Chapter 1

Introduction: Part I – Design and information in biological systems

J. Bryant

School of Biosciences, University of Exeter, Exeter, UK.

Abstract

The term ‘design’ in biology usually refers to fitness for purpose: is the particular structure or mechanism effective in carrying out its function? This must be seen in the light of evolution by natural selection. Organisms which function better in a given environment than their close relatives and therefore have a greater reproductive success will become more abundant at the expense of less successful individuals. The millions of species of living organisms, from the most simple to the most complex, now present on earth have arisen by this process. Natural selection can only work if a particular advantage exhibited by particular individuals is heritable, i.e. embedded in the ‘genetic machinery’. That genetic machinery is based on DNA, whose structure is elegantly fitted to its two functions: (a) carrying the genetic information that regulates the development, growth and functioning of the organism; (b) passing on that information to subsequent generations. Genetic information is carried in the order of deoxyribonucleotides in a DNA molecule. The double helical structure of DNA, coupled with the way that the bases within the deoxyribonucleotides pair specifically between the two chains of the double helix, provides a template mechanism for passing on the information. DNA’s role as the regulator of minute-by-minute function is achieved by the copying of specific tracts of DNA (genes) into mRNA and the translation of the code in mRNA to make proteins. In evolution, it is the subtle changes in the order of deoxyribonucleotides (mutations) that generate the heritable variation based on which natural selection works. We are ignorant as to how these mechanisms originated, but it is thought that early in the development of life, the genetic material was RNA, which in addition to carrying genetic information could also mediate a limited range of the functions now performed by proteins.

1 Design, function and elegance

When design is spoken of in the day-to-day world we can discern two separate strands of meaning. The first of these is *fitness for purpose*. Does the object perform effectively the functions that it is meant for? Will a bridge support appropriate loads under all weather conditions? Will a toaster

warm and brown the bread evenly and without burning? Will a raincoat actually prevent the wearer from getting wet? It will be obvious that if any such objects fail to fulfil their function, then we can talk about a design fault and thus, used in this sense, design and function are inexorably linked. However, in day-to-day life, design also incorporates the rather more elusive term 'style' and thus possesses an aesthetic element. A bridge may carry traffic across a river but may also be an eyesore. A raincoat may keep the rain off but may do nothing to enhance the appearance of the wearer. These examples also show us that ideas of style may be transient: ideas of what is acceptable style change. In architecture, for example, the stark modernity of many mid-20th century buildings, where beauty was equated with function, is now largely regarded as ugly and obtrusive. And, of course, the extreme of this transience is seen in fashion where firstly function may be sacrificed for style and secondly what is regarded as 'stylish' one year may be rejected the next. Further, ideas of style may also be personal: what someone likes, another may dislike intensely as seen, for example, in the reactions to the 'ziggurat' student residences at the University of East Anglia (a prize-winning design by Sir Denys Lasdun in the late 1960s; Fig. 1a) or to the starkly modernist style of many of the buildings on the east campus of the University of Illinois at Chicago (Fig. 1b).

Although we have separated the two elements of fitness for purpose and style, they may in fact be linked. When an engineer solves a design problem in a particularly neat way or when an IT expert writes a new program that replaces an older, more cumbersome and less user-friendly version, then we often speak of elegance. Thus our aesthetic sense appreciates the cleverness of the way that a problem has been solved.

This element of elegance – fitness for purpose achieved by a neat and economical mechanism – leads to specific consideration of design in biological systems. In biology, the major implication of the term 'design' is fitness for purpose. The particular structure or system performs the necessary tasks within the life of a particular living organism. However, we also recognise that the structures and systems that have evolved in response to particular problems are often very elegant, indeed to the biologist they may be beautiful. (This emphasises a point that the author has made elsewhere [1, 2]: science is neither value-free nor free from the scientist's own particular set of values. It is entirely legitimate to speak of beauty.) In the author's own field [3], i.e. replication of the genetic material (DNA), the prevention of unscheduled replication is achieved by an array of interacting, subtly regulated and very effective mechanisms providing a system of control which, even after many years of work on the subject, I still find beautiful. Further, these elements of neatness and economy in relation to fitness for purpose have been admired not only by biologists but also by those designing objects for use in human society. Engineers, for example, have turned frequently to nature and some of the results of that are described in this and other volumes in the series. However, for the time being we must return to the specifically biological aspects.

