Radboud Universiteit

Master’s thesis Philosophy of Natural and Life Sciences

How Random is Random Mutation?

An investigation of different meanings of randomness in biology

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Student Number
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Word count
14.735

June 25, 2025

In biology, the nature of mutations is often described as “random”. In an evolutionary context, this represents the canonical view that mutation is not directed towards providing favourable traits for an organism. However, “mutation” can also refer to alterations in DNA, in which “mutation is random” is a vastly different and extensively debated claim within genetics. I investigate what the statement “mutation is random” means in an evolutionary and a genetic context and how different interpretations of “random” affect its meaning. I argue that using different definitions of randomness interchangeably has far-reaching implications, such as the confusion of epistemological and ontological claims, (accidental) Lamarckian conclusions, and that it raises questions about reductionism in biological science.

Thesis to obtain the degree “Master of Arts” in philosophy at Radboud University in Nijmegen.

Hereby I, Mila S. Burger, declare and assure that I have composed the present thesis with the title *How Random is Random Mutation?* independently, that I did not use any other sources or tools other than indicated and that I marked those parts of the text derived from the literal content or meaning of other works — digital media included — by making them known as such by indicating their source(s). Nijmegen, June 25, 2025.

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Chapter 1

Introduction

Chance, when strictly examined, is a mere negative word, and means not any real power, which has any where, a being in nature — David Hume[1]

Once every few years, the field of biology is stirred up by new findings on mechanisms of "non-random" mutation.[2,3,4] "Random mutations" has been a commonly accepted idea ever since Darwin's formulation of the theory of evolution, but modern genetics seems to cause cracks in this belief. The fact that genetic research is used to imply that mutations are not random in evolution, is remarkable at the very least. It invokes questions about the definition of the term "randomness", which, upon examination, turns out not to be singular but pluralistic.[5] Does the word "random" signify the same in a genetic and in an evolutionary context? How does it apply to mutations? Consequently, what implications do different interpretations of "randomness" have?

In this thesis, I investigate the "randomness" of mutations in different domains of biology, and reflect on the implications of interpretations of randomness on a reductionist approach to biology. I do this by first providing an account of what the randomness of mutations signifies in evolutionary biology and molecular genetics, respectively. Subsequently, I clarify that although "mutation is random" is a phrase used in evolutionary biology and molecular genetics, the ambivalent meaning of the term "random" creates a situation in which the distinctions between ontological and epistemological claims, as well as the distinction between cause and consequence, become unclear. Furthermore, I provide my own distinction between evolutionary and genetic randomness to attack authors who argue in favour of alleged non-random mutations, who, in my view, make an illegitimate and reductionist argument.

1. David Hume, *An Enquiry Concerning Human Understanding*, ed. Peter Millican (New York: Oxford University Press, [1748] 2007), 69.
2. Barbara E. Wright, "A Biochemical Mechanism for Nonrandom Mutations and Evolution," *Journal of Bacteriology* 182 (1999): 2993–3001.
3. Iñigo Martincorena, Aswin S. N. Seshasayee, and Nicholas M. Luscombe, "Evidence of Non-Random Mutation Rates Suggests an Evolutionary Risk Management Strategy," *Nature* 485 (2012): 95–98.
4. J. Grey Monroe et al., "Mutation Bias Reflects Natural Selection in Arabidopsis Thaliana," *Nature* 602 (2022): 101–105.
5. Christoph H. Lüthy and Carla Rita Palmerino, "Conceptual and Historical Reflections on Chance (and Related Concepts)," in *The Challenge of Chance: A Multidisciplinary Approach from Science and the Humanities*, ed. Klaas Landsman and Ellen van Wolde (Springer Open, 2016).

1.1 Biological background

To be able to investigate the randomness of mutations in an evolutionary and genetic context, some background knowledge is required on the molecular basis of mutations. This section gives a brief introduction to genetics and mutation, providing the most important mechanisms and some details that will prove to be of importance later. At moments where I simplify biological mechanisms or leave out some context, I use footnotes to explain phenomena in proper biological jargon. Readers with less background in molecular biology can disregard these footnotes (all starting with "For the biologist:"). Readers with more knowledge about the molecular mechanisms of cell biology might be inclined to skip over this section. I would, however, advise against this, as I make some distinctions that might not be commonplace in the field. I start this section by explaining the basic structure of genetic material and introduce a definition of mutation. Then, I provide some context on how often mutations occur and how they are involved in evolution.

1.1.1 The basic structure of our genome

Before I can define and describe genetic mutations, one first needs to understand the basic mechanisms involved in synthesis and heredity of our genetic material; deoxyribonucleic acid (DNA). All known living species have DNA as their hereditary material and therefore, all the features described

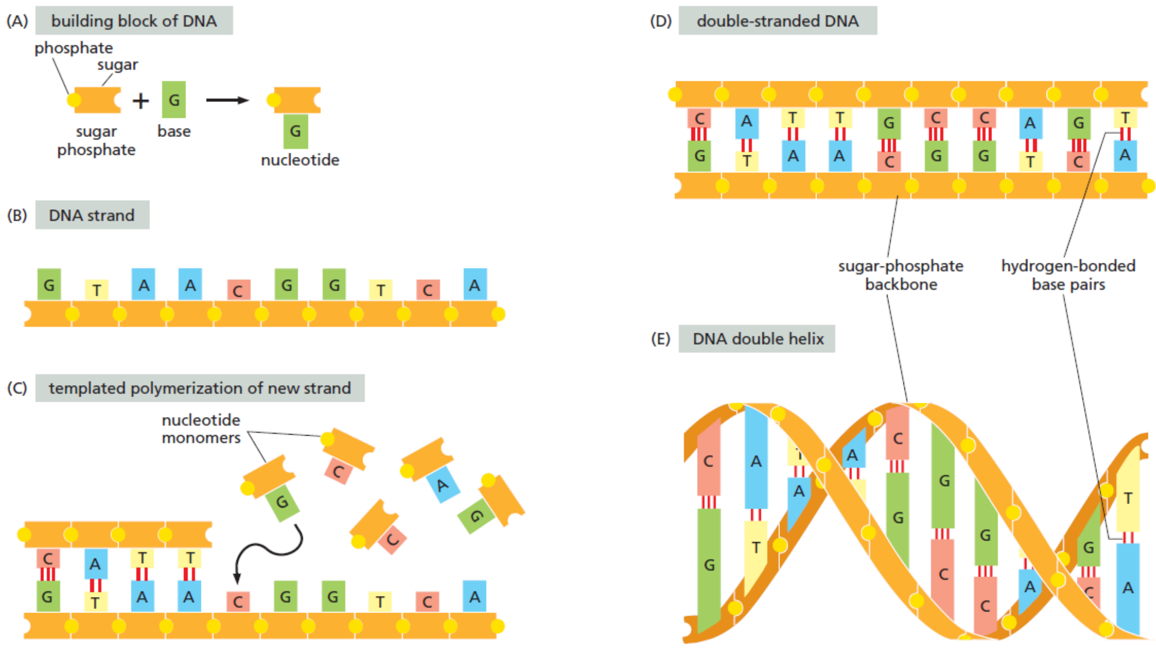

Figure 1.1 The building blocks of DNA. (A) Nucleotides are composed of a sugar phosphate and one of four possible bases. (B) A DNA strand is formed by a chain of sugar-phosphates, often called the *backbone*. Each base is a side group of this backbone. (C) Corresponding nucleotides form *base pairs*. (D) DNA forms a double-stranded molecule. The upper and lower strand are considered *complementary* strands. (E) Due to the chemical structure of the DNA molecule, it will fold itself into a stable *double-helix*. [6]

6. Adapted from Figure 1-2 in Bruce Alberts et al., *Molecular Biology of the Cell*, 6th ed. (Garland Science, 2015), 3

in this section apply to all living organisms.[7,8] In many species, DNA molecules are structured in the form of *chromosomes*, each chromosome being one long DNA molecule. Other organisms, such as bacteria, have a single, circular DNA molecule. As depicted in Figure 1.1, a DNA molecule can be seen as a long string of smaller components called nucleotides. In DNA, there are four types of nucleotides: adenine (`A`), cytosine (`C`), guanine (`G`), and thymine (`T`). Each of these letters, often referred to as *bases*, can form a pair with another base: the nucleotide `A` pairs with `T` and `C` pairs with `G`. Because these base pairs stick together, DNA will form a double strand.

DNA is synthesised in a process called *replication*. The double helix structure of DNA is unwound and the strands are "zipped" open, so that one of the strands can function as a template. Due to the bases forming their specific pairs, the newly synthesised strand is identical to the *other* strand (that did not function as a template, see also Figure 1.1C).[9] DNA can thus be copied, but it can also be transcribed into an analogous molecule, called RNA. This process, *transcription*, is very similar to replication, except for two details. First, `A` will not pair with `T`, but with a fifth type of nucleotide: uracil (`U`). Second, after transcription is done, the RNA strand will not remain paired with the DNA strand. Instead, it will be detached, transported, and used in *translation*. Translation is the process of reading an RNA molecule and simultaneously synthesising a protein. Each set of three nucleotides, called a *triplet*, codes for a specific amino acid — this is *the genetic code*. A string of amino acids will fold into a three-dimensional shape and become a protein. Proteins are responsible for most processes in living organisms; each type of protein carries out a specific function, including synthesis, transportation, alteration, or decomposition of other molecules. In fact, replication, transcription, and translation are also carried out by proteins. The part of the DNA that encodes for one protein is a *gene*.[11] Figure 1.2 provides a visual overview of the mechanisms involved in the processing of genetic material. A salient detail here is the directionality of these processes. There are organisms capable of reverse transcription, meaning that they make DNA from reading an RNA template. To date, no organism is known to be capable of reverse *translation*: synthesis of RNA

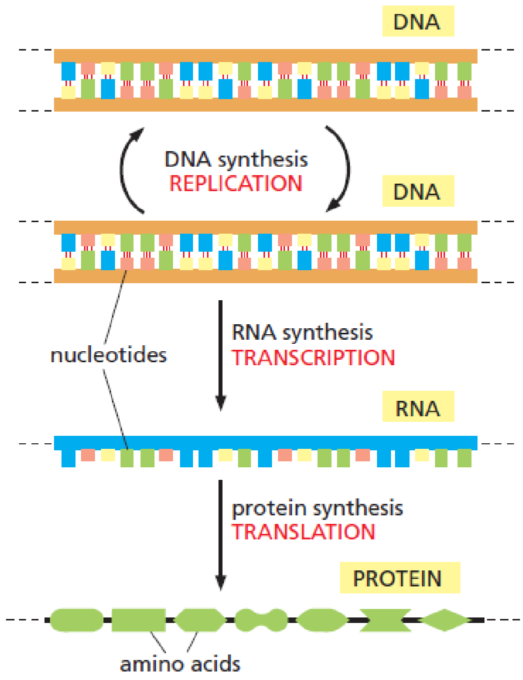

Figure 1.2 The processes from genetic material to protein. DNA is copied in a process called *replication*. Specific DNA sequences encode for specific proteins. In order to synthesise these proteins, DNA needs to be *transcribed* into RNA and RNA is then *translated* into a protein. Proteins are composed of a string of *amino acids*.[10]

7. For the biologist: I realise that this statement might be too radical and that future research might prove DNA-less life or life forms that we today cannot conceive. "All" in this case stands for "as far as we know now".
8. Akira Hiyoshi et al., "Does a DNA-less Cellular Organism Exist on Earth?," *Genes to Cells* 16, no. 12 (2011): 1146–1158.
9. For the biologist: newly synthesised strands will not be exactly identical to the coding strand because of misinsertions. I will explain this phenomenon later. Furthermore, in replication *both* strands serve as a template, resulting in two double-stranded DNA molecules, but for clarity, I have ignored this fact.
10. Adapted from Figure 1-4 in Alberts et al., *Molecular Biology of the Cell*, 4
11. Alberts et al., 3–6.

or DNA from a protein sequence. Translation thus appears to be a strictly unidirectional process, although this is based on empirical evidence only, and is conceptually conceivable.[12]

Because proteins carry out most cellular processes, they are in large part responsible for our *phenotype*; our physically visible traits. This includes, for example, eye colour, body height, and also (disposition for) disease.[13] However, not all genes are transcribed all the time. Protein synthesis is regulated; the *expression* of genes, determines whether or not they are used. This is vital to an organism's function, because not all processes are needed at all times. Hence, the *genotype* of an individual — the total set of genes — combined with the expression of these genes, determines the phenotype of the individual.[14]

1.1.2 Mutations

Now that we know the basic structure and mechanisms involved in genetics, we can dive into how mutations play a role in this system. *Mutation* can be interpreted in two ways; it refers either to the process of alteration of a DNA sequence or to the altered form of the sequence.[15] Because this dual meaning of the word "mutation" as both an event and a difference is confusing, I eschew the use as "a variation". Instead, I use the word "polymorphism" to refer to a DNA sequence that is different in individuals of the same species. Note that a polymorphism only describes a difference in DNA sequence, not necessarily a phenotypic difference. Some mutations cause changes in phenotype, while others have no effect.

