Spring 2021 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 14 and 15 (April 20 & 27)

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

Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

Books (Reserve in Library)

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.

Literature

Nilsson EE, Ben Maamar M, Skinner MK. Environmentally Induced Epigenetic Transgenerational Inheritance and the Weismann Barrier: The Dawn of Neo-Lamarckian Theory. J Dev Biol. 2020 Dec 4;8(4):28.

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Venney CJ, Love OP, Drown EJ, Heath DD. DNA Methylation Profiles Suggest Intergenerational Transfer of Maternal Effects. Mol Biol Evol. 2020 Feb 1;37(2):540-548.
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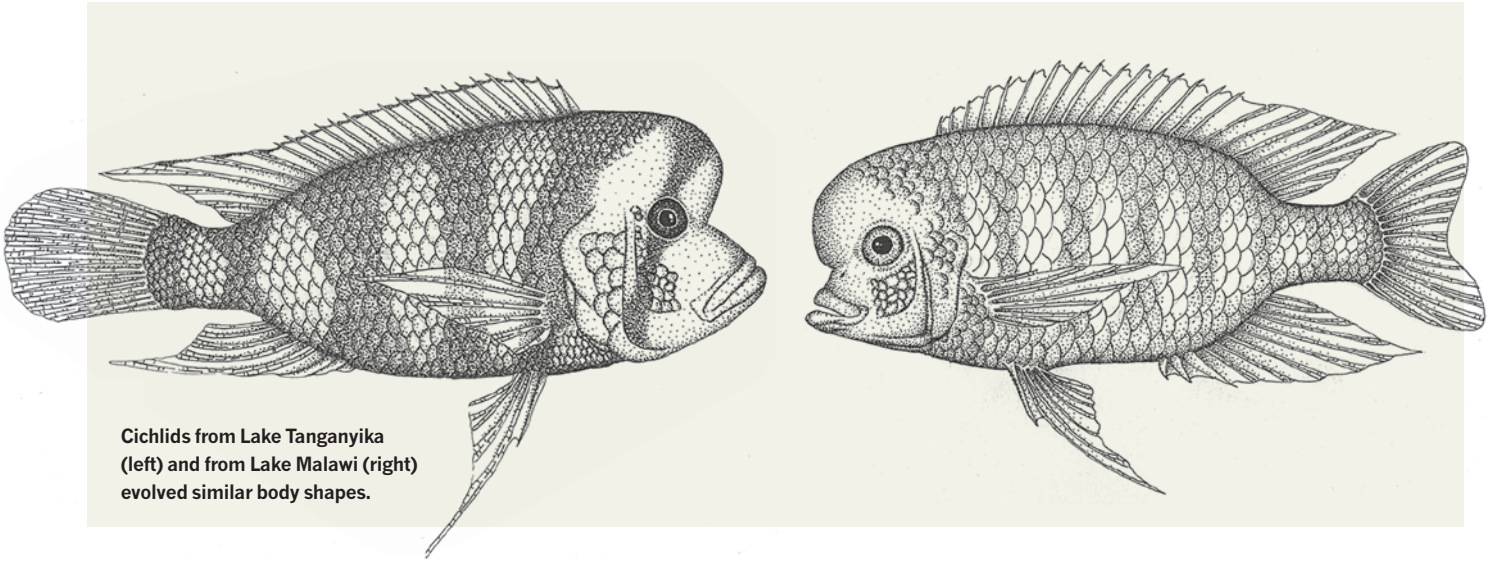
COMMENT



Cichlids from Lake Tanganyika (left) and from Lake Malawi (right) evolved similar body shapes.

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.*

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[1] (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.*

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*[11] 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** ▶

ILLUSTRATION BY R. CRAIG ALBERTSON

POINT: YES, URGENTLY ▶ evolution works. We hold that organisms are constructed in development, not simply 'programmed' to develop by genes. Living things do not evolve to fit into pre-existing environments, but co-construct and coevolve with their environments, in the process changing the structure of ecosystems.

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[1,2]. 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 tearoom, 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).

Plasticity: commodore butterflies emerge with different colours in dry (left) and wet seasons.

ORANGE: PETER CHADWICK/SPL; BLUE: LAWRENCE LAWRY/SPL

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[3]. 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[3].

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[4]. 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[4,5]. Rather than selection being free to traverse across any physical possibility, it is guided along specific routes opened up by the processes of development[5,6].

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[5,6]. In other words, often it is the trait that comes first; genes that cement it follow, sometimes several generations later[5].

Studies of fish, birds, amphibians and insects suggest that adaptations that were, initially, environmentally induced may promote colonization of new environments and facilitate speciation[5,6]. 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 reproductive 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[7].

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[7]. This 'niche construction', like developmental bias, means that organisms co-direct their own evolution by systematically changing environments and thereby biasing selection[7].

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 PAGE 164 ▶

COUNTERPOINT: NO, ALL IS WELL ▶ during the 1920s, when a handful of statisticians and geneticists began quietly laying the foundations for a dramatic transformation. Their work between 1936 and 1947 culminated in the 'modern synthesis', which united Darwin's concept of natural selection with the nascent field of genetics and, to a lesser extent, palaeontology and systematics. Most importantly, it laid the theoretical foundations for a quantitative and rigorous understanding of adaptation and speciation, two of the most fundamental evolutionary processes.

In the decades since, generations of evolutionary biologists have modified, corrected and extended the framework of the modern synthesis in countless ways. Like Darwin, they have drawn heavily from other fields. When molecular biologists identified DNA as the material basis for heredity and trait variation, for instance, their discoveries catalysed fundamental extensions to evolutionary theory. For example, the realization that many genetic changes have no fitness consequences led to major theoretical advances in population genetics. The discovery of 'selfish' DNA prompted discussions about selection at the level of genes rather than traits. Kin selection theory, which describes how traits affecting relatives are selected, represents another extension[12].

Nonetheless there are evolutionary biologists (see 'Yes, urgently') who argue that theory has since ossified around genetic concepts. More specifically, they contend that four phenomena are important evolutionary processes: phenotypic plasticity, niche construction, inclusive inheritance and developmental bias. We could not agree more. We study them ourselves.

But we do not think that these processes deserve such special attention as to merit a new name such as 'extended evolutionary synthesis'. Below we outline three reasons why we believe that these topics already receive their due in current evolutionary theory.

NEW WORDS, OLD CONCEPTS

The evolutionary phenomena championed by Laland and colleagues are already well integrated into evolutionary biology, where they have long provided useful insights. Indeed, all of these concepts date back to Darwin himself, as exemplified by his analysis of the feedback that occurred as earthworms became adapted to their life in soil.

Today we call such a process niche construction, but the new name does not alter the fact that evolutionary biologists have been studying feedback between organisms and the environment for well over a century[13]. Stunning adaptations such as termite mounds, beaver dams, and bowerbird displays have long been a staple of evolutionary studies. No less spectacular are cases that can only be appreciated at the microscopic or molecular scale, such as viruses that hijack host cells to reproduce and 'quorum sensing', a sort of group think by bacteria.

Another process, phenotypic plasticity, has drawn considerable attention from evolutionary biologists. Countless cases in which the environment influences trait variation have been documented — from the jaws of cichlid fishes that change shape when food sources alter, to leaf-mimicking insects that are brown if born in the dry season and green in the wet. Technological advances in the past decade have revealed an incredible degree of plasticity in gene expression in response to diverse environmental conditions, opening the door to understanding its material basis. Much discussed, too, was a book[5] by behavioural scientist Mary Jane West-Eberhard that explored how plasticity might precede genetic changes during adaptation.

So, none of the phenomena championed by Laland and colleagues are neglected in evolutionary biology. Like all ideas, however, they need to prove their value in the marketplace of rigorous theory, empirical results and critical discussion. The prominence that these four phenomena command in the discourse of contemporary evolutionary theory reflects their proven explanatory power, not a lack of attention.

MODERN EXPANSION

Furthermore, the phenomena that interest Laland and colleagues are just four among many that offer promise for future advances in evolutionary biology. Most evolutionary biologists have a list of topics that they would like to see given more attention. Some would argue that epistasis — complex interactions among genetic variants — has long been under-appreciated. Others would advocate for cryptic genetic variation (mutations that affect only traits under specific genetic or environmental conditions). Still others would stress the importance of extinction, or adaptation to climate change, or the evolution of behaviour. The list goes on.

We could stop and argue about whether 'enough' attention is being paid to any of these. Or we could roll up our sleeves, get to work, and find out by laying the theoretical foundations and building a solid casebook of empirical studies. Advocacy can take an idea only so far.

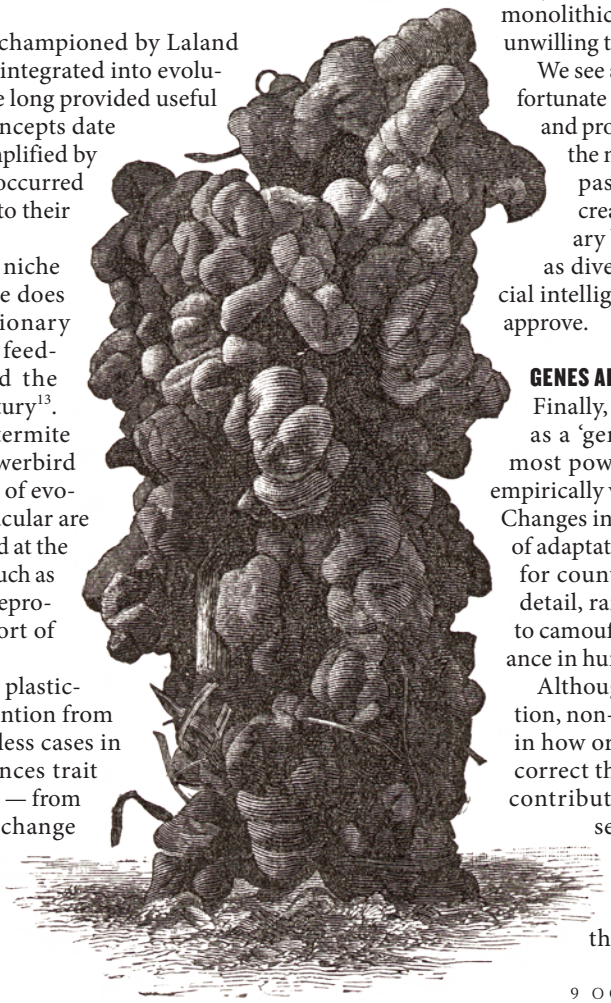
What Laland and colleagues term the standard evolutionary theory is a caricature that views the field as static and monolithic. They see today's evolutionary biologists as unwilling to consider ideas that challenge convention.

We see a very different world. We consider ourselves fortunate to live and work in the most exciting, inclusive and progressive period of evolutionary research since the modern synthesis. Far from being stuck in the past, current evolutionary theory is vibrantly creative and rapidly growing in scope. Evolutionary biologists today draw inspiration from fields as diverse as genomics, medicine, ecology, artificial intelligence and robotics. We think Darwin would approve.

GENES ARE CENTRAL

Finally, diluting what Laland and colleagues deride as a 'gene-centric' view would de-emphasize the most powerfully predictive, broadly applicable and empirically validated component of evolutionary theory. Changes in the hereditary material are an essential part of adaptation and speciation. The precise genetic basis for countless adaptations has been documented in detail, ranging from antibiotic resistance in bacteria to camouflage coloration in deer mice, to lactose tolerance in humans.

Although genetic changes are required for adaptation, non-genetic processes can sometimes play a part in how organisms evolve. Laland and colleagues are correct that phenotypic plasticity, for instance, may contribute to the adaptedness of an individual. A seedling might bend towards brighter light, growing into a tree with a different shape from its siblings'. Many studies have shown that this kind of plasticity is beneficial, and that it can readily evolve if there PAGE 164 ▶



JOHN VAN WYHE/DARWIN-ONLINE.ORG.UK

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[8]. In addition, extra-genetic inheritance includes socially transmitted behaviour in animals, such as nut cracking in chimpanzees or the migratory patterns of reef fishes[8,9]. It also encompasses those structures and altered conditions that organisms leave to their descendants through their niche construction — from beavers' dams to worm-processed soils[7,10]. 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 not[7–9]. 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.

"There is more to inheritance than genes."

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 seabed[10]. 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 ecosystems[10].

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 development of alternative hypotheses, and stimulates empirical work. No longer a protest movement, the EES is now a credible framework inspiring useful work by bringing diverse researchers under one theoretical roof to effect conceptual change in evolutionary biology. ■

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COUNTERPOINT: NO, ALL IS WELL ▶ is genetic variation in the response[14]. 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 assimilation[15]. 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.

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.

"What matters is the heritable differences in traits, especially those that bestow some selective advantage."

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 advanced[16].

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"[17]. ■

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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

Table 1
Evolution Theory Components

Neo-Lamarckian concept
Environment directly alters phenotype generationally
Darwinian evolution theory
Natural selection acts on phenotypic variation
Neo-Darwinian evolution theory
Genetic mutations promote phenotypic variation on which natural selection acts
Unified evolution theory
Environmental epigenetic alterations promote genetic mutations to alter genotypic variation Environmental epigenetics and genetic mutations both promote phenotypic variation on which natural selection acts

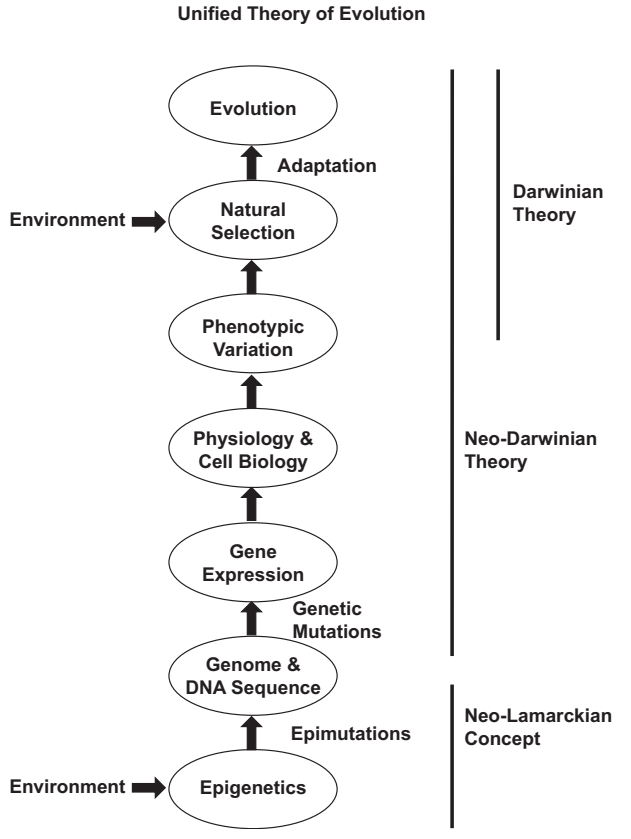

Fig. 1.—Schematic of the unified theory of evolution. No dominance is suggested by the appearance of specific circles (e.g., epimutations vs. genetics) such that all are equally important components.

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 pangenesis, 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

(great-grand-offspring) were obtained to assess alterations in mate preference behavior (Anway et al. 2005). A dramatic alteration in mate preference was observed (Crews et al. 2007) along with epigenetic alterations (termed epimutations) in the germline (sperm) (Guerrero-Bosagna et al. 2010). Transgenerational transcriptome changes in the brain regions correlated with the alterations in mate preference behavior (Skinner et al. 2008). Therefore, an environmental factor that altered sexual selection was found to promote a permanent alteration in the sperm epigenome in an imprinted-like manner that was inherited for multiple generations (Crews et al. 2007; Skinner et al. 2010). These studies suggest that environmental epigenetics may play an important role in evolutionary change. The role of epigenetics in mate choice and evolution has been further discussed (Zeh JA and Zeh DW 2008; Bonduriansky and Day 2013). Indeed, several recent reviews have suggested a role for epigenetics in microevolution and macroevolution (Jablonka and Raz 2009; Rebollo et al. 2010; Skinner et al. 2010; Day and Bonduriansky 2011; Kuzawa and Thayer 2011; Flatscher et al. 2012; Klironomos et al. 2013; Badyaev 2014; Jaeger and Monk 2014; Skinner 2014a).

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 is supported by environmental and transgenerational epigenetic studies (Crews et al. 2007; Koonin and Wolf 2009; Koonin 2014; Skinner, Gurerrero-Bosagna, Haque, et al. 2014). Therefore, the first aspect of the unified theory involves the ability of environment to impact epigenetic programming generationally to alter phenotypic variation (fig. 1).

The well-established aspect of Darwinian evolution is the ability of environment through natural selection to act on phenotypic variation within an evolutionary event (Darwin 1859; Olson-Manning et al. 2012). The classic neo-Darwinian view is that genetic mutations and genetic variation are the primary molecular mechanism involved in generating the phenotypic variation (Nei and Nozawa 2011; Olson-Manning et al. 2012) (table 1). Although epigenetics can also have a critical role in the establishment and maintenance of phenotypic variation, the genetic mutations and genotype of the phenotype will be critical. This neo-Darwinian natural selection event for evolution is the other component of the unified theory (fig. 1).

A combination of environmental epigenetic impacts on phenotypic variation and the ability of environment to mediate natural selection will both be important for evolution. Therefore, 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; Badyaev 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; Badyaev 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 alter 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, Gurerrero-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.

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Associate editor: Dan Graur

Spring 2021 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 14 and 15 (April 20 & 27)

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

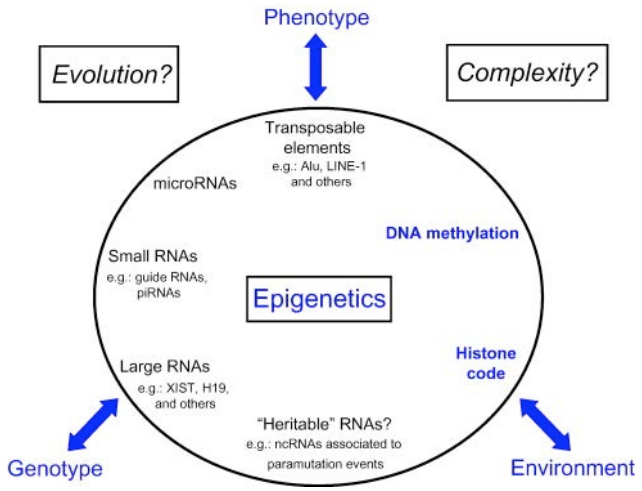
Required Reading

Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

Books (Reserve in Library)

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.



Darwinian Evolutionary Biology

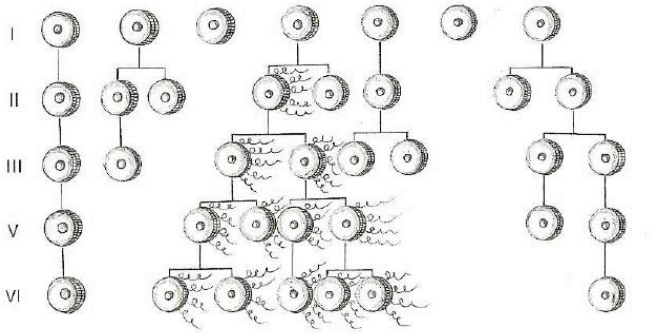
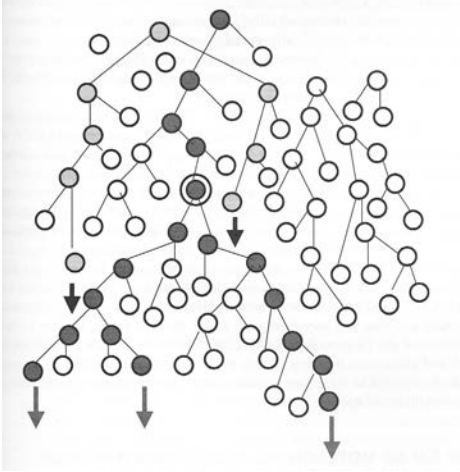


Figure 1.1
Universal Darwinism: the frequency of the hairy entity, which first appears in generation II, increases in subsequent generations because it survives better and multiplies more than its competitors.



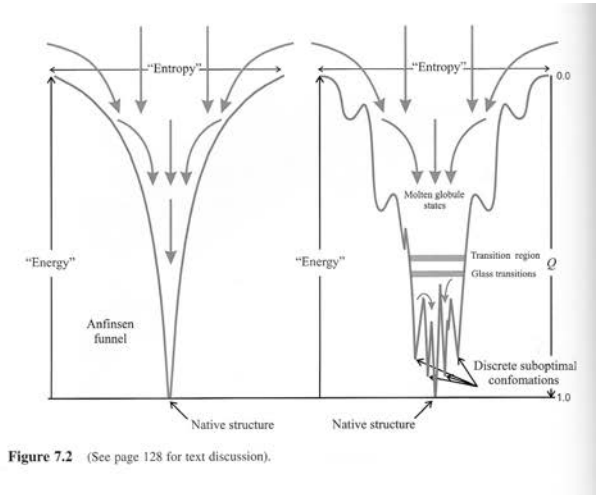
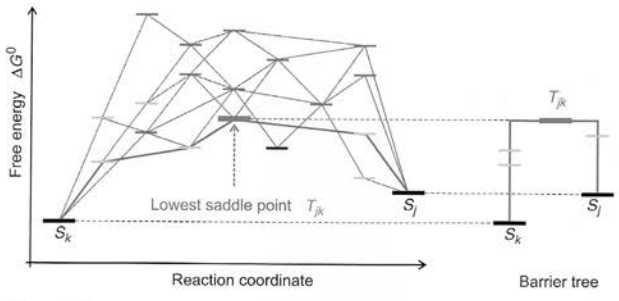


Figure 7.2 (See page 128 for text discussion).



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

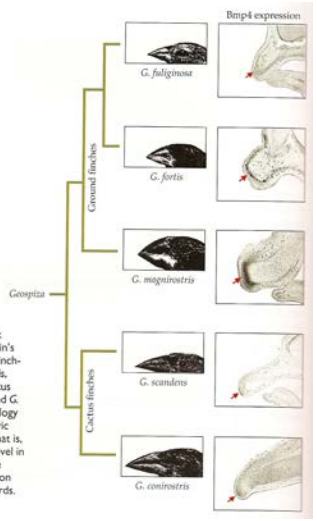


FIGURE 9.13 Correlation between beak shape and the expression of *Bmp4* in Darwin's finches. In the genus *Geospiza*, the ground finches (represented here by *G. fuliginosa*, *G. fortis*, and *G. magnirostris*) separated from the cactus finches (represented here by *G. scandens* and *G. conirostris*). The differences in beak morphology correlate to heterochronic and heterometric changes in *Bmp4* expression in the beak. That is, *Bmp4* is expressed earlier and at a higher level in the seed-crushing ground finches. This gene expression difference provides an explanation for the role of natural selection on these birds. (From Abzhanov et al. 2004.)

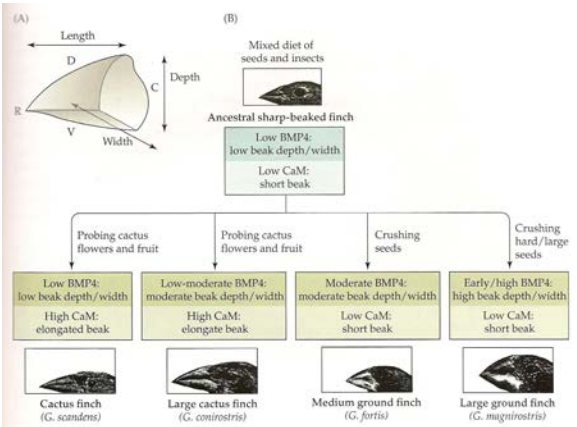


FIGURE 9.15 Beak evolution among Darwin's finches. (A) Bird beaks are three-dimensional structures that can change along any of the growth axes. C, caudal (tailward); D, dorsal (spineward); R, rostral (forward); V, ventral (belly). (B) A sharp-beaked finch represents the basal morphology for *Geospiza*, as the ancestral species is thought to have had such a morphology. The model for BMP4 and calmodulin involvement explains development of both the elongated and the deep/wide beaks of the derived species of *Geospiza*. (After Abzhanov et al. 2006.)

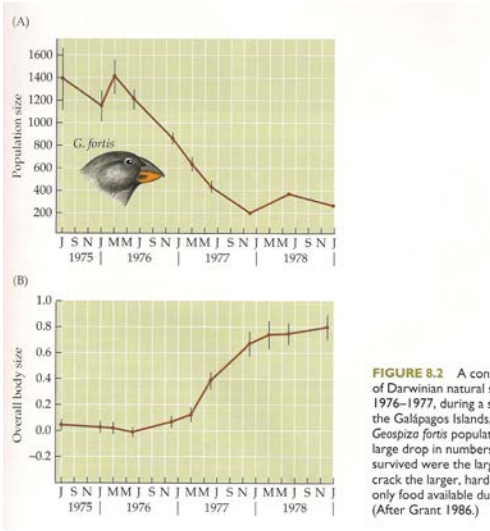


FIGURE 8.2 A contemporary example of Darwinian natural selection. (A) In 1976–1977, during a severe drought in the Galápagos Islands, the ground finch *Geospiza fortis* populations underwent a large drop in numbers. (B) Those that survived were the larger birds that could crack the larger, hard-shelled seeds—the only food available during the drought. (After Grant 1986.)

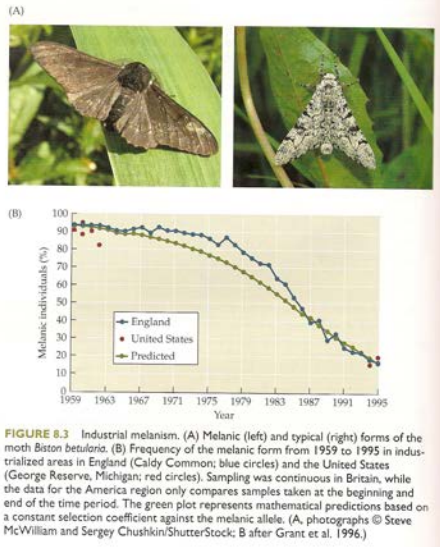
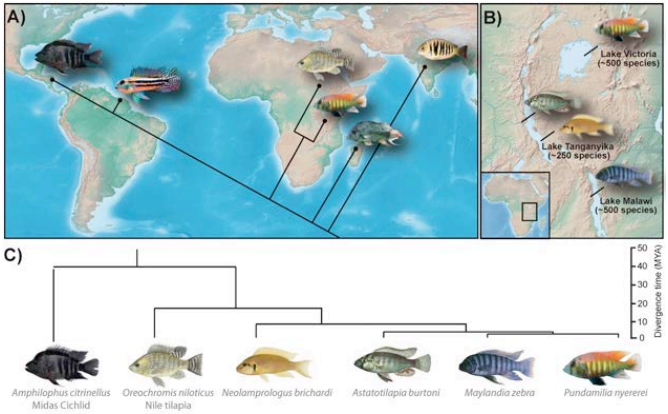


FIGURE 8.3 Industrial melanism. (A) Melanic (left) and typical (right) forms of the moth *Biston betularia*. (B) Frequency of the melanic form from 1959 to 1995 in industrialized areas in England (Caldy Common; blue circles) and the United States (George Reserve, Michigan; red circles). Sampling was continuous in Britain, while the data for the America region only compares samples taken at the beginning and end of the time period. The green plot represents mathematical predictions based on a constant selection coefficient against the melanic allele. (A, photographs © Steve McWilliam and Sergey Chushkin/ShutterStock; B after Grant et al. 1996.)



