Philosophy of Molecular Biology

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Ingo Brigandt

University of Alberta, Edmonton, Canada

Introductory article

Abstract

Ongoing empirical discoveries in molecular biology have generated novel conceptual challenges and perspectives. Philosophers of biology have reacted to these trends when investigating the practice of molecular biology and contributed to scientific debates on methodological and conceptual matters. This article reviews some major philosophical issues in molecular biology. First, philosophical accounts of mechanistic explanation yield a notion of explanation in the context of molecular biology that does not have to rely on laws of nature and comports well with molecular discovery. Second, reductionism continues to be debated and increasingly be rejected by scientists. Philosophers have likewise moved away from reduction toward integration across fields or integrative explanations covering several levels of organization. Third, although the gene concept has undergone substantial transformation and even fragmentation, it still enjoys widespread use by molecular biologists, which has prompted philosophers to understand the empirical reasons for this. At the same time, it has been argued the notion of 'genetic information' is largely an empty metaphor, which generates the illusion of explanatory understanding without offering an adequate explanation of molecular and developmental mechanisms.

Key Concepts

- Mechanistic explanation yields a notion of explanation for molecular biology that does not have to invoke laws of nature.
- Philosophical accounts of mechanistic explanation mesh well with how discovery in molecular biology works.

- The idea that all biological knowledge can be reduced to one fundamental theory or that all explanations are reductive has largely been abandoned.
- Reductionism tends to be replaced in favour of integration across fields or explanations combining features from different levels of organization.
- The concept of the gene has undergone substantial transformation throughout its history. Despite its more recent fragmentation, the gene concept is still widely used.
- The notion of 'genetic information' is largely a metaphor, generating the illusion of explanatory understanding, and cannot be articulated in a manner conforming to mechanistic explanations of molecular and developmental processes.

Keywords: mechanism, mechanistic explanation, reduction, integration, gene concept, genetic information

Introduction

As a discipline independent from general philosophy of science—which originally focused on physics as the model of science—philosophy of biology originated in the 1970s. In addition to merely taking an observer point of view and investigating how theorizing and practice in different parts of biology works, philosophers of biology have collaborated with biologists and made contributions to various conceptual and methodological debates across biology. While a good deal of philosophy of biology was concerned with evolutionary biology, the new molecular genetics also provided material for philosophical discussion. This article critically reviews some of the major philosophical issues in molecular biology: mechanistic explanation, reductionism, the gene concept, and the notion of genetic information.

Mechanisms and mechanistic explanation

Does molecular biology possess scientific laws? Although laws from physics and chemistry can play a role in molecular biology, the standard answer is that molecular biology is not in the business of establishing scientific laws. And admitting this is no problem for a contemporary understanding of science and its diversity, which does not make a discipline's status as being science contingent on it uncovering laws of nature. However, one may still wonder how molecular biology puts forward *scientific explanations*—a question that becomes particularly pressing given that philosophy of science used to construe explanation in terms of laws.

The influential philosophical view of explanation by Hempel and Oppenheim (1948) assumed that offering a scientific explanation consists in showing how the phenomenon to be explained follows from a scientific law. This has been called the 'covering law model,' as the explanation reveals an event to be an instance of some law of nature. In the last two decades, philosophers have come to accept that not all explanations found in science follow this model, and have put forward additional models of scientific explanations, for instance, accounts of causal explanations where a phenomenon can be explained by citing one of its causes rather than some scientific law (Woodward, 2003).

Based on close attention to the practice of molecular biology, philosophers have developed accounts of *mechanistic explanation*, and more generally made the notion of a mechanism a core notion of contemporary philosophy of biology (Bechtel and Richardson, 1993/2010). A *mechanism* has component parts that are organized so as to produce some phenomenon of interest. A traditional example is the mechanism of protein synthesis, which includes DNA, RNA polymerases, mRNAs, ribosomes, and tRNAs among its component parts (see Figure 1). Mechanism components can be entities (e.g., double stranded DNA, RNA polymerase) as well as

activities such as binding and activating (in our example the unwinding of the double stranded DNA, the transporting of the mRNA into the cytoplasm, and the binding of complementary tRNAs to the mRNA). The components of a mechanism need not be molecular entities, but can be from all levels of organization—even mechanisms studied in molecular biology may involve whole chromosomes, axons, and cells. Beyond the very component parts, what is crucial for a mechanism to be able to produce its characteristic phenomenon is the mechanism's organization. This not only includes the spatial organization of the various components, but also their temporal-procedural organization, e.g., transcription taking place before translation can occur (Machamer et al., 2000). Consequently, a mechanistic explanation accounts for a phenomenon by pointing to its underlying mechanism, including the mechanism's components and their organization. On the old covering law model, an explanation provides understanding by means of logical derivation from laws. In contrast, in a mechanistic explanation understanding is generated by mentally simulating the operation of the mechanism, typically aided by a mechanism diagram. Indeed, a law is represented by a quantitative formula or other written statement, but mechanisms typically are visually represented by various diagrams and reasoning about such diagrams is widespread within molecular biology (Bechtel and Abrahamsen, 2005).