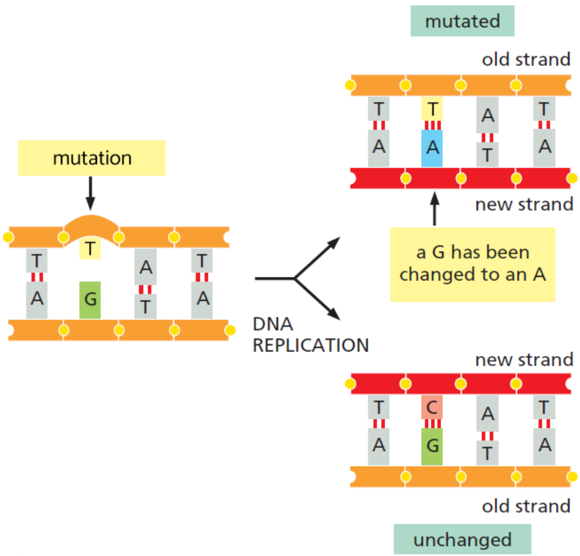

Figure 1.3 Mutation introduces a polymorphism after DNA replication. The mutation from `C` to `T` introduces a *mispaired base*. In DNA replication, both strands get used as a template. Because `T` pairs with `A`, in the mutated strand, an alternative base pair, a *polymorphism*, will arise.[16]

Different molecular mechanisms of mutation are known: single nucleotides can be substituted, inserted, or deleted, but it is also possible for larger parts of DNA to be duplicated, removed, or translocated. Figure 1.3 shows how a mutation results in a polymorphism. The location of a polymorphism determines whether it could have an effect on phenotypic traits. Some mutations make no difference at all, for instance, because every amino acid has multiple corresponding triplets. Take for example the sequence `GCC`,

12. Adhityo Wicaksono, Viol Kharisma, and Arli Aditya Parikesit, "New Perspectives on Reverse Translation: Brief History and Updates," *Universitas Scientiarum* 28 (2023): 1–20.
13. These traits all have genetic components, but I would not dare to assert that no other factors could possibly be involved in causing these phenotypes.
14. Anthony J.F. Griffiths et al., *Introduction to Genetic Analysis*, 11th ed. (New York, NY: W.H. Freeman, 2015), 7, 32.
15. Griffiths et al., 32.
16. For the biologist: the mutation shown here is deamination of 5-methylcytosine to thymine. Figure adapted and altered from Figure 5-40A in Alberts et al., *Molecular Biology of the Cell*, 269

which codes for the amino acid alanine. Suppose the second `C` is replaced by an `A`, the triplet would now be `GCA`. This triplet also codes for alanine, which means that the protein encoded remains unchanged.[17] Furthermore, in more complex organisms,[18] there are (large) portions of the genome that do not encode for any protein. While some of these regions have regulatory functions, others are called *junk DNA*: of these regions, no function is known (at least to date). This probably means that mutations in these regions have no, or at least very limited, effect on the phenotype of an individual. On the other hand, a single nucleotide polymorphism may very well have a substantial effect on the phenotype of an individual. An illustrative example is that for some people, coriander tastes like soap. This heritable phenotypic trait is caused by a single nucleotide being different from the one in individuals who like the taste of coriander. Exactly the same is the case for sickle cell disease, a severe, often fatal blood disorder in humans that decreases the ability of red blood cells to transport oxygen.[19,20]

Lastly, it is important to provide some context for the frequency with which mutations occur. To illustrate the mutation rate in humans: one specific type of mutation occurs approximately one hundred times per day, per cell.[21,22] The human body is composed of more than 10^{13} cells, meaning that this type of mutation occurs at least one quadrillion times per day in an adult person. This is only one of several types of mutation, illustrating the enormous number of mutations that take place in an organism all the time. Fortunately, there are mechanisms that repair the vast majority of mutations. As a matter of fact, of the over one quadrillion mutations caused by the mechanism I just described, almost 100% is repaired.[23] However, this does not apply to all types of mutation. Mutations that are not repaired will be paired with a different nucleotide(s) in the next DNA replication cycle, resulting in a polymorphism (see again Figure 1.3.[24] Polymorphisms can be a single nucleotide long — for example, in substitutions — but they can also span larger portions of DNA, such as with insertions, duplications, or deletions.

1.1.3 Heredity and evolution

But how do polymorphisms affect evolution? The first thing that is important to grasp is that in the context of evolution, mutation only plays a role if it happens in cells that will be passed on to offspring. In single-celled organisms like bacteria, the cell will undergo cell division, which will generate a new individual. Hence, all the polymorphisms that a single-celled organism acquires are inherited by its daughter cells. Multicellular, sexually reproducing organisms, such as human beings, have a *germ cell line*, illustrated in Figure 1.4. The purple cell, the *zygote*, is a fertilised egg cell. This cell generates the *somatic cells*, depicted in blue. These are the cells that our bodies consist of, while the red dots, *germ-line cells*, can form *gametes*. Gametes are also known as *reproductive cells*, that is,

17. Alberts et al., 238.
18. For the biologist: eukaryotes.
19. Griffiths et al., *Introduction to Genetic Analysis*, 219–220.
20. For the biologist: Insertions or deletions causing frameshift mutations is another example of a relatively small polymorphism that can have large effects on phenotype.
21. For the biologist: I am referring to deamination, the decay from cytosine to uracil or from 5-methylcytosine to thymine nucleotides.
22. Alberts et al., *Molecular Biology of the Cell*, 267–268.
23. Alberts et al., 267, Table 5-3.
24. Alberts et al., 269, Figure 5-40.

egg cells or sperm cells.[25,26] Since only germ-line cells are inherited, only mutations that occur in these cells are inherited by offspring and could therefore play a role in evolution.

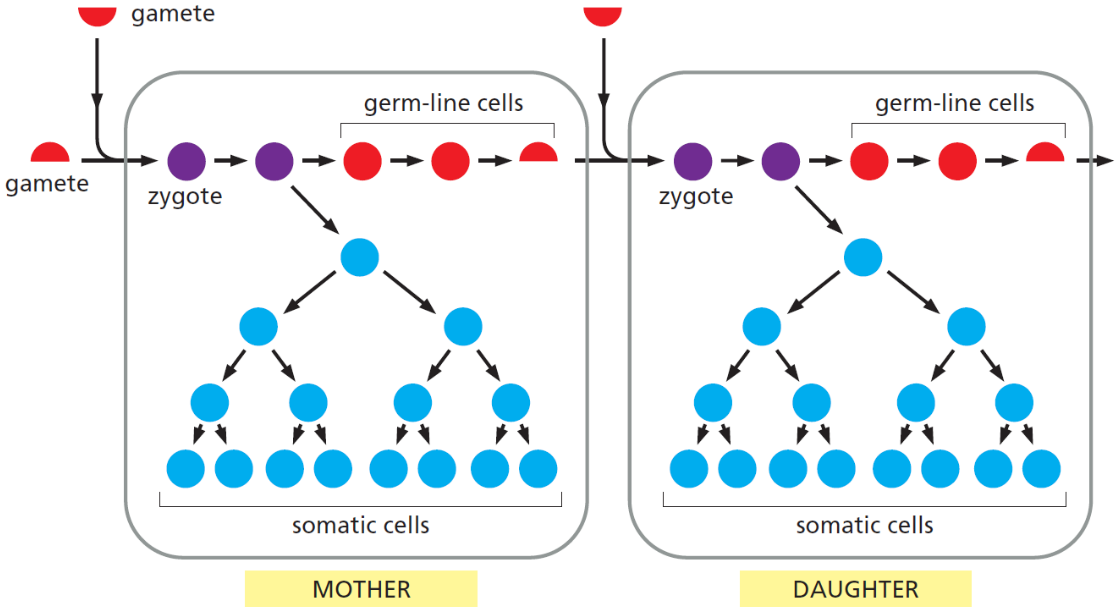

Figure 1.4 Germ-line and somatic cells. In embryogenesis, a fertilised egg cell is the product of two *gametes*. This cell, the *zygote*, produces the somatic cells that the body consist of, as well as a specialised germ cell-line, that will yield new *gametes*.[27]

I will briefly revisit the previously used example of soap-like coriander taste and sickle cell disease. Now that we know of germ-line cells, we can infer that the single nucleotide mutation that causes these phenotypes must have taken place in a germ-line cell. Subsequently, an individual that inherits a germ cell with this polymorphism will express the polymorphism in all of their cells, including their taste-bud cells or blood cells. Only then will the corresponding phenotype of tasting soap or being ill become expressed.

The last thing that warrants attention before we can investigate the problem of the randomness of mutation is Mendelian inheritance.[28] In humans this works as follows: each cell of the offspring has two copies of every chromosome, one inherited via the gamete of its mother and the other from that of its father. This means that an individual has two copies of each gene, and chances are that the trait encoded on the genes is not the same.[29] Recall once more the example of sickle cell disease. The disease is caused by a *recessive* copy of the gene, which means that a person will only have the disease — that is, express the phenotype — if they have inherited the faulty polymorphism from *both* their parents.[30,31] If they only receive one copy of the faulty gene, they will not have sickle

25. Alberts et al., *Molecular Biology of the Cell*, 238–239.
26. Griffiths et al., *Introduction to Genetic Analysis*, 4.
27. Adapted from Figure 5-1 in Alberts et al., *Molecular Biology of the Cell*, 239
28. I return to the discoveries of Mendel himself in Section 2.1.2. Here, I describe only the ideas that are still canonical as of today.
29. Griffiths et al., *Introduction to Genetic Analysis*, 4.
30. Griffiths et al., 219–220.
31. For the biologist: In sickle-cell anemia, the allele for sickling cells is actually codominant with the allele for normal cells. However, heterozygous individuals do not have sickling red blood cells under normal conditions, only under low oxygen concentrations (see Griffiths et al., 219–220). Therefore, I have regarded sickling cells as a recessive trait.

cell disease, but will be a carrier of the disease. For dominant traits, an individual needs only one copy in order to express the phenotype.[32,33]

In summary, while genotype and phenotype are linked, there is not a one-to-one correlation between the two. Mutations can be silent and have no effect on phenotype, but other single nucleotide polymorphisms could cause crippling disease. In sexually reproducing organisms, not all mutation-caused polymorphisms are inherited; only those in germ-line cells will be passed on to the next generation. Finally, not all parts of the genome — and therefore not all polymorphisms — are visible in phenotype; not only do noncoding regions (*junk DNA*) prove this, but also the fact that recessive traits are not phenotypically shown if a dominant copy is present.

1.2 Mutation in different contexts

We have seen so far that mutation is a molecular process, but it has evolutionary implications: the alteration of a base pair in DNA may result in an altered phenotype in the affected individual. Individuals are subject to natural selection, in which altered phenotype can prove to be positive, negative, or neutral. It is often said that "mutation is random with regard to evolution",[34] but what exactly does this mean? Furthermore, the term is also used in genetics to describe the molecular mechanisms of mutation. This often happens by invoking related terms, such as "spontaneity", or by connecting the biology of mutation to quantum mechanics.[35,36]

Thus, the term "randomness" is used in both evolutionary biology and molecular genetics. As "randomness" lacks a singular definition, the question arises of whether the same interpretation of randomness is used in both fields of biology. In Chapters 2 and 3 respectively, I investigate the use of the word "random" with regard to the concept of mutation in evolutionary biology and molecular genetics. Chapter 4 provides a reflection on the implications of different uses of "randomness", in which I address the importance of distinguishing ontological from epistemological claims, explanations of causes from those of consequences, and evolutionary randomness from genetic randomness.

32. For the biologist: I have only explained inheritance in diploid organisms, as the existence of polyploid sexually reproducing organisms is not relevant for the argument I make in this thesis. The existence of germ-cell lines and the mechanism of inheritance are.
33. Griffiths et al., *Introduction to Genetic Analysis*, 3–4.
34. Arlin Stoltzfus, *Mutation, Randomness, and Evolution* (New York: Oxford University Press, 2021), 231–236.
35. Alberts et al., *Molecular Biology of the Cell*, 267–268.
36. Louie Slocombe, Marco Sacchi, and Jim Al-Khalili, "An Open Quantum Systems Approach to Proton Tunnelling in DNA," *Communications Physics* 5 (1 2022): 2399–3650.

Chapter 2

Evolutionary randomness

A curious aspect of the theory of evolution is that everybody thinks he understands it.
— Jacques Monod[1]

It could be said that the pinnacle of biological knowledge is the theory of evolution. Theodosius Dobzhansky, one of the great geneticists of the 20th century, published an essay under the title "Nothing in Biology Makes Sense, Except in the Light of Evolution", in which he quoted his contemporary Pierre Teilhard de Chardin:

> Is evolution a theory, a system, or a hypothesis? It is much more — it is a general postulate to which all theories, all hypotheses, all systems must henceforward bow and which they must satisfy in order to be thinkable and true. Evolution is a light which illuminates all facts, a trajectory which all lines of thought must follow — this is what evolution is.[2]

The interpretations of randomness in the evolutionary context are twofold. First, it can be interpreted as an opposition to directed mutation, to which the notion of (neo-)Lamarckism is connected. Secondly, the randomness of mutation within an evolutionary context could signify independence of mutations with regard to fitness effect, which is a broad interpretation of randomness as non-directed. In this chapter, I elucidate how these two interpretations of randomness in evolution are used and what they imply, after providing the necessary historical context for evolutionary thought.

2.1 Brief history of evolutionary thought

Two common interpretations of "mutation is random" in evolution are non-directed mutation, or mutation that is independent of fitness effect. To fully understand this first conception of randomness, a short history of evolutionary theory is needed, because directed mutation is often referred to as "Lamarckian", while random mutation would be "Darwinian". In this simplified history of evolutionary thought, I highlight the role of directedness and chance in the evolutionary theories of Lamarck and Darwin, describe the research that led to the rejection of Lamarckism, and touch on the origin of the phrase "mutation is random".

1. Jacques Monod, "On the molecular theory of evolution," in *Problems of Scientific Revolution: Progress and Obstacles to Progress in the Sciences. The Herbert Spencer Lectures 1973*, ed. Rom Harré (Oxford: Clarendon Press, 1975), 12.
2. Theodosius Dobzhansky, "Nothing in Biology Makes Sense Except in the Light of Evolution," *The American Biology Teacher* 35, no. 3 (1973): 129.

2.1.1 Lamarck and Darwin

Although he was certainly not the first natural philosopher to formulate an evolutionary theory, Jean-Baptiste de Lamarck (1744-1829) formulated what is considered the predecessor of Darwinism. In 1809, he published his *Philosophie Zoologique*,[3] the book in which he postulated two central laws on his theory of evolution. Lamarck's First Law explains how variation comes about, and his Second Law has to do with the inheritance of traits. The First Law describes a positive correlation between the use of an organ and its strength.[4] So, the more a heart muscle is exercised, the stronger and larger it becomes, or the more a giraffe stretches its neck to reach the highest leaves of a tree, the longer it will become. In these two examples, the acquisition of traits seems to be caused by an act of the individual, but this is not a necessity; it could also be exposure to warmth that causes a thinner coat in an individual. This means that an individual can strengthen, or even newly develop, traits during its lifetime.[5] Lamarck's Second Law states that these acquired characteristics are then genetically encoded and passed on to offspring.[6] This genetic encoding happens only by virtue of the adaptive needs of the individual; the giraffe genetically encodes its elongated neck *only if* it provides it with an advantageous characteristic.[7] In this manner, beneficial traits are inherited by the offspring, while unprofitable traits are not.

