types than in the ancestral state, but this prediction has not yet been tested.

Epigenetic inheritance and evolution: A paternal perspective on dietary influences.

Soubry A.

Epigenetic variations in heredity and evolution.

Jablonka E.

Fine-tuning evolution: germ-line epigenetics and inheritance.

Stringer JM, Barrand S, Western P.
Inbreeding, Epigenetics and Evolutionary Biology

The genetics of inbreeding depression

Deborah Charsworth* and John H. Willis*

Abstract | Inbreeding depression — the reduced survival and fertility of offspring of related individuals — occurs in wild animal and plant populations as well as in humans, indicating that genetic variation in fitness traits exists in natural populations. Inbreeding depression is important in the evolution of outcrossing mating systems and, because intercrossing inbred strains improves yield (heterosis), which is important in crop breeding, the genetic basis of these effects has been debated since the early twentieth century. Classical genetic studies and modern molecular evolutionary approaches now suggest that inbreeding depression and heterosis are predominantly caused by the presence of recessive deleterious mutations in populations.

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Table 1: Detecting inbreeding depression and genetic load

| Type of organism | Method | Quantities estimated | Ref.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverse species (genetic or pedigree information)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-compatible</td>
<td>Comparison of offspring produced by self-fertilization</td>
<td>0 for one generation of selfing</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>by outcrossing</td>
<td>6 for one generation of selfing</td>
<td></td>
</tr>
<tr>
<td>Cyclically self-compatible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mating females with their brothers from the same sexual clone; this is generally equivalent to self-fertilization</td>
<td>0 for one generation of selfing</td>
<td>39</td>
</tr>
<tr>
<td>Organisms with separate sexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inbreeding load</td>
<td>180, 141</td>
<td></td>
</tr>
<tr>
<td>Haploidy species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mother-in-breeding (generating higher inbreeding coefficients than ordinary diploid inbreeding)</td>
<td>None (detection only)</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inbreeding load</td>
<td>None (detection only)</td>
<td>148</td>
</tr>
<tr>
<td>Allergens</td>
<td>Analysis of the relationship between trait values and inbreeding coefficients based on pedigree information</td>
<td>Inbreeding load</td>
<td>148</td>
</tr>
<tr>
<td>Infertility detection (using genetic markers)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of inbreeding coefficients estimated from frequencies of homozygotes and heterozygotes for genetic markers in 2NPs</td>
<td>Inbreeding load</td>
<td>146-149</td>
</tr>
<tr>
<td>Allergens</td>
<td>Examination of genetic ratios at marker loci: allelic deficiency of one homoygote in family or a significant heterozygote excess in family (or in inbred lines relative to the heterozygote frequency predictor neutral alleles by the inbreeding coefficient) suggests inbreeding depression due to identity-by-descent for a gene linked to the marker</td>
<td>Inbreeding load</td>
<td>146-149</td>
</tr>
<tr>
<td></td>
<td>Cytological aberrations</td>
<td>Detection of an increase in heterozygote frequency over several generations</td>
<td>None (detection only)</td>
</tr>
</tbody>
</table>

Figure 1: Summary of the main genetic hypotheses for inbreeding depression. These hypotheses were developed by making genetic tests in the nineteenth century but are only beginning to be tested in modern contexts. The increased homozygosity of inbred individuals lowers fitness, thus because of deleterious mutations with recessive effects, which cause homozygotes to have lower survival or fertility (in addition to inbreeding depression, it causes loss of viable alleles that result in the higher fitness of heterozygotes (overdominance). Bottom right: For dominance and pseudo-dominance (mutational) hypotheses, the figure shows how the higher heterozygote frequencies for recessive deleterious mutant alleles (indicated at 1 and 2) among inbred individuals will cause lower fitness than in non-inbred individuals or hybrids. In the epistasis hypothesis, inbred individuals are less likely to have lethal or recessive deleterious mutant alleles (indicated at 3) and will therefore have lower fitness. See Table 1 for a more detailed explanation of these hypotheses.
Inversion
Rearrangement in which part of a chromosome is inverted in order with respect to a homologous chromosome in the same species or in a different species.

Melanic drive regions
Regions containing genes that have non-Mendelian segregation in heterozygotes because one allelic version of the region is rendered non-functional during meiosis.

Complementation
Restoration of function in heterozygotes for two genes with recessive loss-of-function mutations unless both mutations are in the same configuration in the same gene, so that neither allele is functional.