Overview of cichlid fishes. A: Worldwide geographic distribution of cichlids with representatives from India and Madagascar forming the most basal lineages and the monophyletic African and South and Central American lineages as sister-groups. B: The cichlids' center of biodiversity is East Africa, where more than 1,500 cichlid species are recognized. Estimated species numbers for the big lakes Victoria, Tanganyika and Malawi are given in brackets. C: Phylogenetic tree of the six cichlid species from Central America (A. citrinellus) and Africa with high-quality genome drafts. Divergence times are based on the lower timescale of [51].

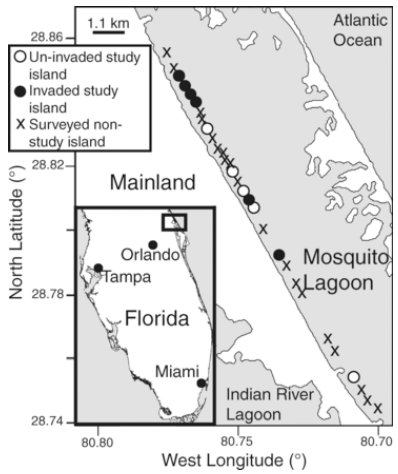
Rapid evolution of a native species following invasion by a congener.

Science. 2014 Oct 24;346(6208):463-6.

Stuart YE, Campbell TS, Hohenlohe PA, Reynolds RG, Revell LJ, Losos JB.

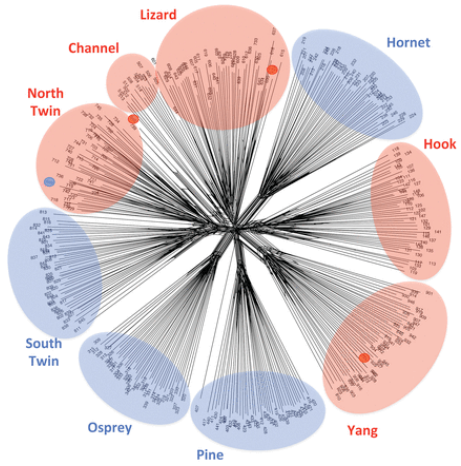
Abstract

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.



2010 study islands along the Intracoastal Waterway.

Anolis carolinensis inhabits all study islands. Six study islands were invaded by *A. sagrei* sometime between 1995 and 2010 (closed circles), and five study islands remain un-invaded today (open circles). Nineteen additional non–study islands were surveyed ["x"; (12)]; 17 of these contained *A. carolinensis* and were invaded by *A. sagrei*; and two were empty of both species.

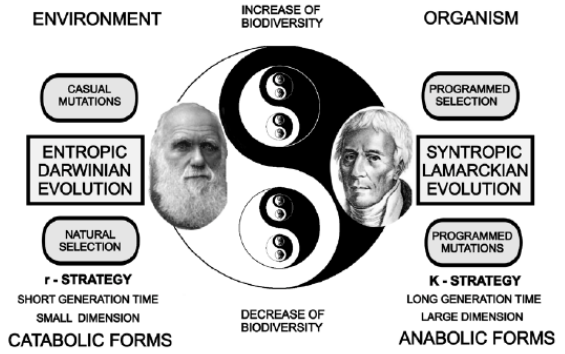


Neighbor-net analysis of genetic distance for *A. carolinensis* individuals from invaded (red) and un-invaded (blue) islands (12).

Small shaded areas enclose individuals that do not cluster with their own island; the color of these areas represents invasion status of their home islands.

Lamarck's

Environment and Evolutionary Biology

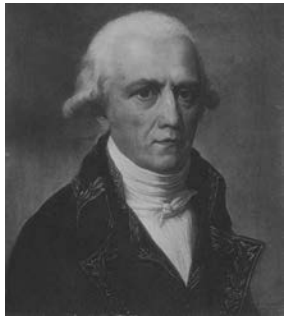


Lamarckian inheritance was based on physiology, behavior, and phenotypic plasticity: if you used your muscles, they grew bigger. Moreover, such muscular changes would be passed on to subsequent generations, so that the offspring of run-

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.

Lamarck, evolution, and the inheritance of acquired characters.
Genetics. 2013 Aug;194(4):793-805.
Burkhardt RW Jr.



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.

Is Lamarckian evolution relevant to medicine?
Handel AE, Ramagopalan SV.
BMC Med Genet. 2010 May 13;11:73

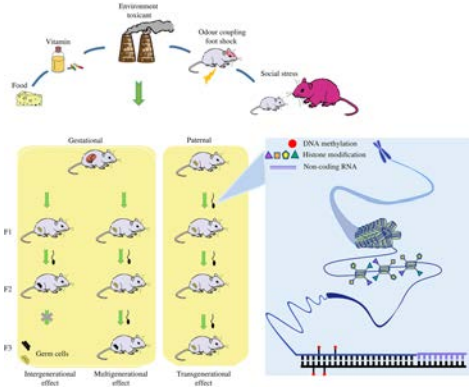
Abstract

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.

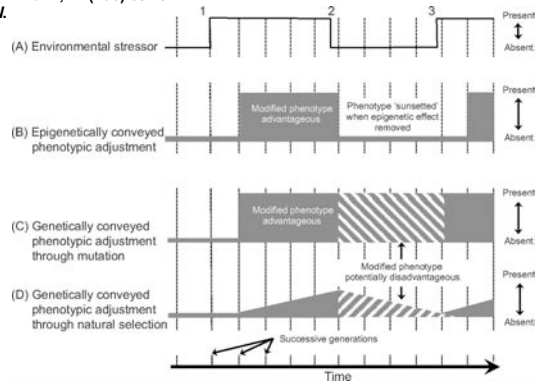
DISCUSSION: Lamarckian concepts, long thought of no relevance to modern evolutionary theory, are enjoying a quiet resurgence with the increasing complexity of epigenetic theories of inheritance. There is evidence that epigenetic alterations, including DNA methylation and histone modifications, are transmitted 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.

Lamarck rises from his grave: parental environment-induced epigenetic inheritance in model organisms and humans.
Biol Rev Camb Philos Soc. 2017 Nov;92(4):2084-2111.
Wang Y, Liu H, Sun Z



Epigenetics as a source of variation in comparative animal physiology - or - Lamarck is lookin' pretty good these days.
J Exp Biol. 2014 Mar 1;217(Pt 5):682-9.
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 or disappears (2), the epigenetically maintained phenotype (with its associated advantages but also its costs) disappears, 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.

History

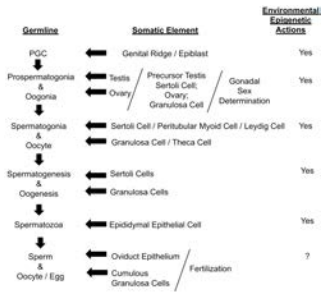
Environment and Evolutionary Biology

Environmentally Induced Epigenetic Transgenerational Inheritance and the Weismann Barrier: The Dawn of Neo-Lamarckian Theory

Nilsson EE, Ben Maamar M, Skinner MK.
J Dev Biol. 2020 Dec 4;8(4):28.

Table 1. Weismann's Germ Plasm Theory Components.

(1)	Germ cells are the only cells to transmit molecular heredity information between generations.
(2)	Germ cells are the only cells with a full set of instructions (germplasm) for development of the next generation. The determinants of germ plasm are divided up among the somatic cells of the embryo. The full set of instructions is kept intact by germ cells from generation to generation by the continuity of the germ line.
(3)	Germ cell molecular determinants are not impacted by changes in somatic cells (germ line—somatic barrier).



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.


Kammerer


Weiss


von Frisch


Steinach

Hans Przibram, Director, Biologische Versuchsanstalt
Institute of Experimental Biology or 'Vivarium'
1903-1938. Spent remainder of life (to 1944) in Theresianstadt.

State-of-the-art research on experimental developmental biology, including first constant temperature rooms. Focus of Institute was to derive the laws (statistical regularities or patterns) governing development of individual organism and its relationship to the environment. Sought to explore a 'third way' between determinism and chance by capturing "the complexity of the interaction between the organism and its environment". In other words, systems biology and the concept of emergence.

Paul Alfred Weiss

Doctoral thesis (1922) under Hans Prizbram 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.

Evolutionary systems biology: what it is and why it matters.
Bioessays. 2013 Aug;35(8):696-705.
Soyer OS, O'Malley MA.

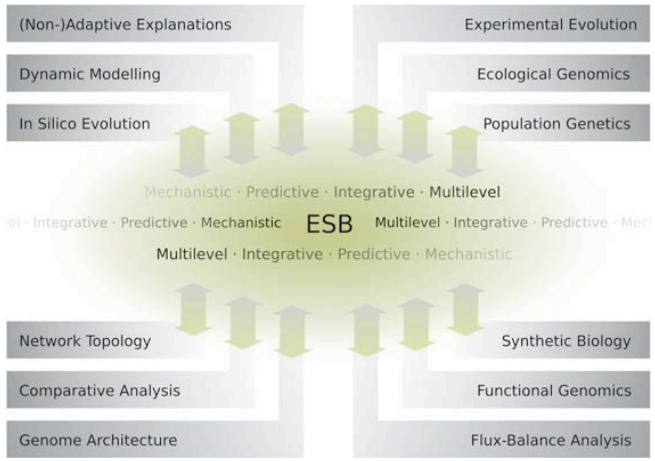


Table 1.1

Type of theory	Hereditary transmission	Unit of variation	Origin of variation	Target of selection	Unit of evolution
Darwin's Darwinism	Gemmules transferred from the soma to sex cells	Gemmule	Random + induced in the soma	Individual (sometimes also the group)	The population of individuals
Weismann's neo-Darwinism	Transfer of determinants through the germ line	Determinant	Random + induced in the germ line	Individual (mainly) + determinants, cells, organs	The population of individuals, cells, or determinants
Modern Synthesis neo-Darwinism	Transfer of genes in the germ line	Genes in the germ line	Random mutation	Individual	The population of individuals
Molecular neo-Darwinism	DNA replication	DNA sequence	Random DNA changes; rarely also directed changes (see chapter 3)	Mainly the individual (also the gene, the group, lineage, and species)	Mainly the population of individuals
Selfish gene neo-Darwinism	DNA replication	DNA sequence	Random DNA changes	The gene, the individual, the group	The population of alleles of the gene

NEO-DARWINIAN EVOLUTION

Molecular and Genetic Aspects

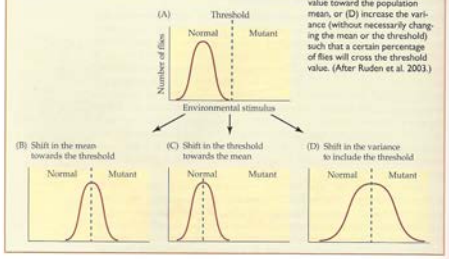
of Evolutionary Biology

Thresholds of Genetic Assimilation

One mechanism for genetic assimilation is based on changing the threshold at which a given environmentally induced phenotype is seen. Bateman (1959a) proposed that genetic assimilation can occur by three major routes. Molecular biology has since found evidence that each of these mechanisms may work to produce the genetic fixation of a phenotype that was originally induced by environmental factors.

Bateman's models posit an original population in which the norm and most deviation fall short of a threshold value needed to see a particular phenotype (Figure A). In the first model, stress shifts the norm toward the threshold value (Figure B). For example, if a certain Hsp90 expression phenotype occurs at a particular threshold temperature, no fly in the original population will express that phenotype at a lower temperature. But stress, leading to Hsp90 deficiency, causes numerous mutant individuals to express the induced phenotype, altering the distribution of flies in the populations. Now there are some individuals who are over the threshold and who will express the phenotype under certain conditions.

In the second model, the threshold is shifted toward the mean of the variation (Figure 10.4C). In other words, the variation is still centered around the same point, but the threshold temperature for the production of the new phenotype is genetically changed. In the third model, the threshold and the norm remain the same, but the amount of variation increases such that some fraction of the population is over the threshold value (Figure 10.4D).

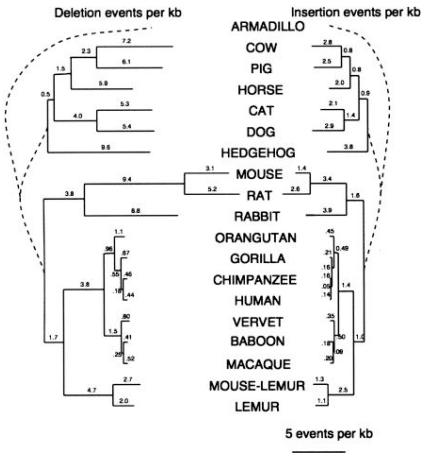


Three models of genetic assimilation. (A) Initial, unstressed situations in which the phenotype is not expressed in the population. (B–D) The stress-induced phenotype can be fixed genetically by genes that (B) shift the mean of the population toward the threshold value, (C) shift the threshold value toward the population mean, or (D) increase the variance (without necessarily changing the mean or the threshold) such that a certain percentage of flies will cross the threshold value. (After Ruden et al. 2003.)

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

Operation	Original	Target
(a) Operations affecting gene orders		
Reversal	1 2 3 4 5	1 −3 −2 4 5
Translocation	1 2 3 4 5 6 7 8 9	1 2 3 8 9 6 7 4 5
Fusion	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Fission	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Transposition	1 2 3 4 5 6 7 8	1 4 5 6 2 3 7 8
Block interchange (special)	1 2 3 4 5 6 7 8	1 4 5 6 2 3 7 8
Block interchange (general)	1 2 3 4 5 6 7 8	1 6 7 4 5 2 3 8
(b) Operations affecting gene contents		
Duplication	1 2 3 4 5	1 2 3 2′ 3′ 4 5
Insertion	1 2 3 4 5	1 2 3 6 4 5
Deletion	1 2 3 4 5	1 4 5

Blanchette M, Green ED, Miller W, Haussler D. (2004) Reconstructing large regions of an ancestral mammalian genome in silico. Genome Res. 14(12):2412-23.



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.

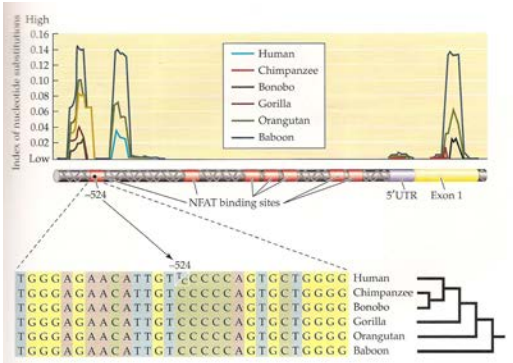


FIGURE 9.16 Heterometry (a change in the amount of a gene product expresses) can help drive evolution. (A) Regions of variability in the enhancer of the gene for interleukin-4 (IL4) among primates. Several regions are highly conserved, or invariable, indicating that any change (i.e., mutation) in these nucleotide sequences usually results in decreased fitness. These regions include the enhancers for the IL4 genes. (B) At position −524, in the midst of a highly conserved enhancer sequence, a mutation in the human population has created a new binding site for the NFAT transcription factor, enabling *IL4* to be transcribed in greater amounts. Although this has negative fitness consequences in many populations, it functions positively for the survival of individuals living in places where worm parasites are common. Heterometry is caused by mutation in the enhancer site of the *IL4* gene. (After Rockman et al. 2003.)

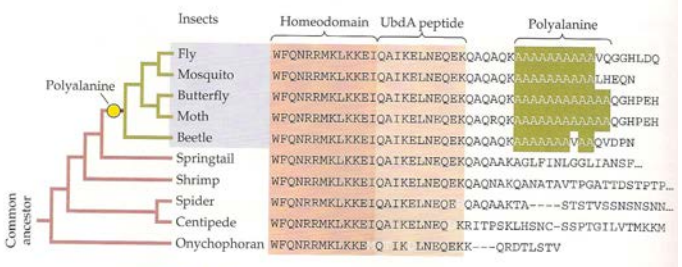


FIGURE 9.17 Changes in Ubx protein associated with the insect clade in the evolution of arthropods. Of all arthropods, only the insects have Ubx protein that is able to repress *Distal-less* gene expression and thereby inhibit abdominal legs. This ability to repress *Distal-less* is due to a mutation wherein a stretch of polyalanine residues is encoded in the carboxyl terminus of the Ubx protein. This mutation is seen only in the insect *Ubx* gene. (After Galant and Carroll 2002 and Ronshaugen et al. 2002).

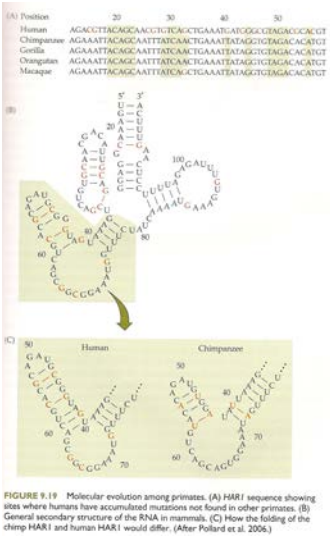


FIGURE 9.19 Molecular evolution among primates. (A) *HAR1* sequence showing sites where humans have accumulated mutations not found in other primates. (B) General secondary structure of the RNA in mammals. (C) How the folding of the chimp HAR1 and human HAR1 would differ. (After Pollard et al. 2006.)

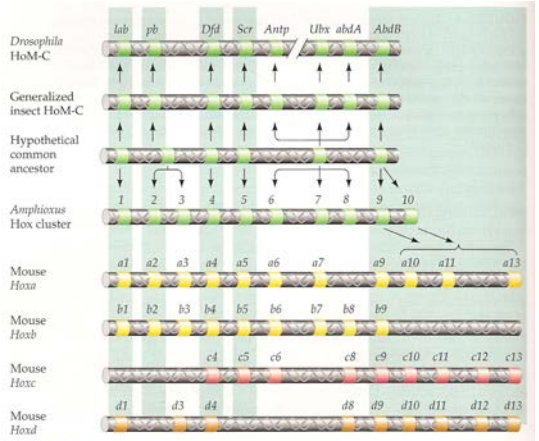


FIGURE 9.2 Postulated ancestry of the Hox genes from a hypothetical ancestor of both protostomes and deuterostomes. The deuterostome, *Amphioxus*, has only one set of Hox genes, just like the protostomes. Vertebrates, derived from an *Amphioxus*-like organism, have four Hox clusters, none of which is complete. (After Holland and Garcia-Fernández 1996.)

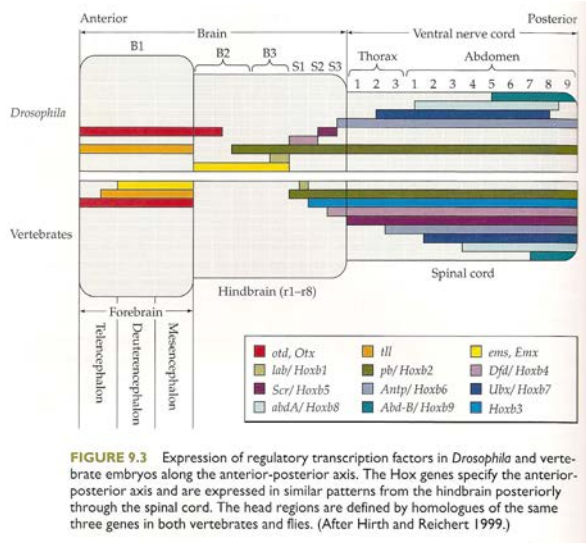


FIGURE 9.3 Expression of regulatory transcription factors in *Drosophila* and vertebrate embryos along the anterior-posterior axis. The Hox genes specify the anterior-posterior axis and are expressed in similar patterns from the hindbrain posteriorly through the spinal cord. The head regions are defined by homologues of the same three genes in both vertebrates and flies. (After Hirth and Reichert 1999.)

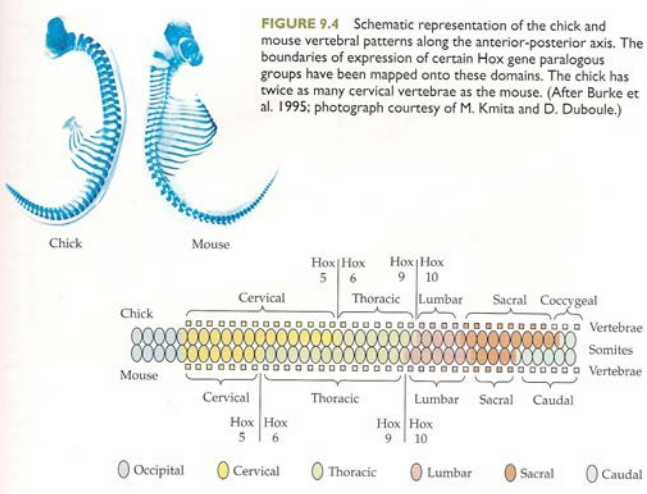


FIGURE 9.4 Schematic representation of the chick and mouse vertebral patterns along the anterior-posterior axis. The boundaries of expression of certain Hox gene paralogous groups have been mapped onto these domains. The chick has twice as many cervical vertebrae as the mouse. (After Burke et al. 1995; photograph courtesy of M. Kmita and D. Duboule.)

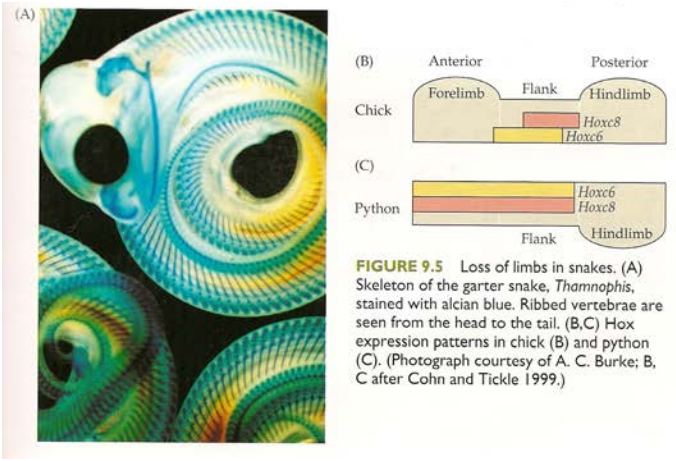


FIGURE 9.5 Loss of limbs in snakes. (A) Skeleton of the garter snake, *Thamnophis*, stained with alcian blue. Ribbed vertebrae are seen from the head to the tail. (B,C) Hox expression patterns in chick (B) and python (C). (Photograph courtesy of A. C. Burke; B, C after Cohn and Tickle 1999.)

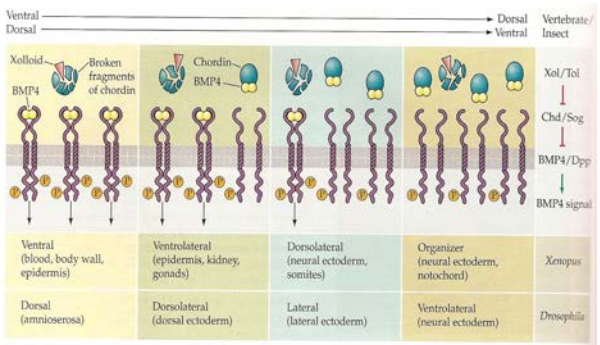
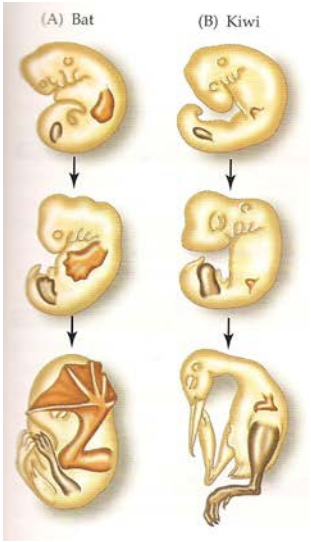


FIGURE 9.6 Homologous pathways specifying the central nervous system and the dorsal-ventral axes of flies and vertebrates. Both pathways involve a source of chordin/Sog protein (the most dorsal region of the vertebrate embryo; the most ventral region of the fly embryo) and a source of BMP4/Dpp (the ventral region of the vertebrate; the dorsal region of the fly). These two regions form antagonistic gradients. Those regions with the most chordin/Sog become central nervous tissue—on the dorsal side of the vertebrate body and on the ventral side of the fly body). The side with the BMP4/Dpp becomes epidermis. In both instances, the gradiant is shaped by a constant supply of Xolloid/Tolloid protein, which degrades chordin/Sog. (After Dale and Wardle 1999.)

TABLE 9.1 Developmental regulatory genes conserved between protostomes and deuterostomes

Gene	Function	Distribution
achaete-scute group	Cell fate specification	Cnidarians, *Drosophila*, vertebrates
Bcl2/Drob-1/ced9	Programmed cell death	*Drosophila*, nematodes, vertebrates
Caudal	Posterior differentiation	*Drosophila*, vertebrates
delta/Xdelta-1	Primary neurogenesis	*Drosophila*, *Xenopus*
Distal-less/DLX	Appendage formation (proximal-distal axis)	Numerous phyla of protostomes and deuterostomes
Dorsal/NFκB	Immune response	*Drosophila*, vertebrates
forkhead/Fox	Terminal differentiation	*Drosophila*, vertebrates
Fringe/radical fringe	Formation of limb margin (apical ectodermal ridge in vertebrates)	*Drosophila*, chick
Hac-1/Apaf/ced 4	Programmed cell death	*Drosophila*, nematodes, vertebrates
Hox complex	Anterior-posterior patterning	Widespread among metazoans
lin-12/Notch	Cell fate specification	*C. elegans*, *Drosophila*, vertebrates
Otx-1, Otx-2/Otd, Emx-1, Emx-2/ems	Anterior patterning, cephalization	*Drosophila*, vertebrates
Pax6/eyeless; Eyes absent/eya	Anterior CNS/eye regulation	*Drosophila*, vertebrates
Polycomb group	Hox expression/cell differentiation control	*Drosophila*, vertebrates
Netrins, Slit proteins, and their receptors	Axon guidance	*Drosophila*, vertebrates
RAS	Signal transduction	*Drosophila*, vertebrates
sine oculus/Six3	Anterior CNS/eye pattern formation	*Drosophila*, vertebrates
sog/chordin, dpp/BMP4	Dorsal-ventral patterning, neurogenesis	*Drosophila*, *Xenopus*
tinman/Nkx 2-5	Heart/blood vascular system	*Drosophila*, mouse
vnd, msh	Neural tube patterning	*Drosophila*, vertebrates

Source: After Erwin 1999.



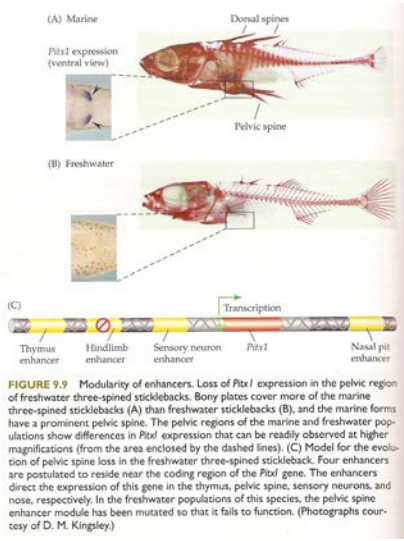


FIGURE 9.9 Modularity of enhancers. Loss of *Pitx1* expression in the pelvic region of freshwater three-spined sticklebacks. Bony plates cover more of the marine three-spined sticklebacks (A) than freshwater sticklebacks (B), and the marine forms have a prominent pelvic spine. The pelvic regions of the marine and freshwater populations show differences in *Pitx1* expression that can be readily observed at higher magnifications (from the area enclosed by the dashed lines). (C) Model for the evolution of pelvic spine loss in the freshwater three-spined stickleback. Four enhancers are postulated to reside near the coding region of the *Pitx1* gene. The enhancers direct the expression of this gene in the thymus, pelvic spine, sensory neurons, and nose, respectively. In the freshwater populations of this species, the pelvic spine enhancer module has been mutated so that it fails to function. (Photographs courtesy of D. M. Kingsley.)