2 Evolution and design

When we observe a particular structure or system in biology we are observing the current results of an ongoing evolutionary process. The diversity of living organisms and their occupation of particular ecological niches has arisen by the process of change driven by a set of mechanisms known as natural selection. In essence, this means that in a given population, the individuals that are more fitted for the particular environment will be more successful than those that are less fitted. In general, success here means reproductive success: individuals that produce more offspring will eventually come to dominate the population, even if the differential is very small. It is specifically in this context that the word 'fit' must be understood. The term 'survival of the fittest'

Figure 1: (a) Student residences at the University of East Anglia, Norwich, UK. Downloaded by permission from http://www.uea.ac.uk/slideshow_pages/slideshow1.html. (b) The east campus of the University of Illinois at Chicago, IL, USA. Downloaded by permission from <http://www.uic.edu/depts/oar/virtualtour/slideshow/index.html>.

has provoked hostile reactions and has been extensively misapplied. Indeed, the term was never used by Darwin but was coined by Herbert Spencer [in his book *Principles of Biology* (1864)] in what was probably a misunderstanding of what natural selection actually involves. Nevertheless, the term is now used frequently in the context of evolution where it means fitness for existence in a particular environment and does not refer directly to the ‘health’ of the organism. A perfectly

healthy organism may be less fitted for an environment and thus have less reproductive success than another equally healthy organism.

We need to note that the process of evolution has led to the existence of living organisms exhibiting a huge range of levels of complexity, from simple single-celled micro-organisms such as bacteria to very complex multicellular organisms such as mammals. This is not the place to become involved in a discussion of the evolution of complexity. However, we do need to consider design in the light of complexity.

Design is fitness for purpose: the structure or system performs the necessary function and that structure has evolved to be fit for purpose under the pressure of natural selection. A particular individual in which a particular function is performed more efficiently may enjoy a reproductive advantage and thus the 'improved' version that enables more efficient performance of function will be favoured. Some structures or systems occur almost universally across the vast spectrum of living organisms, performing at similar levels of efficiency (i.e. exhibiting similar fitness for purpose) across that range while other systems are developed to very different levels of complexity and efficiency in different types of organism. Thus, for example, the compound eye of the insect is a less efficient visual organ than the mammalian eye. However, within the level of complexity exhibited by the insects, the mechanisms involved in the development and function of the mammalian eye are not possible. But no one can say that the insects are 'unsuccessful': there are more species of insects than of any other group of animals. The complexity of design of many features may thus be related to the complexity reached by a particular group during evolution.

Finally, we need to note that there are many very elegant examples of evolution that involve two or, sometimes, more types of organism. Some of this involves organisms living together in close association; this is called symbiosis. In many cases, the symbiosis is of benefit to both organisms, in which case we use the term 'mutualism'. Usually, in mutualistic relationships, there is close cellular relationship between the two organisms; for example, mycorrhizal fungi form sheaths around the roots of their host plants. In some instances, the tissues of the two organisms are so intimately associated that the combination of the two looks like a completely new species, e.g. when a fungus combines with either a photosynthetic blue-green bacterium or a photosynthetic alga to form a lichen. Interestingly, the study of DNA sequences and gene organisation suggests that lichen-style symbioses have evolved independently at least five times during the long history of life on earth [4]. All such close associations imply a history of co-evolution as the two organisms adapted to become more and more mutually interdependent.

However, co-evolution is not confined to these close relationships: there are also instances in which there is no intermixing or intimate contact at the cell or tissue level. Two examples out of many will suffice. First, many plants are insect-pollinated. In visiting flowers to obtain nectar and/or pollen, the insect in question transfers some pollen to other flowers of the same species thereby bringing about cross-fertilisation. Amongst the orchids, several groups attract pollinating insects because the flowers strongly resemble the females of the pollinating species. In attempting to mate with the flower, the male picks up pollen which will be transferred to the next flower at the next unsuccessful copulation attempt. The insect receives no reward: there is no nectar, the pollen is unavailable to the insect (being contained in structures called pollinia) and, of course, sex is not at all satisfactory. It is hardly surprising that this is called 'deceit pollination'. The second example also concerns plants and insects. Many wild plants accumulate in their leaves chemical compounds that are toxic to predatory insects. The biochemical pathway that leads to the synthesis of these compounds is fit for the purpose of deterring predators. However, some insects have evolved a defence against the plant defences either by the possession of detoxification mechanisms, or, more sophisticated still, by accumulating the plant toxins so that the insects themselves become toxic in turn to their potential predators.