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<table>
<thead>
<tr>
<th>Nature of the difference</th>
<th>Inbreeding depression</th>
<th>Heterosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic variation</td>
<td>Must be present within the species or population</td>
<td>Can appear in F1 individuals between genetically uniform populations or strains</td>
</tr>
<tr>
<td>Effect of genetic drift in small population</td>
<td>Lower inbreeding depression due to mildly deleterious mutations in small populations</td>
<td>Heterosis due to mildly deleterious mutations is highest for small populations or highly inbreeding populations. May lower the magnitude of heterosis</td>
</tr>
<tr>
<td>Likelihood of outbreeding depression and its consequences</td>
<td>Unitary without strong isolation or local adaptation and therefore unlikely to affect the magnitude of inbreeding depression within a population</td>
<td></td>
</tr>
<tr>
<td>Complementary interactions between different deleterious recessive mutations</td>
<td>Can cause inbreeding depression. Note, no homogeneity for the genotypic range less than fitness (genetic variance, see No. 1)</td>
<td>Can cause heterosis even if loci are additive and even if heterozygous alleles at the two locus phenotypes that are between those at homozygous (FF, SS)</td>
</tr>
</tbody>
</table>

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Summary Epigenetics and Evolutionary Biology
The concept of a genotype-phenotype (G-P) map is a widely used metaphor for the multiple ways in which genotypic information influences the phenotype of an organism. The term dates at least to 1970 when Jim Burns proposed linking population genetic and biochemical variation, but the importance of the relationship between genotype and phenotype has long been apparent. Two early versions of the G-P map concept are the epigenetic landscape of Conrad Hal Waddington and Richard Lewontin’s concept of evolution as taking place in the space of all possible genotypes (G space) and the space of all possible phenotypes (P space).

This relationship is shown in part a of the figure, which indicates the mean position of a population in G and P spaces over two generations. There are four key parts to the evolutionary process, shown as numbered arrows: (1) the epigenetic process creates the phenotype using genotypic information; (2) natural selection acts in P space to change the average phenotype of parents away from the average phenotype of all individuals; (3) the identity of successful parents determines which genotypes are preserved; and (4) genetic processes such as mutation and recombination alter position in G space.

An alternative concept of the G-P map at the level of the individual is shown in part b of the figure. An individual can be conceptualized as occupying a single point in G space, and this position plus the environment (including other individuals, such as parents) combine to create the internal phenotypic state of the organism. These internal phenotypes include cellular, tissue level and physiological properties. These internal phenotypes in turn shape internal phenotypes such as morphology and behaviour. Phenotypes can in turn shape the environment that an individual occupies, creating complex feedback relationships between genes, environments and phenotypes. The importance of the environment suggests that we should explicitly broaden the G-P map to the genotype-environment-phenotype (G-E-P) map.
Epigenetics and the evolution of Darwin’s Finches.

Epigenetic variation between urban and rural populations of Darwin’s finches.
McNew SM, Beck D, Sadler-Riggleman I, Knutie SA, Koop JAH, Clayton DH, Skinner MK.

An Epigenetic Perspective on the Midwife Toad Experiments of Paul Kammerer (1880-1926).
Vargas AO, Krabichler Q, Guerrero-Bosagna C.

Alternation of generations - unravelling the underlying molecular mechanism of a 165-year-old botanical observation.
Horst NA, Reski R.
Epigenetic Alterations Promote Genetic Instability

<table>
<thead>
<tr>
<th>Genetic Mutation</th>
<th>Epigenetic Alteration</th>
<th>DNA Sequence Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Mutation (SNP)</td>
<td>DNA Methylation (CpG)</td>
<td>Susceptibility C → T Conversion</td>
</tr>
<tr>
<td>Copy Number Variation (CNV)</td>
<td>Hypomethylation (Repeats)</td>
<td>Susceptibility Repeat Element</td>
</tr>
<tr>
<td>Transposon Migration</td>
<td>Hypomethylation DNA</td>
<td>Susceptibility Transposon Migration</td>
</tr>
<tr>
<td>Translocation</td>
<td>DNA Methylation and Histone</td>
<td>Susceptibility Translocation at</td>
</tr>
<tr>
<td>Telomere Length</td>
<td>DNA Methylation Alteration</td>
<td>Break Point</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alteration in Telomere Length</td>
</tr>
</tbody>
</table>

Table 1: (IL) Inbred C57BL6 F3 Generation Sperm Genome-wide CNV and Epimutations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1 Generation</th>
<th>F1 Generation</th>
<th>F3 Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sperm CNV</td>
<td>Sperm CNV</td>
<td>Sperm Epimutations</td>
</tr>
<tr>
<td>Number (Single Probe)</td>
<td>5402048 Gain / 246 Loss</td>
<td>49526084 Gain / 284 Loss</td>
<td>9032</td>
</tr>
<tr>
<td>Number (L7 Probe)</td>
<td>3921 Gain / 18 Loss</td>
<td>38640 Gain / 14 Loss</td>
<td>951</td>
</tr>
<tr>
<td>Mean Size Base</td>
<td>11,633</td>
<td>12,087</td>
<td>2130</td>
</tr>
<tr>
<td>Mean CpG Density (CpG/100 bp)</td>
<td>1.3</td>
<td>1.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Epigenetic Transgenerational Inheritance of Sperm Epimutations Promotes Genome Instability and Genetic Point Mutations
McCarrey JR, Lehle JD, Raju SS, Wang Y, Nilsson EE, Skinner MK
(2016) PLoS One

Sperm Epimutations Promotes Epigenetic Transgenerational Inheritance of Genetic Mutations

Environmental Factor

No alterations in genetic point mutations (SNP) or copy number Variation (CNV)

Increased susceptibility in genetic point mutations (SNP) or copy number Variation (CNV)