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Epigenetic Inheritance and the Modern Evolutionary Synthesis

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ABSTRACT
Advocates of Extended Evolutionary Synthesis claim that the gene-centric framework of Modern Synthesis (MS) inadequately addresses epigenetics and extended heredity. Historically, epigenetic inheritance relates to Lamarck's inheritance of acquired characters, which was widely accepted before the dominance of MS. In this talk, I argue that the challenge posed by epigenetic inheritance to the gene-centric view arises partly from the ambiguous use of "gene," "phenotype," and "environment" concepts. A functional analysis of the gene concept played in the formal evolutionary models shows that the gene can include materials like exogenes, demonstrating the flexibility of evolutionary theory beyond the verbal MS. Properly understanding the evolutionary gene concept reveals that incorporating epigenetic inheritance does not demand a radical revision of the contemporary evolutionary theory.

KEYWORDS
Epigenetic Inheritance; Gene-centric view; Modern Synthesis; Evolutionary Gene; Molecular Gene

This work was initially about my paper on epigenetic inheritance with Pierrick Bourrat. Later, it became the central argument of my PhD thesis. Our basic idea is to investigate how epigenetic inheritance challenges modern evolutionary synthesis. So, I have the talk title today, Epigenetic Inheritance and the Modern Evolutionary Synthesis.

First, let me introduce some background. Although the discipline of epigenetics started almost 80 years ago, philosophical thinking about it in a systematic way began in 1995, with a book written by Jablonka and Lamb entitled *Epigenetic Inheritance and the Evolution*. The subtitle of the book is *the Lamarckian Dimensions*. In this book, they introduced many examples of how changes in epigenetic modifications can lead to the inheritance of certain traits for several generations and even for more than ten generations. The idea is that not only DNA can play the role of heritable material but also epigenetic modifications. And because environmental clues can easily change those modifications, this represents a mechanism for the Lamarckian idea of inheritance of acquired characters. Therefore, they are calling for a revival of Lamarckian evolution. Their 2005 book, reprinted in 2014, explores not only epigenetic inheritance in the biological context but also the behavioral and symbolic variation in the history of life. They generally wanted to call for a broad understanding of heredity or inclusive inheritance. In 2011, Jablonka communicated with some biologists from other fields and philosophers to discuss how Lamarckism should be reconsidered

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after so many years of rejection by modern synthesis (Gissis, Jablonka and Zeligowski 2011). The thought of how epigenetic inheritance and Lamarckism are linked converged to another huge movement: the Extended Evolutionary Synthesis. In 2010, Pigliucci and Muller published a book to argue for an extension of the modern synthesis. And in 2014, there was an article in *Nature* asking the question of whether evolutionary theory needs a rethink (Laland and Uller, et. al. 2014). There seems to be a clear divide between two camps: One from ecologists, developmental biologists, and others, thinking it is urgent to rethink evolutionary theory and a call for an extended evolutionary synthesis, in short, EES. Others, mostly evolutionary biologists, claim that all is well with the current understanding of evolutionary theory. In 2016, the Royal Society in London organized a panel discussion focusing on the new trends in evolution.[1] They invited philosophers such as Nancy Cartwright and biologists to discuss how development, which was "black-boxed" by the modern synthesis (MS), can contribute to the trajectory of evolution and explore whether MS needs a revolution. The public has quickly noticed this. In 2022, *The Guardian* published a long story: do we need a new theory of evolution? Soon, the Chinese WeChat official account Leviathan (利维坦) also discussed this story (Buranyi 2022). A new institute exclusively looking at evolutionary theory was launched by Zhejiang University in 2022. Today, I will focus on epigenetic inheritance within the whole EES movement.

When talking about inheritance, we need to distinguish two conceptions. First is heredity. Usually, it refers to the phenomenon of organisms sharing similar traits, such as skin colors or some behaviors with their parents. For example, two Hello Kitties will give birth to a little Hello Kitty rather than a dog or other animals. Another concept is inheritance, which refers to the process or the mechanism for the phenomenon of heredity. So, we use some theories of inheritance to explain the phenomenon of heredity. Intuitively, we would think that the parents must transfer certain substances to the offspring, which influence the offspring's development, resulting in traits similar to their parents.

Back in history, Hippocrates provided the first theory of inheritance called Pangenesis (Zirkle 1935). As the father of medicine, Hippocrates thinks that all organs of the body of an organism have some invisible "seeds." These seeds were transmitted during sexual intercourse, and reassembled themselves in the mother's womb. During an individual's development, when a certain body part changes, its "seeds" change accordingly. If Pangenesis is correct, the inheritance of acquired characters, in short, IAC, can happen. In particular, IAC means that changes an organism acquires through its own experiences or interactions with the environment can be passed on to its offspring.