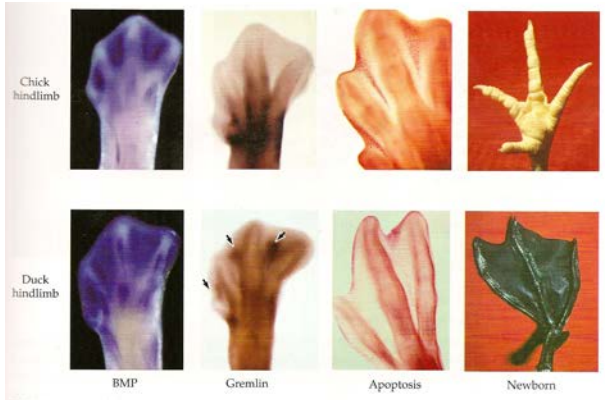


FIGURE 9.10 Heterotopy exemplified by the role of BMPs in the generation of webbed feet in ducks. BMPs cause apoptosis in the interdigital webbing. Autopods of chick feet (upper row) and duck feet (lower row) are shown at similar stages. The in situ hybridizations show that while BMPs are expressed in both the chick and duck hindlimb webbing, the duck limb shows expression of Gremlin protein (arrows) in the webbing as well. Gremlin is an inhibitor of BMPs. The pattern of cell death (shown by neutral red dye accumulation) becomes distinctly different in the two species. (Photographs courtesy of J. Hurle and E. Laufer.)

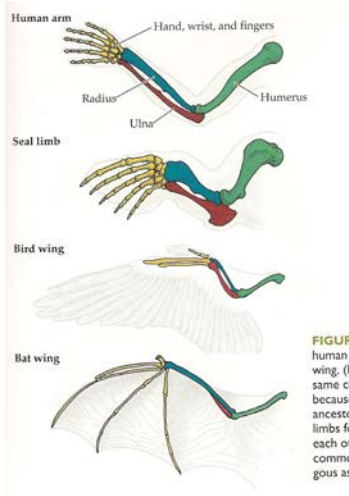
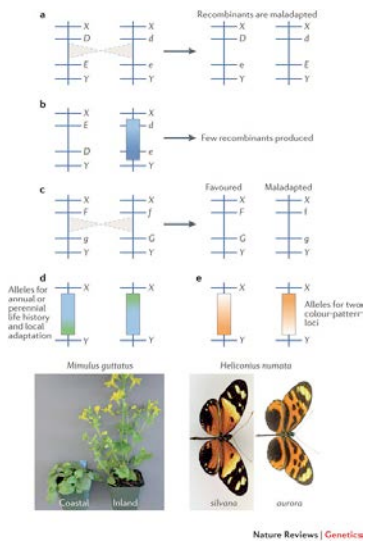
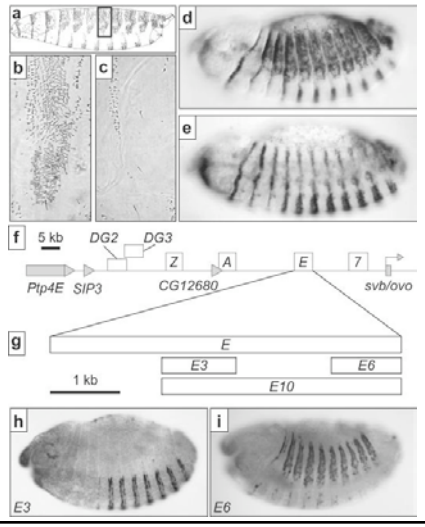


FIGURE 8.1 Homologies of structure among a human arm, a seal forelimb, a bird wing, and a bat wing. (Homologous structures are shown in the same color.) All four are homologous as forelimbs because they derive from a common tetrapod ancestor. The adaptations of bird and bat forelimbs for flight, however, evolved independently of each other, after the two lineages diverged from a common ancestor. Therefore they are homologous as forelimbs but analogous as wings.

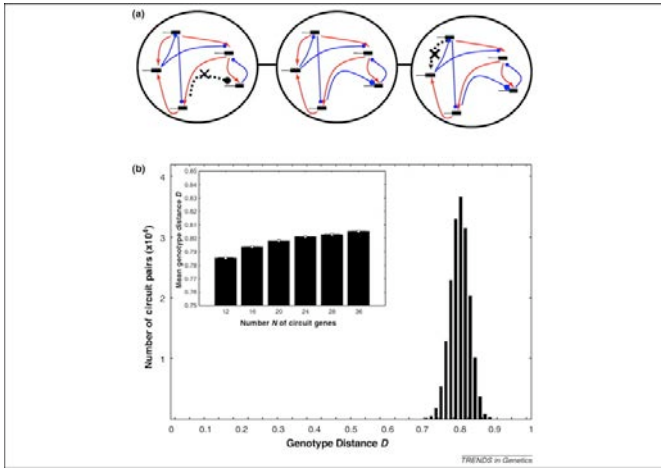


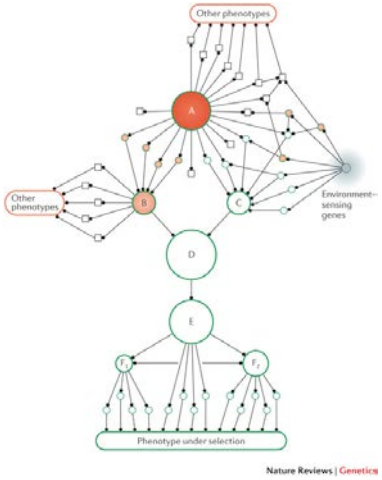
The dual nature of recombination.
a | Consider two ecologically important genes, D and E, segregating for alleles that are adapted to different environments. Alleles D and E are best suited to environment 1, and alleles e and d are best in environment 2. Finally, genes X and Y are neutral loci. Mating between DE and de can produce maladaptive haplotypes De and dE. b | An inversion on the DE haplotype will repress recombination between these loci and increase fitness of these alleles in their favoured environment. c | 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. d | 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 combinations81. e | Heliconius butterflies are a classic example of Mullerian mimicry. Many species of the genus Heliconius (for example, Heliconius numata silvana and Heliconius numata aurora) mimic the wing patterns of Melinae spp. to avoid predators. Each of these wing patterns requires a distinct combination of alleles that influence colour and shape, and recombinants between these distinct types are maladapted. The different Heliconius mimics are closely related and occur sympatrically, yet hybrids are rarely found in nature. It has been shown that two phenotypically distinct mimics have an inversion that harbours at least two colour-pattern loci97. 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.

Frankel N, Erezyilmaz DF, McGregor AP, Wang S, Payre F, Stern DL. (2011) Morphological evolution caused by many subtle-effect substitutions in regulatory DNA. Nature. 29;474(7353):598-603.



Wagner A. (2011) The molecular origins of evolutionary innovations. Trends Genet. 27(10):397-410.





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 sizes are 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 on other traits). Square nodes have no effect on the target phenotype owing to the directionality of the network, but they may influence other phenotypes. Small black circles indicate the directions of the interactions in the network; modes of interaction are not specified. 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. Compared with protein A, the gene encoding protein B has 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 with both high centrality and high connectivity (E) may be influenced by large-effect, adaptive alleles. Genes encoding downstream, peripheral proteins (F1 and F2) may have small to moderate effects and are more likely to accumulate neutral or nearly neutral variants than relatively upstream genes of large effect (D and E), which may evolve under positive and then purifying selection.

Box 2 | **Key issues in network evolution**

Integrating targeted genome engineering with laboratory evolution and computational modelling could considerably increase our understanding of the following open issues in network evolution.

Impact of network rewiring on metabolic functioning
What is the adaptive value of introducing new enzymatic reactions or rewiring regulatory links in particular environments? Systematic network modifications by means of genome engineering[80] will allow researchers to map the fitness landscape of metabolic networks and also explore the space of plausible alternative molecular circuits.

Neutral evolution and emergence of key innovations
How does the neutral evolution of metabolic networks influence the emergence of evolutionary innovations[81]? A computational study showed that the presence of alternative metabolic circuits with the same phenotype is a key facilitator of evolutionary novelty (that is, the ability to utilize new nutrients)[82]. In principle, this prediction can be tested experimentally by measuring the fitness of alternative network circuits under various environmental conditions.

Role of promiscuous enzyme activities in network evolution
Promiscuous functions — weak activities for which the enzyme is not directly selected — have been suggested to have important roles as raw materials for future adaptive evolution[83,84]. Generating large pools of mutations in numerous targeted promiscuous enzymes and exposing the mutant strains to repeated rounds of selection will shed light on how novel promiscuous pathways evolve.

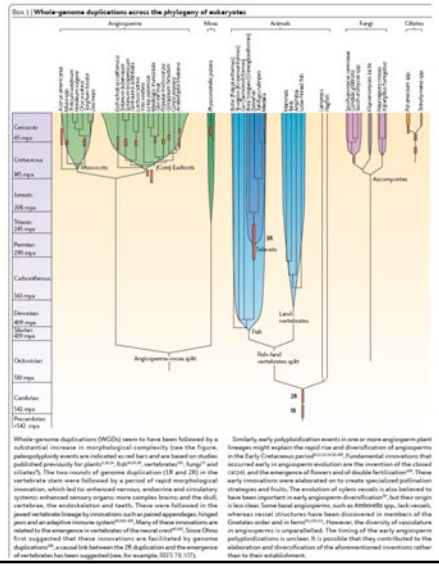
Importance of regulatory versus structural mutations in adaptive evolution
Phenotypic changes could arise through mutations in *cis*-regulatory sequences or coding regions, but their relative importance remains intensely debated[85]. This issue could be addressed by directed evolution *in vitro*[81] by modifying the targets of available genetic variation.

Convergent evolution of network structure and function
How frequent is convergent evolution at the network level[86]? Replaying adaptive network evolution in the laboratory would allow the prevalence of convergence to be estimated and computational predictions on the availability of alternative evolutionary trajectories to be tested.

The evolutionary significance of ancient genome duplications.

Van de Peer Y, Maere S, Meyer A.

Nat Rev Genet. 2009 Oct;10(10):725-32.



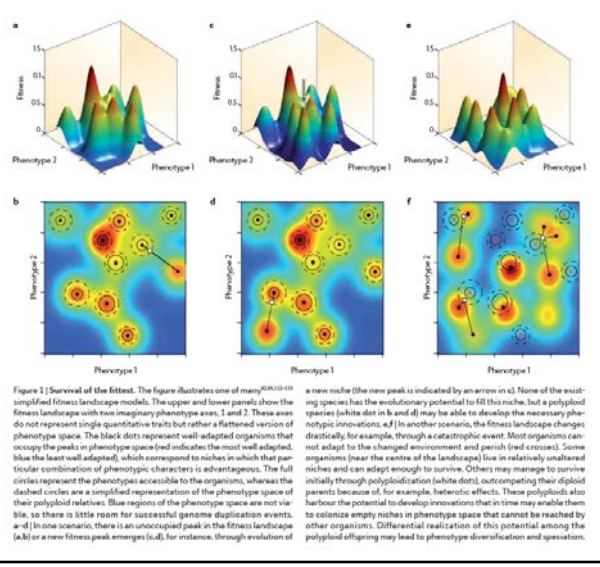
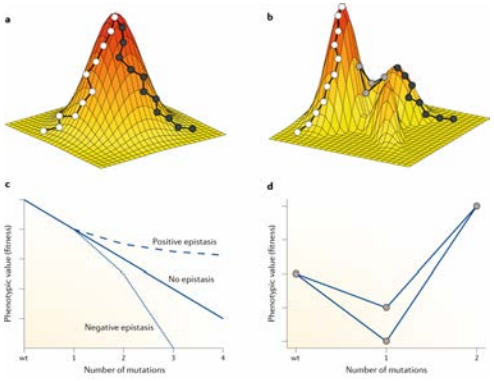
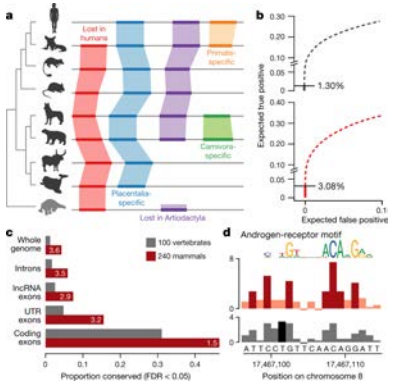


Figure 1 | Survival of the fittest. The figure illustrates one of many[82,83,113] simplified fitness landscape models. The upper and lower panels show the fitness landscape with two imaginary phenotype axes, 1 and 2. These axes do not represent single quantitative traits but rather a flattened version of phenotype space. The black dots represent well-adapted organisms that occupy the peaks in phenotype space (red indicates the most well adapted, blue the least well adapted), which correspond to niches in which that particular combination of phenotypic characters is advantageous. The full circles represent the phenotypes accessible to the organisms, whereas the dashed circles are a simplified representation of the phenotype space of their polyploid relatives. Blue regions of the phenotype space are not viable, so there is little room for successful genome duplication events. **a**–**d** | In one scenario, there is an unoccupied peak in the fitness landscape (**a**,**b**) or a new fitness peak emerges (**c**,**d**), for instance, through evolution of a new niche (the new peak is indicated by an arrow in **c**). None of the existing species has the evolutionary potential to fill this niche, but a polyploid species (white dot in **b** and **d**) may be able to develop the necessary phenotypic innovations. **e**,**f** | In another scenario, the fitness landscape changes drastically, for example, through a catastrophic event. Most organisms cannot adapt to the changed environment and perish (red crosses). Some organisms (near the centre of the landscape) live in relatively unaltered niches and can adapt enough to survive. Others may manage to survive initially through polyploidization (white dots), outcompeting their diploid parents because of, for example, heterotic effects. These polyploids also harbour the potential to develop innovations that in time may enable them to colonize empty niches in phenotype space that cannot be reached by other organisms. Differential realization of this potential among the polyploid offspring may lead to phenotype diversification and speciation.

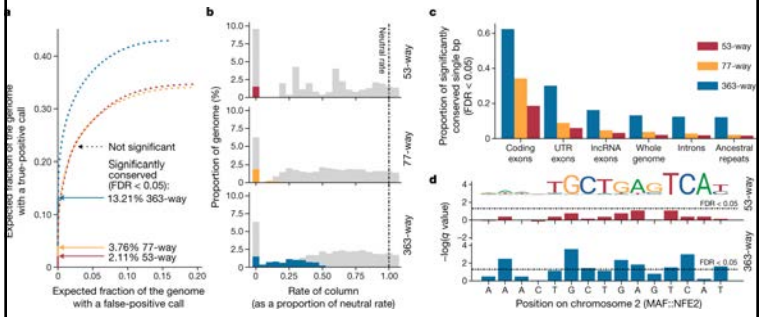
The causes of evolvability and their evolution.
Nat Rev Genet. 2019 Jan;20(1):24-38.
Payne JL, Wagner A.



A comparative genomics multitool for scientific discovery and conservation.
Zoonomia Consortium.
Nature. 2020 Nov;587(7833):240-245.



Dense sampling of bird diversity increases power of comparative genomics.
Feng S, Stiller J, Deng Y, et al.
Nature. 2020 Nov;587(7833):252-257.



Hopeful Monsters and Evolutionary Biology

The proper place of hopeful monsters in evolutionary biology.

Theissen G.
Theory Biosci. 2006 Mar;124(3-4):349-69.

Abstract

Hopeful monsters are organisms with a profound mutant phenotype that have the potential to establish a new evolutionary lineage. The Synthetic Theory of evolutionary biology has rejected the evolutionary relevance of hopeful monsters, but could not fully explain the mechanism and mode of macroevolution. On the other hand, several lines of evidence suggest that hopeful monsters played an important role during the origin of key innovations and novel body plans by saltational rather than gradual evolution. Homeotic mutants are identified as an especially promising class of hopeful monsters. Examples for animal and plant lineages that may have originated as hopeful monsters are given. Nevertheless, a brief review of the history of the concept of hopeful monsters reveals that it needs refinements and empirical tests if it is to be a useful addition to evolutionary biology. While evolutionary biology is traditionally zoocentric, hopeful monsters might be more relevant for plant than for animal evolution. Even though during recent years developmental genetics has provided detailed knowledge about how hopeful monsters can originate in the first place, we know almost nothing about their performance in natural populations and thus the ultimate difference between hopeful and hopeless. Studying the fitness of candidate hopeful monsters (suitable mutants with profound phenotype) in natural habitats thus remains a considerable challenge for the future.

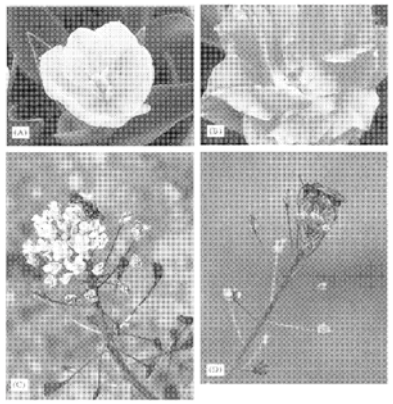
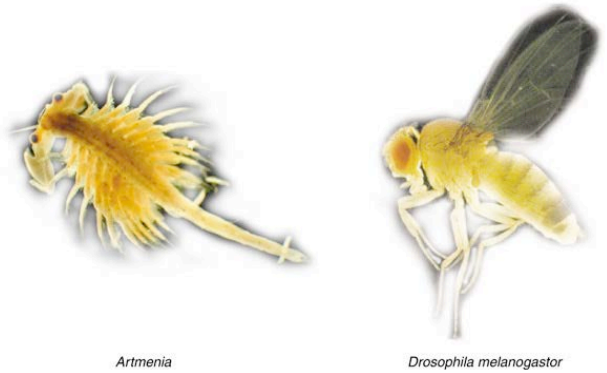


Fig. 1. A putative hopeless (B) and hopeful monster (D). In the upper row, a wild-type flower of tulip (*Tulipa gesneriana*, left) is compared to a "double flower" or "filled flower" mutant (right); while the wild-type flower has male (stamens) and female reproductive organs (carpels) in the centre, the filled flower is sterile, because all reproductive organs are transformed into showy yet sterile perianth organs, thus hampering sexual reproduction and undermining fitness. The lower part shows inflorescences of Shepherd's purse (*Capsella bursa-pastoris*). While wild-type flowers have four different types of floral organs including petals (the white organs in C), all petals are transformed into stamens in the "decandric" variety shown in D, which hence has 10 stamens and 2 carpels in all of its flowers and is fully fertile. Note that while evolutionary biology usually favours animal model systems (an attitude known as zoocentrism), the insects shown here are only decorative elements. (Pictures courtesy of Hanneloore Simon (upper row) and Janine Zermann (lower row)).

Hopeful monsters and morphogens at the beach.

Niswander L, Anderson KV.

Nat Cell Biol. 2002 Nov;4(11):E259-62.

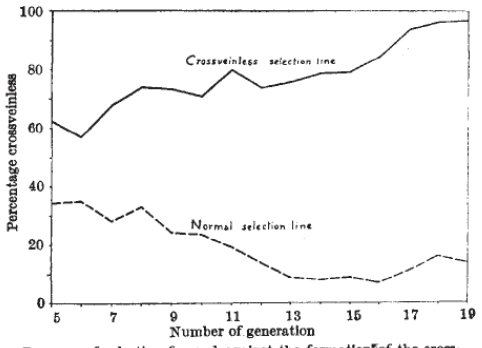


Crustaceans such as *Artemia* have 11 pairs of legs (left), whereas *Drosophila* has three pairs of legs. A change in a phosphorylation site of *Artemia* Ubx appears to alter the protein such that development is not respressed in the *Artemia* abdominal segements. See text for further details.

"*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)

Waddington

Environment and Evolutionary Biology



Progress of selection for and against the formation of the crossveinless phenocopy, from the fifth generation onwards, the temperature shock being applied to pupæ aged 21–23 hr.

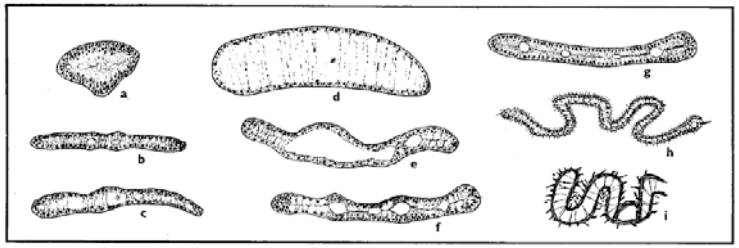


FIGURE 1 – *Diagrammatic drawings of sections of the developing wing in the fruit-fly* Drosophila. *Notice how the wing is at first quite solidly constructed. (Figure* 1 b *is of about the same age as figure* 2 A.) *Then it becomes hollow (figure* 1 d, *which corresponds to figure* 2 B), *contracts again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

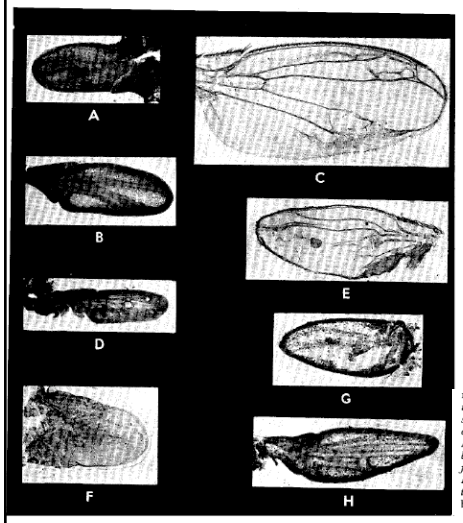


FIGURE 3 – *Some genetically controlled abnormalities in the contraction-phase of wing-development in* Drosophila. *Figures* A, B, *and* C *show wings of the mutant race* net *in which there is a partial failure of contraction, which causes the formation of extra veins in some regions. In figures* D *and* E *the failure of contraction is much more complete, and bubbles of fluid are left between the two wing-surfaces, which remain so far apart that in many areas no veins appear (the mutant* bloated). *In figures* F, G, *and* H *the contraction does not fail, but is abnormal, so that a wing of characteristically elongated form is produced (the mutant* blade *in* D. pseudo-obscura).

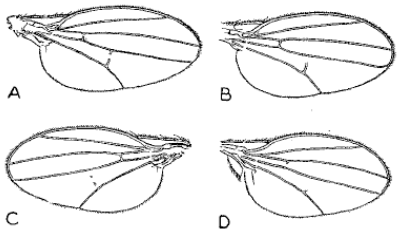


FIG. 1. Four crossveinless wings: *a* grade 4, *b* grade 3, *c* grade 2, *d* grade 1.

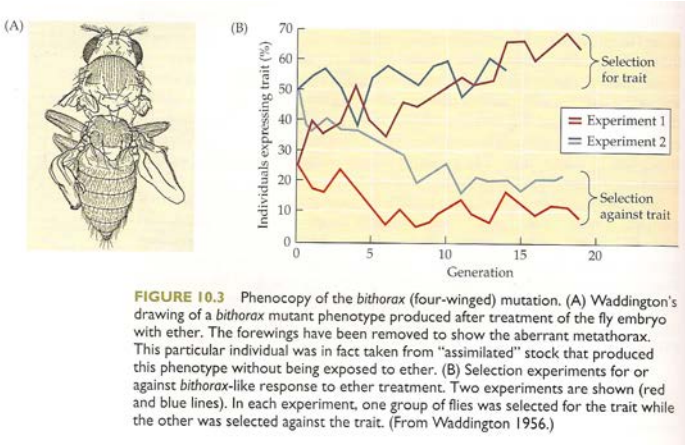


FIGURE 10.3 Phenocopy of the *bithorax* (four-winged) mutation. (A) Waddington's drawing of a *bithorax* mutant phenotype produced after treatment of the fly embryo with ether. The forewings have been removed to show the aberrant metathorax. This particular individual was in fact taken from "assimilated" stock that produced this phenotype without being exposed to ether. (B) Selection experiments for or against *bithorax*-like response to ether treatment. Two experiments are shown (red and blue lines). In each experiment, one group of flies was selected for the trait while the other was selected against the trait. (From Waddington 1956.)

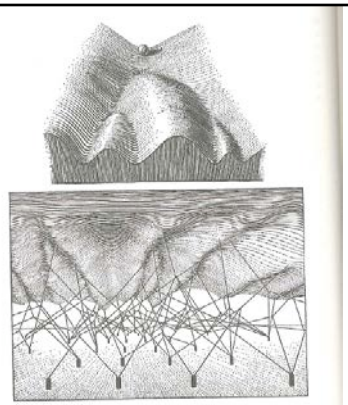
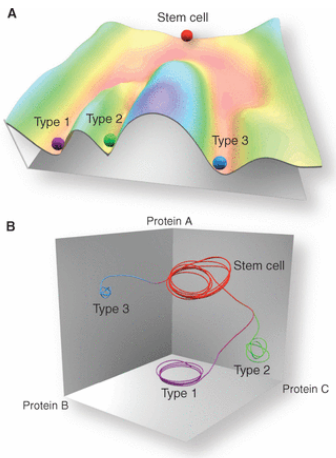
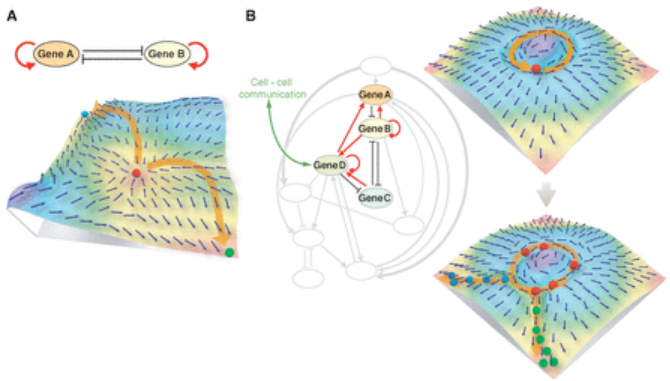


Figure 2.5
Waddington's pictures of epigenetic landscapes. His legend for the upper picture began "Part of an epigenetic landscape. The path followed by the ball, as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg." The lower picture had the legend "The complex system of interactions underlying the epigenetic landscape. The pegs in the ground represent genes; the strings leading from them the chemical tendencies which the genes produce. The moulding of the epigenetic landscape, which slopes down from above one's head towards the distance, is controlled by the pull of these numerous guy-ropes which are ultimately anchored to the genes." (Reproduced with permission from C.H. Waddington, *The Strategy of the Genes*, London, Allen and Unwin, 1957, pp. 29, 36.)

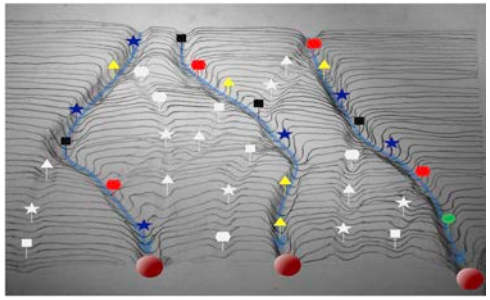


(A) Waddington's epigenetic landscape. The development of a cellular state is represented by a ball rolling down a landscape of bifurcating valleys, each representing different cell types. (B) Dynamical-systems representation of cellular states. Each axis represents the expression of a protein whose time development is depicted as a trajectory in space. Final states are attractors and correspond to distinct cell types.