3 Evolution and information

In the discussion of evolution, the concept was introduced that subtle differences between otherwise very similar individuals could lead to differences in reproductive success. However, in order for this difference in reproductive success to be maintained, it must be heritable. Having a selective advantage in one generation but not in the next will not lead to evolution. Now, although natural selection acts on the phenotype (i.e. on the features of the actual living organism resulting from an interaction between genes and the environment), long-term heritable differences must ultimately be based in the genes. It is the genes that carry heritable information. It is therefore helpful, at this point in this introductory chapter, to briefly discuss gene function.

In all cellular life, genes are made of DNA. (There are some classes of virus in which the genetic material is RNA. However, although we may regard this as a throwback to a time in early evolution when the prevalent genetic material may have been RNA, we cannot regard present-day viruses as primitive life forms because they rely on cellular organisms for their own multiplication.) Indeed, the discovery in 1944 that DNA is the almost universal genetic material [5] was the real turning point in biology and led to intense efforts to understand the structure of this vital molecule. These efforts led, of course, to the discovery in 1953 of the double helix [6, 7]. This structure is ‘design in nature’ at its most elegant. The genetic material needs to fulfil two major functions. First, it must carry the genetic information. Further, that genetic information must be in a form that is readily usable in the life of the organism. Secondly, the genetic information must be passed on faithfully from generation to generation, i.e. must be heritable.

How then does DNA carry genetic information? Although DNA molecules are large, their chemical structure is relatively simple: each single strand of DNA is a chain of nucleotides (to be more specific, deoxyribonucleotides, which are often called, incorrectly, bases; however, it is the components of the deoxyribonucleotides known as bases that provide the differences between the deoxyribonucleotides and whose interactions maintain the double helix.). There are only four types of these, and one of the puzzles raised by the discovery that DNA is the genetic material was how such a structure could contain the information needed for life. Of course, the answer is now well known. Although there are only four deoxyribonucleotides, the length of DNA molecules means that the linear array of these four building blocks can be immense. Further, there are no constraints as to which deoxyribonucleotide is next to another: they can occur in any order. This immediately raises the possibility that a specific linear array of deoxyribonucleotides can be a coded source of information just as a linear array of the 26 letters of the alphabet can be a coded source of information (provided we can read the language in which those 26 letters are deployed). The function of the code in DNA is discussed below. In the meantime, we focus on the second function of the genetic material, passing on information from generation to generation.

In order to be a faithful transmitter of hereditary information from generation to generation, the coded information must be accurately reproduced and this is ensured by the structure of DNA, the double helix. We have already noted that there are no constraints in placing deoxyribonucleotides next to each other along a single DNA strand. However, there are constraints on the deoxyribonucleotides that can exist opposite each other in the two strands of the double helix. This constraint lies in the properties of the bases (as already noted, these are the variable moieties within deoxyribonucleotides) and thus from this point the discussion is framed in terms of bases. The constraint on what base occurs opposite another in the two strands of the double helix is a result of specific base pairing: adenine can pair only with thymine and cytosine can pair only with guanine. The pairing depends on the ability to form hydrogen bonds from particular positions in each base molecule (Fig. 2). Adenine and thymine form two hydrogen bonds between each other, cytosine and guanine three. This means that the position of a particular base in one strand defines

Figure 2: (a) The double helical structure of DNA. (b) Pairing between the bases of DNA. Both figures reproduced by permission from Bryant, J.A. (ed.), *Molecular Aspects of Gene Expression in Plants*, Academic Press: London and New York, 1976.

what base will be opposite it in the other. It can be seen straightaway that this structure preserves the genetic information. When the DNA is replicated, the two strands of the helix separate and each is able to act as a template for the formation of a new strand; the order of bases in the new strand being defined by the order of bases in the template strand. The enzymes (protein molecules that act as biocatalysts) that mediate DNA replication (enzymes mediate all cellular chemical transformations) are thus guided and indeed constrained by the order of bases in the template strands. The pre-existing strands really do provide the information to build the new strands. Thus two double helices now exist where before there was one; in this sense – the specification of the base sequence in the new strand by the base sequence in the old strand – DNA is a self-replicating molecule (but see Section 5).