But Aristotle did not like Pangenesis. He gave some very interesting counterexamples. First, certain body parts are composed of dead tissues like nails and hair. The question is, how do offspring inherit those parts from their parents? Second, why do newborn babies not have facial hair like their fathers if the "seeds" in their fathers have already changed? Third, according to the Pangenesis, each parent produced their own set of "seeds." Then why is the offspring not a monstrous creature with two heads and four arms? Aristotle has his own theory of inheritance (Aristotle 1943). He thinks the mother's blood provides the material for the fetus, and the father's semen contains some "form-giving principles" that govern the direction of the offspring's development. Those "form-giving principles" determine the essential and unchanging traits of the offspring or the whole species. In contrast, some traits acquired due to the developmental environment can only be accidental. According to this understanding of inheritance, IAC, although it can happen, is not crucial for our knowledge of heredity.

Later, we have the evolutionary theory against essentialism. According to essentialism, species

1 *New trends in evolutionary biology: Biological, philosophical and social science perspectives | Royal Society*. (n. d.). Retrieved August 24, 2023, from https://royalsociety.org/science-events-and-lectures/2016/11/evolutionary-biology/

are determined by their essence, and essence remains constant and unchanging. This means species do not change. But evolutionary theory, in a minimal sense, is the idea that species can change; species can evolve. In the mid to late 18th century, French naturalist Buffon proposed that species may change. In 1802, Lamarck, in his book *Researches on the Organization of Living Bodies*, provided a systematic theory about how species can evolve from simple to complex forms (Burkhardt 2013). In 1859, Darwin published *The Origin of Species*, which laid the foundation for the theory of biological evolution.

Conceptually speaking, if we want to hold an evolutionary theory of life, we should provide two mechanisms. First, to explain the source of variations. Second, to describe the inheritance of those new variations. IAC seems to be a perfect candidate because parents can acquire new traits during their lifetime, and these new variations can be inherited by offspring. It is unsurprising that both Lamarck and Darwin will think of IAC as an important mechanism for evolution.

Lamarck's book *Zoological Philosophy* (1809) gave his theory of evolution (Burkhardt 2013). To use a classic example of giraffes. First, some environmental changes might cause some changes in survival needs. For instance, if fewer leaves are at a low height, the giraffes need to reach higher leaves. The change in the needs will change the habits of the giraffe. This means it will increase or decrease the use of certain organs or tissues. For instance, giraffes develop the habit of extending their necks to reach high leaves. Here comes the first law to explain the source of variation: frequently used organs tend to develop; otherwise, they tend to degenerate. This means the necks of giraffes gradually become longer. Then, according to the second law, to explain the inheritance of variation, acquired traits are inherited by the next generation. This means the long-neck trait is inherited by offspring. After several generations or more, the neck of giraffes in the population becomes longer and longer.

Contrary to what most people would think about Lamarckism and the relationship between IAC and Lamarckism, according to the historian Burkhardt (2013), Lamarck himself did not provide a mechanistic explanation for IAC because the inheritance of acquired traits at that time was common knowledge, and almost no one would reject it. The significant contribution from Lamarck is to emphasize the principle of use and disuse. Ironically, Darwin is a supporter of IAC. For example, in *On the Origin of Species*, Darwin explicitly asserted that the principle of "use and the disuse" is one of the sources of variation. In *The Variation of Animals and Plants under Domestication* (1868), Darwin proposed a theory of Pangenesis to explain heredity. He replaced "seeds" with "gemmules" in cells, but the basic idea is the same (Darwin 1868).

Many historians agree that Lamarck's idea has influenced Darwin's own theory of evolution. Their difference lies in how new variation arises. For Lamarck, it appears from the use and disuse by the organism directly in response to environmental changes. This means that variation is non-random. However, Darwin believed that indirect environmental effects also play a role in leading to random variations. He thought most variations were random and proposed the evolution by natural selection, which, very simply put, takes three steps. First, due to random mutation, there are giraffes with long necks and giraffes with short necks within one population. This means a trait variation. Second, giraffes with long necks can reach more food, thus producing more offspring, which means differential fitness. And third, on average, giraffes with long necks have long-neck offspring. After several generations, the population will have an increasing number of individuals with long necks. Thus, evolution happens.

Compare Lamarck with Darwin. For a variation to be preserved, whether this variation is led by use and disuse or by random mutation, it requires those variations to be heritable. Hence, there's no conflict between Lamarck and Darwin regarding inheritance. Their conflict lies in the primary driving force of evolution. For Lamarck, organisms develop variations through "use and disuse" in response to environmental changes. So, the driving force of evolution lies in the organism's own

efforts. But for Darwin, because most variations are random, whether a variation is preserved depends on whether it allows individuals to leave more offspring in their current environment. In this sense, natural selection is the driving force of evolution.