In 1859, Charles Darwin (1809-1882) published *On the Origin of Species*,[8] the book in which he proposed a new theory of evolution. Darwin's evolutionary theory was based not on the acquisition of favourable traits but on their selection. His theory could be summarised in three central principles, described by Curtis Johnson in *Darwin's Dice* (2014) as follows:

1. Variation. All creatures that reproduce (...) will produce offspring that vary slightly from themselves. An offspring might have slightly longer legs, or a slightly shorter beak, or slightly more hair, than its parents, and so it is said to *vary*. It is important to say that Darwin often claimed that he did not know *how* or *why* variations occur, only that they do occur. (...) Darwin could often do no better than to say that any variation from parent to child is due to what we must, in our ignorance, call *chance*.
2. Heritability. Variations are often passed along in reproduction. Children with longer legs or more hair are likely to have children with these same traits, or even with these same traits more pronounced, and so on down the line of generation. In other words, variations often have a tendency to be *preserved*.
3. Competition for survival. More creatures are born in every species or group than can normally survive. (...) Therefore, some — actually many — must perish, as a regular fact of life. Only the few ever survive. This phenomenon came to be called by Darwin "survival of the fittest," an expression that was invented by Herbert Spencer and

3. Jean-Baptiste Lamarck, *Philosophie Zoologique, ou Exposition des Considérations Relatives à l'Histoire Naturelle des Animaux* (Brussels: Culture et civilisation, [1809] 1983).
4. Stoltzfus, *Mutation, Randomness, and Evolution*, 48.
5. Elliott Sober, *The Nature of Selection: Evolutionary Theory in Philosophical Focus* (Chicago: University of Chicago Press, 1984), 106.
6. Stoltzfus, *Mutation, Randomness, and Evolution*, 48–49.
7. Sober, *The Nature of Selection*, 106.
8. Charles R. Darwin, *The Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life.*, 6th edition (London: John Murray, 1872).

brought to Darwin's notice by the co-discoverer of the theory of natural selection, A. R. Wallace.[9]

Through variation, heritability of traits, and competition for survival, natural selection takes place. Individuals best suited to their environments have a greater chance of surviving and reproducing themselves, carrying on their favourable traits to offspring.[10] Ergo, in Darwin's theory, variation is not informed by the advantageousness of the trait. Rather, variation occurs due to "chance", after which natural selection preserves favourable variants. When describing the origin of variation, Darwin uses the word "chance". However, throughout his work, he employed multiple definitions of the word in different contexts, the two main interpretations being the *probability of survival* of an individual and the *fortuity of variation*.[11] The latter definition connects to mutation, for it describes the nature of variation. Darwin did not pretend to know why or how variation arises and sometimes defined the origin of variation as "what we, in our ignorance, must call chance".[12] This interpretation of chance as "unknown cause" could be interpreted as implying that the cause is *knowable*, just as of yet not known to us. However, according to Johnson, Darwin himself did not explicitly state this.[13]

The pivotal difference between Lamarck's and Darwin's accounts of evolution is that the former formulated a *developmental* theory, while the latter theory is *selectional*. The distinction between the two types can be illustrated by making an analogy with a school class of children. Suppose that there is a classroom with 10 schoolchildren in it. All students have a certain level of reading proficiency, say, a third grade level. This fact could be explained in two different ways. Firstly, in a developmental approach, the reason is that the children have learnt this skill inside the classroom, they have developed the trait *because* they are in the classroom. In a selective model, the children were only allowed access to the room if they were already able to read at the required level.[14] Drawing on this analogy, the schoolchildren represent organisms that are well-fitted to their environments. In the Lamarckian theory of evolution, these individuals have acquired, or *developed*, those characteristics. By contrast, in the Darwinian theory of evolution, these individuals have been selected because of the traits they already had.

However, to conclude from this that Lamarckism and Darwinism are mutually exclusive would be misleading.[15] In *On the Origin of Species*, Darwin frequently mentions the mechanism of use and disuse that Lamarck proposed, as a force additional to natural selection.[16] Darwin also did not repudiate the possibility of inheritance of acquired traits. In his theory of inheritance, which he called *Pangenesis*, he proposed that minuscule molecules within cells, called gemmules, contained information about traits.[17] These gemmules could travel from cell to cell throughout the body and could even be influenced by external factors. Gemmules would aggregate in reproductive cells (what we now call gametes), by means of which they are inherited by offspring.[18] In the 6th edition of *On*

9. Curtis Johnson, *Darwin's Dice: The Idea of Chance in the Thought of Charles Darwin* (Oxford: Oxford University Press, 2015), xiv-xv. Emphasis in original.
10. Johnson, xv.
11. Johnson, xxi.
12. Johnson, 12.
13. Johnson, xxii–xxiii.
14. Sober, *The Nature of Selection*, 148–150.
15. Stoltzfus, *Mutation, Randomness, and Evolution*, 49.
16. Sober, *The Nature of Selection*, 109.
17. For the biologist: Darwin's gemmules are not to be confused with the buds involved in the asexual reproduction of sea sponges.
18. Yongsheng Liu, "Darwinian Evolution Includes Lamarckian Inheritance of Acquired Characters," *International Journal of*

the Origin of Species, Darwin wrote:

> I have now recapitulated the facts and considerations which have thoroughly convinced me that species have been modified, during a long course of descent. This has been effected chiefly through the natural selection of numerous successive, slight, favourable variations; aided in an important manner by the inherited effects of the use and disuse of parts; and in an unimportant manner, that is in relation to adaptive structures, whether past or present, by the direct action of external conditions, and by variations which seem to us in our ignorance to arise spontaneously. It appears that I formerly underrated the frequency and value of these latter forms of variation, as leading to permanent modifications of structure independently of natural selection.[19]

In this passage, Darwin acknowledges the influence of the theory of use and disuse, as well as the inheritance of traits that are acquired through external conditions. These two mechanisms are Lamarckian mechanisms, indicating that a hard dichotomy between Darwinism and Lamarckism is an illusion. Indeed, the main point of dispute between the two authors concerns the developmental or selective nature of their theories of evolution, not the origin of variation.[20]

2.1.2 The Weismann barrier and Mendelian inheritance

I have mentioned that Lamarck postulated genetic encoding of acquired characteristics and that Darwin proposed theory of inheritance called Pangenesis. However, the observant reader might have noticed that I have described a different mechanism in Section 1.1.3. This is due to the fact that in the late 19th century, Darwin's theory of Pangenesis was experimentally tested, challenged, and finally disputed. Francis Galton (1822-1911) performed experimental testing of the Pangenesis theory by transfusing blood from white, orange, and black rabbits into grey individuals. He found that neither the transfused individuals nor their progeny showed any change in colour. This led him to believe that the gemmules that Darwin proposed were either not circulating in the rabbits' blood or did, in fact, not exist at all. Darwin denied that he ever claimed that gemmules would travel through blood, but were transmitted from cell to cell.[21] This argument did not undermine Galton's findings, who could still state that "(...) the doctrine of Pangenesis pure and simple, as I have interpreted it, is incorrect".[22] The idea that gemmules did not exist was endorsed by the findings of August Weismann (1834–1914), a German biologist who suspected that alterations in somatic cells could not be passed on via reproductive cells. To test this hypothesis, he amputated the tails of several generations of rats and discovered that the tail length of newborn individuals did not deviate from that of individuals with ancestors who had kept their tails.[23] Weismann called his hypothesis of separate cell lines for germ cells and somatic cells "theory of the germ-plasm", but today we know it as the Weismann barrier.

Epidemiology 45, no. 6 (2016): 2206–2207.

19. Darwin, *The Origin of Species*, 421.
20. Sober, *The Nature of Selection*, 110.
21. With contemporary biological knowledge, it is hard to fathom what this would look like, because we now know that blood is abound with cells
22. Elof Axel Carlson, *Mutation: The History of an Idea from Darwin to Genomics* (New York: Cold Spring Harbor Laboratory Press, 2011), 17–18.
23. Carlson, 18.

The Weismann barrier challenges not only Darwin's Pangenesis theory, but also the Lamarckian mechanism of evolution. Further objections to Lamarck's theory of evolution came from the rediscovery of the work of Austrian biologist Gregor Mendel (1822–1884) on pea plants. When Mendel conducted his experiments, the commonly accepted proposed mechanism of inheritance was the *blending theory*, where the traits of two parents would blend with each other in their offspring. However, when crossing pea plants with purple and white flowers, the flowers of the offspring plants (called *hybrids*) were not pink, as would be expected according to the blending theory, but a mix of purple and white. By self-pollinating the hybrid plants — meaning that the plant generates offspring with itself — Mendel worked out a 3 to 1 ratio between purple and white flowers.[25] After finding the same ratio for six other traits, including pea colour and pod shape, Mendel hypothesised that each plant had two *particles* — we now know that these are chromosomes — that each carried a trait and of which only one was passed to progeny.[26,27] Mendel also correctly theorised that traits could be *dominant* over another, if plants had two different *particles*, see Figure 2.1. Mendel's findings, substantiated by later research, refuted the Lamarckian idea of inheritance of acquired traits.

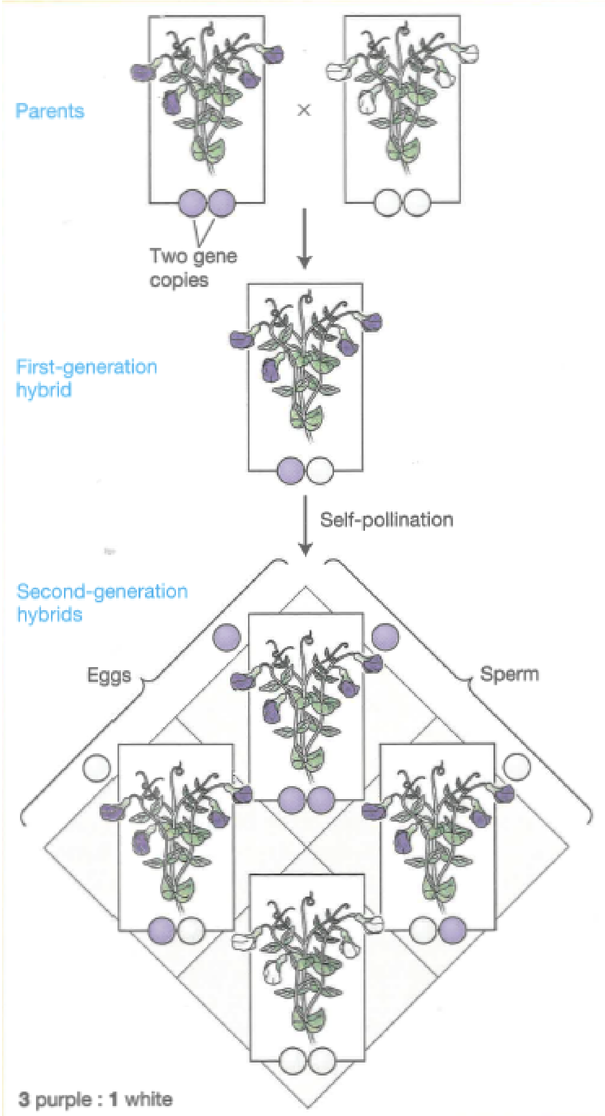

Figure 2.1 A schematic overview of Mendelian inheritance. Two plants with each a pair of gene copies are crossed. Their offspring, a *hybrid* plant, is then self-pollinated, shown in the table. The plant passes on either its purple gene or its white one. The offspring plants that received two white genes will have white flowers and those that received two purple copies will have purple ones. Because the purple trait is *dominant*, the plants receiving one purple and one white copy, will also generate purple flowers. The ratio of purple:white flowers in the offspring will thus be 3:1. [24]

2.1.3 Modern Synthesis

At the turn of the century, the discoveries of Weismann and Mendel not only refuted Lamarckism but also induced a project to synthesise these findings with Darwin's theory of evolution. During this so-called Modern Synthesis, links between the field of evolution and genetics were

24. Adapted from Figure 1-3 in Griffiths et al., *Introduction to Genetic Analysis*, 587
25. Griffiths et al., 3–4.
26. Carlson, *Mutation*, 25–27.
27. Griffiths et al., *Introduction to Genetic Analysis*, 4.

drawn, resulting in an integrated theory on the basic mechanisms of all life. I briefly summarise the main discoveries of this period, which roughly spanned the decades between 1920 and 1960, and pay some attention to the Luria-Delbrück experiment, an experiment that significantly altered our understanding of mutation in an evolutionary context.

The Modern Synthesis is characterised by a cluster of vast discoveries packed into a relatively short period of time. At the end of it, virtually all the mechanisms described in Section 1.1 were discovered. This includes the formulation of the *chromosome theory*, the *multifactorial hypothesis* (the idea that phenotypic traits can be determined by multiple genes), the *one-gene-one-enzyme hypothesis* (that every gene encodes for one protein), the discovery of the structure of hereditary material (DNA) and the discovery of gene expression.[28] In the late 1950's, one the discoverers of the double helix structure of DNA, Francis Crick, introduced the term "central dogma of molecular biology" to indicate the basic molecular mechanisms present in living organisms (see also Figure 1.2). Accidentally expressed very strongly — Crick was under the impression that the word "dogma" was synonymous with "hypothesis" — the phrase has since grown into its name and survived to the present day.[29] One could say that the discovery of the central dogma of molecular biology and its fit within the Darwinian framework of evolution were the main products of the Modern Synthesis.