By investigating the nature of mechanistic explanation, philosophers have enlarged the spectrum of types of explanation previously considered, and carved out an account capturing molecular biology (and also other scientific domains). But in addition to explanations as the product of science, philosophical studies of mechanisms and mechanistic research have at the same time paid attention to *discovery* in molecular biology (Craver and Darden, 2013). Research in molecular biology is geared toward the discovery of mechanisms, where one major strategy is to understand a complex phenomenon (e.g., signal transmission across neurons) by uncovering the parts that make it up (e.g., axons, neurotransmitters, and receptors) and how these parts

interact and are organized (e.g., in terms of neurotransmitters being released by one neuron and then activating receptors and postsynaptic signalling pathways in another neuron; see Figure 2). The philosophers Bechtel and Richardson (1993/2010) dubbed the strategy of finding and differentiating relevant mechanism components 'decomposition.' Discovery in molecular biology is always a piecemeal affair. But the idea of mechanistic research comports well with this, given that often many aspects of the actual mechanism are still unknown and several possible mechanisms (that could account for the phenomenon of interest) are still being considered by scientists, where more and more missing parts are added to a model of the mechanism. Initial mechanism diagrams may still contain gaps or black-boxes that yet have to be filled, for example, an account of protein synthesis may cover transcription and translation (as in Figure 1), without detailing how in eukaryotes the intermediate step of post-transcriptional mRNA processing by means of splicing works.

In addition to examining what strategies are used for mechanism discovery (Craver and Darden, 2013) and how reasoning using mechanism diagrams works (Abrahamsen et al., 2018), the attention of philosophers of biology has recently turned to systems biology, especially the complex molecular and cellular networks revealed by contemporary large data collection procedures. These philosophical discussion centre on whether complex systems (with unclear boundaries and unclear constituent functional parts) can count as mechanisms, whether some explanations found in systems biology (explaining in terms of mathematical models or abstract network structure) are non-mechanistic explanations of molecular-cellular phenomena (Bechtel and Abrahamsen, 2010; Brigandt et al., 2018; Issad and Malaterre, 2015), and whether the investigation of complex networks is in continuity with traditional mechanistic discovery or also adds completely new scientific strategies (Green et al., 2017).

Reductionism in molecular biology

Questions about the relations of different fields and levels of organization have exercised scientists throughout the centuries. In contemporary philosophy of biology, reductionism became a subject of debate with the rise of molecular biology. Here the question originally centred on whether classical genetics could be reduced to molecular genetics, or to biochemistry. Given that objections against 'reduction' targeted certain philosophical models of what a reduction is, the debate actually concerned not only whether reduction is possible, but what notion of reduction is the scientifically relevant one.

Following Nagel's (1949) account, philosophical models of reduction in science first focused on theories (which were often taken to include scientific laws), and the reduction of one whole theory to another, more fundamental theory. Successful reduction was construed in terms of logical derivation. In the context of biology, Schaffner (1976) proposed that such a reduction of classical to molecular genetics should be possible, so that the challenge was to logically derive all of the tenets of classical genetics from some theory of molecular biology. The feasibility of reduction on this model was immediately challenged by other philosophers of biology (Hull, 1976). The proponents of reduction insisted that reduction was possible *in principle*, but this simply underscored the critics' point that accounts of *theory reduction* in terms of logical derivation failed to capture reductions as they actually take place in molecular biology.

Subsequently the philosophical focus shifted to models of *explanatory reduction* (Sarkar, 1998; see also Kaiser 2015). These pertain not to a whole theory being reduced, but to an explanation of an individual fact being reductive, in the sense that the explanation is in terms of lower-level entities. This is similar to the notion of mechanistic explanation covered in the previous section, so that (unlike theory reduction's focus on logical derivation) models of

explanatory reduction explicitly capture the widespread idea that a reductive explanation in molecular biology accounts for a complex whole in terms of its lower-level parts. Moreover, we have already seen that such reductive explanations are established in a piecemeal fashion, resulting in a philosophical account that effectively captures the practice of molecular biology (as opposed to pondering whether logical relations among theories can in principle be set up by some finished science).