According to the mainstream story, IAC' s historical demise was due to Weismann's famous tail-cutting experiment (Haig 2007). The experimenters cut the tails of the newborn mice, let them reproduce, and see whether their offspring still has tails. This experiment goes through more than 20 generations. As a result, not surprisingly, the infant mouse baby still has the tail. However, according to the "use and disuse" principle, the tail should gradually degenerate. Therefore, Lamarckism is false. But if we look closely, this is not a conclusive experiment that can refute IAC. The conclusion is instead that certain acquired traits cannot be inherited. This does not mean all acquired traits cannot be inherited. Moreover, the tail was cut rather than degenerated by the mice's efforts. Hence, this is not consistent with Lamarck's context. It means the very famous experiment alone does not refute IAC.

In fact, the demise of IAC is due to the Germ-Plasm theory proposed by Weismann in 1893. The basic idea is that the organism is divided into germ plasm and somatic plasm, with the germ plasm containing the determinants of biological traits, while the somatic plasm constitutes the rest. The germ plasm determines the somatic plasm, but changes in the somatic plasm do not affect the germ plasm. This means that use and disuse during an individual's lifetime can only lead to changes in the somatic plasm; acquired traits cannot be inherited through the germ plasm. Later, Weismann became a major figure of Neo-Darwinism, as did Wallace (Kutschera and Hossfeld 2013). They are new because they want to emphasize that natural selection *alone* is sufficient to explain all evolutionary phenomena. If this is the case, according to Occam's razor, we do not need any other mechanism, such as IAC, to explain other evolutionary phenomena. It leaves no room for IAC.

By the 1940s, the marriage between Neo-Darwinism and Mendelian genetics was integrated into a consensus known as the modern evolutionary synthesis, MS. This synthesis provided the theoretical foundations for a quantitative understanding of evolution. It has been regarded as the paradigm for evolutionary theory over the last 70 years. Here, Mendelian genetics provides the inheritance mechanism for Neo-Darwinism. In Mendel's story, as known by almost everyone, he observed some traits and patterns of phenotypic heredity in peas, and he posited that those phenotypical phenomena are determined by factors inside the organism following specific laws. The basic idea is that genotype determines phenotype, and inheritance is the transmission of those genes. Mendelian genetics also provides a methodology of quantitative statistics for modeling evolution. Before, we looked at the population focusing on the traits and their changes, because we assumed that genotypes determine those phenotypes; we see phenotypes through genes when we look at the population again. In this sense, gene frequency is the heritable composition of a population, which is quantified by the population genetic models. If the population's phenotype changes, it means a change in gene frequencies. In this sense, evolution is regarded as the change in gene frequency within a population. In other words, the gene-centric framework changes how we look at populations and their evolution.

Now we get to the question: does the evolution theory composed by MS need a rethink? The primary target for EES is the core claims of MS. The claims include new variations arising from 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. EES claims that there have been many new findings in biology indicating some missing pieces of MS. The missing parts are from four aspects. First, instead of being randomly generated, the appearance of new traits is influenced by developmental constraints. This is developmental bias. The second is phenotypic plasticity. The same genotype may respond differently to different environmental conditions, resulting in different phenotypes. These two together propose a non-random, non-

genetic way of generating phenotypic variation. Then there is epigenetic inheritance, not the transmission of DNA, but DNA methylation patterns across generations. Some of you might notice that the combination of phenotypic plasticity and epigenetic inheritance provides a mechanism for IAC. Fourthly, it's niche construction. Organisms may not simply be selected by the environment but can modify their environments, which in turn influence the selection process.

Here, I will focus on epigenetic inheritance. The term epigenetics was first introduced by Waddington in 1942 to refer to the study of the interactions between genes and their products during development. More recently, epigenetics has been defined as the study of heritable changes in gene expression that are not caused by changes in the DNA sequences (Haig 2004). Accordingly, epigenetic inheritance refers to the transmission of epigenetic modifications via cell division across generations (Griffiths and Stotz 2013, p. 112). Typical epigenetic modifications include histone modification, RNA interference, and DNA methylation. In a broader sense, supported by some philosophers, epigenetic inheritance also includes the inheritance of phenotypic features through causal pathways other than the inheritance of nuclear DNA—a very inclusive concept.

Here is an example (Youngson and Whitelaw 2008). In rats, the quality of a mother's care behavior, like licking and grooming their babies, causes the development of different traits in the babies. A stressed mother who does not lick and groom her baby will cause a decreased level of serotonin. Serotonin is a neurotransmitter associated with nerve impulses. This decreased serotonin in the baby's brain increases the DNA methylation pattern on a certain gene, leading to high levels of stressed reactive behavior in the offspring. The result is that stressed mothers produce stressed daughters who become stressed mothers themselves. In this example, the mother's behavior is reproduced in later generations by means that are not DNA-based but instead via the reconstruction during the development of a complex network of interactions that includes DNA methylation patterns. This and similar examples strongly indicate that nuclear DNA cannot be the sole heritage of the material influencing the production of phenotypic inheritance.