An especially important discovery when it comes to the "randomness" of mutations was made by Salvador Luria and Max Delbrück, who were awarded the 1969 Nobel Prize in Physiology or Medicine for proving that mutations were not directed by evolutionary outcome.[30] In their experiment, depicted in Figure 2.2, they cultured *Escherichia coli* (E. coli) bacteria for several generations and tested the youngest generation for resistance to a bacterium-specific virus. The figure shows four pedigrees of bacteria, with the ancestor at the top and their progeny below. Figure 2.2a and 2.2b represent the predicted outcome of the experiment under two different hypotheses. 2.2a shows a pattern of resistant bacteria (depicted in blue) that would be expected under the hypothesis that the presence of the virus induced resistance in a percentage of the bacteria. This means that the resistant bacteria would be approximately equally distributed over the four different pedigrees. The other hypothesis, shown in Figure 2.2b, proposes that the mutation making the bacteria resistant occurs independently of exposure to the virus, in other words, at "random". Under this hypothesis, so-called "hot-spots" are expected; clusters of closely related bacteria that are all resistant to the virus. This suggests that a common ancestor of the resistant bacteria had mutated and transmitted the trait of being resistant to the virus, without ever having been exposed to it.[31] When testing these hypotheses, Luria and Delbrück found the pattern depicted in Figure 2.2b, indicating that the cause of these mutations is "random": "The original variants are predisposed to survival by random physiological variations (...)."[32] The fact that the mutation arose prior to exposure to the virus proves that the mutation could not have been induced by evolutionary selective pressure and therefore could not have arisen directed by its evolutionary outcome. The authors summarise:

28. Griffiths et al., 5–7.
29. Griffiths et al., 9.
30. Stoltzfus, *Mutation, Randomness, and Evolution*, 24–25.
31. Griffiths et al., *Introduction to Genetic Analysis*, 586–587.
32. Salvador E. Luria and Max Delbrück, "Mutations of Bacteria from Virus Sensitivity to Virus Resistance," *Genetics*, no. 6 (28 1943): 492.

> The distribution has been studied experimentally and has been found to conform with the conclusions drawn from the hypothesis that the resistant bacteria arise by mutations of sensitive cells independently of the action of virus.[33]

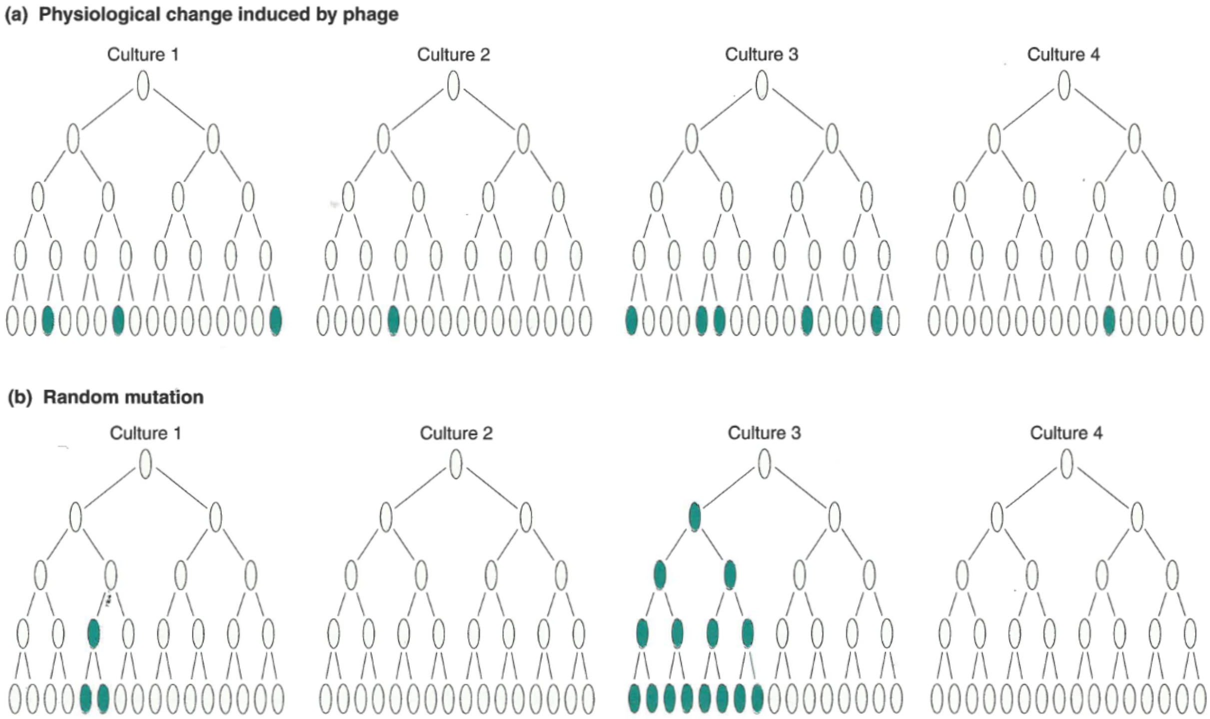

Figure 2.2 Cell pedigrees depicting the two contrasting hypotheses of the Luria-Delbrück experiment. (a) The pattern of resistant bacteria that is expected under the hypothesis of induced mutation. Of the youngest generation, 10 of the 64 bacteria are resistant to the virus, meaning ±16% of bacteria are resistant. The resistant bacteria are equally distributed over the four pedigrees. (b) The pattern of resistant bacteria under the hypothesis of random mutation. Again, ±16% of bacteria are resistant, but now they are clustered together in hot-spots, indicating that a common ancestor acquired the mutation. [34]

2.2 Randomness as opposition to directed mutation

After the Modern Synthesis, during which it was established that mutations were not directed, advances in biology did not grind to a halt. Although in contemporary evolutionary biology, the Darwinian framework still prevails, new interpretations of the Lamarckian theory also emerge.[35] Given the enormous amount of knowledge we have of cellular processes compared to the age of Lamarck and Darwin, contemporary interpretations of their theories of evolution are referred to as neo-Darwinian and neo-Lamarckian. Although these movements lack clear definitions, it is important to distinguish them from the original Darwinian and Lamarckian views. As justly noted by Arlin Stoltzfus, evolutionary biologist and author of the 2021 book *Mutation, Randomness, and Evolution*:

33. Luria and Delbrück, "Mutations of Bacteria from Virus Sensitivity to Virus Resistance," 510.
34. Adapted from Figure 16-5 in Griffiths et al., *Introduction to Genetic Analysis*, 587
35. I return to this subject in depth in Chapter 4.

> The names of Darwin and Lamarck should not be invoked in the same sentence as the word "mutation," except to note the anachronism of doing so.[36]

Nevertheless, neo-Lamarckism is sometimes used to assert the non-randomness of mutations, the implications of which I discuss in Chapter 4. The definition of randomness as non-Lamarckian is particularly difficult to pinpoint, for it is often not clear which tenet of Lamarckism is being denied. The inheritance of acquired traits was already disproven by Galton's and Weismann's experiments, so in that sense Lamarckism is indeed opposed. However, this opposition to Lamarckism is not a sense of randomness of mutation, but rather of the mechanism of inheritance on which the evolutionary theory relies. Moreover, the inheritance of acquired traits is not an original idea of Lamarck himself, but rather a commonly held belief at the time.[37]

Alternatively, it is the instructive nature of the (neo-)Lamarckian theory that is rejected. In this view, variation — which nowadays we know is caused by mutation — is not propagated to the next generation because of its beneficial evolutionary outcome. In line with Luria and Delbrück's paper, one could also say that mutations do not happen because of their evolutionary outcome. This idea is corroborated by the *central dogma of molecular biology*; living organisms can "reason" from genetic material to phenotype,[38] but not from phenotype to genotype (see also Figure 1.2).

In conclusion, mutation could be referred to as "random" in the sense of nondirectedness toward evolutionary positive outcomes. This was established by the Luria-Delbrück experiment, which proved that viral resistance in bacteria was not caused by exposure to the virus. As this refutes the idea of instructive or directed mutations, it poses a challenge to Lamarckism. Interestingly, there are contemporary biologists who argue in favour of neo-Lamarckian mechanisms, either by providing evidence of alleged directed mutations or via non-Mendelian inheritance. This topic will be investigated more thoroughly in Chapter 4.

2.3 Independence of fitness effect

In contemporary evolutionary biology, the Darwinian framework of evolution remains; we still believe that evolution works through "survival of the fittest by means of natural selection". Darwin used "survival of the fittest" and "natural selection" as synonyms, but in contemporary biology, the term "fitness" refers to a more specific concept.[39,40] In this section, I describe what role the concept of fitness plays in contemporary evolutionary biology. Subsequently, I show in what ways the randomness of mutations relates to the concept of fitness.

2.3.1 What is fitness?

"Fitness", like "randomness", is a term that lacks a single definition. Often, it is invoked in the context of the phrase "survival of the fittest". However, when defining who the "fittest" are, it is easy to

36. Stoltzfus, *Mutation, Randomness, and Evolution*, 50.
37. Stoltzfus, 49.
38. They can do this though transcription, translation, and gene expression, see Section 1.1.1.
39. Darwin, *The Origin of Species*, 49, 62, 98.
40. Elliott Sober, *Philosophy of Biology* (Oxford: Oxford University Press, 1993), 69.

resort to "those who survive". "Those who survive" are then, consequently, the "fittest". This is, of course, a tautology. We need to define "fitness" more clearly. We can start by linking fitness to how *well adapted* an organism is to its surroundings, but then we need to define "well adaptedness". Philosopher of biology Eliott Sober proposes the following definition, in terms of probability of survival and fecundity.

> Trait X is fitter than trait Y if and only if X has a higher probability of survival and/or a greater expectation of reproductive success than Y.[41]

Although this definition is more helpful than the previous one, it still fails to adequately describe three important aspects of fitness. It misses some nuance with regard to reproductive success, it refers to traits instead of individuals, and it is relational. Explaining these shortcomings will enable me to formulate an more complete definition.

First, Sober's definition relies on survival *and/or* reproductive success, while the Darwinian framework of evolution requires both survival *and* reproductive success.[42] We might even say that: "The survival of an old man, if he is quite unable to have any children, is of no importance whatever to the theory of evolution."[43] Moreover, in order to reproduce, of course an individual *has* to survive at least until it has reached its reproductive age. We could therefore describe "fitness" just in terms of reproductive success.

Second, it refers to traits instead of individuals. In the definition posed by Sober, it appears as if traits are capable of surviving and reproducing, which of course they are not. Traits are in a sense capable of "still being present in a population after numerous generations", but this is not the same as surviving or reproducing. Additionally, an individual can be better or worse adapted to its environment, while a gene or trait cannot. Consequently, fitness is not a property of traits (or genes), but rather of individuals.

Third and last, Sober's definition is relational; it describes the fitness of a trait in relation to another trait. In order to investigate its relationship to mutation, we should be able to describe the fitness of a single individual, for a mutation in an individual will change only their phenotype and fitness. When we take these three concerns into account, we end up with the following definition of "fitness":

> The fitness of an individual describes how well adapted it is to its environment by measure of its probability of reproductive success.

2.3.2 Fitness and mutation

Now that we have established a somewhat clear definition of "fitness", we can investigate its connection with randomness and mutation. Stoltzfus asks the same question: "(...) we want to know whether the chance of a mutation from genotype A to B is uncorrelated with the fitness effect of replacing A with B."[44] He contends that mutation and fitness can never be completely independent, as a change in genotype (caused by a mutation) can alter the organism's fitness.[45] This, however,

41. Sober, *Philosophy of Biology*, 70.
42. Griffiths et al., *Introduction to Genetic Analysis*, 696.
43. Monod, "On the molecular theory of evolution," 17.
44. Stoltzfus, *Mutation, Randomness, and Evolution*, 53.
45. Stoltzfus, 53–54.

only proves that fitness is dependent on mutation, not that mutation is dependent on fitness.

Whether mutation is dependent on fitness effect was tested by Luria and Delbrück, described in Section 2.1.3. They found that exposure to a bacterial virus did not induce mutations causing resistance to the virus. In the years following the publication of the paper, the experimental setup of Luria and Delbrück was repeated several times, also in other species and testing other phenotypic traits. The findings predominantly corroborated Luria and Delbrück's theory, strengthening its status.[46] However, the Luria-Delbrück experiment and related experiments do not categorically prove that there exists not a single mutational mechanism in which mutation is dependent on fitness effect.[47] The claim of independence of mutation and fitness effect can neither be proven on the basis of biological laws, nor can it be empirically verified.

Notwithstanding the impossibility of turning the independence of mutation and fitness effect into a universal biological law, independence is still observed in the vast majority of experiments. It does, however, mean that finding a single mechanism in which mutation is dependent on fitness effect will overturn the randomness doctrine of mutation. There are authors who claim that this evidence has been found, which will be thoroughly examined in Chapter 4.

2.4 Randomness in evolution

In this chapter, I have investigated where the idea of "random" mutations in evolution originated and how it is regarded in contemporary evolutionary biology. The main interpretations of "randomness" in evolutionary biology are "non-directedness to beneficial evolutionary outcomes" (in the Luria-Delbrück sense) and "independence of fitness effect". In a historical context, non-directed mutation could either be opposed to Lamarckism, or signify the fact that mutations were not induced by the environment, as shown in the Luria-Delbrück experiment. Random mutations as independent of fitness effect implies that mutations do not occur because they would alter an individual's likelihood of propagating.

Although the two interpretations of evolutionary randomness are very similar, they are not identical. The central claim of non-directed mutations is that mutations are not inclined to cause only evolutionary *beneficial* outcomes. By contrast, the independence hypothesis states that the fitness of an organism does not influence mutations in that organism. This makes randomness as independence a different type of claim than randomness as non-directed.

In conclusion, I have found two interpretations of evolutionary randomness: opposition to Lamarckism, opposition to directed mutation, and independence of fitness effect. Opposition to directed mutation can be seen as a part of opposition to Lamarckism, for Lamarckism supposed both directed mutations and the inheritance of acquired traits. The second interpretation of the randomness of mutations in an evolutionary context is that mutations would be independent of fitness effect.