It is thus apparent that the faithful copying of the genetic material (and, as described in Section 4 below, its function in providing the information for the ongoing life of the organism) is based on a truly elegant structure. But we need to highlight two more features that further illustrate the beauty of this molecule. When Watson and Crick first hit on the idea of a double helix defined by specific base-pairing they modelled both strands of the helix as being in the same orientation – both the same way up. However, the bases did not fit together perfectly in their pairs; the double helix was distorted, under strain and therefore likely to be less thermodynamically stable than it should be. However, if one strand is turned upside down in relation to the other, i.e. if the two strands are *anti-parallel*, then specific base pairing can occur along the full length of the double helix. There is no distortion or strain and the molecule is in the most stable configuration thermodynamically (the configuration of least energy). This inspired guess or wonderful intuition on the part of Watson and Crick was readily confirmed by direct experimentation. The second feature concerns the forces that hold the helix together, namely hydrogen bonds between the two strands and Van der Waal's interactions up and down the molecule. These interactions are strong enough to stabilise the helix but weak enough to allow ready separation of the strands when needed, e.g. for replication. This is a truly elegant molecule with its functions based beautifully in

its properties. Stuart Kauffman, a founder-member of the notable Santa Fe Institute states that the chemistry of DNA, ‘this beautiful double helix aperiodic structure’ fits it ‘almost miraculously ... for the task of being the master-molecule of life’ [8].

4 Using the information

4.1 Introduction

In order for the coding information in DNA to be used by the cell, it must first be copied or transcribed and then the information in the copy must be translated. The products of translation are proteins, which are the working molecules of cells, carrying out functions from catalytic (as with enzymes) to structural. Thus the code in DNA provides the information for the synthesis of proteins. In this section, the basic mechanisms involved in this process are described (see Fig. 3). In the next chapter, the more complex aspects are discussed in greater detail.

4.2 Transcription

It has already been noted that the formation of specific base pairs is the mechanism by which the genetic information is faithfully copied. It is the same base-pairing mechanism that enables the coding regions of DNA, the genes, to be transcribed into working copies. These working copies are built not with deoxyribonucleotides but with ribonucleotides (Fig. 4). They are thus RNA molecules and are known as messenger RNA (mRNA). Each mRNA molecule is transcribed from one strand of a coding region (gene) of DNA and because of the specific base-pairing involved in transcription, it is complementary to the DNA strand from which it is transcribed.

As with DNA replication, transcription is carried out by enzymes, and a question that immediately arises is how do the transcription enzymes ‘know’ where to start and stop along the length of a DNA strand that contains many genes. Part of the answer lies in the structure of DNA itself. In addition to the genes which provide information that is transcribed into RNA molecules, the sequence of bases provides other types of information, including sequences ‘upstream’ of genes

Figure 3: Diagram illustrating the basic mechanisms involved in gene function. ‘Upstream’ of the gene is a DNA sequence called the promoter which is involved in turning the gene on and off. A gene which is ‘on’ is copied into a complementary mRNA molecule. The code contained within the sequence of the mRNA is translated, enabling the cell to form the particular protein encoded in the RNA.

Figure 4: General structures of ribonucleotides (a) and deoxyribonucleotides (b). The two general structures differ only in the absence of oxygen on position 2' in the sugar moiety. Reproduced by permission from Voet, D., Voet, J.G. & Pratt, C.W., *Fundamentals of Biochemistry*, John Wiley and Sons: New York, 1998.

that enable the transcription enzymes (RNA polymerases) to bind to the DNA. These upstream recognition sequences are known as promoters; immediately 'downstream' of a promoter is a base sequence which marks the point at which transcription starts. Further, at the other end of a gene there is a sequence of bases that marks the point at which the RNA polymerase stops transcribing the gene. Thus, DNA contains, in addition to the sequences that code for proteins, sequences that enable the process of transcription (and, as described in the next chapter, replication) to take place. This is similar in some respects to a computer program that contains within it not only the digital information involved in the program itself but also the information that enables the program to be run. This embedding of different types of function into the base sequence of DNA has been described as the 'many-sidedness' of DNA [9].