Two basic types of arguments against reduction have been repeatedly raised (Hull, 1976). Broadly speaking, the two are based on the one–many and many–one relation, respectively, between higher-level and molecular phenomena. First, a higher-level phenomenon such as dominance in genetics (an allele being dominant over another one) can be due to a variety of underlying molecular situations. (Philosophers call this one–many situation a higher-level kind being 'multiply realized' on the lower level.) As a result, expressing the notion 'dominance' from classical genetics purely by means of molecular or biochemical terms would require a complex list of all the possible DNA sequences and molecular background conditions that yield a dominant genotype, based on what the phenotype resulting from the molecular configuration is. The significance of this is that while it may *in principle* be possible to translate any biological account into (an extremely complex concatenation of) purely molecular terms, explanations better include reference to some higher-level phenomena. Not only can this yield a more general account (a higher-level phenomenon encompassing many different molecular situations) than an explanation focussing on one molecular situation, but it may also capture the level at which the relevant causes operate. For instance, Mendelian segregation is explained in terms of the behaviour of whole chromosomes during meiosis as the relevant working entities, rather than in terms of the nucleotides and other molecular entities making up the chromosomes (Darden, 2005).

The second common argument against reduction points out that the behaviour or effect of a molecular phenomenon is in some cases dependent on its context. For example, the phenotypic impact of a molecular gene varies with this DNA sequence's regulatory context and the downstream signalling and developmental pathways that lead to the phenotype—a many–one relation in the sense that many higher-level situations can arise from a molecular phenomenon. Proponents of reductionism have responded that if the context matters, the reductive explanation can simply include it. But this fails to appreciate the nature of reductive explanations, because a reductive explanation derives its power from situations where the explanation can simply represent the component entities and interactions of a system largely *in isolation*, without taking the system's larger context into account, and without capturing how a component part may be influenced by its systemic context (Kaiser, 2015). But there are many examples of complex molecular systems where the operation of the system *changes* the properties and impact of its components (Bechtel and Richardson, 1993/2010), in which case the explanation has to take the context-sensitive features of the interacting parts into account and cannot proceed in a thoroughly reductive fashion.

A reductive explanation has important virtues, in particular if it can account for a biological object by only representing its molecular parts (in a context-independent fashion) and their interactions. Yet many important explanation found in biology are not reductive (Kaiser, 2015). This is also the case when the explanation is not exclusively in terms of lower-level entities. The above discussion of mechanistic explanation indicated that some explanations in molecular biology appeal to features on different levels at the same time, such as ions and neurotransmitters (as molecules), receptors (embedded in a cell membrane), axons (as larger parts of a cell), and synapses or whole cells engaged in cell-cell interactions (see Figure 2). Indeed, contemporary philosophical accounts have emphasized the *multilevel* nature of many mechanistic explanations

(Craver, 2005; Craver and Darden, 2013). And even when a mechanistic explanation is in terms of lower-level entities only, beyond the mechanistic decomposition of a system into its parts, the explanatory challenge is to *recompose* the system again, by means of understanding how the parts' complex organization and interactions generates the phenomenon of interest (Bechtel, 2010).

The outdated vision of theory reduction matched with the 'layer-cake' model of scientific fields, which assumed a linear hierarchy of disciplines (sociology, psychology, biology, chemistry, and physics), where one can be fully reduced to the other. Yet the relations among fields are more complex, and pertain to only some items of knowledge across fields, resulting in a network of scientific facts, models, and explanations that changes as discovery proceeds. Consequently, moving beyond arguments for or against reduction, philosophers have come to focus instead on studying the nature of *integration*, and how interdisciplinarity across different biological fields works (Brigandt, 2013; Darden and Maull, 1977). Philosophical accounts of mechanistic explanation have likewise contributed to this, highlighting how different fields shed light on the components of a mechanism, so as to result in multifield explanations. Indeed, whereas the reductionism debate in the philosophy of biology started with the question of whether classical genetics can be reduced to molecular genetics, the processes studied by both fields are better seen as different yet serially connected mechanisms, making the two fields non-reducible to each other, while mechanistically related (Darden, 2005). See also: DOI: 10.1002/9780470015902.a0003356.pub2

Generally, in contrast to philosophers' original attempt to articulate a unique notion of reduction, 'reductionism' as used by biologists refers to different ontological, methodological, or epistemic commitments in different contexts. This explains why advocacy for the experimental

fruitfulness of (reductive) system decomposition can be found together with the admonition that a (non-reductive) recomposition and integration of molecular parts is essential. Likewise, discussions about the possibility and impossibility of reductionism are typically not asserted across the board (for all of biology), but concern specific biological cases, for instance, whether protein folding can be explained solely in terms of the internal, primary structure of proteins (its amino acid sequence), or whether factors external to a folding protein such chaperones have to be taken into account.