46. Stoltzfus, 25.
47. Stoltzfus, 55.

Chapter 3

Genetic randomness

Mutations are often described as accidental, random, undirected, chance events. Just what do these epithets mean? — Theodosius Dobzhansky[1]

Now that we have investigated the potential role of "random" mutations in an evolutionary context, we should look at the other domain, genetics. As we saw in Section 1.1.1, mutation is a molecular mechanism with evolutionary implications, and we will now focus on the molecular mechanisms of mutation and the ways in which randomness could be involved. At first glance, it may seem as if "mutation is random" in a genetic context were a misinterpretation; that it is a statement made in evolutionary biology that is not to be interpreted in different contexts. However, the randomness of mutations is also questioned in contemporary molecular genetics.[2] Additionally, in Stoltzfus's book *Mutation, Randomness, and Evolution* (mentioned earlier in Section 2.2) identifies several ways ways in which the molecular basis of mutation could be interpreted as random. In this chapter, I investigate an array of different definitions of "randomness" in the context of molecular genetics, discuss their respective implications, and test them to empirical evidence in contemporary genetics. Where necessary, I explain some of the molecular mechanisms of mutation using two canonical handbooks, used by both students and scientists, namely *An Introduction to Genetic Analysis* by Griffiths et al. and *Molecular Biology of the Cell* by Alberts et al.[3,4,5]

3.1 Equal probability

Randomness is sometimes interpreted in a statistical sense. A random distribution in statistics would look like an equal probability distribution: every possible option is equiprobable.[6] This can be compared by the throw of a die: every side of the die has an equal probability, $\frac{1}{6}$, of ending up facing upward.[7]

1. Theodosius Dobzhansky, *Genetics of the Evolutionary Process* (New York: Columbia University Press, 1970), 65.
2. Laura Nuño de la Rosa and Cristina Villegas, "Chances and Propensities in Evo-Devo," *The British Journal for the Philosophy of Science* 73, no. 7 (2022): 513–514.
3. I emphasise the use of handbooks instead of individual scientific publications because in this way, I try to approximate the scientific consensus instead of individual interpretations of the term "random".
4. Griffiths et al., *Introduction to Genetic Analysis*.
5. Alberts et al., *Molecular Biology of the Cell*.
6. Stoltzfus, *Mutation, Randomness, and Evolution*, 17.
7. Interestingly, Stoltzfus refers to Laplace when explaining a uniform probability distribution. Although Laplace did develop such a theory, he uses this argument to develop a system in which an equal probability distribution signifies the *absence* of randomness and, therefore, implies determinism. Stoltzfus uses the argument in the exact opposite direction.

When the proposition "mutation is random" is meant in a statistical sense, this could be interpreted in four different ways. Firstly, one could argue that all types of mutation (such as insertions, deletions, substitutions, and translocations) have an equal probability and would in theory be observed the same number of times within a defined time frame. Secondly, random distribution could mean that a specific single nucleotide somewhere in the genome, for example, an adenine (`A`) nucleotide, has an equal probability of mutating into a `C`, `G`, or `T`.[8] A third interpretation of a uniform distribution of mutation is that each nucleotide in a locus (e.g., a gene) has an equal probability of mutating. If this probability is known, then the probability that a mutation will take place somewhere in a certain gene can be calculated by the length of the sequence alone.[9] A fourth possible interpretation would be that a mutation has the same probability of turning out to be beneficial or deleterious in the context of evolution.[10] This interpretation differs from evolutionary randomness in the sense that it does not describe a tendency or informed-ness of mutation, but rather a statistical distribution of their evolutionary effects, generated with hindsight knowledge.

Empirical evidence from molecular biology contradicts the applicability of all these interpretations of "probabilistic randomness". The first interpretation is invalidated by the fact that the rates of different types of mutation can be 10 orders of magnitude apart. For example, the number of repeats a short tandem repeat sequence (a sequence of between one and six nucleotides that repeats itself a number of times) consists of changes much more often than a single base pair insertion or deletion.[11] The second claim is refuted because the substitution of, say, $\texttt{A} \to \texttt{G}$ is much more common than $\texttt{A} \to \texttt{T}$. This can be explained by the structure of the nucleotides: `A` and `G` are structurally more similar, decreasing the "distance" that must be covered to go from an `A` to a `G`, compared to `A` to `T`.[12] The third interpretation of randomness as uniformity does not hold either: the sequence of nucleotides in a specific locus can influence the mutation rate. The probability of short insertions and deletions is increased in so-called homopolymeric sequences, sequences with repetitions of the same nucleotide.[13] The fourth interpretation, of equal probability of benefit or burden, can be refuted on logical grounds.[14] As Sober put it: "Random tinkering with a watch is more apt to make it run worse than better; by the same token, the odds are that a mutation will diminish rather than enhance an organism's fitness."[15]

3.2 Unpredictable

The "randomness" of a process is also often associated with the unpredictability of its outcome. The throw of a die is random in the sense that it seems impossible to predict with accuracy which number the next throw will yield. Mathematician and astronomer Pierre-Simon Laplace argued that this does not mean that the outcome of the throw is undetermined. He argued that the result of

8. For the biologist: or `U`.
9. Stoltzfus, *Mutation, Randomness, and Evolution*, 17.
10. Sober, *The Nature of Selection*, 105.
11. Stoltzfus, *Mutation, Randomness, and Evolution*, 17.
12. For the biologist: `A` and `G` are both purines, whereas `C`, `T` and `U` have pyrimidine structures. Single nucleotide changes within the same class of nucleotides are called transitions, and cross-class changes are transversions.
13. Stoltzfus, *Mutation, Randomness, and Evolution*, 18.
14. Disproving it on empirical grounds is equally possible, see Adam Eyre-Walker and Peter D. Keightley, "The Distribution of Fitness Effects of New Mutations," *Nature Reviews Genetics* 8 (2007): 610–618.
15. Sober, *The Nature of Selection*, 105.

the throw could be predicted by a supreme intelligence — nowadays known as "Laplace's demon" — given that it has perfect knowledge of the entire system: the starting conditions plus force, grip, motion, and all other factors that influence the outcome of the throw.[16] Laplace writes:

> We ought then to regard the present state of the universe as the effect of its anterior state and as the cause of the one which is to follow. Given for one instant an intelligence which could comprehend all the forces by which nature is animated and the respective situation of the beings who compose it (...); for it, nothing would be uncertain and the future, as the past, would be present to its eyes.[17]

Thus, according to Laplace, the universe is *deterministic*; all future events are determined by preceding ones. Here, Laplace draws from the *principle of sufficient reason*.[18] For Laplace's demon with its supreme intelligence, all these causes are intelligible. For humans, on the contrary, this universal knowledge of the world is impossible. Laplace continues:

> The human mind offers, in the perfection which it has been able to give to astronomy, a feeble idea of this intelligence.[19]

In summary, Laplace concludes that the world is deterministic. Every event, however vast or minute, can be predicted by a supreme intelligence. This is because, according to the principle of sufficient reason, nothing happens without a cause. For humans, this comprehensive knowledge of the world is inaccessible.

How does this translate to the biology of mutations? When asserting the unpredictability of mutations, are we stating that even Laplace's demon could not predict the time and place of a mutation? In what follows, I investigate what unpredictability of mutation means for humans and for Laplace's demon.

3.2.1 Scientifically unpredictable

It is evident that contemporary science does not have perfect knowledge of every mechanism of mutation. Some types of mutation are fairly well known and therefore predictable to us, whereas others remain totally unpredictable.[20] One could say that the mechanisms that are poorly understood by science are *scientifically unpredictable*.[21] However, randomness as scientifically unpredictability is not synonymous to "science does not know yet". Stoltzfus argues that the "observer effect" known from physics is also, to some extent, applicable to biology.

Consider the following scenario: we know that UV radiation can damage DNA. It does not induce mutation directly, but the repair mechanisms for UV damage are error prone, increasing the probability of a mutation. This repair mechanism consists of a variety of molecules and complexes,

16. Pierre-Simon Laplace, *A Philosophical Essay on Probabilities*, 6th ed., trans. Frederick W. Truscott and Frederick L. Emory (New York: Wiley, 1902), 4.
17. Laplace, 4.
18. Laplace, 3.
19. Laplace, 4.
20. Stoltzfus, *Mutation, Randomness, and Evolution*, 22–23.
21. Stoltzfus employs this exact interpretation of randomness as well, but calls it *subjective unpredictability*. As a philosopher, I feel that Stoltzfus' term implies the existence of a concomitant term, *objective unpredictability*, which is an implication that I do not wish to make.

the identity, location, and momentum of all of which we would have to know in order to predict whether damage will be repaired with or without introducing a mutation. Laplace's demon would obviously know all of this information and would be able to create a model out of these data that is able to make accurate predictions. However, as Stoltzfus argues, science depends on measuring techniques, such as X-rays or magnetic resonance, which will inevitably interfere with the cellular processes that are being studied.[22] This view of Stoltzfus implies that techniques capable of mapping out cellular content will inherently disturb cellular processes. Although a non-interfering technique able to identify particles as small as single ions seems incomprehensible today, this might be different in the future. This claim to randomness is thus purely epistemological. Whether the mechanisms of the causes of mutation will remain unpredictable or not is dependent on the course of scientific discovery. The acceptance of the statement that at least some mutations are random in the sense of scientific unpredictability does not imply any ontological claim about the nature of the cause of these mutations.

3.2.2 Fundamentally uncaused

The fact that some mechanisms of mutation are unpredictable for current science does not imply that they are fundamentally unpredictable or *indeterministic*. By contrast, only to say that even with perfect knowledge, even for Laplace's demon, mutation is unpredictable would be to say that mutation is indeterministic. The canonical example of this type of indeterminism in science is quantum mechanics. Although, for example, Max Bohm pleads for a deterministic interpretation of quantum mechanics, most people — including physicist Erwin Schrödinger and Stoltzfus — adhere to the Copenhagen interpretation of quantum mechanics. Under this interpretation, quantum mechanical processes introduce indeterminacy into biology.

The first to propose a quantum theory of mutation was Max Delbrück, of the Luria-Delbrück experiment mentioned in Section 2.1.3.[23] Despite the fact that Delbrück himself was not convinced of his own theory (he called it a "silly piece of work"[24]), Schrödinger adopted the idea in his renowned book *What is Life?* (1944).[25] Many distinguished figures in 20th-century biology supported this theory, including biochemist and Nobel laureate Jacques Monod:[26]

> We now know what the nature of mutations is. (...) We know that they are quantum events, that they occur at the level of single molecules, and therefore that they belong in the realm of microscopic physics — in the realm of events that by their very nature cannot be individually predicted (...)[27]

In contemporary science, this idea is represented by the field of *quantum biology*.[28] In very recent research, it was hypothesised that a quantum phenomenon called "proton tunnelling" also occurs within DNA molecules.[29] Quantum tunnelling is a phenomenon where a particle — for example, a

22. Stoltzfus, *Mutation, Randomness, and Evolution*, 23.
23. Carlson, *Mutation*, 76–77.
24. Carlson, 83, n24.
25. Erwin Schrödinger, *What is Life?* (New York: The Macmillan Company, [1944] 1962), 47.
26. Jacques Monod, *Chance and Necessity*, trans. Austryn Wainhouse (London: Penguin Books, 1971), 113–115.
27. Monod, "On the molecular theory of evolution," 19–20.
28. Thomas Heams, "Randomness in Biology," *Mathematical Structures in Computer Science* 24, no. 3 (2014): 19.
29. Slocombe, Sacchi, and Al-Khalili, "An Open Quantum Systems Approach to Proton Tunnelling in DNA."

proton — crosses an energetic barrier which, according to classical physics, it should not be able to pass. In order to cross the barrier, it needs a sufficient amount of energy. In quantum tunnelling, the particle does not have enough energy, but it still passes the barrier.[30] In quantum biology, it is hypothesised that the protons in the bonds connecting a base pair[31] undergo quantum tunnelling, resulting in a bond between a mismatched pair, which is considered a mutation.[32,33]

Of course, this is not conclusive evidence that many, let alone all mutations are caused by quantum effects, but it does provide a first piece of evidence that some mutations might. Under the indeterministic Copenhagen interpretation of quantum mechanics, this means that the quantum processes causing mutation are indeterminate, introducing indeterminacy in mutational events.

In the future, quantum mechanical processes could provide a direct explanation for mutations, but they could also turn out to indirectly influence mutation. As discussed in 3.2.1, UV radiation causes damage, which is repaired by error-prone repair mechanisms. This radiation is ultimately caused by nuclear fission in the Sun, which is considered to be an indeterminate process.[34] Thus, even without more evidence from the emerging field of quantum biology, some mutational mechanisms can be considered to be indeterminate.

3.3 Independent

Mutation could also be described as "independent": as we saw in Section 2.3. I have demonstrated that mutation could be seen as independent from fitness effect in an evolutionary context. However, randomness as independence can also apply to mutation in a genetic context, as independent of other mutations, other cellular processes, or external agents. The latter category is generally opposed to "induced mutations", and is called "spontaneous". However, we will see that the term "spontaneity" has many connotations, both in biology and philosophy.

3.3.1 Relational independence

It seems logical to regard mutation as a singular event. Some mutations have larger effects than others, but generally the accumulation of mutations leads to variance in phenotype upon which selection takes place. In this view, mutations would be relationally independent of other mutations: a mutation at a certain site would be independent of a mutation at another site.[35] This idea of randomness approximates Aristotle's idea of chance.[36] Things that happen by chance could fall into different categories, but have in common that they are caused by *accidents*. In Aristotle's example, two people meet each other "accidentally" at a marketplace, and although they both deliberately decided to go to the market, each with his own purpose, they did not intend to meet one another

30. Slocombe, Sacchi, and Al-Khalili, "An Open Quantum Systems Approach to Proton Tunnelling in DNA," 1–2.
31. For the biologist: hydrogen bonds
32. For the biologist: tautomeric base pairing
33. Slocombe, Sacchi, and Al-Khalili, "An Open Quantum Systems Approach to Proton Tunnelling in DNA," 1.
34. Stoltzfus, *Mutation, Randomness, and Evolution*, 22.
35. Stoltzfus, 28.
36. Aristotle, "Metaphysics," in *The Complete Works of Aristotle*, ed. J. Barnes, trans. W.D. Ross (Princeton: Princeton University Press, 1984), 1064b30-1065b6.

there.[37,38] While Aristotle's teleological world view does not match that of our scientific understanding of mutation, the idea of two events with their respective causes coinciding does correspond.