Not only about heredity, epigenetic inheritance can also influence the evolutionary process. For example, a study (Dia and Ressler 2014) shows that mice acquired a fear of a sweet smell when researchers gave the mice a mild foot shock every time the smell was present. The fear is associated with a decreased level of DNA methylation on a particular gene sequence. The epigenetic pattern is transmitted stably, causing the descendants to fear that smell, even if they have never confronted that smell in their lives. In this example, non-random or direct effect leads to a heritable phenotype. An environmental change causes some epigenetic modification, which leads to new phenotypic variation. This is the process of phenotypic plasticity. The new trait is heritable via epigenetic inheritance. If the selective environment favors the fear trait, natural selection can lead to evolution. Here, Lamarck's first law and the second law both play roles in explaining evolution. Jablonka et al. (2014) gives a similar argument defending Lamarckian evolution.

Now, the question is whether evolutionary theory requires a significant revision to incorporate the phenomenon of epigenetic inheritance. There seems to be a spectrum from a conservative to a revolutionary view. Some philosophers think that epigenetic inheritance is an augmentation of the classic view of genetic inheritance. However, others claim that incorporating epigenetic inheritance would be a substantial change or even a revolution to the gene-centric view of MS. To answer this question; I think the first thing to do is to clarify the gene concept in evolutionary theory. We claim that evolutionary genes should be understood more broadly and abstractly. It should not be restricted to DNA materials but can encompass heritable epigenetic modifications that affect the phenotype. Once the evolutionary gene is understood this way, evolutionary theory would not require a major revision to incorporate epigenetic inheritance. To apply our view to the spectrum, it would be somewhere in the middle. On the one hand, the understanding of evolutionary genes should be extended to include other heritable materials. On the other hand, we claim this extension

corresponds well to the core of MS and will not substantially change evolutionary theory.

Original MS is the marriage between Darwinian evolution and Mendelian genetics, resulting in population genetics and qualitative genetics, which is a formal version of evolutionary theory. But the MS, which we are very familiar with, is a verbal expression of formal population genetics.

The concept of genes in MS is from Mendelian genetics that is primarily defined through their effects on phenotypes, not by appealing to their intrinsic physical structures. When the structure of DNA was established in 1953, DNA seemed to be a perfect physical candidate to fit the functional role of the gene. Since then, especially with the development of molecular biology, it has been common for biologists to refer to genes as molecular DNA in their verbal accounts. We call the gene that is defined by DNA with the name of *Molecular gene*, but this does not mean that the concept of the gene in evolutionary theory, which we call *Evolutionary gene,* should restrict itself to only DNA materials. Logically speaking, if some physical material other than DNA can affect the phenotype and can be transmitted across generations, this material can also be included in the evolutionary gene. In other words, the physical condition of the gene as DNA is a generalization, which is not necessary for the concept of the gene in evolutionary theory.

Thomas Morgan (1935 p. 315), the father of classical genetics, noted in 1935 that "there is no consensus of opinion amongst geneticists as to what genes are-- whether they are real or purely fictitious--because at the level at which genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle."

The next task is defining a notion of evolutionary genes corresponding to the current formal evolutionary theory. We think David Haig's (2012) account of the strategic gene would be a good start. The strategic gene is a set of gene tokens, mainly DNA sequences, as the unit that can be considered a strategist in an evolutionary game played with other strategic genes. Here, the genes are seen as heritable units that can affect phenotypes in a population in an evolutionary game. Although Haig mentioned that the strategic genes are mainly DNAs, We think it should be explicit that evolutionary genes are open to other materialized instances that give rise to the same effects or functions.

Here is another example (Rassoulzadegan et al. 2006): a mutant allele at the kit gene will produce a white tail tip in mice, and the offspring of heterozygote parents with two normal alleles are supposed to have a normal phenotype without a white tail tip. However, experiments show that most offspring with two normal alleles at the kit gene still had a white tail tip. Later research shows this is because the male parent with the mutant kit gene manufactures particular RNA molecules, and those RNAs are delivered directly to the offspring through the sperm, which causes the white tail tip. Here, the difference makers that cause phenotypic differences are particular RNA molecules. Therefore, RNA, like DNA, can also be transmitted and influence phenotypic production. This gives us a good reason to extend Haig's strategic gene to include both DNA and RNA sequences. Once we take this step, it seems natural to include other inherited epigenetic modifications into materialized evolutionary genes.