The gene concept and the notion of genetic information

The concept of the gene is obviously a core notion for molecular biology. Given the astonishing transformation this concept has undergone throughout its long history, for several decades geneticists, historians of biology, and philosophers of biology have been discussing the development of the gene concept (Falk, 1986; Griffiths and Stotz, 2013; Keller, 2000; Moss, 2003; Portin, 1993; Rheinberger and Müller-Wille, 2017). Classical genetics defined genes as alleles, basically construed in terms of their phenotypic *function*: different alleles at the same locus result in different phenotypes (in two individuals). The advent of molecular genetics can be seen as the discovery of the underlying molecular structure, resulting in a *structural* characterization of genes as certain segments of DNA, e.g., as open reading frames bounded by a start and stop codon and preceded by a promotor (which initiates the transcription of this molecular gene). One difference to the classical gene is that a molecular gene's function is to code for a polypeptide (forming a protein), and not for some gross phenotypic trait. But this comports with the agenda of molecular genetics to understand how molecular genes figure in

biochemical and molecular mechanisms within cells (as opposed to primarily investigating inheritance across generations). Moreover, the relation between classical genes and phenotypes is many–many. Classical geneticists were well aware of the fact that a gene impacts several phenotypic traits, and that several classical genes are needed for one phenotype. Moving the focus from gross phenotype to a gene's *molecular* product (a polypeptide) seemed to yield a scientifically advantageous one–one relation between molecular genes and their products (historically foreshadowed by the one gene–one enzyme hypothesis of Beadle and Tatum, 1941, well before the advent of the discovery of the structure of DNA).

Yet from the mid-1970s onward, research has uncovered more and more of the enormous complexity regarding the structure and function of eukaryotic genes (Griffiths and Stotz, 2013). Structurally, genes are organized into exons and non-coding introns. Molecular genes may overlap, by one gene being contained in the intron of another gene. Or whereas normally only the sense strand of the double stranded DNA is transcribed and codes for a protein, there are genes consisting of an *antisense* strand segment, overlapping with a very different gene on the sense strand. Functionally, the organization into exons and introns requires the post-transcriptional process of splicing, which removes the introns from the transcribed pre-mRNA. There is the process of alternative splicing, where different combinations of exons are selected from each of the pre-mRNA transcripts of the *same* gene, upon translation resulting into many *different* protein products. In the case of trans-splicing, two non-contiguous DNA segments with different promotors (two separate genes?), possibly located on different chromosomes, are transcribed, and then exons from both pre-mRNAs are merged to form *one* mature mRNA that is translated to one polypeptide product. Alternative and trans-splicing reveal that the relation between DNA segments and molecular gene products is *many–many*, after all. Some further post-transcriptional processes include RNA editing and translational recoding. Especially the former shows that in

general a gene product's amino acid sequence is *not* specified by the DNA's nucleotide sequence in accordance with the genetic code, given that pre-mRNA transcribed from the DNA is edited before translation to polypeptide (Stotz, 2006a, 2006b). Generally, although in the early stages of molecular genetics a purely structural definition of genes seemed possible, the advent of functional genomics and transcriptomics has made plain that an account of what genes are or whether a DNA segment counts as a gene has to include considerations of molecular function (Griffiths and Stotz, 2013; Rheinberger and Müller-Wille, 2017).