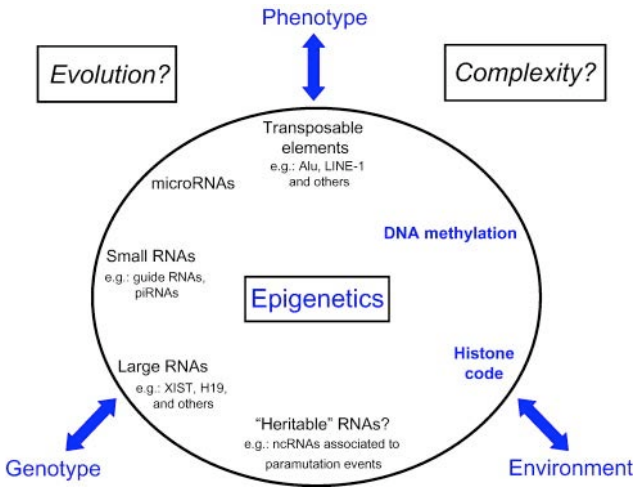
Dynamical-systems view on the differentiation dynamics of a stem cell. (A) By adding self-activation (top, red arrows) to a toggle-switch network, i.e., two mutually repressing genes (9), (bottom) an attractor (red) with balanced expression of the two genes is added between A-activated and B-activated 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.

The "evolutionary field" hypothesis. Non-Mendelian transgenerational inheritance mediates diversification and evolution.
Prog Biophys Mol Biol. 2018 May;134:27-37.
Spadafora C.

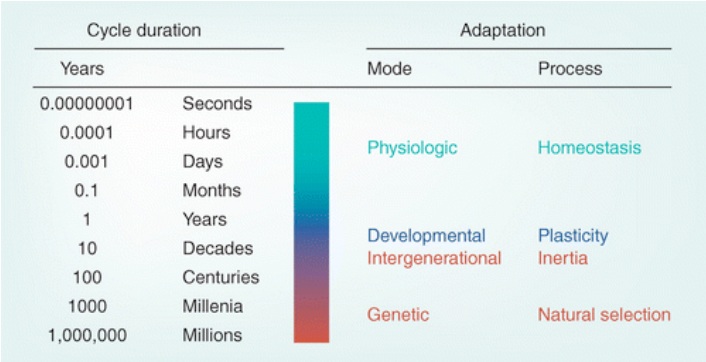


Building of the genome regulatory networks. Colored symbols represent retrotransposal insertions that provide a variety of DNA recognition sites (i.e. transcription- or hormone-binding sequences, promoters, enhancers, splicing sites, insulators etc) required for the assembly of functional regulatory networks and also contribute to expand the copy number of miRNA and trRNA 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

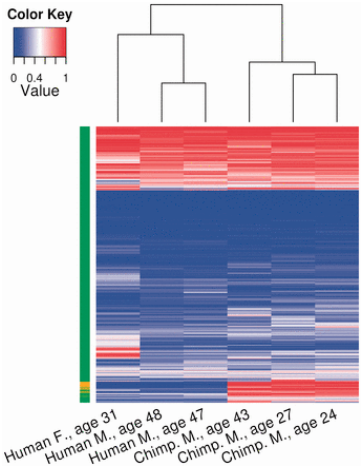


Kuzawa CW, Thayer ZM. (2011) Timescales of human adaptation: the role of epigenetic processes. Epigenomics. ;3(2):221-34.



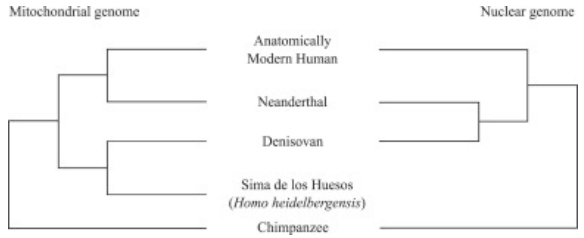
Cycle duration		Adaptation	
Years		Mode	Process
0.00000001	Seconds		
0.0001	Hours	Physiologic	Homeostasis
0.001	Days		
0.1	Months		
1	Years	Developmental	Plasticity
10	Decades	Intergenerational	Inertia
100	Centuries		
1000	Millenia	Genetic	Natural selection
1,000,000	Millions		

Epigenetics and evolution.
Integr Comp Biol. 2014 Jul;54(1):31-42
Mendizabal I, Keller TE, Zeng J, Yi SV.

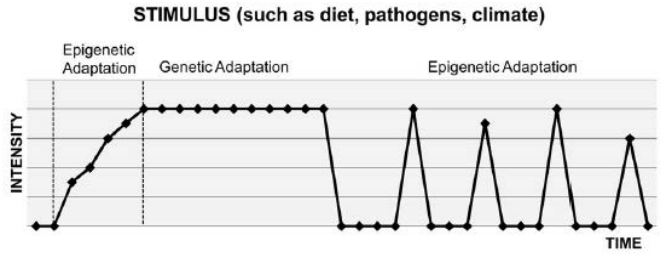


Levels of DNA methylation of 12,063 orthologous promoters in three humans and three chimpanzees analyzed by Zeng et al. (2012). Hierarchical clustering both within and between species was performed using the average methylation of promoters to generate a heatmap. The column to the left of the heatmap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

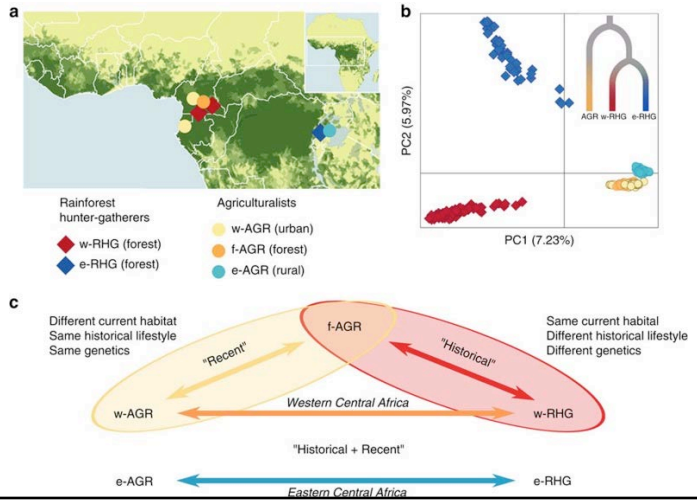
Major transitions in human evolution revisited: a tribute to ancient DNA.
J Hum Evol. 2015 Feb;79:4-20.
Ermini L, Der Sarkissian C, Willerslev E, Orlando L.



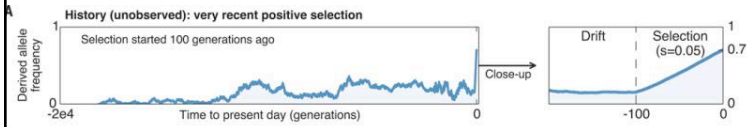
The epigenetic side of human adaptation: hypotheses, evidences and theories.
Ann Hum Biol. 2015 Jan;42(1):1-9.
Giuliani C, Bacalini MG, Sazzini M, Pirazzini C, Franceschi C, Garagnani P, Luiselli D.

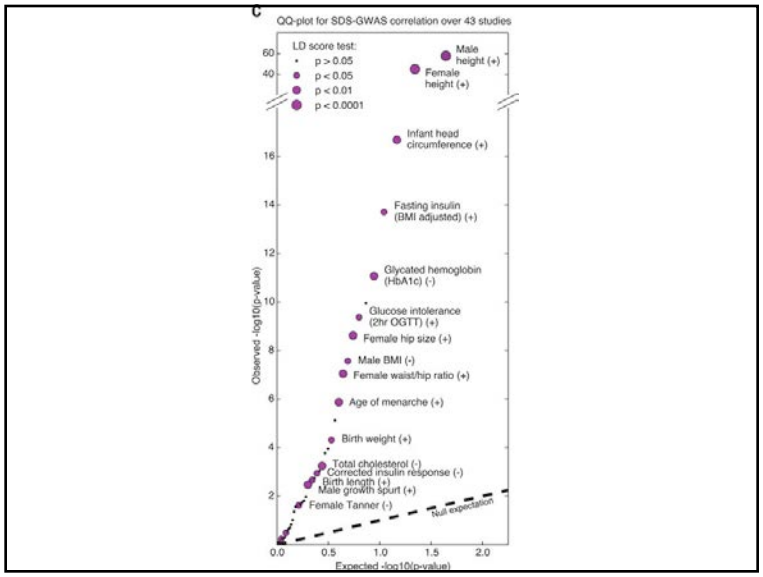


The epigenomic landscape of African rainforest hunter-gatherers and farmers.
Fagny M, Patin E, MacIsaac JL, et al.
Nat Commun. 2015 Nov 30;6:10047.



Detection of human adaptation during the past 2000 years.
Field Y, Boyle EA, Telis N, et al.
Science. 2016 Nov 11;354(6313):760-764.

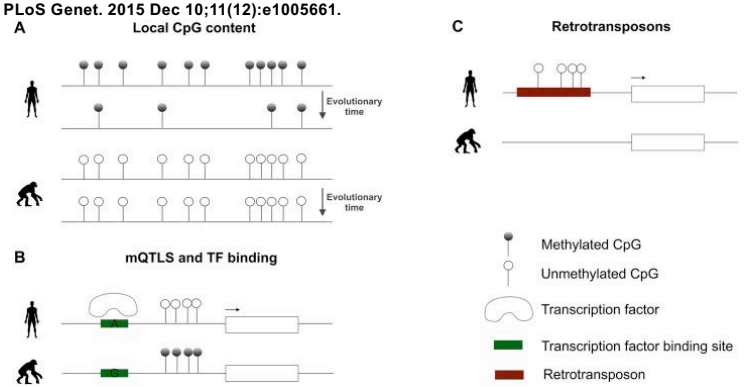




DNA Methylation: Insights into Human Evolution.

Hernando-Herraez I, Garcia-Perez R, Sharp AJ, Marques-Bonet T

PLoS Genet. 2015 Dec 10;11(12):e1005661.



The interplay between the genome and the methylome.

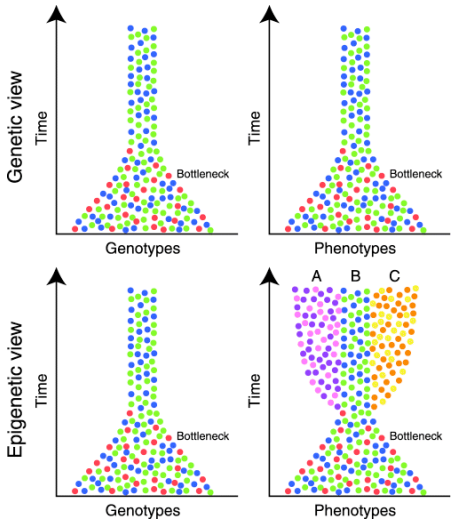
A) Methylated cytosines tend to deaminate over evolutionary time and, thus, the methylation state of cytosines in different species influences the evolution of the underlying genome sequence. B) Species-specific nucleotide changes that disrupt transcription factor (TF) binding sites can alter the methylation 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.

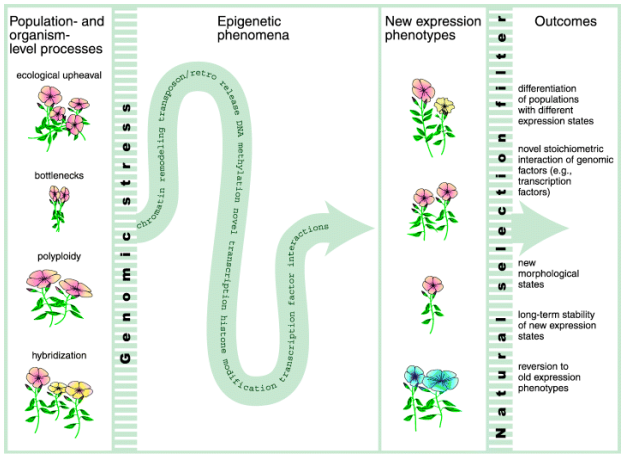
Table 1. Comparative studies of DNA methylation patterns in primates.

Reference	Species	Methodology	Tissue	Highlights
Wang, J. (2012)	Human, Macaque	MeDIP-chip and SEQUENOM MassARRAY	Prefrontal cortex	>100 differentially methylated regions; Validated DMRs associated with genes with neural functions and with schizophrenia and Alzheimer's disease
Pai, A. (2011)	Human, Chimpanzee	Illumina 27K array	Liver, heart, and kidney	14.5% of promoter CpG sites are differentially methylated between tissues; 8.6% of promoter CpG sites are differentially methylated between species; Interspecies differences in promoter methylation underlie 12%–18% of gene expression differences
Molaro, A. (2011)	Human, Chimpanzee	Whole-genome bisulfite sequence	Sperm	70% of genes are hypomethylated in both chimpanzee and human sperm; 6% and 35% of orthologous SVAs had a methylation level below 50% in chimpanzee and human sperm, respectively
Martin, D.I.K. (2011)	Human, Chimpanzee, Orangutan	MethylSeq	Neutrophils	10% of CpG islands-like regions present different methylation states between chimpanzees and humans; Regions with differential methylation might have diverged in gene regulatory function
Fukuda, K. (2013)	Human, Chimpanzee	MeDIP-chip (chromosomes 21 and 22)	Peripheral blood leukocytes	16 sDMRs between chimpanzees and humans in chromosomes 21 and 22; Genetic changes underlying these differences in methylation include gain/loss of CTCF-binding sites and changes in CpG density
Hernando-Herraez, I. (2013)	Human, Chimpanzee, Bonobo, Gorilla, Orangutan	Illumina 450K array	Peripheral blood	~9% of the assayed CpG sites showed significant methylation differences between chimpanzees and humans; 184 genes perfectly conserved at protein level show significant epigenetic differences between chimpanzees and humans
Hernando-Herraez, I. (2015)	Human, Chimpanzee, Gorilla, Orangutan	Whole-genome bisulfite sequence	Peripheral blood	72% of the hypomethylated regions (HMRs) were shared among all four species; 42.6% of HMRs were on human CpG islands; 52.6% of HMRs were on human CpG shores
Gokhman, D. (2014)	Neandertal, Denisovan	Deamination rate as a proxy for DNA methylation	Femur, costae, and tibia bones	>2,000 DMRs between archaic and present-day humans; Substantial changes in methylation in the *HOXD* cluster
Fraser, H. B (2012)	Human	Illumina 27K array	Lymphoblastoid cell lines	21.4% of CpG sites differed in methylation between populations; 5.4% of these CpG sites were strongly associated with local SNPs
Heyn, H. 2013	Human	Illumina 450K array	Lymphoblastoid cell lines	439 population-specific differentially methylated CpG sites (pop-CpG); Significantly decreased gene expression associated to promoter hypermethylation in 12.9% (13 out of 101) of pop-CpG; Significantly increased gene expression associated to gene body methylation in 23.9% (27 out of 113) of pop-CpG

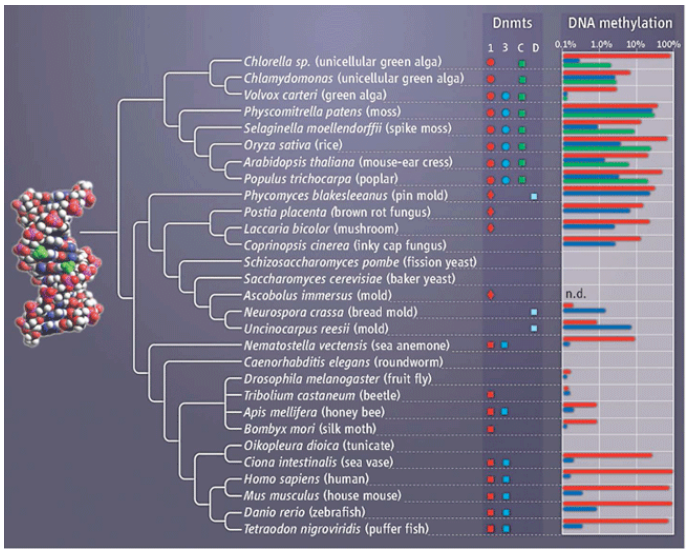
doi:10.1371/journal.pgen.1005661.t001

Rapp RA, Wendel JF. (2005) Epigenetics and plant evolution. New Phytol. 168(1):81-91.





Conceptualization of the interaction between epigenetics and evolutionary change. A number of population-level processes (left) cause genomic stress, leading to the induction of epigenetic phenomena (large 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.

Epigenetics. 2009 Nov 16;4(8):551-6.

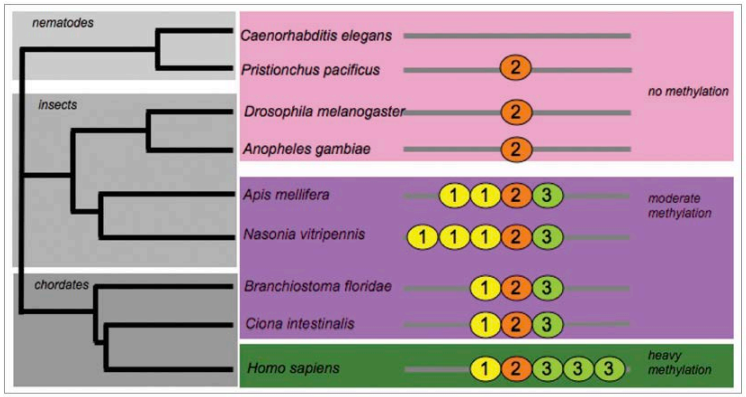


Figure 1. The numbers of different *dnmts* in sequenced animal genomes. Different *dnmt* loci are depicted as different color circles. *dnmt2* exists in single copy and shows the most widespread distribution in animal genomes, but bears an unclear relationship with presence of functional CpG DNA methylation. In contrast, *dnmt1* and *dnmt3* families undergo frequent duplications and loss events, and seem to be associated with genome methylation.[5,17,62,63] Phylogenetic relationships among chordates are following Putnam et al.[64]

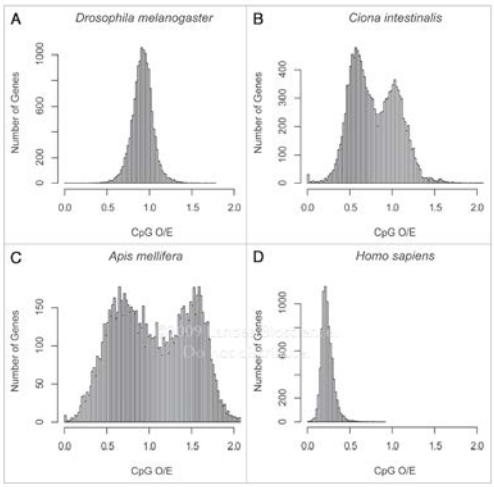
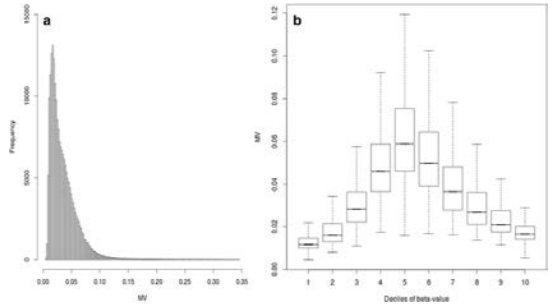
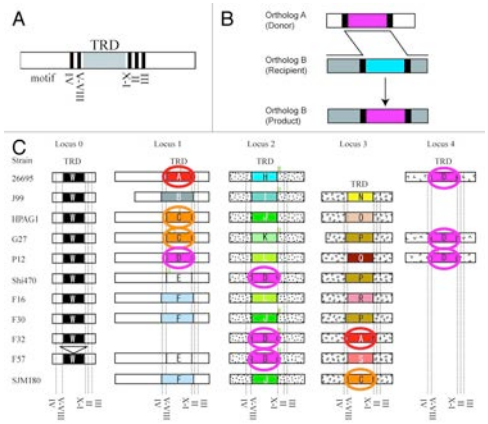


Figure 2. Distributions of CpG O/E values from different genomes indicate divergent patterns of genomic DNA methylation. (A) CpG O/E values from genes in *D. melanogaster* genome show a Gaussian distribution with the mean around 1, as expected in a system without DNA methylation. In contrast, genes in (B) *C. intestinalis* and (C) *A. mellifera* genomes exhibit distinctive 'bimodal' distributions, likely caused by the division of the genome into hyper- and hypo-methylated classes of genes. (D) CpG O/E values from human genes are around 0.2, demonstrating significant depletion of CpG dinucleotides explained by 'heavy' genomic DNA methylation.

DNA Methylation variability among individuals is related to CpGs cluster density and evolutionary signatures.
BMC Genomics. 2018 Apr 2;19(1):229.
Palumbo D, Affinito O, Monticelli A, Cocozza S.

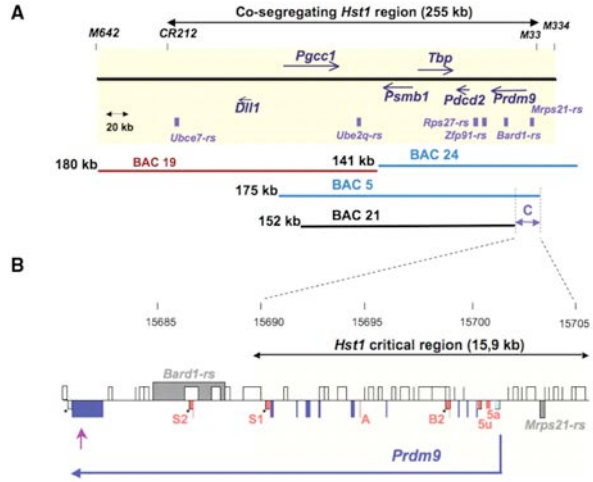


Furuta Y, Kobayashi I. (2012) Mobility of DNA sequence recognition domains in DNA methyltransferases suggests epigenetics-driven adaptive evolution. Mob Genet Elements. 1;2(6):292-296.

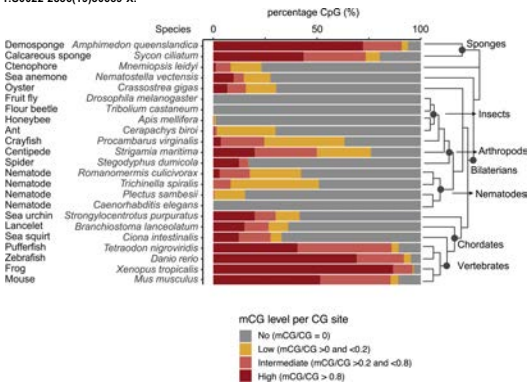


Movement of target DNA recognition domains between non-orthologous genes of Type III mod genes. (A) Gene organization in mod genes. TRD, target recognition domain. Roman numerals, amino-acid sequence motifs conserved among m6A DNA methyltransferases. (B) A likely process of the movement of target recognition domains: DNA recombination at conserved DNA sequences flanking the target recognition domain that encode the conserved amino-acid motifs. (C) Repertoire of orthologs of mod genes in global strains of Helicobacter pylori. Members of the same homology group of target recognition domains are in the same color. Small vertical bars in green and small vertical bars in orange: start codon and stop codon generated by frameshift mutations. Modified from Furuta et al.

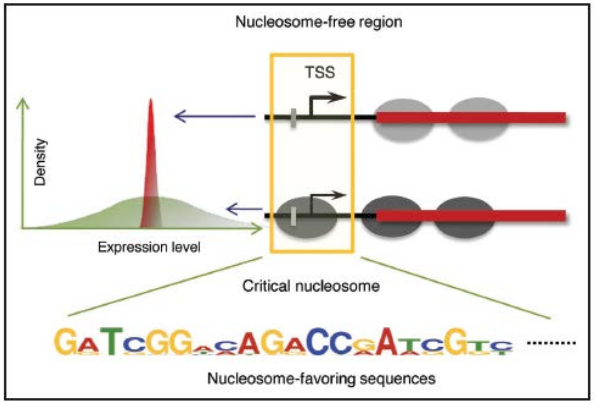
Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J. (2009) A mouse speciation gene encodes a meiotic histone H3 methyltransferase. Science. 16;323(5912):373-5.



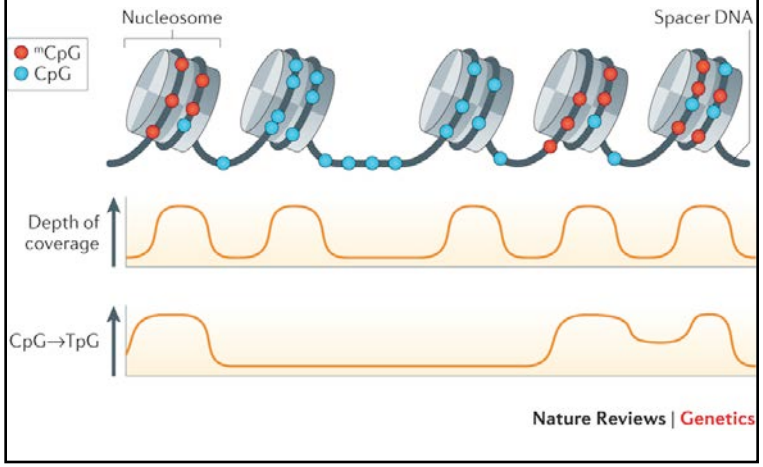
Evolution of DNA Methylome Diversity in Eukaryotes
de Mendoza A, Lister R, Bogdanovic O. J
Mol Biol. 2019 Nov 11:S0022-2836(19)30659-X.



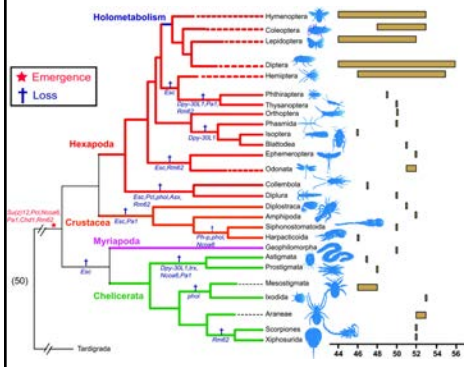
Choi JK, Kim YJ. (2009) Implications of the nucleosome code in regulatory variation, adaptation and evolution. Epigenetics. 1;4(5):291-5.



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

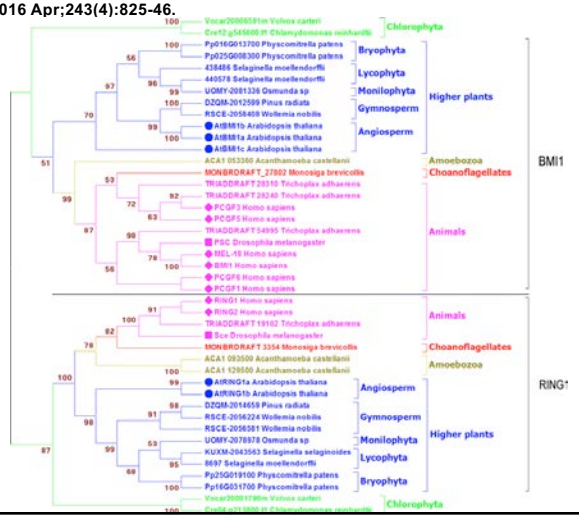


Genomic data reveal high conservation but divergent evolutionary pattern of Polycomb/Trithorax group genes in arthropods.
Insect Sci. 2019 Feb;26(1):20-34.
Jiang F, Liu Q, Liu X, Wang XH, Kang L.