Starting with Haig, we arrive at Griffiths and Neumann-Held's (1999) conception of the evolutionary gene, which is defined as a heritable atomistic change that causes phenotypic differences. This definition strips down the DNA material restriction and corresponds to the spirit of the formal evolutionary models. Therefore, any physical structure that can be transmitted across generations and causes phenotypic resemblance between generations should be seen as an instance of evolutionary genes. To have an extended gene-centric framework, some coherent notions of the phenotype and the environment should also be defined.

The phenotype is defined as the gene's effects relative to some alternatives (Haig 2012 p. 461). The gene's phenotype is everything the gene makes a difference in when compared to another gene under the same conditions. The evolutionary notion of environment, which is consistent with

the concept of evolutionary genes and the phenotype, should be understood as any variable that is not causally influenced by evolutionary genes and that causally influences the phenotype.

This whole set of gene, phenotype, and environment concepts is different from what people usually mean. There are at least two ways of partitioning the biological world. The evolutionary approach focuses on evolutionary genes and the traditional approach is centered on organisms. Traditionally, the environment refers to the environment external to the physical boundaries of an organism. But in our framework, the phenotype is the gene's effect that can refer to traits of an organism as well as traits external to the organism, such as the dam of the beaver proposed by Dawkins. Hence, the evolutionary gene and its phenotypic effect can be part of the organism's environment (Dawkins 1982). Correspondingly, physically speaking, the gene's environment can include other alleles in the same locus, other parts and mechanisms inside the organism, and the parts external to the organism. Suppose one understands genes solely as DNA sequences, which are part of an organism but do not constitute all of it, and the environment as the external environment of the organism. In this case, indeed, there is organic material other than genes within the physical boundaries of the organism that will affect the process of development and evolution. We must keep in mind that different ways of partitioning the world should not be mixed up.

The immediate objection from epigenetic inheritance is that DNA is not the sole heritable material. A classic example comes from a study of the Agouti Locus in mice (Morgan et al. 1999). Mice with similar genotypes display a range of phenotypes on the color of their fur due to a difference in DNA methylation patterns on the promoter of the dominant agouti allele. This study shows that patterns of DNA methylation can be inherited through generations and further cause phenotypic inheritance. Since evolutionary genes do not have to commit to DNA as the sole material support for genes, DNA methylation, in this example, is also an instance of evolutionary genes. There is no fundamental conflict between a pluralistic view of heredity and the extended evolutionary gene-centric view.

The second objection relates to phenotypic plasticity. The change of a given environmental inducer might cause a phenotypic change through some epigenetic modifications. If the change in epigenetic modifications can be passed on to offspring, which will cause the same phenotype in offspring, the phenotypic variation is maintained by epigenetic inheritance. And if the alternative phenotype has a different adaptive value in the population, evolution can happen without a change in DNA. The response is immediate. The heritable epigenetic modification is an instance of the evolutionary gene. In this sense, the phenotypic variation can be seen as caused by genetic variation. So, the evolutionary genotype determines the phenotype. The evolutionary process based on this non-DNA mutation can be seen as changing evolutionary gene frequencies within a population.

Another potential objection is about non-random mutation during development. The mutation is non-random when the selective environment favors the environmentally induced phenotype. Moreover, phenotypic plasticity arises from developmental processes, which means natural selection is sometimes guided along specific routes opened up by the development processes. In other words, development plays the role of initiating and directing adaptive evolution. Here, I follow Peter Godfrey-Smith (2007, p.493). According to him, Darwinian evolution can occur on the variation that is directional, even adaptively directed. In these cases, natural selection may have less explanatory importance than it has when variation is random, but it can still exist. That is to say, non-random mutation only undermines the extent to which natural selection can produce or explain complex structures. Yet, natural selection is only one of several processes creating evolutionary change, and the current evolutionary theory can accommodate non-random sources of variation, which is compatible with Darwinism. The verbal accounts of MS indeed give a lot of weight to random mutations, and it is fair for people to claim that epigenetic inheritance challenges this idea

(Merlin 2010; Fuyuyma 2006, p.12). However, MS itself, in the formal version, is more flexible and can accommodate other evolutionary forces beyond natural selection, including non-random variation or neutral evolution.

Here are the conclusions. Before the prevalence of Neo-Darwinism, IAC, inheritance of acquired characters was recognized as common. There's no dispute about IAC. I have argued that the challenge posed by epigenetic inheritance to the gene-centric view is partly caused by the ambiguous use of concepts of "gene," "phenotype," and "environments". My analysis of the concept of the gene from a formal perspective reveals that the evolutionary gene is open to incorporate other materials such as exogenes, and the evolutionary theory is much more flexible than the verbal MS. If the concept of genes in evolutionary theory were appropriately understood, incorporating epigenetic inheritance would not require a radical revision.