This development of the last three decades has occasionally been described as the 'fragmentation' of the gene concept. In any case, it has been a significant historical transformation from a more unified molecular concept of the gene to a situation where different geneticists may use different conceptions of what a gene is and where there is in many cases no unique answer to the question of whether a given segment of DNA is a gene (or merely one part of a gene). Given their specific investigative contexts, researchers may use different structural and functional considerations when employing a conception of the gene and when deciding how to annotate a certain genomic region. For instance, when due to trans-splicing two DNA segments form one product, this suggests to some that the two non-contiguous segments taken together should be viewed as forming one gene; yet the situation that one such DNA segment also independently codes for another product supports the alternative view that these are two separate genes. While this situation is all too familiar after the many challenging empirical findings of the last two decades, the fate of the molecular gene concept was presciently foreseen by geneticists turned historian of genetics Falk (1986, p.165): "But beyond this belief [that genes are made of DNA], what is meant by the use of the terms can only be gathered from the context. Sometimes 'gene' is used to denote a specific unit, sometimes it is a collective term for genetic units and quite often it is avoided completely." Moreover, even something very much like the

classical gene concept still continues to be used in molecular biology, at least in medical genetics (Moss, 2003).

Nowadays many terms apart from ‘gene’ are available and can be used in combination to offer a more precise account of what aspects of gene structure or function one is talking about in a concrete case, terms such as ‘transcription unit’ and ‘exon’. This has led some to argue that the very word ‘gene’—laden with significant historical baggage—has outlived its usefulness and better be abandoned in favour of other, more modern terms (Keller, 2000). At the same time, the term ‘gene’ still enjoys widespread popularity among molecular geneticists, where stereotypical accounts of what genes are employed as a stepping-stone (concomitant with the acknowledgement that more precise construals are actually needed to capture individual empirical cases) and where the meaning of ‘gene’ depends on and varies with the context. In the light of this, rather than endorsing the elimination of the gene concept or attempting to still recover some common core encompassing all uses of ‘gene’, some philosophers of biology have adopted the investigative project of trying to understand the empirical reasons for the diversification of the molecular gene concept, and the scientific motivation for preferring a particular construal of ‘gene’ in a certain context (Stotz and Griffiths, 2004).

In the context of genetics, a further philosophical issue has been the very idea of *genetic information*. While the notion was not used in classical genetics, information talk became popular after the advent of molecular genetics (Maynard Smith, 2000). At the same time, many commentators have been critical of this, charging that ‘genetic information’ is for the most part an empty metaphor that does not do any explanatory work, while also having misleading connotations, in particular for the general public (Griffiths and Stotz, 2013; Moss, 2003; Robert, 2004). A major problem is that the two major ways of articulating what ‘information’ actually is

are unsuitable for the purposes of molecular genetics. One prominent definition of information stems from mathematical information theory (proposed by Shannon). However, this approach does not pertain to the content of an information bearing entity (e.g., what trait a gene would code for), but only to the quantity of information a communication channel can transmit. Moreover, all sorts of physical states count as containing information, as long as there are some correlations among states, *regardless* of the direction of causation. The presence of fire tells us that (contains the information that) there is smoke nearby, and likewise, the presence smoke yields the information that there is a fire. Consequently, on the mathematical information theory approach, a genotype does contain information about the phenotype, but also this phenotype permits an inference about and thus contains information about the genotype. Weak correlations also exist with the states of the environment, so that the environment (and not only the genotype) contains some information about the phenotype and even about the genotype. Obviously, this prominent definition of information does not underwrite the idea that only genes contain information about phenotypic traits.

The second way of articulating information (called 'teleosemantics' by philosophers) invokes natural selection. The basic idea is that in the past, a gene had phenotypic effects, some of which were favoured by natural selection, and the information that the gene now possesses is to code for those traits (including morphological and behavioural traits) that were selected for in the past. Some feel that an attractive aspect of this approach is that it yields a sense in which a gene is still 'meant' to generate a phenotype (because of natural selection in the *past*) even if due to environmental interferences this phenotype is not *currently* produced. At the same time, such a definition in terms of past selection does not align with how explanations in molecular genetics work, which are about the current operation and effects of molecular mechanisms. This definition of information does not even comport with the common idea that a molecular gene

codes for an amino acid sequence—which for molecular biologists is the amino acid sequence that a DNA segment now produces (or does not produce) *in a given cell*, and not some (possibly different) amino acid sequence that may have been favoured by natural selection in the remote past.