4.3 Translation

In the linear array of ribonucleotides in a particular mRNA molecule, there is encoded a recipe to build a particular protein from its individual building blocks, the amino acids. The decoding of this recipe is known as translation. The code is read in groups of three nucleotides, (these triplets are known as codons) each of which specifies the addition of a particular amino acid to the growing protein chain (Fig. 5). Specific base-pairing is also involved in this process: each amino acid is brought into position by a specific carrier molecule called transfer RNA (tRNA). An example will help to clarify this. The three-letter codon that specifies the amino acid methionine is AUG (ribonucleotides containing the bases adenine, uracil and guanine); the tRNA that carries methionine contains the anti-codon sequence UAC (ribonucleotides containing the bases uracil, adenine and cytosine), which is complementary to and therefore can base pair with AUG. It will not have escaped the reader's notice that each tRNA molecule must carry the amino acid that is specified by a particular triplet of bases, otherwise the translation mechanism would not work. This linkage of particular amino acids with particular tRNA species is of course carried out by enzymes (enzymes whose catalytic activity embodies this dual specificity).

The participation of tRNA in the translation of the code during protein synthesis shows that there are other types of RNA in addition to mRNA. These include RNA molecules known as ribosomal RNA (rRNA) which, together with an assemblage of proteins, make up a subcellular organelle called the ribosome. These particles are intimately involved in translation, providing the specific locations at which the mRNA codons base pair temporarily with the tRNA anti-codons during protein synthesis (Fig. 5). Like mRNA, both tRNA and rRNA are transcribed from genes. However, unlike mRNA, these other types of RNA do not embody a code that specifies synthesis of a particular protein. Instead, they participate in the actual mechanism of protein synthesis.

Figure 5: Diagram of the process of protein synthesis – translation of the code in mRNA. Ribosomes engage with the mRNA and move along it (from left to right in this diagram). The amino acids – building blocks for the protein – are brought to the ribosome by tRNA molecules. Each type of tRNA recognises the particular three-base sequence (codon) that specifies the amino acid that the tRNA is carrying. Reproduced by permission from Mathews, C.K. & van Holde, K.E., *Biochemistry*, 2nd edn, Benjamin/Cummins: Menlo Park, CA, 1996.

In the next chapter, we discuss further aspects of DNA replication, gene transcription and protein synthesis, including the roles of yet more types of RNA. In the meantime, we consider the relationship between these basic processes and evolution.

4.4 Genetic information and evolution

It has been emphasised already that natural selection works on the phenotype, the actual living individual, and that the process favours the individuals that are best fitted to a particular environment. This implies that individuals within an interbreeding population (or species) differ from each other. Some of those differences may not be heritable, e.g. those that are caused by direct nutritional or environmental effects on the growth or development of the individual. Other differences are however heritable because they are based in the genes and it is the selection of such differences that is the basic mechanism of evolution. How do genetic differences arise between individuals? Although the process of DNA replication is extremely accurate, it happens on very rare occasions that the wrong deoxyribonucleotide is inserted into the growing DNA strand. This causes a mutation, simply meaning a change (despite the sinister overtones that many people mistakenly attach to the word). Some of these changes may be deleterious or even lethal, others may confer an immediate advantage but most are completely neutral. Further, many of these neutral changes may not cause, in a given environment, any visible differences and are therefore hidden. Thus in the human species, *Homo sapiens*, any two individuals are likely to differ in about one in every thousand base pairs but many of those do not produce discernible differences at the level of the phenotype. So, within a particular species there will be a lot of hidden genetic variation between individuals.

At this point, we need to note that generation of genetic diversity simply by mutation of existing genes would be limited if the number of genes was small: there simply would not be enough spare genetic capacity to carry much genetic change. However, it is clear that evolution involves other types of genetic change in addition to mutation. These include the acquisition of extra DNA sequences so that the amount of DNA in more complex organisms is greater than in bacteria.

This is discussed more completely in the next chapter, but the main points to be made here are, first, that acquiring more DNA in itself provides a genetic difference from the cell or organism without the extra DNA and, secondly, it provides more capacity for carrying genetic mutation, as discussed by Brown [10].

We also need to note that in organisms which reproduce by the coming together of specialised sex cells or gametes, the reproductive process itself will set up new mixes of genes. This is firstly because of a mechanism called recombination which functions in many organisms during the formation of the gametes. Secondly, it is because in organisms where outbreeding is obligatory, two different versions of the organism's genome, one from the female parent and the other from the male parent, provide a new combination of genetic variants in the offspring.