Discussion

Audience: I think you made a good case that, in general, epigenetics does not kind of force one to alter the version that you read. But can you suggest if there's a way in which that changes ideologically, or once you say, of course, we should recognize more than one main factor in driving evolution? I mean, isn't that something like an interesting change? And maybe the question is going to be about how weighted those factors are and what that shows about evolution. What do you think if this kind of formal question is not really an issue?

Qiaoying Lu: I think the challenges to MS cannot be only about epigenetic inheritance. As I said, Lamarck and Darwin do not quarrel about inheritance. At least we can separate the steps of the rise of variation and the inheritance of variation. My contribution is that if some revolutionary, Kuhn's paradigm shifts happen, it is not because of epigenetic inheritance alone. On the other hand, if phenotypic plasticity is combined with epigenetic inheritance. Empirical evidence shows this is real and can support some kind of Lamarckism evolution. This is a more interesting way, I think, to see how MS can be changed or modified in a way that incorporates the developmental process and how the developmental process can govern the evolutionary process.

Audience: My question may be in the same vein. I always thought that what's awesome about Darwin is that there is this model where it can make sense of seemingly random changes producing something amazing. And I guess back then, when they were talking about God and stuff. It's kind of this almost miracle explanation if you think about it, where randomness produces something so complex, and I guess some people think it looks like divine or something. And so I always thought the core of Darwinism is not that nothing that there are no other mechanisms that can be plugged into, but that some stupid mechanisms can at all ever introduce these amazing changes. And I feel like as long as that is preserved. It sort of makes sense to call it Darwinism, and I don't know why there would be threats to call it a revolution. So is that core preserved that random mutations often can produce these amazing seemingly directional, seemingly intentional changes?

Qiaoying Lu: I agree with that. In fact, nowadays, the consensus is that, as you said, Darwin's evolution by natural selection provides a very simple mechanical process to explain very complex adaptations, which it was previously thought must be created by God or the divine agents.

There's an argument in history to object to the evolution by natural selection by arguing that this process can only be a selection process. But there's no creativity here to be explained. The procedure would be some variations that have already been there. And natural selection will select

those which are fitter. The major reply to this argument is that natural selection also explains creativity in some sense. For complex traits like human eyes, the evolution of the final eye cannot be taken in a single step; usually, it takes many steps. The means that there are intermediate steps that would lead to the final mutation of the full-eye trait. If, let's say, before the final step, we have a mutation like G2. Only G2 can have a chance to mutate to G3 as the full-eye trait. And natural selection can work in this G2 process. If it can select G2 in a way that increases the rates of G2 in the population, the actual chance of finally getting G3 increases, too. This is how natural selection can contribute to creativity in the whole process for complex structures.

I agree that if there's no natural selection, wholly by random, at least in these intermediate steps, it is hard to imagine how random things can mutate to become eyes. So, natural selection plays a crucial role. But for scientists, they can admit that natural selection is important, they also want to know how the variations can arise in reality. We can give some mechanisms to explain how the environment can affect organisms to produce very amazing mutations.

This also relates to the area of evolutionary developmental biology (evo-devo). They found some HOX genes, which are body plans for different species, across fruit flies to human beings. These are not structural genes that are transcribed to RNA and then translated to proteins; they are regulatory genes that regulate how and when the structural genes should be activated or inactivated. So, it's a whole regulatory network of genes. Just like the switch for the light, those genes can be inserted in different parts of genomes. There are 95% of junk genes in the human genome, previously no one knew the point. But actually, those switch-regulatory genes also play a very important role in development. Basically, it's like a Lego. If you have some materials and plug in some switches in the genome, the whole regulatory network can be realized.

Another amazing thing is if the basic structure remains like Lego, you can access and remove things in many different ways, which also explains the explosion of species variation. It does not require individual multiple times of independent mutation, but only one step; if we get the basic network regulatory genes, only small changes will be needed to lead to diverse organisms. Like evo-devo, if they don't explore this, that knowledge will not come. So people are arguing that we should focus not only on evolution by natural selection but also on those developmental and regulatory mechanisms that can give rise to variation.

Audience: I thought you were asking the question of whether we should see these new developments as augmentation or revolution. And then you were saying that's an augmentation for lots of reasons. But I just wonder if maybe that's in line with what the balance is saying; I wonder what the revolution scenario would even look like. Because Darwin never says that natural selection is necessary and sufficient for any change. Or that's what I was saying earlier. It seemed to me that it was Darwin against these Lamarckians and maybe against certain religious people, who were giving a mechanism that could account for certain changes. That's something very different than saying it's a mechanism that must account for all changes. How could adding something (epigenetics) ever amount to a revolution, no matter how much stuff you add? If the ambition of Darwin was, at least as far as I proceed with, never to see natural selection as necessary and sufficient. So it's rather a way to explain something previously unexplained, not a theory to explain all the changes that must happen by this one minute.