This conception of causal independence translates to mutations as follows. Two mutations are independent, because even if they happened at the same time, their respective causal chains are independent. Their coinciding at the same moment is, as Aristotle phrased it, "neither necessary, nor usual".[39] An example of independent mutations is the existence of homologous sequences in different species. Although the mutation did not necessarily occur at the same time, it is the exact same point mutation, changing one sequence into the other. Humans and chimpanzees share some of the same single nucleotide polymorphisms, but these polymorphisms must have arisen independently of each other, by independent mutational events, because they emerged in different species.[40,41]

However, there is also evidence that not all mutations are independent of other mutations; so-called "compound mutations". Although they are uncommon, the rate of occurrence of mutation clusters is higher than would be expected when the mutations were totally independent.[42] One possible explanation for this is that all mutations in the cluster have a common source, for example, an external agent (as will be discussed below). Another explanation would be that of elevated chances of mutation at sites that have previously mutated. In this case, mutations would not have a common cause, but one mutation could cause (or increase the likelihood of) a second mutation. Although there is some literature supporting this hypothesis, it is not a widely accepted mechanism.[43]

3.3.2 Independent of cellular processes

Mutations are often, albeit not always, independent of other mutations. A different interpretation of genetic randomness as independence would be to regard mutations as events that are independent of other cellular processes. This idea originates from Richard Dawkins, who in his 1976 book *The Selfish Gene* proposed that DNA is "sealed off from the outside world."[44,45] If mutation were independent of all outside effects, independence from fitness effect, and therefore evolutionary randomness, would be guaranteed. However, there is strong evidence that not all types of mutation are independent of other cellular processes. A simple example is misinsertion during DNA replication. In the process of DNA replication, the zip-like double helix structure of DNA is unzipped, making each of the strands a template to which new nucleotides are matched. The new nucleotides are paired with the template strand by a protein complex called DNA-polymerase, which is not 100% accurate; the mistakes it makes are called misinsertions. DNA-polymerase is involved only in the chaining of nucleotides, not in their synthesis. The "free nucleotides" used by DNA-polymerase are already

37. Lüthy and Palmerino, "Conceptual and Historical Reflections on Chance," 19–20.
38. Actually, Aristotle's idea of chance is more complex than I have described here. For a more complete representation of Aristotle's thought in chance, I refer to the article by Lüthy and Palmerino.
39. Lüthy and Palmerino, 19.
40. For the biologist: The fact that the same SNP is found in both humans and chimpanzees indicates that the same point mutation occurred in both species. Alternative hypotheses of neighbouring nucleotide effects, ancestral polymorphisms, and natural selection on the SNP were excluded, indicating true causal independence of the SNP's. See Alan Hodgkinson, Manolis Ladoukakis, and Adam Eyre-Walker, "Cryptic Variation in the Human Mutation Rate," *PLoS Biology* 7 (2009): e1000027.
41. Stoltzfus, *Mutation, Randomness, and Evolution*, 19, 28.
42. Stoltzfus, 28–29.
43. Stoltzfus, 29.
44. In the cited passage, Dawkins does not refer to DNA directly, but to genes.
45. Richard Dawkins, *The Selfish Gene* (Oxford: Oxford University Press, [1976] 2006), 19.

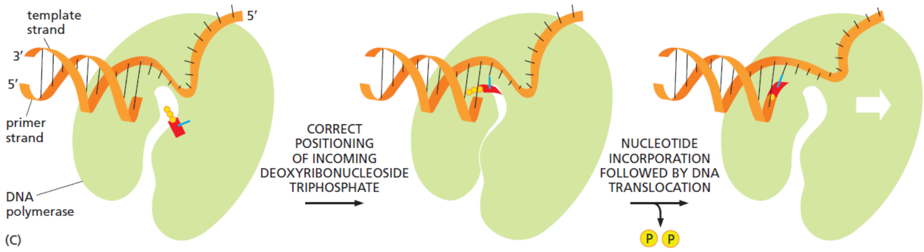

Figure 3.1 The function of DNA polymerase in DNA synthesis. DNA polymerase uses free nucleotides (*deoxyribonucleoside triphosphates*) that are already present and incorporates them in the newly synthesised strand.[47]

present in the nucleus of a cell before DNA replication starts, see Figure 3.1.[46] The production of nucleotides and the activity of DNA-polymerase could therefore be described as independent. However, the probability distribution of misinsertions is not homogeneous: the concentration of free nucleotides in the nucleus is of influence on the misinsertions. Because nucleotide synthesis is a different cellular process, misinsertion can be considered non-independent of cellular processes.

3.3.3 Spontaneous

A term that is very often associated with the nature of mutation is “spontaneity”. “Spontaneous” would be defined here as “without an external cause”, i.e., “not induced by outside agents”. External agents responsible for mutations are often called *mutagens*. Hence, one could divide mutations into those caused by mutagens and “spontaneous” mutations.[48] Interestingly, Griffiths states that “spontaneous mutations arise from a variety of sources”. This is remarkable because in most interpretations of the word “spontaneous”, it refers to phenomena *without* any cause. A good example of this is the conception that the Epicureans had of “spontaneous clinamen”: irregular swerves that happened in atoms. Cicero describes the view of Epicurus as follows:

> Epicurus thinks that the necessity of fate is avoided by the swerve of atoms. (…) That this swerve occurs without a cause he is forced to admit in practice, even if not in so many words. For it is not through the impact of another atom that an atom swerves. How, after all, can one be struck by another if atomic bodies travel perpendicularly in straight lines through their own weight, as Epicurus holds? For it follows that one is never driven from its course by another, if one is not even touched by another. The consequence is that, even supposing that the atom does exist and that it swerves, it swerves without a cause.[49]

“Spontaneous” is used in a similar way in contemporary genetics, but it contains some inconsistencies. The division into *induced mutation* and *spontaneous mutation* implies that spontaneous mutations are not induced by any agent and are therefore uncaused. However, examples of spontaneous

46. For the biologist: In reality, nucleotides are not “free”, but take the form of deoxyribonucleoside triphosphates. As specifics are not important in this case, I have chosen to simplify the matter a bit, to spare the philosophers who have to read this thesis yet another biological term.
47. Adapted from Figure 5-4 in Alberts et al., *Molecular Biology of the Cell*, 241
48. Griffiths et al., *Introduction to Genetic Analysis*, 588.
49. Cicero, “De Fato,” in *The Hellenistic Philosophers*, ed. A. A. Long and D. N. Sedley, vol. 1 (Cambridge: Cambridge University Press, 1987), 104–105.

mutations are errors in DNA replication and so-called *spontaneous lesions*. Errors in DNA replication can lead to transversions, transitions, and deletions.[50] To characterise these mutations as "without a cause" is a little too simplistic, as the cause could be the accuracy of the DNA polymerase protein (see Section 3.3.2). Although it is not fully understood why DNA polymerase misinserts nucleotides, its replication and proofreading mechanisms are far from a black box.[51] While a molecular mechanism explaining misinsertions is not known today, it is known that it can be biased (see Section 3.3.2), and it is certainly conceivable that such a mechanism exists.

The second type of spontaneous mutation approximates the definition of the Epicureans better; that of spontaneous lesions. Here, "spontaneous" is borrowed from chemical thermodynamics, where it means "without addition of external energy". Spontaneous DNA lesions do indeed occur without the need of an energy source or an enzyme.[52,53] However, the use of "spontaneous" is very inconsistent. Alberts et al. uses the term interchangeably with the word "endogenous", meaning with an internal cause, and Griffiths et al. classifies mutations due to interactions with oxygen radicals as spontaneous.[54,55] In summary, while "spontaneous" is a term regularly used to classify types of mutation, there is no consensus on the exact meaning of the concept.

3.4 Randomness in genetics

In this chapter, I have examined a multitude of possible conceptions of randomness in a genetic context. We have seen that mutations are not equiprobable in any sense of the word. Additionally, mutation can be said to be unpredictable in multiple senses, including scientific unpredictability (either for state-of-the-art science or including all future science) and the possibility of fundamental unpredictability through a direct or indirect connection to quantum phenomena. Many mechanisms of mutation can be said to be independent of each other, although compound mutations prove that this does not hold for all mutations. Similarly, many mutations are independent of other cellular processes, but this can also not be categorically proven. Lastly, geneticists describe a group of mutation mechanisms as "spontaneous", in which they use this term inconsistently. Although some mutations are, in a sense, spontaneous, not all mechanisms of mutation are.

In molecular genetics, randomness lacks a conclusive definition, making "mutation is random" an ambiguous statement. None of the examined definitions of randomness apply to all mutations, but it can not be stated that "mutation is *not* random" in a genetic context.

50. Griffiths et al., *Introduction to Genetic Analysis*, 588–589.
51. Alberts et al., *Molecular Biology of the Cell*, 237–254.
52. Griffiths et al., *Introduction to Genetic Analysis*, 589.
53. Alberts et al., *Molecular Biology of the Cell*, 267–268.
54. Alberts et al., 267, Table 5-3.
55. Griffiths et al., *Introduction to Genetic Analysis*, 590.

Chapter 4

What is at stake?

Great is the power of steady misrepresentation; but the history of science shows that fortunately this power does not long endure. — Charles Darwin[1]

In the previous chapters, we have seen that the phrase "mutation is random" has different meanings in evolutionary biology and genetics. Moreover, even within the two fields, the statement is not unambiguous either. In itself, this would not necessarily cause problems, if all sub-meanings were well-delineated and strictly separated. However, we have seen that they are not. This chapter will discuss the problems that arise when the pluriformity of the statement "mutation is random" is not acknowledged. Therefore, I focus on what the phrase "mutation is random" could possibly mean, regardless of whether it is believed to be true. As we will see in Section 4.1, different interpretations of the term exist side by side, resulting in both ontological and epistemological claims, as well as claims about the cause and the result of mutations. Furthermore, I argue that the term "mutational Lamarckism" is both a misrepresentation of Lamarckism and a confusion of genetic and evolutionary randomness (Section 4.2). I suggest that a reductionist approach lies at the base of this confusion in Section 4.3.

4.1 Two discourses of randomness

As we have seen throughout Chapters 2 and 3, the phrase "mutation is random" may be understood differently depending on the definition of "randomness" that is used.

In evolutionary biology, the most common interpretation is that mutations are not directed toward beneficial outcomes. It is important to distinguish this definition from "non-Lamarckian" random mutation, as (neo-)Lamarckism is a specific interpretation of mutation as non-directed (see Section 2.2). Furthermore, it could be argued that in evolution "random mutation" could signal the total independence of mutational processes from fitness effects.

Meanwhile, in genetics, the term "random" has a different set of meanings. "Random mutation" could mean a mutational event that is independent of cellular or external processes (3.3), unpredictable (3.2.1), or even fundamentally uncaused (3.2.2). A recapitulation of the main definitions of randomness in both scientific fields is shown in Table 4.1. I have not included genetic randomness as equiprobable, as all interpretations were empirically disproven.

1. Darwin, *The Origin of Species*, 421.

Evolutionary	Genetic
Not directed	Scientifically unpredictable
Not Lamarckian	Independence of external processes (spontaneous)
Independence of fitness	Fundamentally uncaused

Table 4.1 Different evolutionary and genetic meanings of randomness

4.1.1 Ontological versus epistemological claims

Based on the interpretation of the word "random" in the statement "mutation is random", its meaning can vary drastically. Apart from the meaning of the statement, the *type* of assertion that is made could also change, as it can represent an ontological or epistemological claim. For each definition of randomness, an interpretation of the phrase "mutation is random" could be made. Table 4.2 shows a schematic overview of the possible evolutionary and genetic interpretations of "random" making ontological and epistemological claims.

	Evolutionary	Genetic
Ontological	Not directed; not Lamarckian; Independent of fitness	Fundamentally uncaused; Spontaneous
Epistemological	-[2]	Scientifically unpredictable

Table 4.2 Ontological and epistemological randomness claims with regard to mutation

The majority of the interpretations yield an ontological claim; viz. about how the world *is*. Statements about mutation understood as "not directed towards a beneficial outcome", or as "non-Lamarckian process" are about processes that happen in nature, regardless of an observer. The same is applicable to mutation as "fundamentally uncaused", or "spontaneous" mutation in genetics. However, the use of "random" as "unpredictable", as used in genetics and described in Section 3.2, entails an epistemological claim. This statement does not imply knowledge about the processes that happen, but rather about our ability to observe them. Stating that "mutation is unpredictable" is actually stating that "mutation is unpredictable *to us*". This unpredictability may very well be inevitable, due to phenomena such as the observer effect, but this does not mean that mutation is *ontologically* unpredictable.

This distinction between ontological and epistemological interpretations of randomness is valuable when investigating the (in)deterministic nature of mutations. The term "randomness" is often associated with (in)determinism: when a process is "random", its outcome is considered to be indeterminate. However, it is essential to draw the distinction between ontological and epistemological

2. Ontological evolutionary randomness is conceivable. An example of this is what Thomas Heams calls "individual life histories". He refers to events affecting variation, such as mate selection and recombination during gametogenesis (the production of reproductive cells). Elliot Sober describes a similar kind of chance component that is involved in natural selection. However, I have not discussed or listed this kind of randomness, as it does not concern mutation, but other sources of variation. For more on ontological randomness in evolution, see Heams, "Randomness in Biology" and Sober, *The Nature of Selection*, 103–104.

randomness. Epistemological randomness is equivalent to scientific unpredictability, as mentioned in Section 3.2.1. In contrast, ontological randomness might be found in mechanisms that propose fundamentally uncaused mutations, in which the cause of a mutation is indeterminate (see Section 3.2.2). In this case, the link with ontological randomness in quantum mechanics is evident.