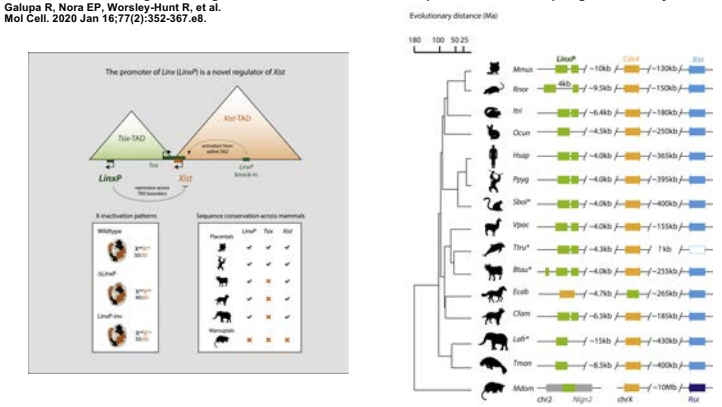


Inference of ancestral state of PcG and TrxG genes along arthropod evolution. The emergence and loss of PcG and TrxG genes are indicated in the internal nodes of the phylogenetic tree. The bars indicate the number ranges of PcG and TrxG genes in each order. The numbers of species in each order are as follows: Amphipoda, 1; Araneae, 2; Astigmata, 1; Blattodea, 1; Coleoptera, 9; Collembola, 1; Diplostraca, 1; Diplura, 1; Diptera, 16; Ephemeroptera, 1; Geophilomorpha, 1; Harpacticoida, 1; Hemiptera, 13; Hymenoptera, 38; Isoptera, 1; Ixodida, 1; Lepidoptera, 9; Mesostigmata, 2; Odonata, 2; Orthoptera, 1; Parachela, 2; Phasmida, 1; Phthiraptera, 1; Prostigmata, 1; Scorpiones, 1; Siphonostomatoida, 1; Thysanoptera, 1; Xiphosurida, 1.

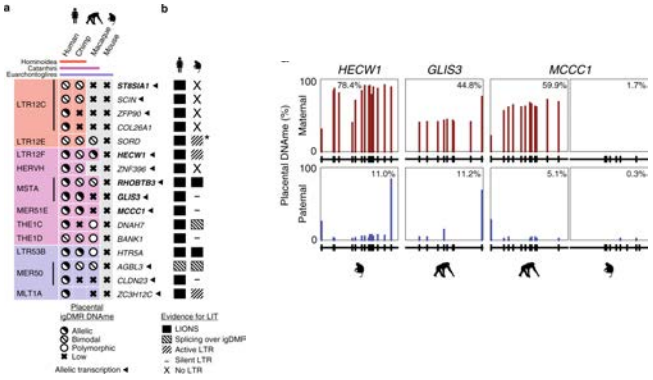
The evolutionary landscape of PRC1 core components in green lineage.
Chen DH, Huang Y, Ruan Y, Shen WH.
Planta. 2016 Apr;243(4):825-46.



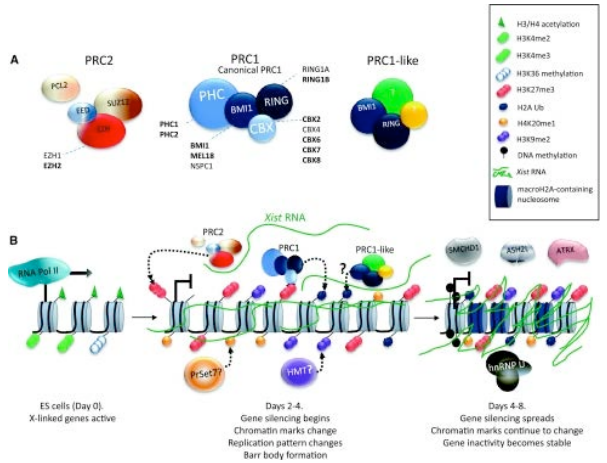
A Conserved Noncoding Locus Regulates Random Monoallelic Xist Expression across a Topological Boundary.
Galupa R, Nora EP, Worsley-Hunt R, et al.
Mol Cell. 2020 Jan 16;77(2):352-367.e8.



Evolution of imprinting via lineage-specific insertion of retroviral promoters.
Bogutz AB, Brind'Amour J, Kobayashi H, Jensen KN, Nakabayashi K, Imai H, Lorincz MC, Lefebvre L.
Nat Commun. 2019 Dec 12;10(1):5674.



Escamilla-Del-Arenal M, da Rocha ST, Heard E. (2011) Evolutionary diversity and developmental regulation of X-chromosome inactivation. Hum Genet. 130(2):307-27.

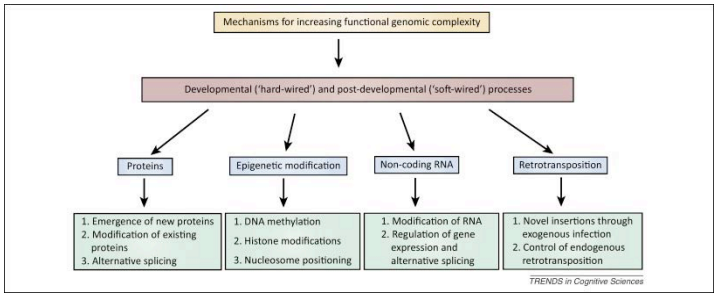


EvoChromo: towards a synthesis of chromatin biology and evolution
Drinnenberg IA, Berger F, Elsässer SJ, et al.
Development . 2019 Sep 26;146(19):dev178962.

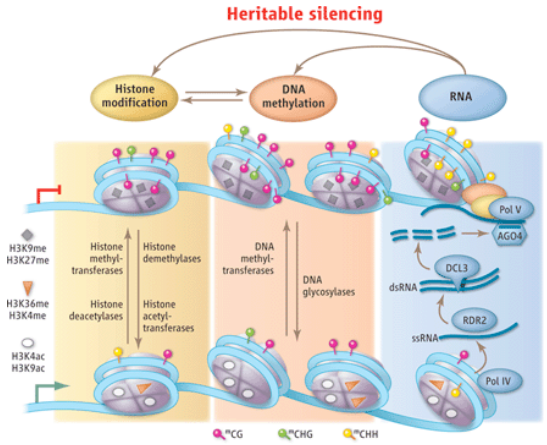
Abstract

Over the past few years, interest in chromatin and its evolution has grown. To further advance these interests, we organized a workshop with the support of The Company of Biologists to debate the current state of knowledge regarding the origin and evolution of chromatin. This workshop led to prospective views on the development of a new field of research that we term 'EvoChromo'. In this short Spotlight article, we define the breadth and expected impact of this new area of scientific inquiry on our understanding of both chromatin and evolution.

Barry G, Mattick JS. (2012) The role of regulatory RNA in cognitive evolution. Trends Cogn Sci. 16(10):497-503.

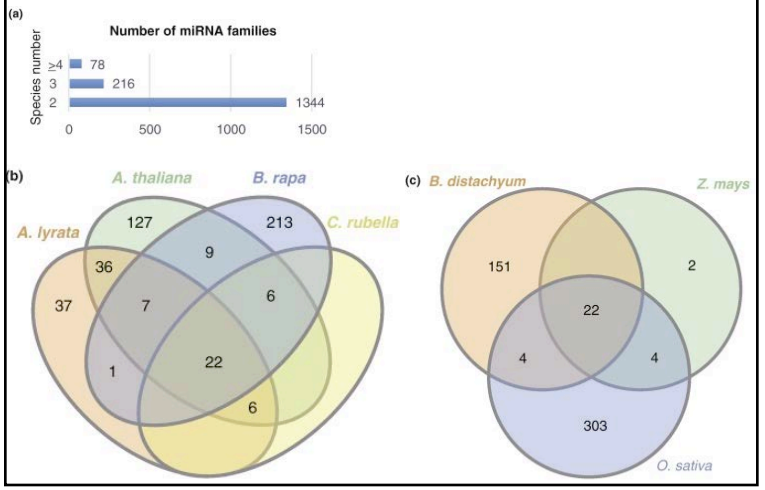


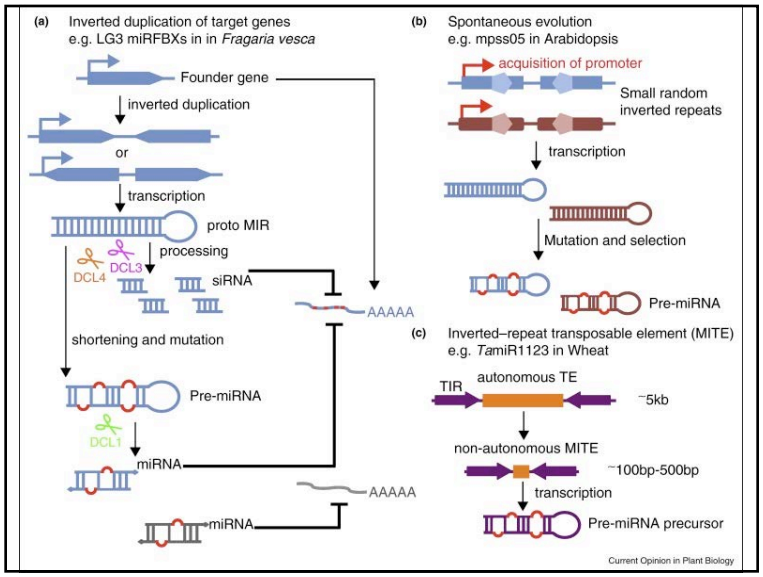
Potential mechanisms for increasing functional genomic complexity. The human brain may have evolved rapidly through a number of mechanisms, including protein innovations, altered epigenetic programs, expansion of regulatory RNAs that direct chromatin modifications, and retrotransposition. Especially 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.



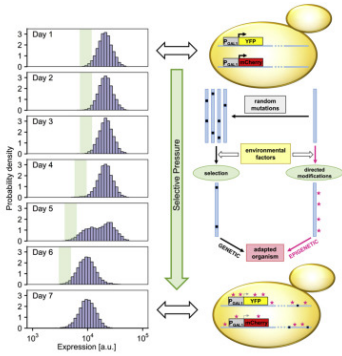
Plant epigenetic mechanisms include DNA methylation, histone modification, and RNA-directed DNA methylation (RdDM). RdDM involves two plant-specific RNA polymerases (Pol IV and Pol V), an RNA-dependent RNA polymerase (RDR2), an enzyme that cleaves double-stranded RNA (DCL3), and an Argonaute-family RNA-binding protein (AGO4). [Adapted with permission from (199)]

The evolution of microRNAs in plants.
Cui J, You C, Chen X.
Curr Opin Plant Biol. 2017 Feb;35:61-67.

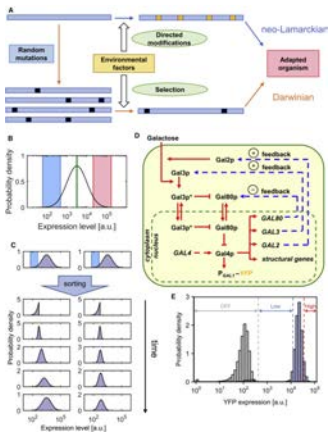




Epigenetic Mechanisms Contribute to Evolutionary Adaptation of Gene Network Activity under Environmental Selection.
Luo X, Song R, Moreno DF, Ryu HY, Hochstrasser M, Acar M.
Cell Rep. 2020 Oct 27;33(4):108306.



In Brief
Luo et al. demonstrate how epigenetic mechanisms contribute to the evolution of gene network activity. Subjecting yeast cells to repeated environmental selection based on the activity of the galactose network, they observe sustained changes in reporter expression level. They characterize the epigenetic and genetic factors contributing to the



Evolution of Epigenetic Regulation in Vertebrate Genomes.

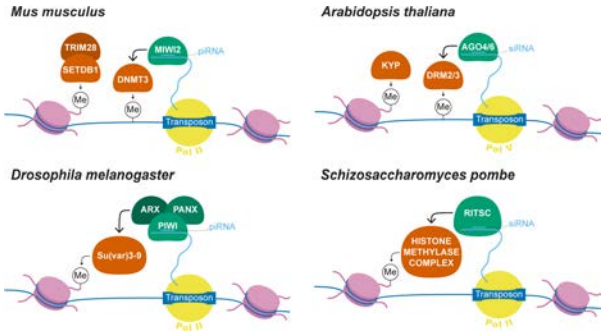
Lowdon RF, Jang HS, Wang T.
Trends Genet. 2016 May;32(5):269-83.

Epigenetic mechanisms	Modification types*	Assay examples	Simplified diagrams
DNA methylation	Low Intermediate High	Chemical-based Bisulfite-treatment # [96] RRBS [97] Enrichment-based MeDIP # [98] Bio-CAP # [99] Enzyme digest-based MRE # [98]	Enhancer Promoter Gene body
Histone PTM	H3K4me1 H3K4me2 H3K4me3 H3K9me3 H3K27ac H3K27me3 H3K36me3	Enrichment-based Histone-specific ChIP # [100]	Key: Nucleosome, Histone tail Enhancer Promoter Gene body
Nucleosome occupancy	DNase I hypersensitive sites (DHS)	Enzyme digest-based DNase I # [101]	Key: DHS Enhancer Promoter Gene body

* = Red and blue terms correspond to repressive and active state, respectively.
= These assays can be quantified by numerous techniques including, but not limited to, gel-imaging, targeted sequencing, RT-qPCR, microarrays and high-throughput sequencing.
96–101] = Reference

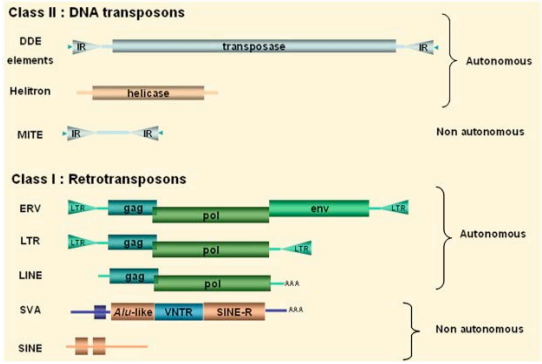
Trends in Genetics

Double-edged sword: The evolutionary consequences of the epigenetic silencing of transposable elements.
Choi JY, Lee YCG.
PLoS Genet. 2020 Jul 16;16(7):e1008872.



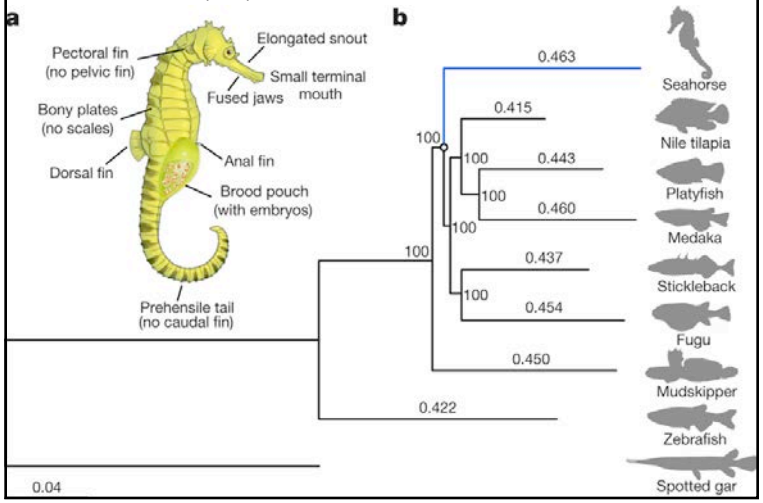
These unique evolutionary consequences indicate that TEs' epigenetic effect is not only a crucial component of TE biology but could also be a significant contributor to genome function and evolution.

Rebollo R, Horard B, Hubert B, Vieira C. (2010) Jumping genes and epigenetics: Towards new species. Gene. 1;454(1-2):1-7.



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 just "cut and paste" their own molecule. Autonomous retrotransposons harbor long terminal repeats in their ends (LTR) or not (LINE-like), and can be infectious 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 thanks to 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.

The seahorse genome and the evolution of its specialized morphology.
Lin Q, Fan S, Zhang Y, et al.
Nature. 2016 Dec 14;540(7633):395-399.



"Epigenetics and Systems Biology"
Spring 2021 (Odd Years)
Biol 476/576
Schedule/Lecture Outline –

Week 1	(Lesson 1)	Systems Biology (History/ Definitions/ Theory)
Week 2	(Lesson 2)	Systems Biology (Networks & Emergence)
Week 3	(Lesson 3)	Systems Biology (Components: DNA to Phenotype)
Week 4	(Lesson 4)	Systems Biology (Genomics / Technology)
Week 5	(Lesson 5)	Epigenetics (History / Molecular Processes)
Week 6	(Lesson 6)	Epigenetics (Molecular Processes & Integration)
Week 7	(Lesson 7)	Epigenetics (Genomics and Technology)
Week 8	(Lesson 8)	Cell & Developmental Biology
Week 9	(Lesson 9)	Epigenetics of Cell & Developmental Biology
Week 10	(Lesson 10)	Environmental Impact on Biology
Week 11	(Lesson 11)	Environmental Epigenetics
Week 12	(Lesson 12)	Disease Etiology
Week 13	(Lesson 13)	Epigenetics & Disease Etiology
Week 14	(Lesson 14)	Evolutionary Biology & Genetics
Week 15	(Lesson 15)	Epigenetics & Evolutionary Biology
Week 16	(Lesson 16)	Grant Review/ Study Section Meeting

Environment, Epigenetic and Evolution

Spring 2021 – Epigenetics and Systems Biology
Lecture Outline (Epigenetics and Evolution)
Michael K. Skinner – Biol 476/576
Weeks 14 and 15 (April 20 & 27)

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

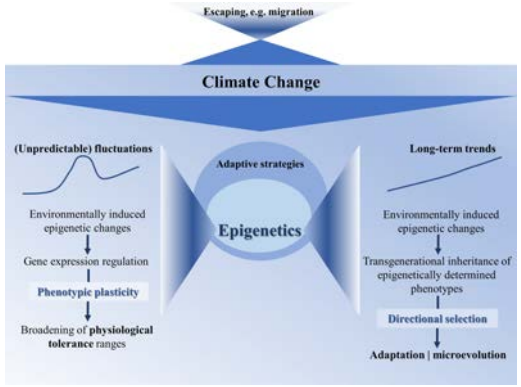
Laland, et al. (2014) Does evolutionary theory need a rethink? Nature 54:161-4

Skinner MK (2015) Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. Genome Biol Evol. 26;7(5):1296-302

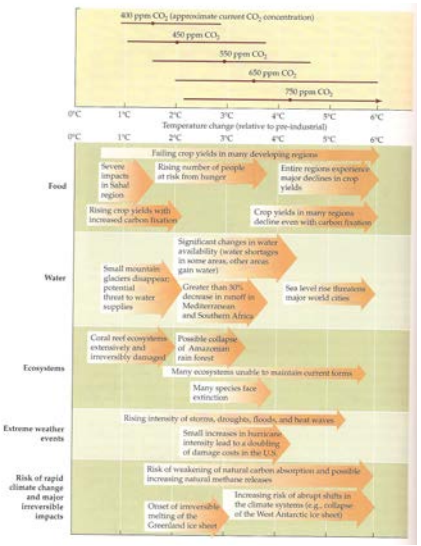
Books (Reserve in Library)

Jablonka, E. & Lamb, M.J. (2014). Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the History of Life. MIT Press, Cambridge.

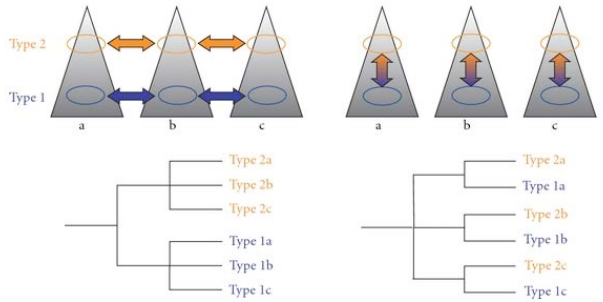
Synthesizing the role of epigenetics in the response and adaptation of species to climate change in freshwater ecosystems.
Mol Ecol. 2018 Jul;27(13):2790-2806.
Jeremias G, Barbosa J, Marques SM, Asselman J, Gonçalves FJM, Pereira JL.



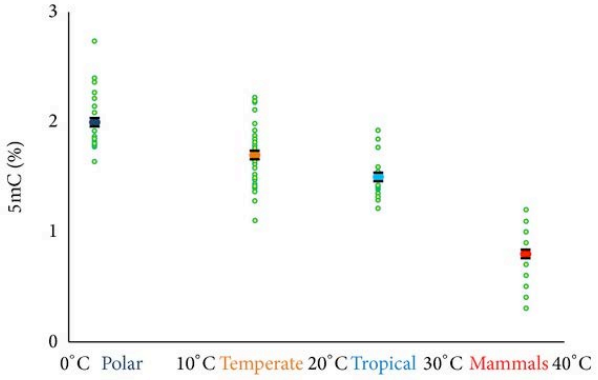
Conceptual diagram representing the role of epigenetics as an adaptive strategy by freshwater organisms while coping to environmental stressors deriving from climate change



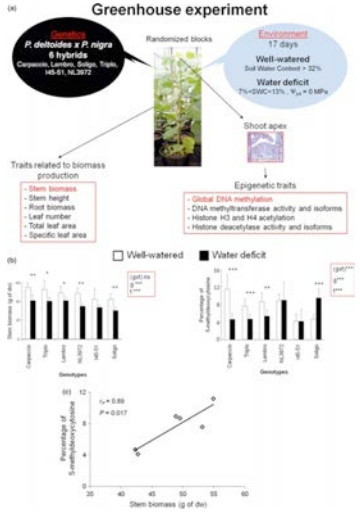
Flatscher R, Frajman B, Schönswetter P, Paun O. (2012) Environmental heterogeneity and phenotypic divergence: can heritable epigenetic variation aid speciation? Genet Res Int. 2012:698421



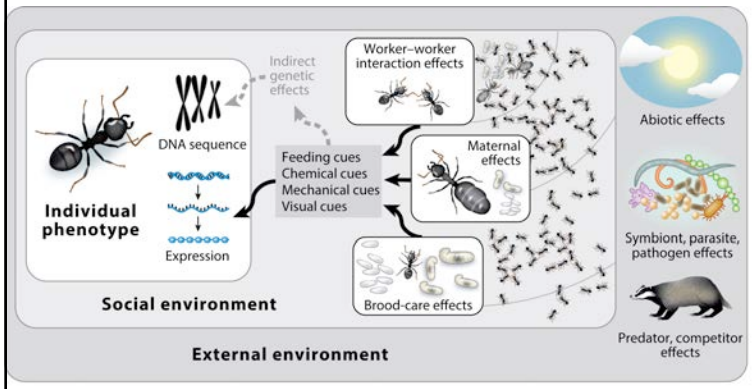
DNA methylation, epigenetics, and evolution in vertebrates: facts and challenges.
Int J Evol Biol. 2014;2014:475981
Varriale A.

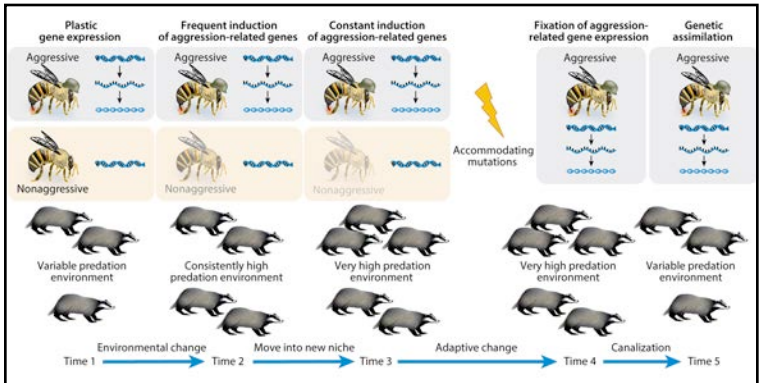


Bräutigam K, et al. (2013) Epigenetic regulation of adaptive responses of forest tree species to the environment. Ecol Evol. 3(2):399-415.



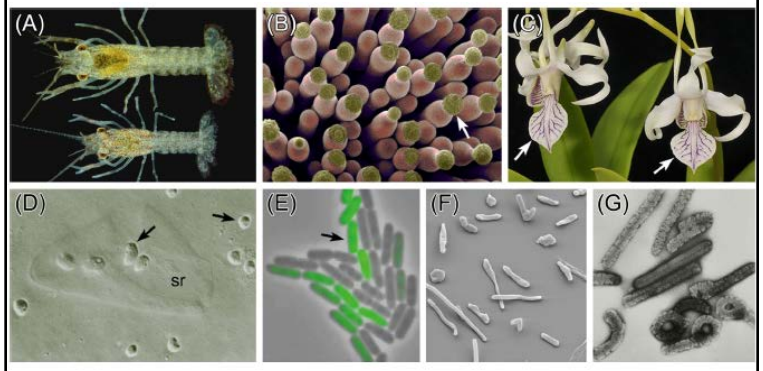
Molecular Evolution of Insect Sociality: An Eco-Evo-Devo Perspective.
Toth AL, Rehan SM.
Annu Rev Entomol. 2017 Jan 31;62:419-442.



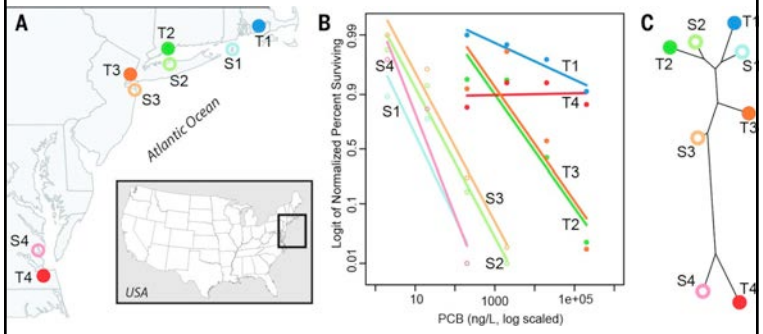


Scenario of genetic assimilation, as applied to the evolution of aggression in honey bees. Initially, individual phenotypic plasticity provides an adaptive response to variable environmental stimuli—for example, aggressive response to predation pressure (time 1). Subsequently, with an environmental change (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).

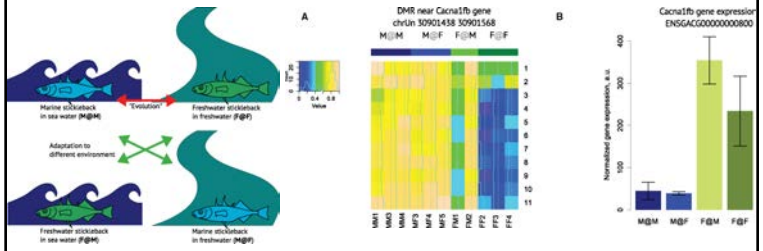
Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences.
Vogt G.
J Biosci. 2015 Mar;40(1):159-204.

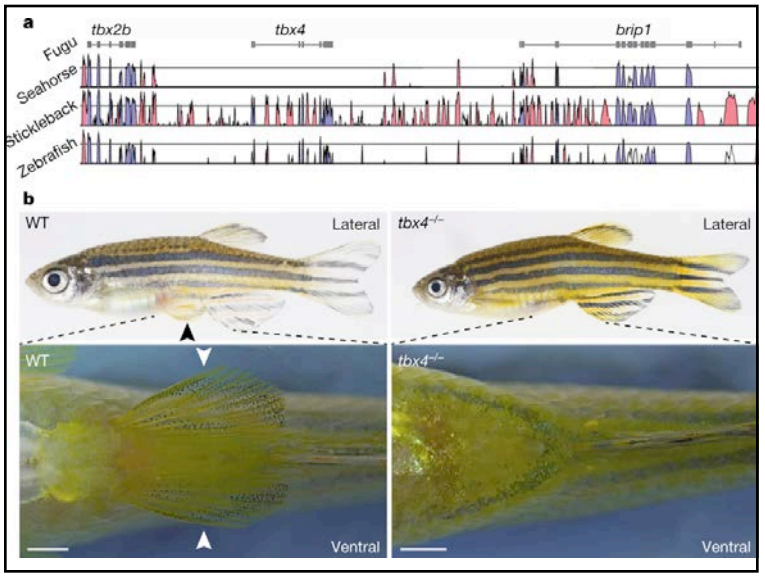


The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish.
Reid NM, Proestou DA, Clark BW, et al.
Science. 2016 Dec 9;354(6317):1305-1308.