Qiaoying Lu: The conflict now is not between Lamarck and Darwin but between Neo-Darwinism and epigenetic inheritance and the EES. The truth is that many people will think that the gene-centric framework is good. Scientists or biologists I talked to believe they cannot work without those frameworks. But philosophers like my previous supervisor, Paul Griffiths at the University of Sydney, who is a major figure in promoting developmental system theory. They say we should abandon the

gene-centric view because it is false. Their main argument is called the parity argument (Griffiths and Gray 2000, pp. 195–218). In general, if you give any argument emphasizing the importance of genes as the cause for the phenotype, then replacing all the genes with the environment and the environment with genes, the argument would still be valid if the previous argument is valid. This means there's no fundamental distinction between genes and the environment as the causal role in causing phenotype. This is very big, and they also published a book with many biologists. They want to propose a theory that does not look at genes but the whole life cycle of individual organisms. Many people agree with and admire this idea. I think developmental system theory makes sense in principle or in theory, but in scientific practice, biologists still need a framework to do their modeling and explain the phenomena. This is why, in fact, my stance is not common. After the publication of our paper, some biologists opened web blogs arguing that this is wrong and unacceptable. We should just abandon the whole gene-centric framework in giving rise to the EES. Our paper was published in 2018.[2] But at that time, our stance seemed rather marginal, and very revolutiuonary people did not like it. Many journals rejected us. But now, in 2023, those revolutionaries who think that EES can provide a revolution against MS. The prominent figure is Kevin Laland, who is an ecologist. But now, in every circumstance, he will emphasize that EES is just a complementary framework that complements the MS rather than replaces it.

Audience: If it's the case that evolutionary genes can include epigenetic changes as well as DNA changes, then my worry is it might be too broad. It can include almost everything, including non-material stuff. For example, the cultural evolution, and when people talk about our studies, it is kind of like an analogy. But now, if we consider the evolutionary gene so broad, then it's not really an analogy. It's just the same thing; it is part of the evolutionary gene. So would that make you worry about it, or is it okay to include everything that explains it?

Qiaoying Lu: That could be a problem if scientists or biologists take this conceptual distinction very seriously. But I think in practice, biologists do not think so many conceptual things. If they see a phenomenon, they want to explain it, and they build some models. If the heritable material is DNA, then it's okay; if epigenetic marks are heritable, they can build the model, too. It does not mean this theoretical construction of evolutionary genes should be fully implemented in scientific practice. It's more like a theoretical work to explore the logical space of the formal MS. In this way, I think, on the one hand, it opens the door for more heritable materials, which might be like DNA methylation patterns. On the other hand, if someone is, in fact, really keen to use it in such a broad way, then they will confront some pragmatic problems because their modeling would not work in any case. Yes, I think it should not be taken very seriously in practice, but conceptually, it makes sense, and I think we defend it rigorously.

Audience: I want to return to your example of the bad and good mice mothers. The good mouse mother produces a good mother in this way and the bad mouse mother does not produce a good mother in this way. But I hesitate to call this kind of causal influence inheritance in a biological sense. Of course, every inheritance is a kind of causal influence, but not every kind of causal influence is an inheritance. Suppose I have a psychological problem, and I keep pressing students, and students become stressed. This is a kind of social phenomenon. This kind is more like a social phenomenon in a very biological sense. So, why call this kind of causal influence inheritance at all?

2 Lu, Q., & Bourrat, P. 2018. The evolutionary gene and the extended evolutionary synthesis. *The British Journal for the Philosophy of Science*, *69*(3), 775–800. https://doi.org/10.1093/bjps/axw035

Qiaoying Lu: This is a very interesting case, not only about some epigenetic marks inside an organism but also about the causal network, including the environmental causes, such as how the mother's behaviors influence offspring. This is also interesting because, as I mentioned, Jablonka and Lamb, in their 2005 work, want to extend the concept of epigenetic inheritance to include more like a behavioral and symbolic inheritance, which, of course, is the field of cultural inheritance. So, this is like a primary exploration of how our understanding of restricted biological epigenetic inheritance can be applied more broadly to include more environmental factors. But you're right that if we compare the cultural and biological evolution models, there is an essential significant mismatch between those two models because the inheritance mechanisms are different, and the fitness is defined differently. I think this is a really interesting question that I cannot answer currently. Their exploration wants to compare how it can be applied more broadly. If it can, in some sense, give some insights about how cultural evolution happens, then it will be a good thing.