Note that the interpretations of both epistemological and ontological randomness come from the domain of genetics. The reason for this is that evolutionary randomness means "not directed" *towards something*, or "independent" *of something*, describing relations between mutation and other phenomena. Describing these relationships has nothing to do with indeterminism or uncausedness, just with excluding certain causes of mutation, such as advantageous outcomes. This leads me to making a distinction between randomness as either describing causes or consequences.

4.1.2 Cause or consequence

In the previous section, I have identified that evolutionary randomness specifies what the consequence of mutation can or cannot be. If mutations are random in the evolutionary sense, then the consequence of these mutations cannot only be positive. Genetic randomness, on the other hand, describes potential causes of mutation.

The distinction I make between genetic randomness as explaining a cause and evolutionary randomness as explaining a consequence, is assisted by the theory of *source laws* and "consequence laws" by Elliott Sober. Source laws describe the cause of a phenomenon in terms of its physical basis.[3] Consequence laws, on the contrary, describe the associated behaviour of the law. For example, the law of gravitation, $F = m \cdot a$, does not describe the physical basis of the origin of the mass or of the acceleration of an object, but it does describe the consequence they will produce, namely the gravitational force.[4] Genetic randomness of mutation provides a source law, as it describes the cause of a specific mutation. The (non-)random origin of mutation could explain where and why mutations arise. Evolutionary random mutations, by contrast, provide a consequence law, as they describe what consequences a mutation can or cannot have. In an evolutionary context, mutations result in altered fitness values and evolutionary randomness implies that these alterations could not be only positive.

4.2 Mutational "Lamarckism"

The context in which the randomness of mutation is asserted is crucial to its meaning. As definitions of randomness are often not very well delineated or explicitly defined, confusion between different meanings of randomness might arise, resulting in claims with unintended connotations.

In the recent literature, the term "mutational Lamarckism" has emerged. This term is used to describe molecular mechanisms of mutation in which phenomena are observed that seem "non-random". This is taken to imply that Lamarckian mechanisms are at play. Mutational Lamarckists often point to either mutation bias as being directed or to non-Mendelian mechanisms of inheri-

3. Sober, *The Nature of Selection*, 47.
4. Sober, 49–50.

tance, such as epigenetics.[5] This section argues that the inference from "non-random mutation" to "mutational Lamarckism" constitutes both a misrepresentation of Lamarckism and a category mistake, as it confuses genetic and evolutionary randomness. A well-known example of a publication that defends mutational Lamarckism is *Evolution in Four Dimensions* (2005) by Eva Jablonka and Marion Lamb. I spell out their argument and then provide a critique based on their definition and use of "Lamarckism", as well as argue that they confuse genetic and evolutionary randomness.

4.2.1 Jablonka and Lamb's argument

In *Evolution in Four Dimensions*, Jablonka and Lamb argue for viewing evolution as a process that happens at four "scales" or in four "dimensions": genetic, epigenetic, behavioural, and symbolic. As part of the genetic dimension, they claim that Lamarckian (instructive) processes are at play within the Darwinian (selective) framework of evolution.[6] Here, unlike in my Section 2.1.1, they oppose instructiveness to selectiveness.[7]. However, because they state that "physiological and developmental changes involve *instruction*" (emphasis in original),[8] it is safe to say they would accept to classify Lamarckism as a developmental theory, as according to them, developed (acquired) traits play a role in inheritance.

The evidence Jablonka and Lamb provide for their claim of instructional Lamarckism is *induced local hypermutation*. For this, they cite an article by Barbara Wright from 1999, who found that in E. coli, environmental stress causes increased mutation rates in genes that are involved in stress-response.[9,10,11] The mechanism at play here is leucine deprivation in E. coli bacteria. E. coli need the amino acid leucine in order to execute their cellular function. Normally, they are able to produce this amino acid by themselves, but in this experiment, a bacterial strain that has a polymorphism in the *LeuB* gene is used. These in bacteria are unable to synthesise leucine, which we will call *LeuB*$^-$ bacteria. The alternative for these non-leucine producing bacteria is to gather leucine from their environment. When leucine also is not available in the environment, this causes environmental stress, as the *LeuB*$^-$ bacteria are then in a life-threatening situation. This stress is directly responsible for activating (actually de-repressing) the *leu* region in their genome, of which the *LeuB* gene is a part.[12] This activation ultimately causes an increased mutation rate (increased mutability), which may or may not result in a mutation that enables the bacteria to synthesise leucine themselves again (*LeuB*$^+$), saving them from the life-threatening situation. The fact that this particular mutation, which results in conversion from *LeuB*$^-$ to *LeuB*$^+$ bacteria, frequently happens provides sufficient reason for Jablonka and Lamb to conclude that this induced local hypermutation is directed towards

5. I will not dive into the topic of epigenetics as proposed form of inheritance of acquired traits. Despite this topic being equally philosophically interesting, it would make me digress from the randomness of mutations. I refer the interested reader to Laurent Loison, "Lamarckism and epigenetic inheritance: a clarification," *Biology & Philosophy* 33, no. 3 (2018) and David Haig, "Weismann Rules! OK? Epigenetics and the Lamarckian Temptation," *Biology and Philosophy* 22 (2007): 415–418.
6. Eva Jablonka and Marion J. Lamb, *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symboli Variation in the History of Life* (Cambridge, Massachusetts: MIT Press, 2005), 87, 102.
7. According to the authors, instructive and selective mechanisms are at play at different levels
8. Jablonka and Lamb, *Evolution in Four Dimensions*, 102.
9. Jablonka and Lamb, 97–98.
10. Francesca Merlin, "Evolutionary Chance Mutation: A Defense of the Modern Synthesis' Consensus View," *Philosophy and Theory in Biology* 2 (2010): 9–10.
11. Wright, "A Biochemical Mechanism for Nonrandom Mutations and Evolution."
12. For the biologist: by "region" I mean the *leu* operon.

adaptive mutations.[13] They write:

> With local [hyper]mutation, there is a measure of randomness in what is produced, but this randomness is targeted or channelled, because the changes occur at specific genomic sites and sometimes in particular conditions. These mutations are particularly interesting, because they are likely to be adaptive. Instead of evolutionary salvation coming from searching for and finding a needle (the exceedingly rare beneficial mutation) in a huge haystack (a large genome), the search is for a needle in a small corner of the haystack, a corner that is well pinpointed. There is still a need to search, but the search is now informed. The cell's chances of finding a mutational solution are enhanced because its evolutionary past has constructed a system that supplies intelligent hints about where and when to generate mutations.[14]

By "the cell's evolutionary past", Jablonka and Lamb refer to the fact that the entire mechanism of induced local hypermutation is itself a product of evolution. The fact that a strain of bacteria employs this mechanism means they are better fit to an environment with fluctuating abundance of leucine. Chances are that at some point in the past, there was evolutionary pressure on exhibiting this trait. The fact that purported mechanisms of directed mutation have evolved from natural selection motivates Jablonka and Lamb to conclude that:

> (…) Darwinian evolution can include Lamarckian processes, because the heritable variation on which selection acts is not entirely blind to function; some of it is induced or "acquired" in response to the conditions of life.[15]

4.2.2 Misinterpretation of Lamarckism

The existence of directed mutations as postulated by Jablonka and Lamb is challenged by Francesca Merlin (2010).[16] According to Merlin, a mutation is either "directed" or a matter of "evolutionary chance" — i.e., "non-directed". Her definition of evolutionary chance corresponds to what I have described as randomness as "non-directed" in sections 2.2 and 4.1. Merlin defines "evolutionary chance mutations" as follows:

> Mutation is "directed" if and only if it fulfills the two following conditions:
>
> 1. It is more probable in an environment where it is beneficial than in another environment where it is deleterious or neutral
> 2. It is clearly more probable in an environment where it is beneficial than other deleterious or neutral mutations (in the same environment)
>
> (…) *A mutation is a matter of "evolutionary chance" if and only if it is not "directed," i.e., if and only if it does not fulfill at least one of the two conditions to be a "directed" mutation*[17]

13. Jablonka and Lamb, *Evolution in Four Dimensions*, 97–101.
14. Jablonka and Lamb, 101.
15. Jablonka and Lamb, 102.
16. Merlin, "Evolutionary Chance Mutation."
17. Merlin, 7 (emphasis in original).

Although Jablonka and Lamb do not provide a clear definition of "directed mutation", it is very likely that they would subscribe to Merlin's two desiderata, as they do propose that the direction of "directed mutation" is towards a beneficial outcome.[18] Merlin's first condition can only be met if the mutation is a *product of* the environment, when there is a correlation between the environment and the emergence of the mutation. The second condition requires this correlation to be causal: the mutation happens only because the environment poses a danger to the organism and the mutation provides a solution for that problem.

Merlin suggests that although the mechanism of hypermutation in the *leu* region fulfils the first criterion of directed mutation, it fails to fulfil the second. The first criterion is met, because the mutation from *LeuB*$^-$ to *LeuB*$^+$ is indeed found more frequently in a leucine deprived environment, i.e., in the environment in which this particular mutation is beneficial. The second criterion, however, requires that the mutation from *LeuB*$^-$ to *LeuB*$^+$ occurs more frequently than other mutations in that specific environment, i.e., that other polymorphisms are observed less often. Merlin argues that we can not prove this, as conversion from *LeuB*$^-$ to *LeuB*$^+$ is particularly easy to detect because of selective pressure, whereas other mutations might go unnoticed.[19]

A second indication of a non-causal correlation between the mutation from *LeuB*$^-$ to *LeuB*$^+$ and its advantageousness is provided in Wright's study. She found an increased mutation rate in the entire *leu* region, not just in the *LeuB* gene responsible for leucine production. The fact that the entire activated region is prone to hypermutability suggests that other physiological mechanisms might play a role.[20] A mechanism that Merlin proposes is based on Wright's research, which indicates that the activation of the genes in the *leu* region is the cause of the hypermutability. Activation of the region means that the genes in this region will be transcribed more frequently, resulting in "unzipping" the double helix more often (for a refreshment of DNA transcription, see Section 1.1.1). The exposed single-stranded DNA is prone to so-called *negative supercoiling*, a change in the DNA's helical structure which is accompanied by increased amounts of mispaired bases. Exposure of single-stranded DNA, negative supercoiling, and concomitant base mispairing are all factors that could elevate local mutation rate.[21] The fact that the full activated region is prone to hypermutability suggests that mechanisms like supercoiling — and not directed mutations — are the more likely cause of this increased mutation rate.[22] These three pieces of evidence suggest that a causal correlation between the mutation and its advantageousness is, at the very least, not established.

Furthermore, Merlin stresses the importance of distinguishing between increased mutability and actual mutations resulting in polymorphisms.[23] If we give Jablonka and Lamb the benefit of the doubt, we could conclude that the stressful environment *is* the direct cause of the increased mutation rate. This would mean that the low fitness value of the *LeuB*$^-$ bacteria caused the environmental stress, which caused a beneficial mutation. From this point of view, it appears that indirectly, mutation is influenced by fitness. However, the low fitness value of the organism resulted in increased mutation *rate*, not only in beneficial polymorphisms. In fact, in this case it has not been proven that the increased mutation rate in leucine-starved E. coli results in more polymorphisms that are favourable

18. Jablonka and Lamb, *Evolution in Four Dimensions*, 87–88.
19. Merlin, "Evolutionary Chance Mutation," 14.
20. Merlin, 13–14.
21. Merlin, 9.
22. Merlin, 13–14.
23. Merlin, 15.

for counteracting leucine starvation than in other types of polymorphisms. Thus, on a genetic level, the polymorphisms caused by the increased mutation rate might still be equally distributed between positive, negative, and neutral alterations.

Lastly, Merlin points out that the mechanism of "directed" mutation and inheritance of acquired traits that Jablonka and Lamb propose is not Lamarckian. Lamarckism interpreted as "exhibiting directed mutations" was ruled out earlier in this section. The other option would be to interpret Lamarckism as "exhibiting the inheritance of acquired traits," thus opposing Weismannism. Merlin argues that this is not the case, as Weismann never excluded the possibility of environmental conditions altering genetic material, he only denied the inheritance of traits that were *not* genetically encoded.[24] To this, I need to add the note that the Weismann barrier is a phenomenon seen only in complex multicellular organisms (see Section 2.1.2). By contrast, the research cited by Jablobka and Lamb is conducted in E. coli, which is a unicellular bacterium. What is deemed impossible about the inheritance of acquired traits is the *transfer* of genetic alterations in somatic cells into germline cells, which is not observed in the cited experiment. Moreover, within the Weismannian paradigm, it is possible for germline cells to acquire polymorphisms due to, for example, radiation and pass those on to offspring. As I have explained in Section 1.1.3, unicellular organisms do not have a Weismann barrier and will pass all of their DNA, including all polymorphisms, on to their offspring. The mechanism Jablonka and Lamb describe is therefore neither anti-Weismannian nor Lamarckist.

4.3 Confusing genetics and evolution

We have just seen that according to Merlin, Jablonka and Lamb's neo-Lamarckian theory fails to prove that the mutational mechanisms they provide are directed and also fails to distinguish between increased local mutation rate and directed mutation. Although I endorse Merlin's objections, I assert that Jablonka, Lamb, and Merlin fail to distinguish between evolutionary and genetic randomness, a shortcoming that takes us back to the central claim of this thesis.

4.3.1 Genetic and evolutionary randomness

Merlin's definition of "evolutionary chance" classifies as what I have called *evolutionary randomness*, as it negates directed mutation, as described in Section 2.2, where I discuss the Luria-Delbrück experiment. Evolutionary randomness describes the consequence of a mutation, its properties with respect to their adaptiveness and their evolutionary outcome. In the words of Sober, it is therefore a consequence law (see Section 4.1.2). Genetic randomness is different from this, because it makes a claim about the *cause* of an individual mutation, not its effect. Ergo, a phenomenon cannot be classified as simultaneously evolutionary and genetically random. Nevertheless, in the argumentation of Jablonka and Lamb, the terms "evolutionary" and "genetic randomness" are applied to the same mechanism. I argue that this constitutes yet another logical flaw in their argumentation.