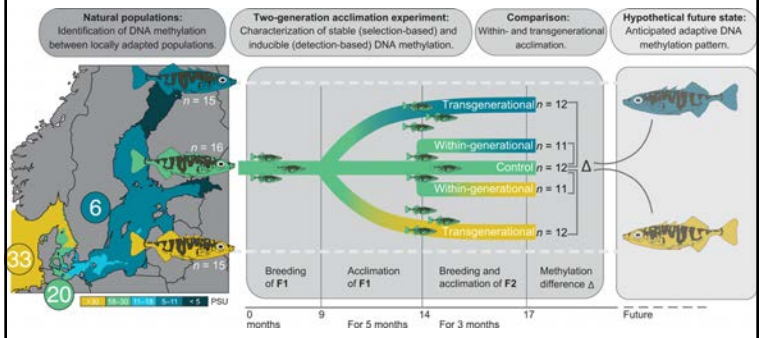


Genome-Wide DNA Methylation Profiling Reveals Epigenetic Adaptation of Stickleback to Marine and Freshwater Conditions.
Mol Biol Evol. 2017 Sep 1;34(9):2203-2213.
Artemov AV, Mugue NS, Rastorguev SM, et al.

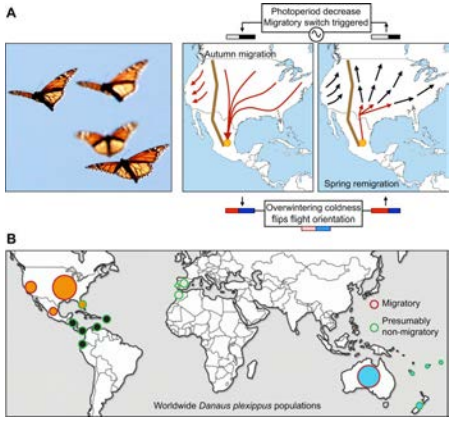




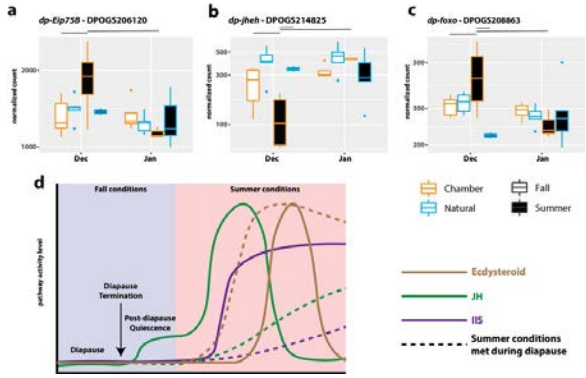
Two different epigenetic information channels in wild three-spined sticklebacks are involved in salinity adaptation
Heckwolf MJ, Meyer BS, Häsler R, Höppner MP, Eizaguirre C, Reusch TBH.
Sci Adv. 2020 Mar 20;6(12):eaaz1138.



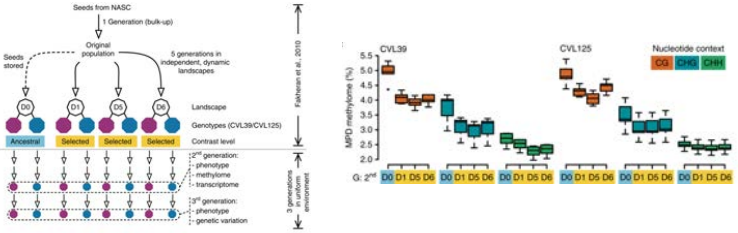
The genetics and epigenetics of animal migration and orientation: birds, butterflies and beyond.
J Exp Biol. 2019 Feb 6;222(Pt Suppl 1).
Merlin C, Liedvogel M.



Monarch butterflies use an environmentally sensitive, internal timer to control overwintering dynamics
Green DA 2nd, Kronforst MR.
Mol Ecol . 2019 Aug;28(16):3642-3655.



Contribution of epigenetic variation to adaptation in Arabidopsis.
Nat Commun. 2018 Oct 25;9(1):4446.
Schmid MW, Heichinger C, Coman Schmid D, et al.

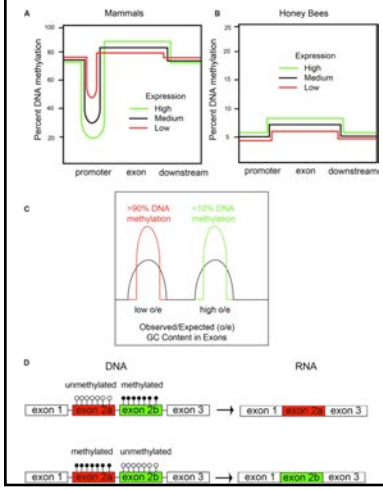


Epigenetic Responses to Temperature and Climate.
McCaw BA, Stevenson TJ, Lancaster LT.
Integr Comp Biol. 2020 Dec 16;60(6):1469-1480.

Abstract

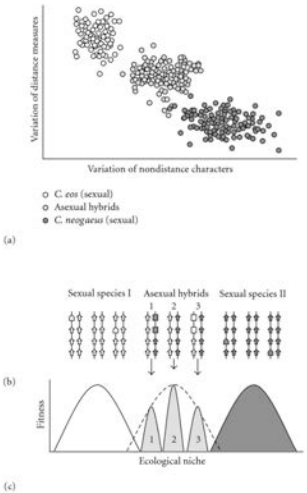
Epigenetics represents a widely accepted set of mechanisms by which organisms respond to the environment by regulating phenotypic plasticity and life history transitions. Understanding the effects of environmental control on phenotypes and fitness, via epigenetic mechanisms, is essential for understanding the ability of organisms to rapidly adapt to environmental change. This review highlights the significance of environmental temperature on epigenetic control of phenotypic variation, with the aim of furthering our understanding of how epigenetics might help or hinder species' adaptation to climate change. It outlines how epigenetic modifications, including DNA methylation and histone/chromatin modification, (1) respond to temperature and regulate thermal stress responses in different kingdoms of life, (2) regulate temperature-dependent expression of key developmental processes, sex determination, and seasonal phenotypes, (3) facilitate transgenerational epigenetic inheritance of thermal adaptation, (4) adapt populations to local and global climate gradients, and finally (5) facilitate in biological invasions across climate regions. Although the evidence points towards a conserved role of epigenetics in responding to temperature change, there appears to be an

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.
Ruden DM, Cingolani PE, Sen A, Qu W, Wang L, Senut MC, Garfinkel MD, Sollars VE, Lu X.



DNA methylation in honeybees correlates with gene expression and alternative splicing. (A) There are two types of DNA methylation in mammals: (1) promoter DNA methylation, which inversely correlates with mRNA expression; and (2) exon DNA methylation, which positively correlates with mRNA expression. (B) Honeybees predominantly have DNA methylation in exons, which, like in mammals, positively correlates with gene expression. (C) There are two types of genes in honeybees: (1) housekeeping genes with low observed/expected (o/e) CG content and high amounts of DNA methylation, and (2) caste-specific and developmental regulatory genes with a high o/e CG content and low amounts of DNA methylation. We have shown that the DNA methylation is at both CpG and CHH sites – CpG methylation primarily in exons and CHH methylation primarily in introns. (D) DNA methylation of cassette exons leads to their exclusion by alternative splicing in honeybees.

The key role of epigenetics in the persistence of asexual lineages.
Genet Res Int. 2012;2012:534289.
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.

Sociobiology and Evolutionary Biology

Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior.

O'Connell LA, Hofmann HA.
Front Neuroendocrinol. 2010 Dec 14.
[Epub ahead of print]

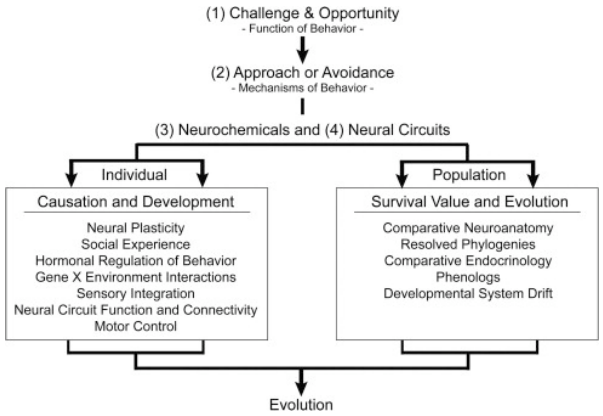
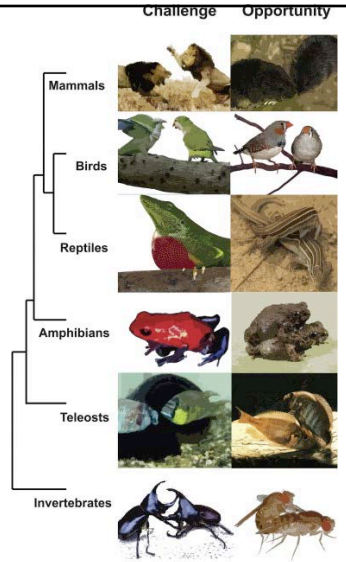


Fig. 1. An integrative framework for the analysis of social behavior and its evolution. Themes for studying both the proximate and ultimate mechanisms of social decision-making are presented on the level of the individual (left panel) and the population (right panel).



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.

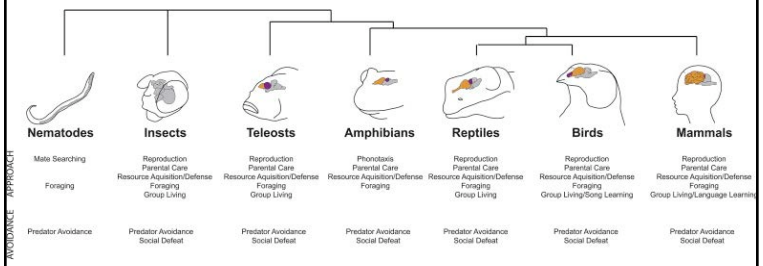


Fig. 3. Approach and avoidance: a mechanistic framework. Quantitative measures of behavioral responses to challenges and opportunities that are tractable in all species provide an important foundation for analyzing the molecular and neural basis of social behavior and its evolution. Brains are shaded differently by forebrain and midbrain.

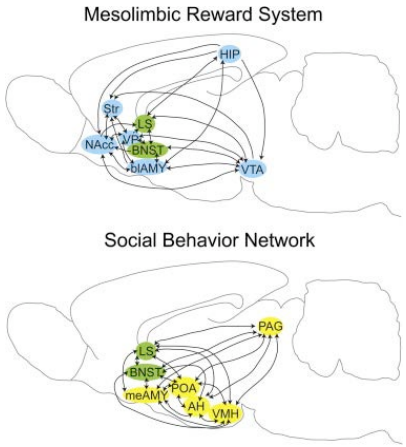


Fig. 4. A neural circuit framework. Schematic representations of a mammalian brain are shown with brain regions of the mesolimbic reward system (blue; top panel) and social behavior network (yellow; bottom panel). Regions shared by both circuits are labeled in green. Adapted from Ref. [199]. Arrows indicated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

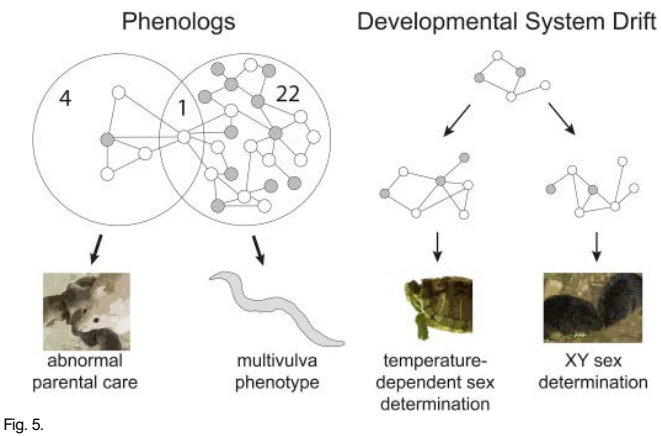


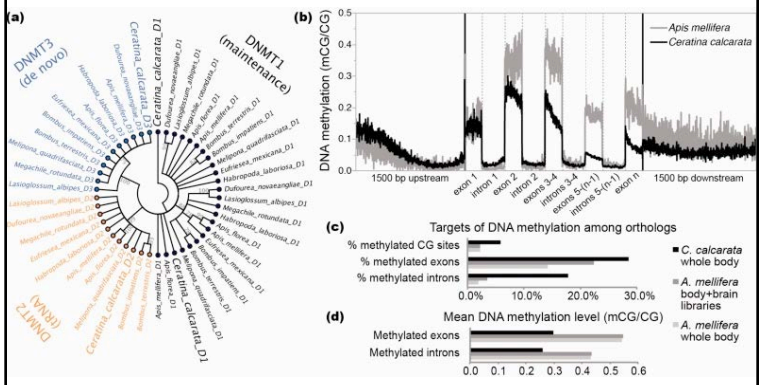
Fig. 5.

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.

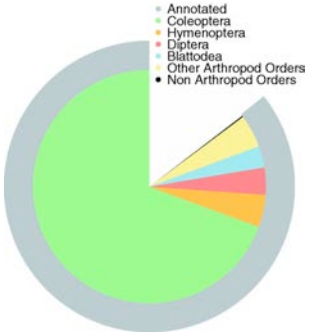
Genome Biol Evol. 2016 May 13;8(5):1401-10.



The Genome and Methylome of a Beetle with Complex Social Behavior, Nicrophorus vespilloides (Coleoptera: Silphidae).

Cunningham CB, Ji L, Wiberg RA, et al.

Genome Biol Evol. 2015 Oct 9;7(12):3383-96.



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.

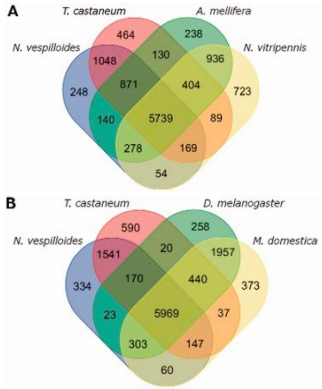
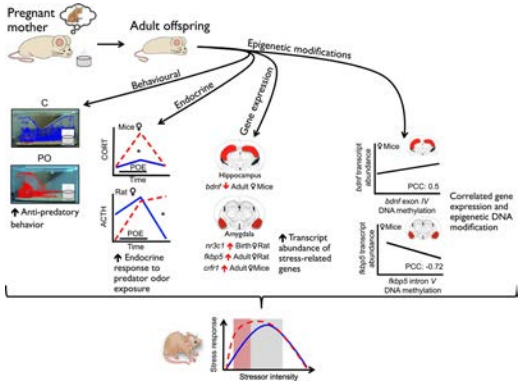


Figure shows the results of the OrthoMCL analysis that clustered the proteomes of *N. vespilloides, T. castaneum, A. mellifera, Na. vitripennis, D. melanogaster,* and *M. domestica* into orthologous groupings. (A) A Venn diagram showing the overlap in the orthologous groupings of the two beetles (*T. castaneum and N. vespilloides*) and the two Hymenoptera (*A. mellifera* and *Na. vitripennis*). (B) A Venn diagram showing the overlap in orthologous groupings of the two beetles (*T. castaneum* and *N. vespilloides*) and the two Diptera (*D. melanogaster* and *M. domestica*).

Adaptation or pathology? The role of prenatal stressor type and intensity in the developmental programing of adult phenotype

Neurotoxicol Teratol. 2018 Mar - Apr;66:113-124.

St-Cyr S, McGowan PO.



Epigenomics and gene regulation in mammalian social systems

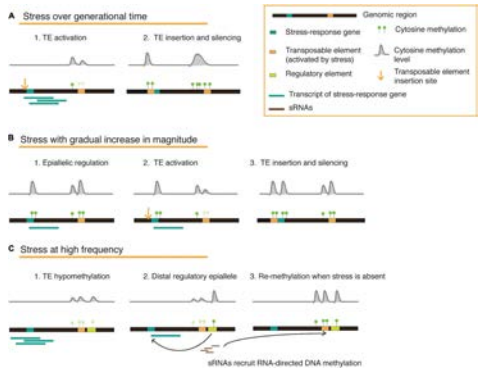
Guerrero TP, Fickel J, Benhaiem S, Weyrich A.

Curr Zool. 2020 Jun;66(3):307-319.

Abstract

Social epigenomics is a new field of research that studies how the social environment shapes the epigenome and how in turn the epigenome modulates behavior. We focus on describing known gene-environment interactions (GEIs) and epigenetic mechanisms in different mammalian social systems. To illustrate how epigenetic mechanisms integrate GEIs, we highlight examples where epigenetic mechanisms are associated with social behaviors and with their maintenance through neuroendocrine, locomotor, and metabolic responses. We discuss future research trajectories and open questions for the emerging field of social epigenomics in nonmodel and naturally occurring social systems. Finally, we outline the technological advances that aid the study of epigenetic mechanisms in the establishment of GEIs and vice versa.

How Stress Facilitates Phenotypic Innovation Through Epigenetic Diversity
Srikant T, Drost H-G.
Front Plant Sci. 2021 Jan 15;11:606800.



Sexual Selection and Evolutionary Biology

On the origin of species by natural and sexual selection.

van Doorn GS, Edelaar P, Weissing FJ.
Science. 2009 Dec 18;326(5960):1704-7.

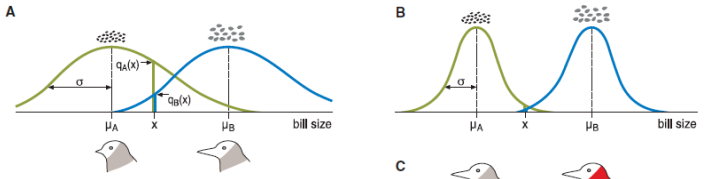


Fig. 1. Illustration of the model structure. Our model considers a patchy environment with differing environmental conditions (small seeds in patch A, large seeds in patch B). Organisms differ in an ecological character (bill size). The green Gaussian curve describes how fitness $q_A(x)$ in patch A varies with bill size x, whereas the blue curve characterizes fitness $q_B(x)$ in patch B. **(A)** In case of a wide fitness curve (large σ), a bird with an intermediate bill size x achieves a higher average fitness across habitats $\frac{1}{2}[q_A(x) + q_B(x)]$ than a small-seed specialist ($x = \mu_A$) or a large-seed specialist ($x = \mu_B$). Hence, selection is stabilizing and favors a generalist food-exploitation strategy (i.e., an intermediate bill size). **(B)** If σ is small, the fitness of the generalist strategy is very low. Selection is disruptive, favoring the two specialist food-exploitation strategies. **(C)** The colored collar represents a sexual ornament that is expressed in a condition-dependent manner. For the same allocation of resources to the ornament, small-billed birds can produce a more attractive (red) ornament in the small-seed patch A (labeled "habitat A" in the figure), whereas large-billed birds can produce a more attractive ornament in the large-seed patch B (labeled "habitat B"). Hence, the ornament functions as an indicator of local adaptation.

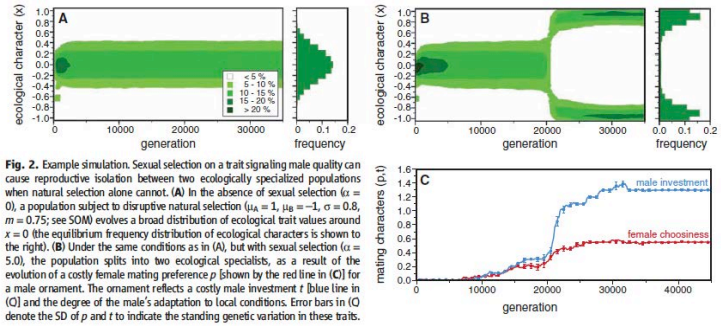


Fig. 2. Example simulation. Sexual selection on a trait signaling male quality can cause reproductive isolation between two ecologically specialized populations when natural selection alone cannot. (**A**) In the absence of sexual selection ($\alpha = 0$), a population subject to disruptive natural selection ($\mu_A = 1$, $\mu_B = -1$, $\sigma = 0.8$, $m = 0.75$; see SOM) evolves a broad distribution of ecological trait values around $x = 0$ (the equilibrium frequency distribution of ecological characters is shown to the right). (**B**) Under the same conditions as in (A), but with sexual selection ($\alpha = 5.0$), the population splits into two ecological specialists, as a result of the evolution of a costly female mating preference p [shown by the red line in (**C**)] for a male ornament. The ornament reflects a costly male investment t [blue line in (C)] and the degree of the male's adaptation to local conditions. Error bars in (C) denote the SD of p and t to indicate the standing genetic variation in these traits.

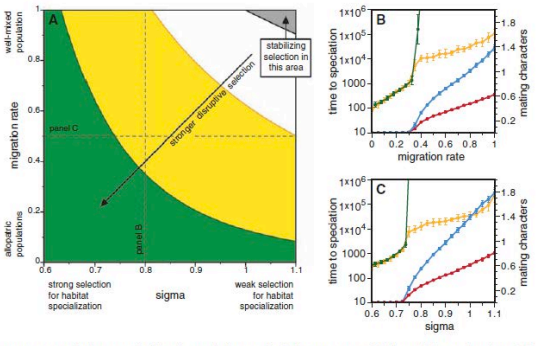
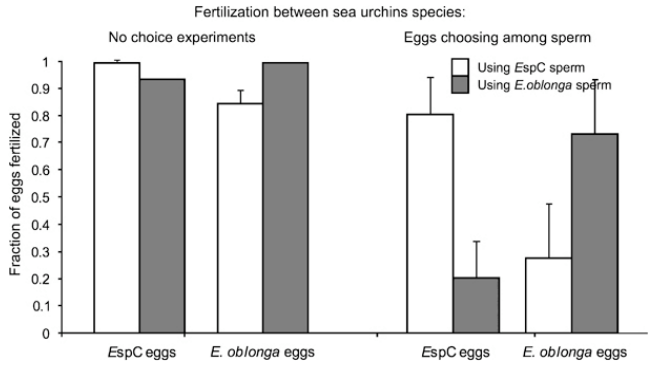


Fig. 3. Effect of ecological parameters on the rate of speciation. (**A**) Without sexual selection, ecological disruptive selection must be strong to induce speciation (green area). When mate choice reinforces ecological disruptive selection, speciation can occur under a broader range of parameters (yellow area). Below the yellow contour, speciation occurred within 10^5 generations in more than 50% of the simulations. (**B** and **C**) Orthogonal transects through parameter space illustrate a sharp increase of the time to speciation (green lines, in the absence of sexual selection) above a certain rate of migration [(B), $m > 0.3$] and below a critical strength of selection on the ecological character [(C), $\sigma > 0.75$]. With sexual selection, the time to speciation (yellow lines) increases gradually: As m and σ increase and ecological disruptive selection becomes weaker, higher values of the mating characters (red, female choosiness; blue, male investment into ornament expression) are required for the population to split. Points are mean ± SD (denoted by error bars) over 20 replicate simulations; other parameters are the same as those in Fig. 2.

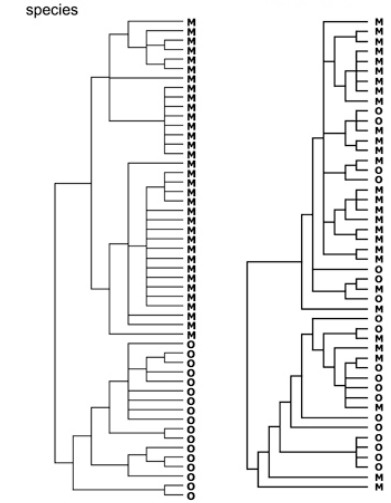
Speciation and the evolution of gamete recognition genes: pattern and process.

Palumbi SR.

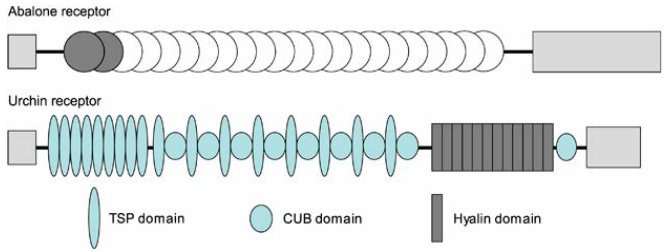
Heredity. 2009 Jan;102(1):66-76.



When eggs of the sea urchins Echinometra oblonga and E. sp. C. 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 tRNA-deacyclase (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.)

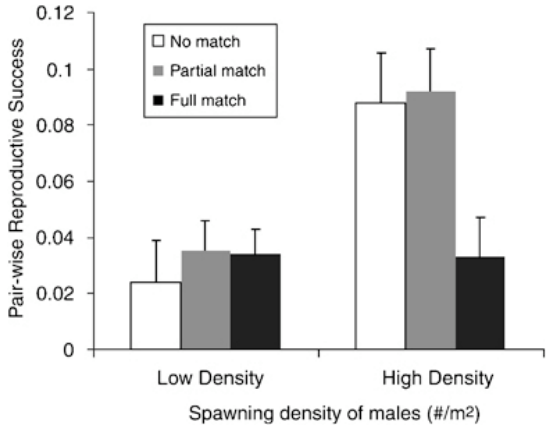


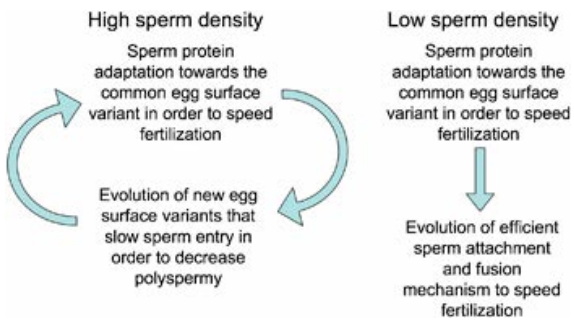
Architecture of sperm receptor proteins in abalone and sea urchins typically includes repeated amino-acid motifs. Motifs that bind sperm proteins are circles in the abalone receptor and rectangles for sea urchins. Motifs under positive selection have dark shading. The sea urchin receptor is modeled after 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 sequence of sea urchin sperm binding motif

SpurpEBR1	PVISGCPSDQNVTTDIGNATAVVIWPPTATDNSGSQTLTSTNNPGDDFPIGNNTVTY
SpurpEBR1	.....
SpurpRepeat_1	..F.....N.....
SpurpRepeat_3	..F.....
SpurpRepeat2	.....A..S.....N.....
SpurpRepeat3	..F.....
SpurpRepeat4	.....A.....N.....
SpurpRepeat5	.....
SpurpRepeat6	..F.....
SpurpRepeat7	.....N.....
SpurpRRepeat8	.....A.....T.....VN.....
Em16	..F.....VLTFN..P.KV..I.T.I.L.....N....D...HS.....H....
Em16	..F.....S.G..S.....T.A.N.....D.....S...Y.....T..N.
Em16	.G.....T.N.FLRKPV.Q.T...N....A.N.....SH.S..T.....T..N.
Em16	..F.....S.N..P...A...T...S.M....T.....N.....
Em16	..F.....S.G.GS.....T.A.N.....D.....S...Y.....T..N.
Eob27	..F.....S.N..P...A...T...S.M....T.....N.....
Eob27	..F.....S.G..S.....A.S...N.....N.I...AS....Y.....
Eob27	..F.....S.N..P.....T...N.....IV.V....S...S.....