As already noted, some new mutations may confer an immediate advantage in a given environment. However, it is more likely that a change in the environment (using the term in the broadest sense) will lead to a selection of variants that had hitherto been neutral and perhaps hidden. This highlights one of the commonest misconceptions about natural selection and evolution, namely that adaptation to changed environments is thought to have to wait for new mutations. In fact, natural selection generally acts on existing genetic variety. Only in times of rapid change is the generation of genetic variety likely to occur too slowly to allow adaptation. Thus, at present, there is concern that some organisms may not adapt quickly enough to the new conditions imposed by global warming and may therefore be heading for extinction.

5 Information and the origin of life

In the preceding section, the basic mechanisms involved in the minute-by-minute use and in the inheritance of genetic information were discussed. But how did all this start? The minimum requirement for life is an ability to self-replicate and thus the double helical DNA with its built-in template system ensuring faithful replication appears to satisfy that requirement. Furthermore, its ability to carry coded information that is conserved in replication suggests that it is indeed the master molecule of life. However, when the situation is examined more closely, it is obvious that this view, although very reasonable in the light of life as we know it, is more difficult to sustain when the origin of life is considered. The problem may be simply put as follows. The DNA codes for proteins but proteins are needed both to read the code and to replicate it. Without DNA there are no proteins but without proteins there is no replication of DNA and no mechanism for making proteins. We are thus in a loop with no obvious way out. Some have suggested that proteins may have been the original molecules of life but they are not self-replicating molecules. Currently, the most widely accepted view is that the original molecule of life was not DNA but RNA [10]. This view is based on the observations that today there are certain types of RNA molecules that are self-replicating and, further, some types of RNA have limited catalytic (equivalent to enzymic) activity, i.e. activity which in the past may have enabled RNA molecules to self-replicate without the need for proteins. Even if the 'RNA world' hypothesis is accepted (and, of course, there is no *direct* way of disproving or proving it), it is still a long way from a self-replicating RNA molecule to the even the simplest of single-celled organisms that are living today, and it is to the organisms of today that we now return.

6 Wider aspects of information transfer

As we have seen, at the heart of life itself, the DNA contains coded information, information that regulates the minute-by-minute biochemical activity of each cell and which is inherited from

generation to generation. Without this coded information, life as we know it would not exist. However, all living organisms, from the simplest single-celled microbe to the most complex mammal, are also dependent on other forms of information transfer. This happens at various levels, including cell to cell (both in single-celled and multicellular organisms), environment to organism, organ to organ (within a complex organism) and organism to organism. The information transfer is often based on chemical signalling but in particular instances may involve other mechanisms such as light perception or the transmission of electrical and electrochemical signals. Further, the effects of the transferred signals/information may be at any level from the core information molecule, DNA itself, to the whole organism (and, in some instances, to populations). A comprehensive treatment of this is outside the scope of this chapter (but will be the subject of a later volume in this series). Here we simply need to note that living organisms as we know them cannot function without a range information transfer and signal transduction mechanisms.

References

- [1] Bryant, J. & Searle, J., *Life in Our Hands*, Inter-Varsity Press: Leicester, 2004.
- [2] Bryant, J., Baggott la Velle, L. & Searle, J., *Introduction to Bioethics*, John Wiley and Sons: Chichester, 2005.
- [3] Bryant, J.A., Moore, K. & Aves, S.J., Origins and complexes: the initiation of DNA replication. *Journal of Experimental Botany*, **52**, pp. 193–202, 2001.
- [4] Raven, P.H., Evert, R.F. & Eichhorn, S.E., *Biology of Plants*, 7th edn, Freeman: New York, 2005.
- [5] Avery, O.T., Macleod, C.M. & McCarty, M., Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation by a desoxyribonucleic acid fraction isolated from *Pneumococcus* type III. *Journal of Experimental Medicine*, **79**, pp. 137–158, 1944.
- [6] Watson, J.D. & Crick, F.H.C., A structure for deoxyribose nucleic acid. *Nature*, **171**, pp. 737–738, 1953.
- [7] Watson, J.D. & Crick, F.H.C., Genetical implications of the structure of deoxyribonucleic acid. *Nature*, **171**, pp. 964–967, 1953.
- [8] Kaufman, S.A., *Investigations*, Oxford University Press: New York and Oxford, 2000.
- [9] Baisnée, P.-F., Baldi, P., Brunak, S. & Pedersen, A.G., Flexibility of the genetic code with respect to DNA structure. *Bioinformatics*, **17**, pp. 237–248, 2001.
- [10] Brown, T.A., *Genomes*, 2nd edn, Bios: Oxford, 2002.