Recall how Jablonka and Lamb observe a phenomenon on a molecular scale, namely the mutation of *LeuB*$^-$ into *LeuB*$^+$ bacteria, specifically when exposed to environmental stress. They conclude that

24. Merlin, "Evolutionary Chance Mutation," 11.

this is a mechanism of "non-random" mutation. We have seen in Section 4.2.2 that Jablonka and Lamb do not prove directed mutation, so the mechanism they describe falls under genetic alleged non-randomness. The claim they make here is that (some) mutational mechanisms are not random in the sense that they are independent of the environment, saying that genetic randomness is false. The non-randomness of mutations they claim for the *LeuB* gene is describing the *cause* of mutations; Jablonka and Lamb propose that the mutation from $LeuB^-$ to $LeuB^+$ is *caused* by the selective pressure in the environment.

Subsequently, from this claim within the genetic domain, Jablonka and Lamb implicitly infer a claim about evolution; that Lamarckian mechanisms should be included into our Darwinian theory of evolution. However, Lamarckism and directed mutation belong to the *evolutionary* domain (see Chapter 2). Moreover, the directedness of mutations describes the *consequence* of mutation, whereas independence of the environment describes the cause (see Section 4.1.2).

Jablonka and Lamb reasoned that the low fitness value of the $LeuB^-$ bacteria caused the environmental stress, which caused the mutation. With this argument, they attempt to deny the directionality of the central dogma of molecular biology; for mutation to be informed by fitness, it must "know" what phenotype would be beneficial in the current environment and therefore which current phenotypic trait needs to be altered. For this, it is necessary to identify the proteins that cause the undesired trait and "reason" from protein to DNA in order to change only the correct nucleotides. Only in this way, fitness could influence the actual mutations (i.e., the polymorphisms) and not only increase mutation rate. However, no mechanism has been observed to date which implies that environmental factors or the fitness of an organism can influence the *actual mutations* that take place. Only when reverse translation is found to be possible, can mutations be truly non-random in an evolutionary sense.

In summary, ignoring the difference between evolutionary and genetic randomness leads Jablonka and Lamb to conclude that Lamarckian processes must be at play without providing legitimate arguments. Mutational mechanisms that show dependence on cellular or environmental processes could never provide proof for directed mutations or Lamarckism. They could, however, provide proof for non-randomness of mutations *in a genetic context*. What happens in the argument of Jablonka and Lamb is that they drag conclusions from the domain of genetics into the domain of evolution, which is, I argue, an illegitimate move.

4.3.2 Reductionism

I have just reasoned that Jablonka and Lamb drag findings from genetics into the domain of evolution and that this is an illegitimate form of reasoning. This closely relates to the problems of reduction in biology, which have been an ongoing topic of discussion since the 1950s.[25] Reductionism of the sciences represents the idea that a phenomenon is entirely explainable by processes on a level *lower* than the level on which the phenomenon is observed. Often times, reductionism in biology is interpreted as the idea that phenomena in biology can be fully explained by theories and laws from chemistry and physics. However, one could also argue that even within the field of biology,

25. Fulvio Mazzocchi, "Complexity and the Reductionism–Holism Debate in Systems Biology," *WIREs Systems Biology and Medicine* 4, no. 5 (2012): 414.

reductionism might play a role. One could try to explain phenomena observed on the level of evolution in terms of underlying molecular genetic mechanisms.

Reductionism can be divided into three types: *ontological*, *methodological*, and *epistemological* reductionism. The question of ontological reductionism in biology is mainly if living systems are constituent on physiochemical entities only, or if there are other forces (such as an “élan vital” or “soul”) at play.[26] Theodosius Dobzhansky summarises: “Most biologists (...) are [ontological] reductionists to the extent that we see life as a highly complex, highly special and highly improbable pattern of physical and chemical processes”,[27] thereby implying a physicalist stance.[28] Methodological reductionism proposes that biological explanations could be obtained only through examination of underlying parts.[29,30] This form of reductionism is less commonly accepted, as its strong version claims that Mendelian genetics or Darwin’s theory of evolution were of no value until their underlying molecular mechanisms were explained.[31] The third form of reductionism, epistemological reductionism, is my main point of focus. It entails that “the theories and experimental laws formulated in one field of science can be shown to be special cases of theories and laws formulated in some other branch of science.”[32]

The confusion of evolutionary and genetic randomness is a form of epistemological reductionism. Evolution and genetics are two distinct fields of biology, each with their own research topics and methods. The fields overlap in subdomains such as population genetics, but the study of mutations also knows an evolutionary and a genetic approach (see Figure 4.1). In both fields, the nature of mutation is being investigated and explained with the term “randomness”. However, the interpretation of the term is distinct in the two fields. I have demonstrated that “mutation is random” in evolution is not equivalent to “mutation is random” in genetics, which means that these statements are not in the domain spanned by both evolutionary and genetic research. Therefore, the two assertions of random mutation must be regarded as theories from two different fields of biology.

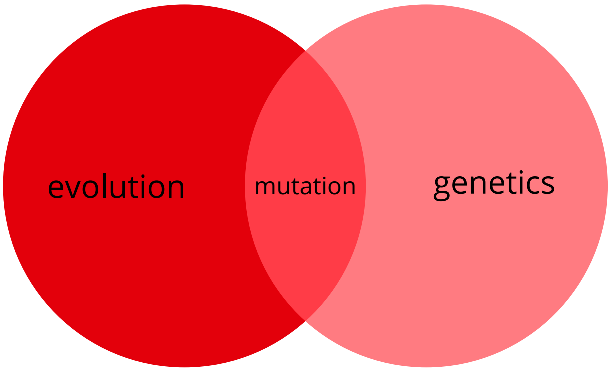

Figure 4.1 The relationship between evolutionary biology and genetics. Mutations are researched in evolutionary biology, in genetics, and in the overlap between the two fields. The concept of “randomness” is not a part of the overlap between evolution and genetics.

26. Francisco J. Ayala and Theodosius Dobzhansky, *Studies in the Philosophy of Biology: Reduction and Related Problems* (Berkeley and Los Angeles: University of California Press, 1974), viii.
27. Ayala and Dobzhansky, 1.
28. Mazzocchi, “Complexity and the Reductionism–Holism Debate in Systems Biology,” 414.
29. Ayala and Dobzhansky, *Studies in the Philosophy of Biology*, viii–ix.
30. Fulvio Mazzocchi, “Complexity in biology,” *EMBO reports* 9, no. 1 (2008): 11.
31. Ayala and Dobzhansky, *Studies in the Philosophy of Biology*, ix.
32. Ayala and Dobzhansky, ix.

Not distinguishing "mutation is random in evolution" from "mutation is random in genetics" is therefore a form of epistemological reduction, since the theory that "mutation is random" that is found and corroborated within the field of evolutionary biology is taken to be an instance of a law in genetics. Disproving mutational randomness in genetics is, by Jablonka and Lamb, seen as a direct threat to the assertion of randomness of mutations in evolutionary theory. This epistemological reduction is, as I defend, not justifiable.

One could argue that a solution to this problem would be to adopt a single definition of randomness, to be employed in both evolutionary biology and genetics. I contest this idea, as this would deprive "randomness" of its explanatory power. In evolution, "randomness" successfully illustrates the long-lived but also debated belief that mutations occur independently of their effect on fitness. By contrast, in genetics it provides a useful null hypothesis, a statement that is disproven but nevertheless this explains something about what the nature of mutation is *not*.[33] In addition, it provides a vehicle for establishing a link between biology and quantum mechanics.[34] The term "randomness" *needs* its pluriform definition to have any explanatory power in the two separate fields of biology.

Alternatives to reductionism in science have been extensively debated in both philosophy and biology.[35] Emerging fields with holistic methods, such as systems biology, are mentioned to provide an alternative to reductionist molecular biology.[36,37,38] Systems biology takes an approach that differs from "traditional" biology by relying on statistical models and big data quantification. It approaches living systems as a whole, instead of investigating the individual parts of the system. This approach has the advantage of circumventing reductions and is also deemed capable of explaining emergent phenomena.[39] Some authors argue that the shift from reductionist molecular biology to holist systems biology should be viewed as a paradigm shift.[40] However, others argue that systems biology should include both holist and reductionist stances.[41] Additionally, questions can be raised about whether the phenomena of the living world can be captured in statistical models. In short, the question of reductionism and its alternatives is still a topic of debate. Further research could focus on the opportunities for a (partly) holist approach to biology.

33. Stoltzfus, *Mutation, Randomness, and Evolution*, 35–45.
34. This does not imply the reductionist stance that molecular biology can be fully explained in terms of (quantum) physics. It merely implies that there might be a connection between the two fields.
35. Ayala and Dobzhansky, *Studies in the Philosophy of Biology*.
36. Mazzocchi, "Complexity in biology."
37. Mazzocchi, "Complexity and the Reductionism–Holism Debate in Systems Biology."
38. Derek Gatherer, "So What Do We Really Mean When We Say That Systems Biology is Holistic?," *BMC Systems Biology* 4 (2010): 22.
39. Maureen A. O'Malley and John Dupré, "Fundamental issues in systems biology," *BioEssays* 27, no. 12 (2005): 1271.
40. Gatherer, "So What Do We Really Mean When We Say That Systems Biology is Holistic?," 6.
41. Mazzocchi, "Complexity in biology," 12–13.

Chapter 5

Conclusion

Every concept arises by means of the equating of the unequal. — Friedrich Nietzsche[1]

In this thesis, I investigated how the concept "random mutations" is being used in two fields of biology, namely evolution and genetics. In evolutionary biology, as we saw in Chapter 2, mutations are regarded as either not directed towards enhancing fitness value or totally independent of fitness effect. Jean-Baptiste Lamarck's theory of evolution proposed that variation in phenotype would become genetically encoded if and only if it concerned a beneficial trait. The inheritance of acquired traits was refuted by the discoveries of August Weismann, and evidence for non-directed mutations was provided by the canonical Luria-Delbrück experiment. Charles Darwin avoided discussing the origin of variation; but according to his model of natural selection, beneficial variations are selected and not instructed as Lamarck had proposed. The second interpretation of "evolutionary randomness", independence of fitness effect, more generally describes the relationship between mutation and evolutionary outcome. It indicates that while fitness depends on mutations, mutations are uninformed by the fitness of an individual.

In Chapter 3, I found that in molecular genetics, "random mutation" can instead be interpreted in a variety of ways, including equally probable, unpredictable, or independent of other mutations, cellular processes, or the environment. Empirical genetic evidence suggests that not all mutations are equiprobable, as some types of mutations occur more frequently than others. A nucleotide does not have equal probability of decaying into every other nucleotide, and the chances of mutation are also not uniformly distributed across different sites in the genome. Mutations can, however, be unpredictable in two ways; either scientifically or fundamentally. Arguments can be made that the observer effect known from physics is also applicable to biology; measuring the contents of a cell will inherently disturb cellular processes, making it impossible to gather all the data required to map out mutational mechanisms. Fundamentally uncaused mutations, on the other hand, connect biology to physics in a different way, as it proposes that mutations might be caused by quantum events, which means that mutation would be indeterministic under the Copenhagen interpretation of quantum mechanics. Finally, mutation could also be seen as independent from other mutations, cellular processes, or the environment. Empirical evidence suggests that none of these interpretations are the case for all known mutational mechanisms, but they certainly all apply to some known

1. Friedrich Nietzsche, "On Truth and Lies in a Nonmoral Sense," in *On Truth and Untruth: Selected Writings*, trans. Taylor Carman (New York: HarperCollins, [1873] 2010), 28.

mechanisms. In conclusion, none of the forms of genetic randomness provides a universal law for all mutational mechanisms, but for each interpretation, some mechanism could be specified for which mutation is “random”.

Having mapped out a variety of possible interpretations of “random mutation”, I observed in Chapter 4 that most interpretations provide ontological claims; (genetic) scientific unpredictability being the only epistemological interpretation. Additionally, I discerned that interpretations of evolutionary randomness provide explanations for the *consequences* of mutation, while genetic randomness describes the *cause* of mutations. Next, I analysed an alleged Lamarckian mechanism of mutation, provided by Jablonka and Lamb. These authors point to a molecular mechanism in which mutations were not independent of the environment — in other words, not genetically random — and conclude from this mechanism that mutations are directed in a Lamarckian sense — thus, that the mutations are not random in an evolutionary sense. I have reasoned that this is an illegitimate argument, caused by the fact that the authors fail to distinguish evolutionary from genetic randomness.

What happens when genetic and evolutionary randomness are not separated, is, in my view, a form of reductionism. Using the same term, “randomness” to refer to processes on a microscopic genetic level, as well as macroscopic evolutionary processes, means assuming that evolution can be fully explained in terms of processes on a lower level, namely genetics. Extrapolating “random mutation” from the domain of genetics to the domain of evolution, as Jablonka and Lamb do, does not recognise that they are fundamentally different domains, each with their own interpretations of “randomness”. I have advanced the idea that this illegitimate move is a form of epistemological reductionism. Proposing a unified definition of “randomness” would solve the problem of this reduction, but would rob the term of its explanatory power. Debates on alternatives for reductionist methods in biology, such as the (partly) holist approach of systems biology, are still ongoing.

In conclusion, the phrase “mutation is random” means fundamentally different things when examined in an evolutionary or a genetic context. Interpretations of evolutionary randomness should not be invoked when discussing genetics of mutation, and likewise, genetic randomness does not belong in the context of evolution. The interpretations of randomness that we apply in these different domains are not interchangeable, and reduction from evolution to processes on a molecular (genetic) scale is, in my view, impossible. Keeping the distinction between evolutionary and genetic randomness sharp will aid both the biological and philosophical research into this one question: How random is random mutation?

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