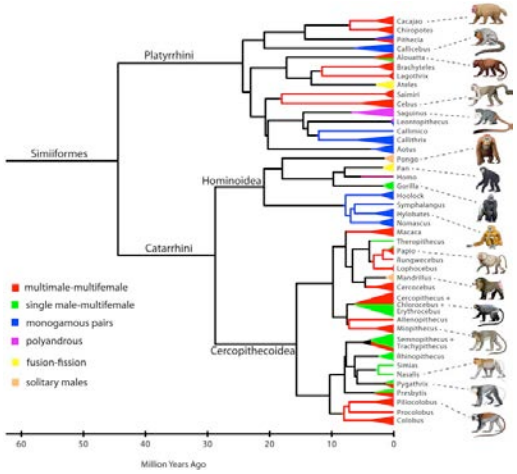
Amino-acid variation in the hyalin-like repeats motifs of the sea urchin sperm receptor within and between species. The top 11 sequences are from different repeats of the EBR1 gene sequenced from Strongylocentrotus purpuratus (Kamei and Glabe, 2003), showing variation at six amino-acid positions. Sequences 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.

Sexual selection and the evolution of behavior, morphology, neuroanatomy and genes in humans and other primates.
Neurosci Biobehav Rev. 2014 Oct 14;46P4:579-590.
Stanyon R, Bigoni F.



A phylogenetic scheme of Similiformes at the genus level. The various colors correspond to the predominant social mating system: red = multimale–multifemale (polygynandrous), green = single male–multifemale, blue = monogamous pairs, pink = polyandrous, yellow = fusion–fission, orange = solitary males. Modified from Springer et al. (2012) (http://creativecommons.org/licenses/by/2.5/); data on social structure are from Fleagle (2013). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Unravelling the role of epigenetics in reproductive adaptations to early-life environment.
Bar-Sadeh B, Rudnizky S, Pnueli L, Bentley GR, Stöger R, Kaplan A, Melamed P.
Nat Rev Endocrinol. 2020 Sep;16(9):519-533.

Key points

- Human reproductive function adjusts to changing environmental conditions.
- Key 'windows of susceptibility' during various stages of early development are the most sensitive to events or exposures that can impart long-term reprogramming of adult reproductive function.
- Epigenetic modifications have a role in regulating the central control of reproduction and pubertal onset and likely mediate much of the adaptive response.
- Human cohort data are useful for identifying methylation in proxy tissues that correlates with phenotypic variation, but determining cause and effect is challenging because hormones affect the epigenome and epigenetic ageing.
- Understanding which of the modifications are functional and responsible

Epigenetic Transgenerational Inheritance

and Evolutionary Biology

Epigenetic Inheritance Systems

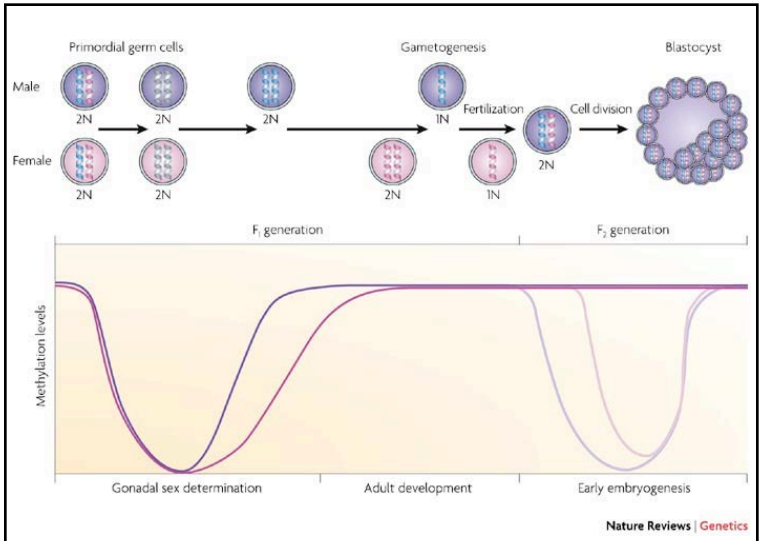
The Inheritance of Environmentally Induced Traits

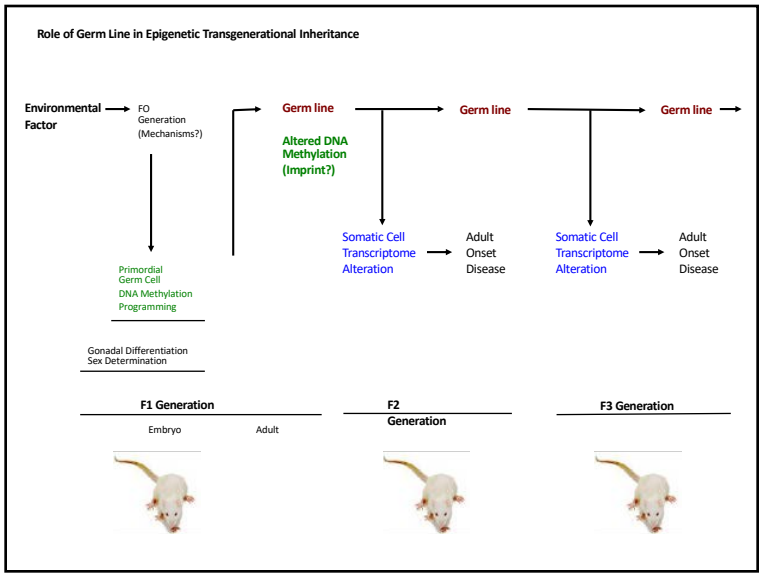
Ecological evolutionary developmental biology, or "eco-evo-devo," has the data to bring two controversial alternative inheritance systems back into the discussion of evolutionary biology. The first idea concerns the inheritance of environmentally acquired traits, an ancient idea usually associated with 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."

The Ghost of Lamarck

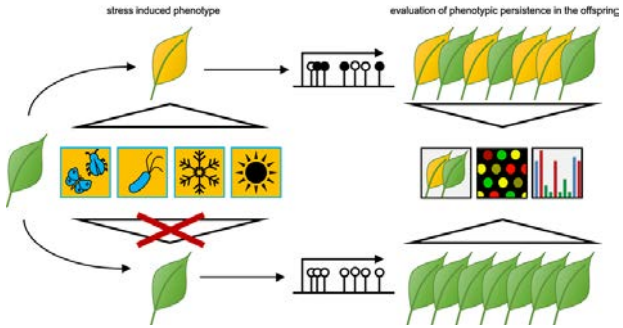
Epigenetic inheritance systems recall the specter of a banished ghost—Lamarckian inheritance. The year 2009 is not only the bicentenary of Darwin's birth and the centenary of the Woltereck and the Johannsen papers described in Chapter 1, it is also the bicentenary of Lamarck's *Philosophie Zoologique*.

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.

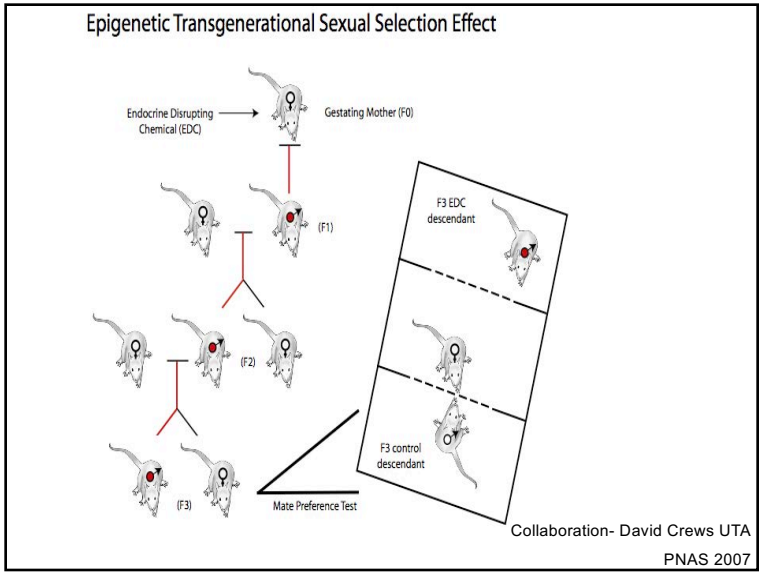


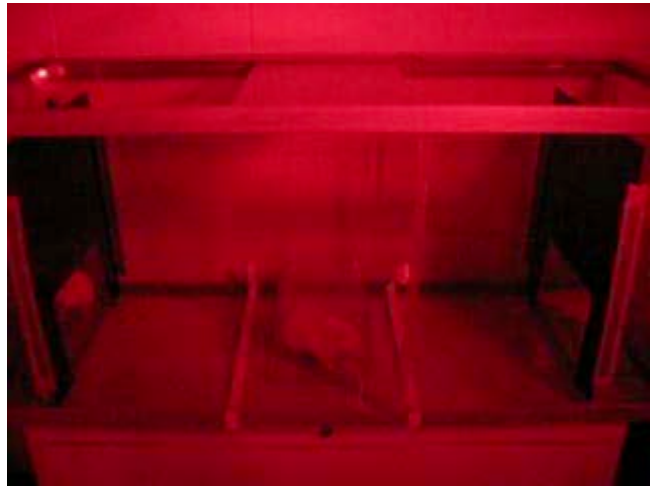


Transgenerational stress-adaption: an opportunity for ecological epigenetics. Plant Cell Rep. 2018 Jan;37(1):3-9.
Weinhold A.



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)





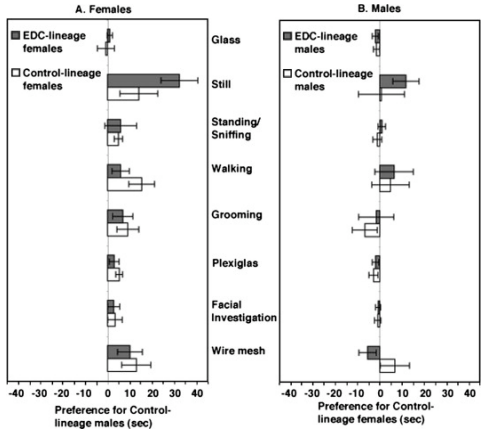
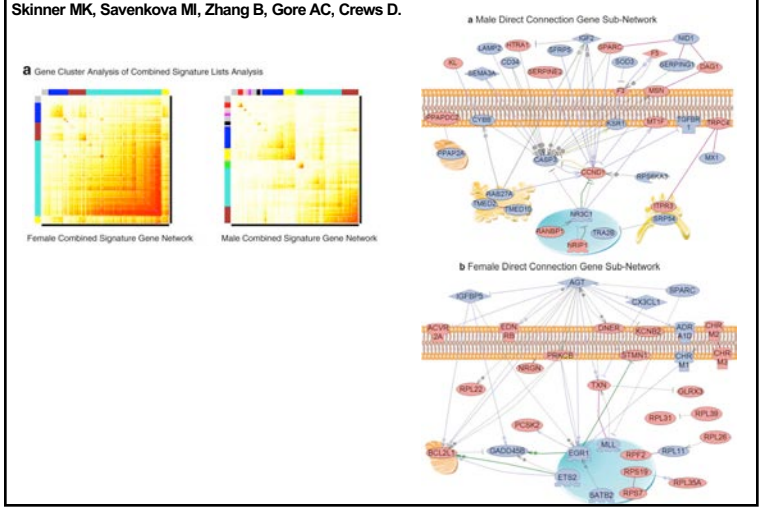
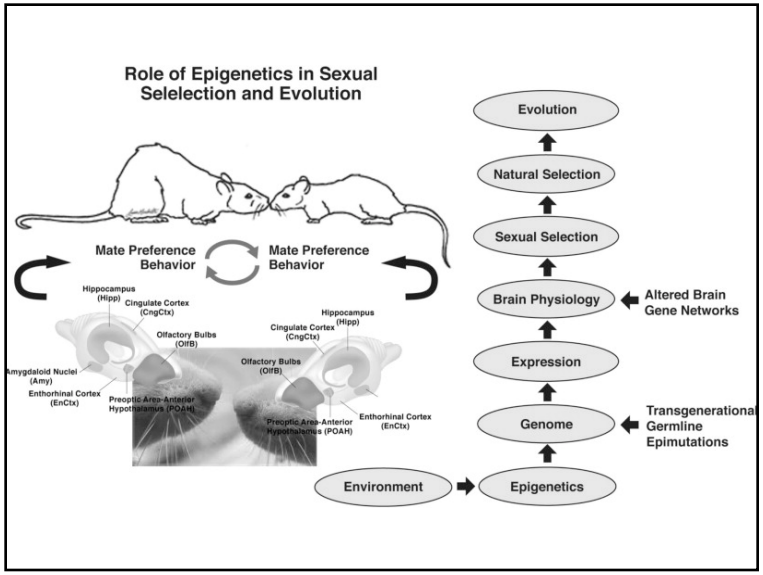
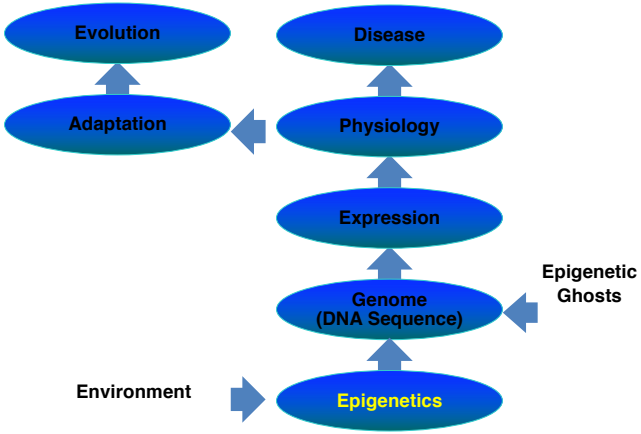


Fig. 7. Third-generation female rats whose progenitors were exposed to vinclozolin, a common-use fungicide with endocrine-disrupting (EDC) properties, and hence epigenetically altered, prefer males from the unexposed Control-lineage. Males do not show this preference. See Fig. 6 for further details. 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].

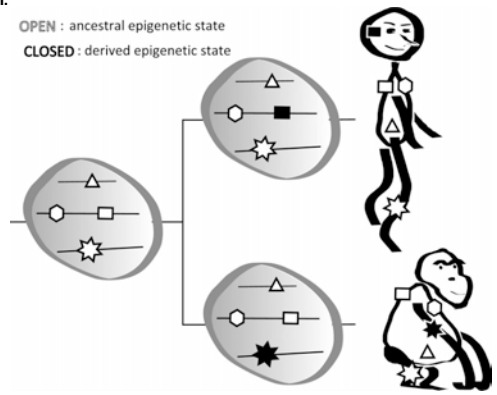
Gene bionetworks involved in the epigenetic transgenerational inheritance of altered mate preference: environmental epigenetics and evolutionary biology.
BMC Genomics. 2014 May 16;15:377.
Skinner MK, Savenkova MI, Zhang B, Gore AC, Crews D.





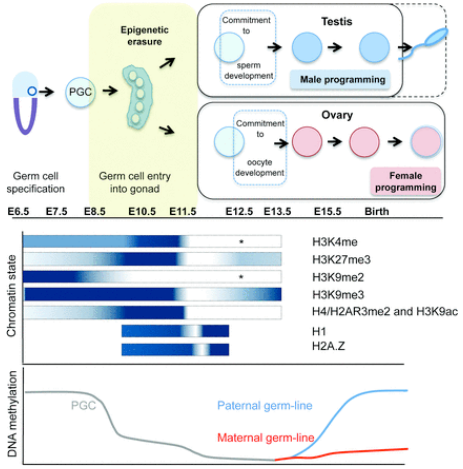


Epigenetic inheritance: a contributor to species differentiation?
DNA Cell Biol. 2012 Oct;31 Suppl 1:S11-6.
Boffelli D, Martin DI.

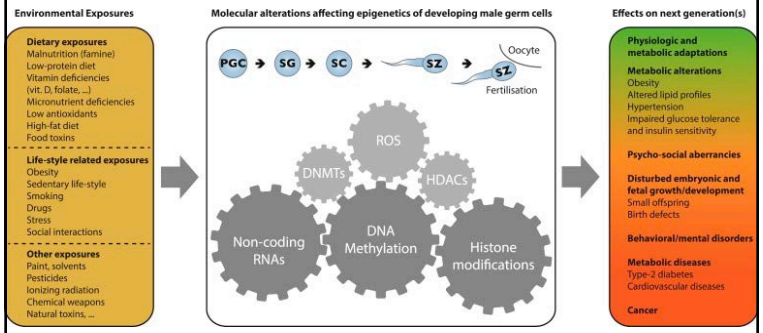


Model for the gain of an active state in somatic tissues following a change of epigenetic state in the germline. We assume that the germline state of certain transcriptional regulatory elements constrains the range of somatic cell types in which those elements will be active (the open elements, representing 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.

Fine-tuning evolution: germ-line epigenetics and inheritance.
Reproduction. 2013 Jun 14;146(1):R37-48.
Stringer JM, Barrand S, Western P.



Epigenetic inheritance and evolution: A paternal perspective on dietary influences.
Prog Biophys Mol Biol. 2015 Mar 10. pii: S0079-6107(15)00033-4.
Soubry A.



Epigenetic variations in heredity and evolution.
Clin Pharmacol Ther. 2012 Dec;92(6):683-8
Jablonka E.

Table 2 Relations between genetic and epigenetic variations (e.g., marks such as methylation patterns) at a particular locus

	Acquisition (induction) of epigenetic variant		
Inheritance of epigenetic variant	**Obligatory**	**Facilitated**	**Independent of DNA sequence variation**
Obligatory	The variant and its inheritance are fully determined by the specific DNA sequence	The DNA sequence affects the likelihood of acquiring particular variants; their inheritance is dependent on the DNA sequence	The DNA sequence does not determine which variant is acquired, but its inheritance is dependent on the DNA sequence
Facilitated	The variant is determined by the DNA sequence; some variants are more likely to be inherited than others	The DNA sequence affects both the likelihood of acquiring particular variants and the likelihood of their inheritance	The DNA sequence does not determine which variant is acquired but does affect the likelihood of it being inherited
Independent of DNA variation	The variant is determined by the DNA sequence, but the likelihood of it being inherited is not	The DNA sequence affects the likelihood of acquiring particular variants but not the likelihood of their being inherited	The DNA sequence determines neither which variant is acquired nor the likelihood of it being inherited

Obligatory acquisition: the specific DNA sequence determines which of several theoretically possible marks can be acquired; *obligatory inheritance*: the DNA sequence determines whether or not the mark is inherited. Changes in the environment do not change the mark, the likelihood of its inheritance, or the fidelity with which it is inherited. *Facilitated acquisition*: the likelihood of acquiring a particular mark is affected by the DNA sequence, but is not fully determined by it; *facilitated inheritance*: the DNA sequence affects, but does not fully determine, the mark's transmission to the next generation. Environmental conditions affect the likelihood of acquiring particular marks, the likelihood that they are inherited, and the fidelity with which they are inherited. *Independent acquisition and transmission*: total independence of DNA variation is, of course, impossible; "independent" acquisition means that for a given genotype, the same DNA sequence can acquire many different marks; "independent" inheritance means that all these different marks can be inherited. The marks acquired and fidelity of transmission are dependent on environmental conditions in ancestral generations.

Short-term heritable variation overwhelms 200 generations of mutational variance for metabolic traits in Caenorhabditis elegans

Johnson LM, Smith OJ, Hahn DA. Baer CF.

Evolution. 2020 Nov;74(11):2451-2464.

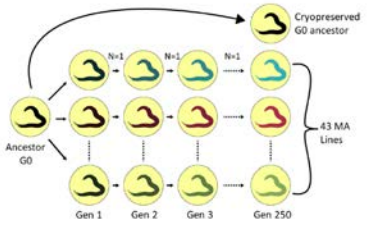
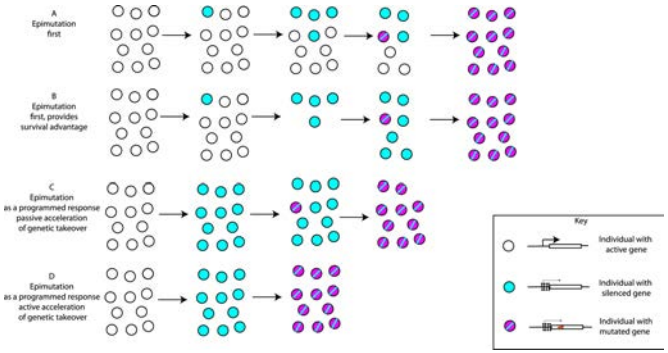


Figure 2. Propagation of mutation accumulation (MA) lines. The G0 ancestor was thawed from a cryopreserved sample and a single hermaphrodite picked onto each of 100 agar plates. MA lines were propagated via single worm descent for ~250 generations. Forty-three MA lines and the G0 ancestor were included in this experiment.

Molecular mechanisms of epigenetic inheritance: Possible evolutionary implications.

Sarkies P.

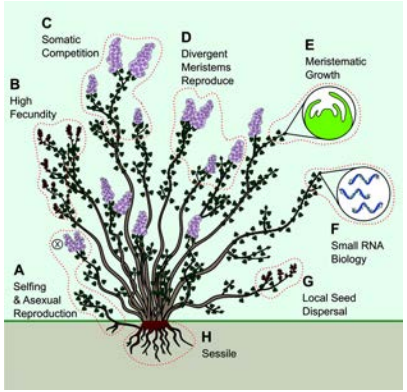
Semin Cell Dev Biol. 2020 Jan;97:106-115.



Does variable epigenetic inheritance fuel plant evolution?

Minow MAA, Colasanti J.

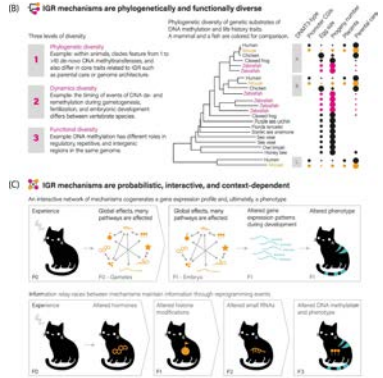
Genome. 2020 May;63(5):253-262.



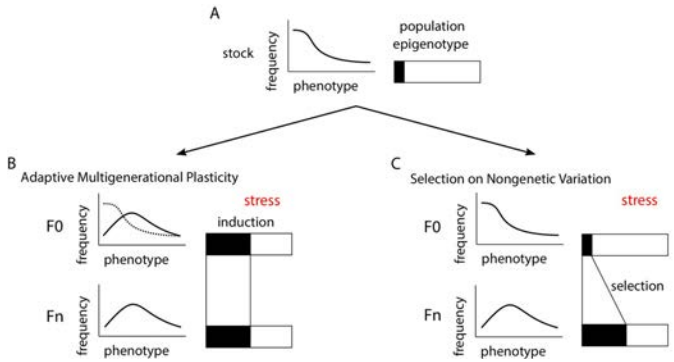
Understanding 'Non-genetic' Inheritance: Insights from Molecular-Evolutionary Crosstalk.

Adrian-Kalchhauser I, Sultan SE, Shama LNS, Spence-Jones H, Tiso S, Keller Valsecchi CI, Weissing FJ.

Trends Ecol Evol. 2020 Dec;35(12):1078-1089.



Nongenetic inheritance and multigenerational plasticity in the nematode C. elegans.
Baugh LR, Day T.
Elife. 2020 Aug 25;9:e58498.



What's all the fuss about? The inheritance of acquired traits is compatible with the Central Dogma.
Camacho MP.
Hist Philos Life Sci. 2020 Jul 20;42(3):32.

Abstract

The Central Dogma of molecular biology, which holds that DNA makes protein and not the other way around, is as influential as it is controversial. Some believe the Dogma has outlived its usefulness, either because it fails to fully capture the ins-and-outs of protein synthesis (Griffiths and Stotz in Genetics and philosophy Cambridge introductions to philosophy and biology, Cambridge University Press, Cambridge, 2013; Stotz in Hist Philos Life Sci 28(4):533-548, 2006), because it turns on a confused notion of information (Sarkar in Molecular models of life, MIT Press, Cambridge, 2004), or because it problematically assumes the unidirectional flow of information from DNA to protein (Gottlieb, in: Oyama, Griffiths, Gray (eds), Cycles of contingency: developmental systems and evolution, MIT Press, Cambridge, 2001). This paper evaluates an underexplored defense of the Dogma, which relies on the assumption that the Dogma and the Inheritance of Acquired Traits, a principle which dates as far back as Jean Baptiste-Lamarck, are incompatible principles (Smith in The theory of evolution, Cambridge University Press, Cambridge, 1993; Judson in The eighth day of creation, Jonathan Cape, London, 1979; Dawkins in The extended phenotype, Oxford University Press, Oxford, 1970; Cobb in PLoS Biol 15(9):e2003243, 2017. https://doi.org/10.1371/journal.pbio.2003243 ; Wilkins in BioEssays 24(10):960-973, 2002. https://doi.org/10.1002/bies.10167 ; Graur The fallacious commingling of

Inbreeding, Epigenetics and Evolutionary Biology

FUNDAMENTAL CONCEPTS IN GENETICS

The genetics of inbreeding depression

Deborah Charlesworth 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.

Table 1 | **Detecting inbreeding depression and genetic load**

Type of organism	Method	Quantities estimated	Refs
Direct detection (experiments or pedigree information)			
Self-compatible hermaphrodite animal or plant (or monoecious plant*)	Comparisons of offspring produced by self-fertilization with offspring produced by outcrossing	δ[‡] for one generation of selfing	1,96
Cyclically asexual animals[§]	Mating females with their brothers from the same asexual clone; this is genetically equivalent to self-fertilization	δ for one generation of selfing	19
Organisms with separate sexes	Sib-mating for one or more generations and other types of mating to produce experimental individuals with various inbreeding coefficients	Inbreeding load	140,141
Haplodiploid organisms	Mother–son inbreeding (generating higher inbreeding coefficients than ordinary diploid sib-matings)	None (detection only)	142
Ferns or mosses	Intragametophyte selfing[‖]	Effect of complete genome homozygosity	143,144
All organisms	Analyses of the relationship between trait values and inbreeding coefficients based on pedigree information	Inbreeding load	145
Indirect detection (using genetic markers)			
All organisms	Use of inbreeding coefficients estimated from frequencies of homozygotes and heterozygotes for genetic markers or SNPs	Inbreeding load	146–149
All organisms	Examination of genetic ratios at marker loci: deficiency of one homozygote in families or a significant heterozygote excess in a family (or in inbred lines relative to the heterozygote frequency predicted for neutral alleles by the inbreeding coefficient) suggests inbreeding depression due to identity-by-descent for a gene linked to the marker	Detection; estimates of selection and dominance coefficients	10, 150–153
Cyclical parthenogens[§]	Detection of an increase in heterozygote frequency over asexual generations	None (detection only)	154

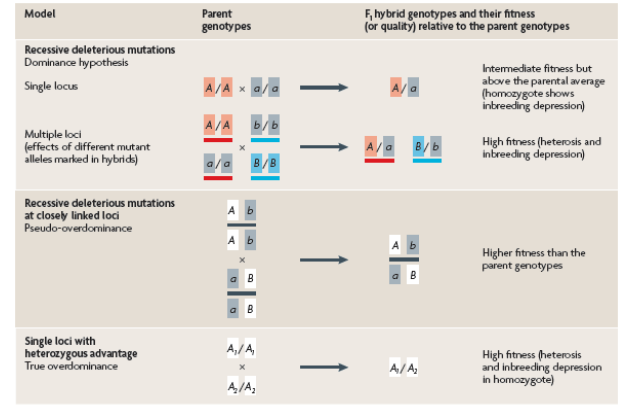


Figure 1 | **Summary of the main genetic hypotheses for inbreeding depression.** These hypotheses were developed by maize geneticists early in the twentieth century but have proved difficult to test (see main text). The increased homozygosity of inbred individuals can lower fitness either because of deleterious mutations with recessive effects, which cause homozygotes to have lower survival or fertility (top and middle rows), or because loci exist with different alleles that result in the higher fitness of heterozygotes (overdominance, bottom row). For the dominance and pseudo-overdominance (mutational) hypotheses, the figure shows how the higher homozygote frequencies for recessive deleterious mutant alleles (indicated as *a* and *b*) among inbred individuals will cause lower fitness than in more heterozygous outbred individuals or hybrids. In the overdominance hypothesis, inbred individuals are less likely to be heterozygous for the two alleles (A_1/A_2) than outbred individuals or hybrids and therefore have lower fitness. See BOX 2 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.