Audience: I am interested in research like gene regulatory networks, which you have discussed before. I'm not a biologist, so I can only do my best. But it sounds all good to me because it seems like a lot of people in that field, scientists, are kind of mad about the modern synthesis because it's not really relevant to their very specific research area where they're just doing system biology, or dynamical systems. Some big-name biologists have written saying modern synthesis is done, and so on. So, it seems there could be a reason to say they are strictly compatible in certain subfields. You can treat them as, you know, non-revolutionary, just kind of addenda to Griffiths' work and Sterenly and all that. But in some fields, you might want to say, this whole Darwinian kind of modern synthesis talk is really kind of getting in the way, and it doesn't really help us.

Qiaoying Lu: When I was teaching the philosophy of biology at PKU, some students from biology majors were working with molecular biologists. They said the same thing; in their research, they do not consider evolution at all. I also talked to some biologists working on genomics and protein research. It seems that if you are doing some specific work, like molecular biologists focusing on very specific molecular mechanisms, certain traits can be developed. Then, of course, it might not require any evolutionary knowledge. But as I talked to Zhejiang University's people in that institute, they think if we really want to understand how life can have this diversity and to compare different species and how their development processes become in homology or different causal pathways, then evolution should be our light in all respects. I agree that maybe in some short period of time, in some specific area of biology, evolutionary theory might just play a very background role, just invisible. But as a whole, if we want to understand biology or life on earth, then it is indispensable.

The EES also currently has some arguments about whether we need a unified evolution theory. If we want to explore how one species evolved during some periods of time, we just look at the species and find what is the most important driving force of evolution. Then that's it. Do we need a unified theory to unify the developments and natural selection to integrate into a general theory to give some general models? I still doubt that. Like in physics, people are still exploring the theory of everything, and if we can get this theory, then our understanding of the world will surely be improved significantly. So, my personal idea right now may change later. But currently, I think we should at least try to find a unified theory for evolution. And that's what EES people are doing, and I really hope they can succeed.

Audience: On my way to this meeting, I listened to a podcast about epigenetics. I think it's a hot topic, and people on the podcast are just talking about eugenics. I think there are many lessons we can learn from the topic. Perhaps one direction is how to understand us, our human beings, how to understand humanity, or how to make our future a better world with better people. I think one

possibility is that we can observe human children. You talk about IAC. I guess we get more or fewer characters from our parents. I mean, a large number of our adult abilities are learned from living time. So we take more time to learn, unlike other animals, just acquired as an instinct directly from inheritance. In fact, it can give us much room for learning. We do not just inherit from our parents. That's one thing.

The other thing is we can also observe that human children have powerful learning abilities. For example, we take a very short time to acquire our mother language. Many scientists or biologists assume this linguistic ability is also a kind of inheritance. What would you think the significance of your topic upon, for example, such topics as eugenics? In what sense, for instance, is it that parents are very important, very responsible for a healthy mind of children?

Qiaoying Lu: I haven't thought about it, but what you're saying might relate to the topic of whether traits are determined by genes, the nature/nurture problem. Usually, we would think if a trait is determined by gene, then it's innate. If it's determined by environments, it's not innate but nurture, which is more plastic. The common consensus is that, of course, genes and environments both play necessary roles in producing traits. I think it's an empirical question of which one is more important. And this is my current research. I want to use structural causal modeling and some quantity to measure the degree of causal strength in particular cases.

Developmental system theory talks about genes and the environment. They are both causes of phenotype. Based on this, they're arguing that there's no fundamental difference between genes and environment. But in fact, what we really want to know is how much the genes play a role and, how much the environments play a role, which one is more important in producing the direction of development. Paul Griffiths, which is very interesting because after he proposed the developmental systems theory, he collaborated with the mathematician who was working on information theory to give a quantitative model for measuring causal specificity. According to their research and applied to genes and the environment, at least initially, we would think genes are more causal specific than the environment. For example, if I drink water and drink much today and then less tomorrow, it will not affect my development. But a slight change in my genes might have a very different effect on my development. So, the causal specificity is different.

Eugenics is done by artificial selection. The direction is determined by people who have limited knowledge about evolution or the prediction about the future. Some evolutionary models show that we can take different time periods to see the evolutionary process based on the same evolutionary setup. Some phenotypes would be adaptive in a short time, but in a longer time, that phenotype would be less adaptive. This means that some phenotypes are good currently but might not be good in the future. So, eugenics is very dangerous. The primary spirit of Darwinian theory is that we should maintain diversity within one population. And this is a final source of variation in the future. So, I would promote multi-value. Not everyone just moves in one direction. This is not right. And I think biology and evolutionary theories support this diversity view rather than the eugenics view.

Also, you are talking about the uniqueness of human beings in IAC, which is very interesting. And thank you for bringing about the example of children learning languages. I think the more complex one species' developmental process is, the more IAC could play a role.

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