Meiotic 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 *trans* configuration in the same gene, so that neither allele is functional).

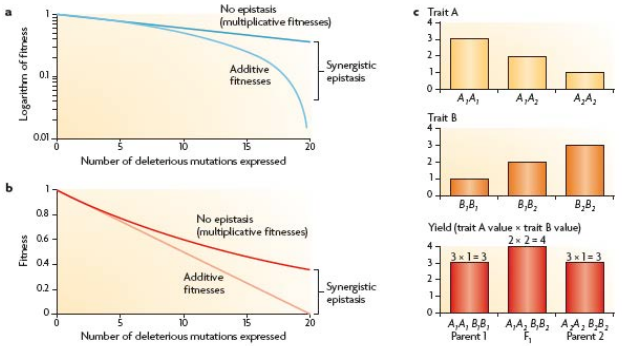
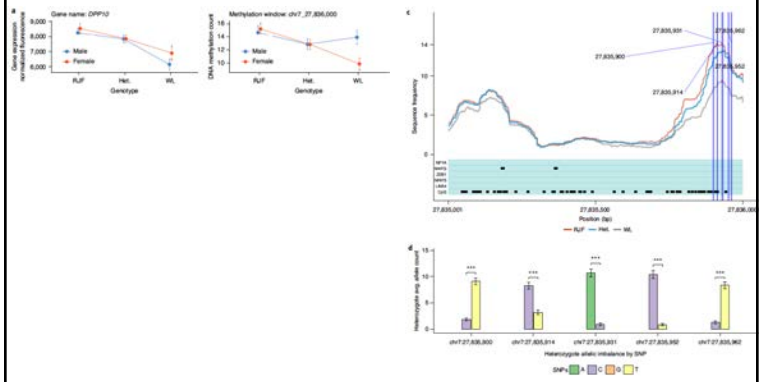


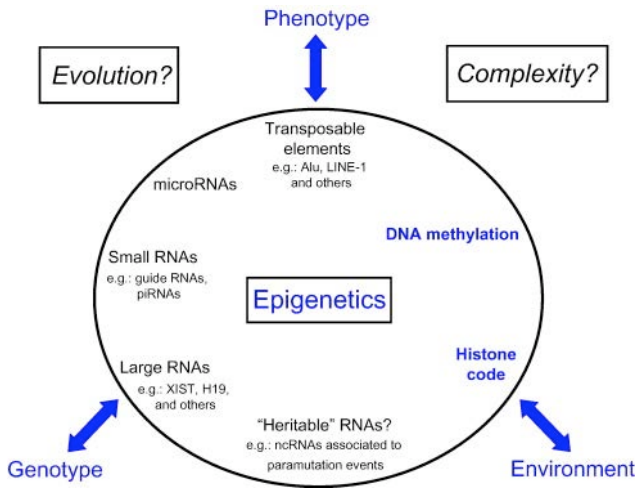
Table 2 | **Differences between inbreeding depression and heterosis**

Nature of the difference	Inbreeding depression	Heterosis*
Genetic variation	Must be present within the species or population	Can appear in F_1 individuals between genetically uniform populations or strains
Effect of genetic drift in small populations	Lowers inbreeding depression due to mildly deleterious mutations in small populations	Heterosis due to mildly deleterious mutations is highest for small populations or highly inbreeding populations
Likelihood of outbreeding depression and its consequences	Unlikely without strong isolation or local adaptation, and therefore unlikely to affect the magnitude of inbreeding depression within a population	May lower the magnitude of heterosis
Complementary interactions between different deleterious recessive mutations	Can cause inbreeding depression if loci are linked, so homozygosity for the genome region lowers fitness (pseudo-overdominance, see FIG. 1)	Can cause heterosis even if loci are unlinked and even if heterozygous alleles at the loci cause phenotypes that are between those of the homozygotes (FIG. 2c)

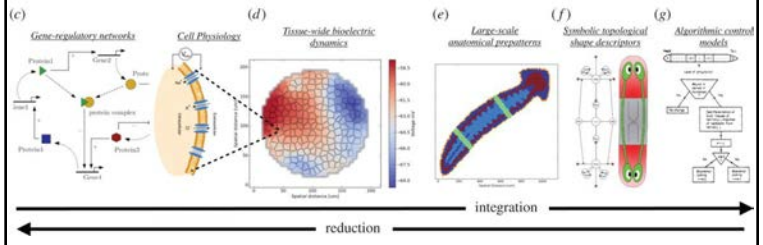
The methylation landscape and its role in domestication and gene regulation in the chicken.
Höglund A, Henriksen R, Fogelholm J, Churcher AM, Guerrero-Bosagna CM, Martinez-Barrio A, Johnsson M, Jensen P, Wright D.
Nat Ecol Evol. 2020 Dec;4(12):1713-1724.

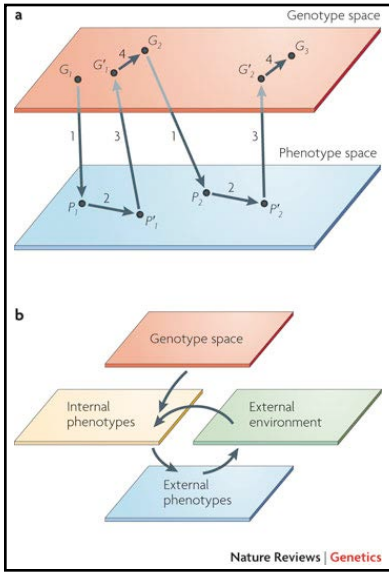


Summary Epigenetics and Evolutionary Biology



Top-down models in biology: explanation and control of complex living systems above the molecular level.
J R Soc Interface. 2016 Nov;13(124).
Pezzulo G, Levin M.





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 variation116, 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 Waddington117 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)118.

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 throughout its life. These internal phenotypes include cellular, tissue level and physiological properties. These internal phenotypes in turn shape external 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.

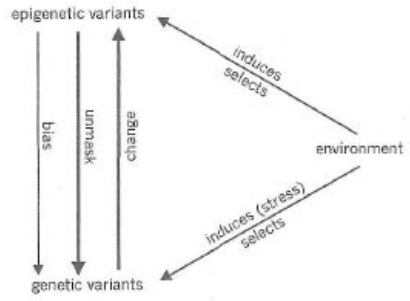


Figure 7.6
The interactions of the genetic and epigenetic systems.

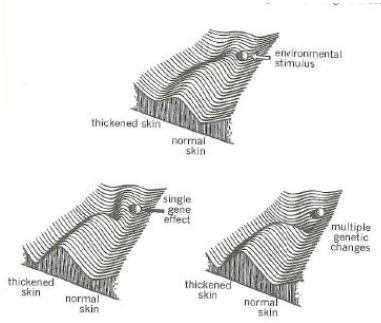
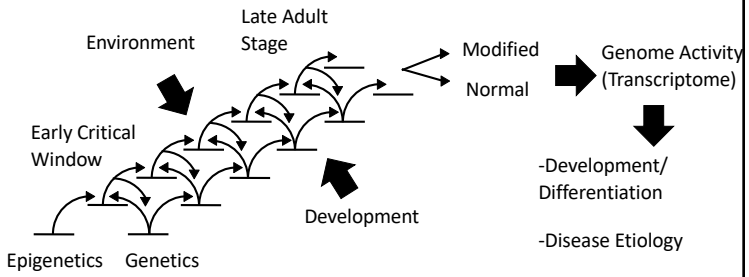


Figure 7.4
Genetic assimilation. At the top, the original epigenetic landscape, in which the main valley leads to normal skin, and a side branch leads to thickened skin. Thick skin is formed only if an environmental stimulus (open arrow) pushes development into the left-hand pathway. Below are two epigenetic landscapes after natural selection has led to genetic assimilation. In both, through selection, the valley leading to thick skin has been tuned and deepened, so that it is an easier path to follow. On the left, a major gene effect (solid arrow) pushes development into this pathway, whereas on the right the selection of variations in many genes has so remodeled the landscape that no stimulus is needed. (Adapted with permission from C. H. Waddington, *The Strategy of the Genes*, Allen and Unwin, London, 1957, p. 167.)



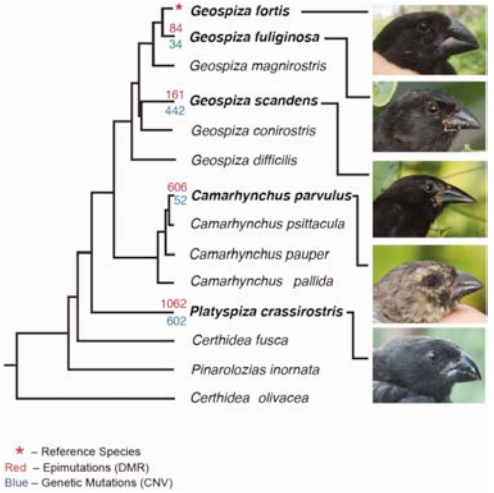
Targeting, constructing, and planning transmitted variation

Inheritance system	Variation is targeted (biased generation)?	Variation subject to developmental filtering and modification?	Variation constructed through direct planning?	Variations can change the selective environment?
Genetic	Generally not, except for the directed changes that are part of development and the various types of interpretive mutation	Usually not, although expressed genetic changes may have to survive selection between cells prior to sexual or asexual reproduction	No	Only insofar as genes can affect all aspects of epigenetics, behavior, and culture
Epigenetic	Yes, a lot of epigenetic variations are produced as specific responses to inducing signals	Yes, selection can occur between cells prior to reproduction; epigenetic states can be modified or reversed during meiosis and early embryogenesis	No	Yes, because the products of cellular activities can affect the environment in which a cell, its neighbors, and its descendants live
Behavioral	Yes, because of emotional, cognitive, and perceptual biases	Yes, behavior is selected and modified during the animal's lifetime	No	Yes, new social behavior and traditions alter the social and sometimes also the physical conditions in which an animal lives
Symbolic	Yes, because of emotional, cognitive, and perceptual biases	Yes, at many levels, in many ways	Yes, at many levels, in many ways	Yes, very extensively, by affecting many aspects of the social and physical conditions of life

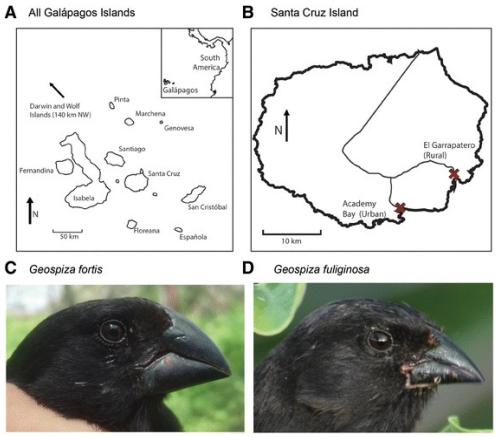
The reproduction of information

Inheritance system	Organization of information	Dedicated copying system?	Transmits latent (nonexpressed) information?	Direction of transmission	Range of variation
Genetic	Modular	Yes	Yes	Mostly vertical	Unlimited
Epigenetic					
Self-sustaining loops	Holistic	No	No	Mostly vertical	Limited at the loop level, unlimited at the cell level
Structural templating	Holistic	No	No	Mostly vertical	Limited at the structure level, unlimited at the cell level
RNA silencing	Holistic	Yes	Sometimes	Vertical and sometimes horizontal	Limited at the single transcript level, unlimited at the cell level
Chromatin marks	Modular and holistic	Yes (for methylation)	Sometimes	Vertical	Unlimited
Organism-level developmental legacies	Holistic	No	No	Mostly vertical	Limited
Behavioral					
Behavior-affecting substances	Holistic	No	No	Both vertical and horizontal	Limited at the single behavior level, unlimited for lifestyles
Nonimitative social learning	Holistic	No	No	Both vertical and horizontal	Limited at the single behavior level, unlimited for lifestyles
Imitation	Modular	Probably	No	Both vertical and horizontal	Unlimited
Symbolic	Modular and holistic	Yes, several	Yes	Both vertical and horizontal	Unlimited

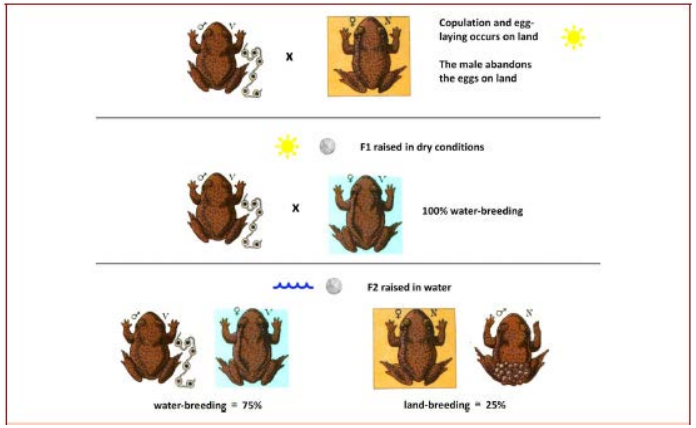
Epigenetics and the evolution of Darwin's Finches.
Genome Biol Evol. 2014 Jul 24;6(8):1972-89.
Skinner MK, Gurerrero-Bosagna C, Haque MM, Nilsson EE, Koop JA, Knutie SA, Clayton DH.



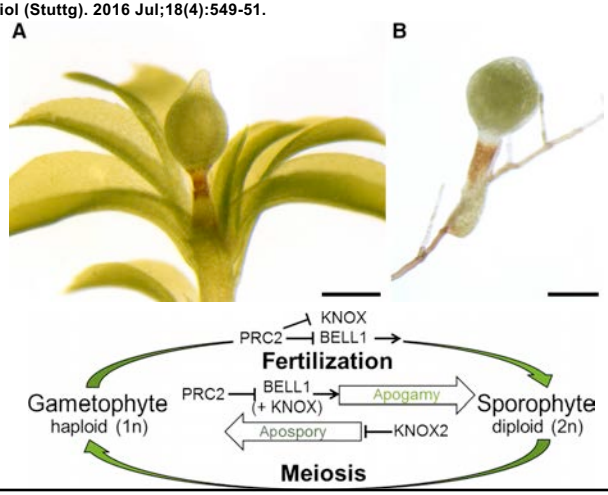
Epigenetic variation between urban and rural populations of Darwin's finches.
BMC Evol Biol. 2017 Aug 24;17(1):183.
McNew SM, Beck D, Sadler-Riggleman I, Knutie SA, Koop JAH, Clayton DH, Skinner MK.



An Epigenetic Perspective on the Midwife Toad Experiments of Paul Kammerer (1880-1926).
Vargas AO, Krabichler Q, Guerrero-Bosagna C.
J Exp Zool B Mol Dev Evol. 2017 Jan;328(1-2):179-192.

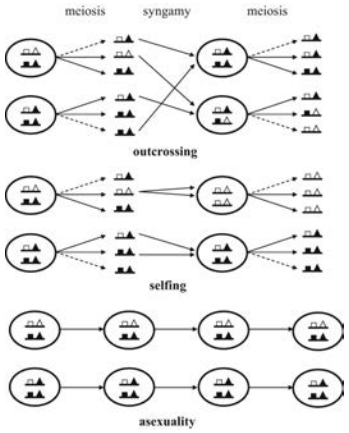


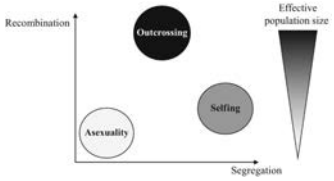
Alternation of generations - unravelling the underlying molecular mechanism of a 165-year-old botanical observation.
Horst NA, Reski R.
Plant Biol (Stuttg). 2016 Jul;18(4):549-51.



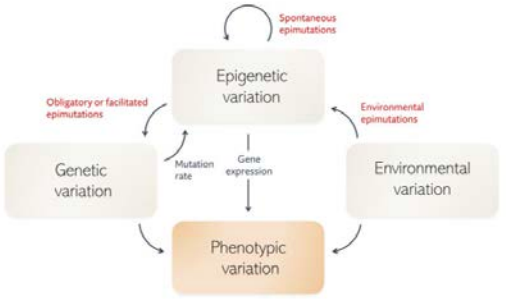
Leapfrog to speciation boosted by mother's influence.
Verzijden M.
Nature. 2019 Oct;574(7776):38-39.

It has now been found that mothers of a species of frog affect the behaviour of their offspring — influencing female mating preferences and aggression between males. Such behaviours might lead to the formation of new species.





The Role of Stochasticity in the Origin of Epigenetic Variation in Animal Populations.
Biwer C, Kawam B, Chapelle V, Silvestre F.
Integr Comp Biol. 2020 Dec 16;60(6):1544-1557.



Epigenetic Alterations Promote Genetic Instability

Genetic Mutation	Epigenetic Alteration	DNA Sequence Alteration
Point Mutation (SNP)	DNA Methylation (CpG)	Susceptibility C ➔ T Conversion
Copy Number Variation (CNV)	Hypomethylation (Repeats)	Susceptibility Repeat Element Alteration (CNV)
Transposon Migration	Hypomethylation DNA	Susceptibility Transposon Migration
Translocation	DNA Methylation and Histone Alterations	Susceptibility Translocation at Break Point
Telomere Length	DNA Methylation Alteration	Alteration in Telomere Length

Environmentally Induced Epigenetic Transgenerational Inheritance of Sperm Epimutations Promote Genetic Mutations

Skinner MK, Guerrero-Bosagna C, Haque M.
Epigenetics 2015; 10:8, 762-771

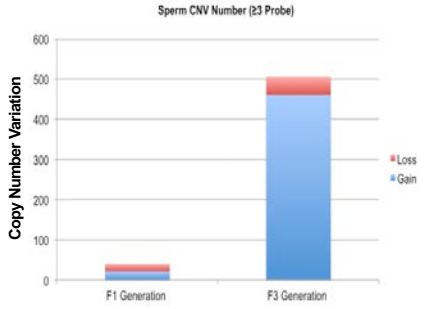
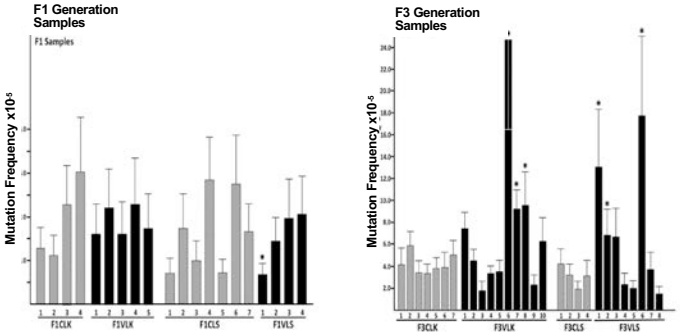


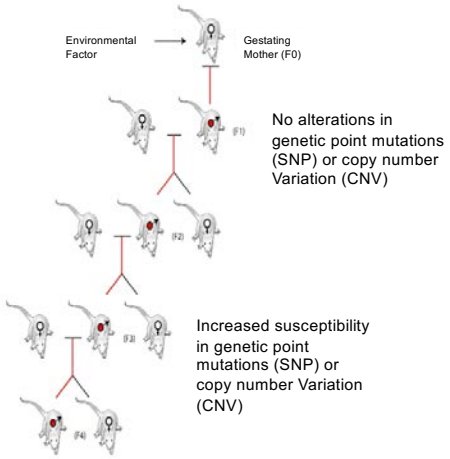
Table 1. (A) Vinclozolin F3 Generation Sperm Genome-wide CNV and Epimutations

Parameters	F1 Generation Sperm CNV	F3 Generation Sperm CNV	F3 Generation Epimutation Sperm
Number (Single Probe)	540(294 Gain / 246 Loss)	4912(4648 Gain / 264 Loss)	9932
Number (≥3 Probe)	39(21 Gain / 18 Loss)	506(461 Gain / 45 Loss)	191
Mean Size (base)	11,633	12,637	2,131
Mean CpG Density (CpG/100 bp)	1.1	1.0	0.9

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

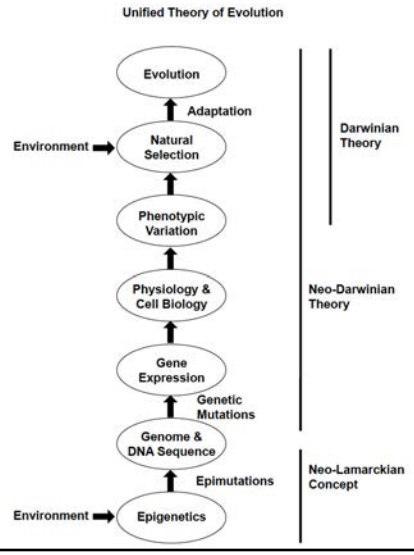


No alterations in genetic point mutations (SNP) or copy number Variation (CNV)

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

Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution.
Skinner MK.
Genome Biol Evol. 2015 Apr 26;7(5):1296-302.

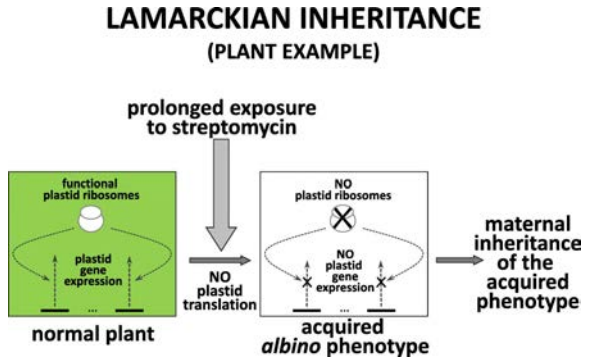
Evolution Theory Components
Neo-Lamarckian concept
Environment directly alters phenotype generationally
Darwinian evolution theory
Natural selection acts on phenotypic variation
Neo-Darwinian evolution theory
Genetic mutations promote phenotypic variation on which natural selection acts
Unified evolution theory
Environmental epigenetic alterations promote genetic mutations to alter genotypic variation Environmental epigenetics and genetic mutations both promote phenotypic variation on which natural selection acts



Epigenetics, Darwin, and Lamarck.
Genome Biol Evol. 2015 May 29;7(6):1758-60.
Penny D.

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.

Heredity determined by the environment: Lamarckian ideas in modern molecular biology.
Tikhodeyev ON.
Sci Total Environ. 2020 Mar 25;710:135521.



Lamarck and Panspermia - On the Efficient Spread of Living Systems Throughout the Cosmos.
Steele EJ, Gorczynski RM, Lindley RA, Liu Y, Temple R, Tokoro G, Wickramasinghe DT, Wickramasinghe NC.
Prog Biophys Mol Biol. 2019 Dec;149:10-32.

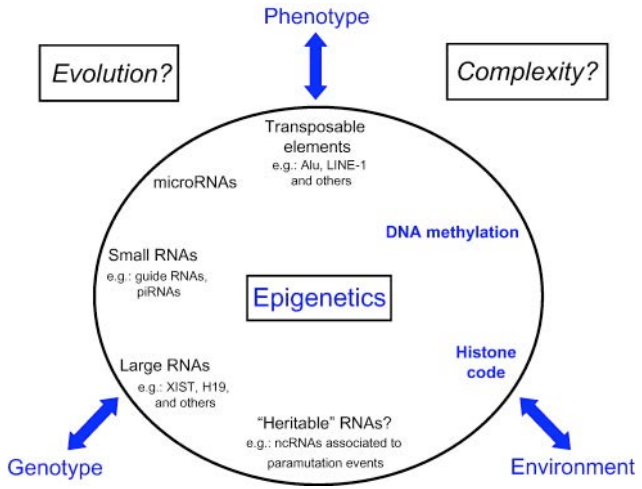
Table 1
Evidence consistent with Lamarckian evolutionary processes.

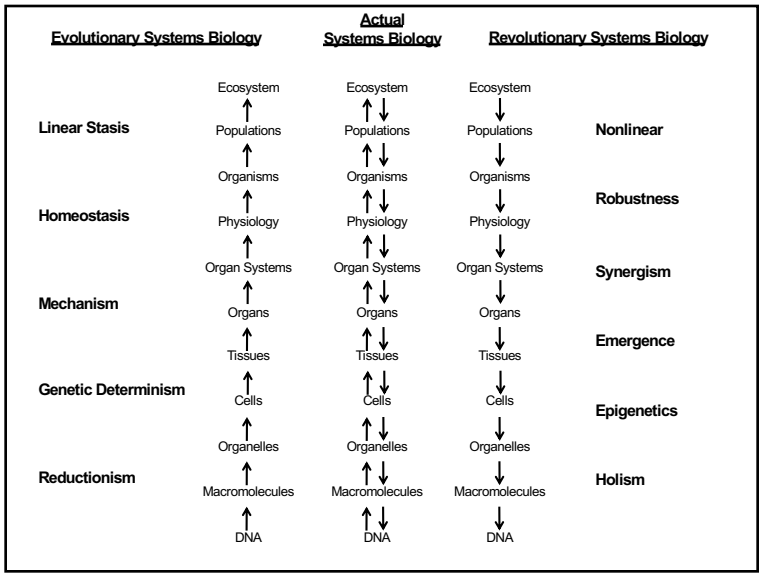
1	Environmental Stimulation as the Directional Mutational Driver
2	Role of Epigenetic Gene Targeting
3	Rapid Genetic Adaptation
4	Penetration of the *Weismann Barrier*
5	Horizontal Gene Transfer (HGT)
6	Central Role of Reverse Transcription

The summaries of evidence for Horizontal Gene Transfer phenomena are well covered at the Wikipedia site https://en.wikipedia.org/wiki/Horizontal_gene_transfer.

Table 2
Cosmic distribution and numbers of living systems.

• Viruses – terrestrial number 10^{31}	10^{53}
• Bacteria/Archaea - terrestrial number $\geq 10^{30}$	10^{52}
• Single cell eukaryotes - terrestrial number 10^{20}-10^{30}	10^{32}–10^{52}
• Complex Metazoans - terrestrial number $\geq 10^{20}$	10^{42}
• Higher plants, terrestrial number $\geq 10^{7}$ species	10^{29}
• Higher animals, terrestrial number $\geq 10^{7}$species	10^{29}





"Epigenetics and Systems Biology"

Spring 2021 (Odd Years)
Biol 476/576
Schedule/Lecture Outline –

Week 1	(Lesson 1)	Systems Biology (History/ Definitions/ Theory)
Week 2	(Lesson 2)	Systems Biology (Networks & Emergence)
Week 3	(Lesson 3)	Systems Biology (Components: DNA to Phenotype)
Week 4	(Lesson 4)	Systems Biology (Genomics / Technology)
Week 5	(Lesson 5)	Epigenetics (History / Molecular Processes)
Week 6	(Lesson 6)	Epigenetics (Molecular Processes & Integration)
Week 7	(Lesson 7)	Epigenetics (Genomics and Technology)
Week 8	(Lesson 8)	Cell & Developmental Biology
Week 9	(Lesson 9)	Epigenetics of Cell & Developmental Biology
Week 10	(Lesson 10)	Environmental Impact on Biology
Week 11	(Lesson 11)	Environmental Epigenetics
Week 12	(Lesson 12)	Disease Etiology
Week 13	(Lesson 13)	Epigenetics & Disease Etiology
Week 14	(Lesson 14)	Evolutionary Biology & Genetics
Week 15	(Lesson 15)	Epigenetics & Evolutionary Biology
Week 16	(Lesson 16)	Grant Review/ Study Section Meeting