Overall, there is nothing wrong with the idea that a molecular gene as a DNA segment codes for a certain amino acid sequences. But this idea can be soberly articulated in terms of the genetic code (i.e., the DNA triplet to amino acid mapping) and the molecular mechanism of transcription and translation—an appeal to information does not add anything to this. In contrast, talk about genes containing 'information' for making morphological traits and behaviours and the related notion of 'genetic programs' (or genetic blueprints) merely employs metaphors that create the illusion of explanatory understanding, without actually offering a mechanistic explanation of how molecular genes bring about traits (Griffiths, 2001; Robert, 2004). Moreover, talk about 'genetic information' and 'genetic programs' suggests—in particular to the general public—that the effect of a molecular gene is context-insensitive (the particular information is just 'inside the gene') and that genes run the whole causal show. Yet even the protein, not to speak of a morphological trait, produced from a molecular gene depends on the cellular context, with alternative splicing and other post-transcriptional processes leading to proteins with different amino acid sequences in different cells (Stotz, 2006b). Transcription factors and various other *non-genetic* entities inside the cell are needed to activate a gene's transcription and thus the generation of some gene product in the first place, where the production of the actual product is modulated by post-transcriptional processes conducted by molecular entities other than DNA. The development of traits is to be explained in terms of interactions among cells and tissues, involving for instance how gene transcription in a cell is activated by signals from another cell, resulting in a plethora of entities other than molecular genes having a significant regulatory

influence (Griffiths and Stotz, 2013). In the previous section we saw that mechanistic explanations often appeal to entities on several levels of organization, which should not make it surprising that explanations in molecular biology include not only genes, and that explanations in developmental biology are epigenetic (Robert, 2004).

Conclusion

This article has reviewed some major philosophical issues in molecular biology. While some have become a subject of debate more recently (e.g., mechanistic explanation), others have been longstanding questions (e.g., reduction and the gene concept). But even in the latter case, new empirical findings have reconfigured the issues, resulting in currently ongoing debates of the matter. Philosophers of biology, attempting to understand how scientific practice works, have contributed to these conceptual discussions and followed the emergence of new empirical findings and methods. Beyond molecular biology narrowly construed, this has also led to philosophers investigating other fields that are nowadays of major scientific importance, such as cell biology (Bechtel, 2006), stem cell research (Fagan, 2013; Laplane 2016) and cancer biology (Bertolaso, 2016), discussing various issues arising within and specific to such a field.

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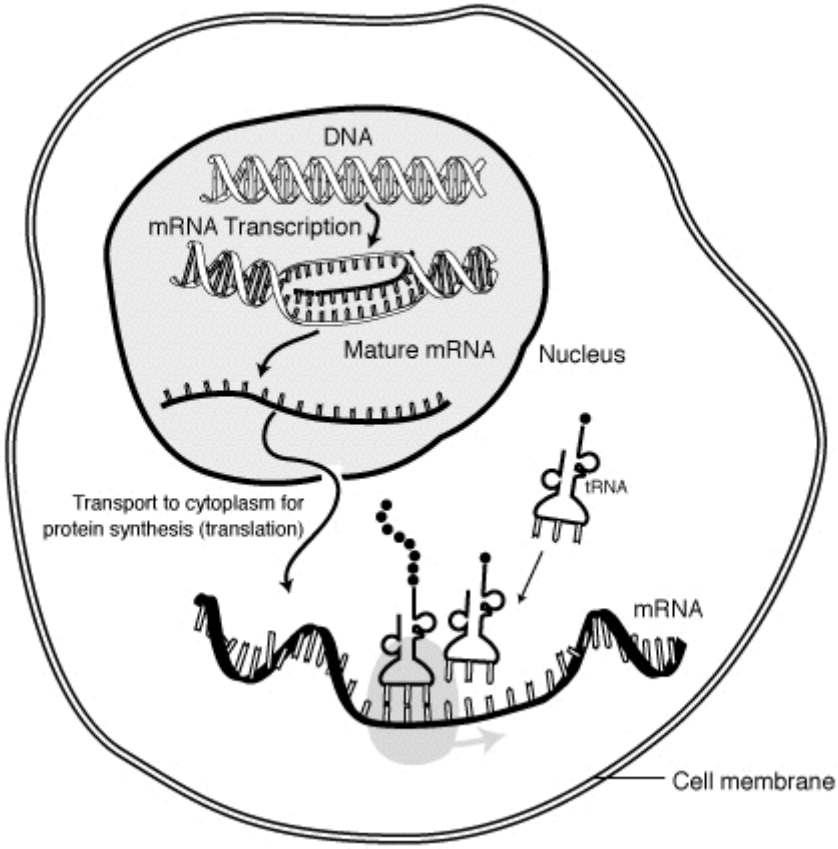

Figure 1: The mechanism of protein synthesis (in eukaryotes). Transcription of the DNA to RNA takes place in the nucleus, while the RNA's subsequent translation to protein (depicted as a chain of black dots) occurs in the cytoplasm. (Image in public domain)

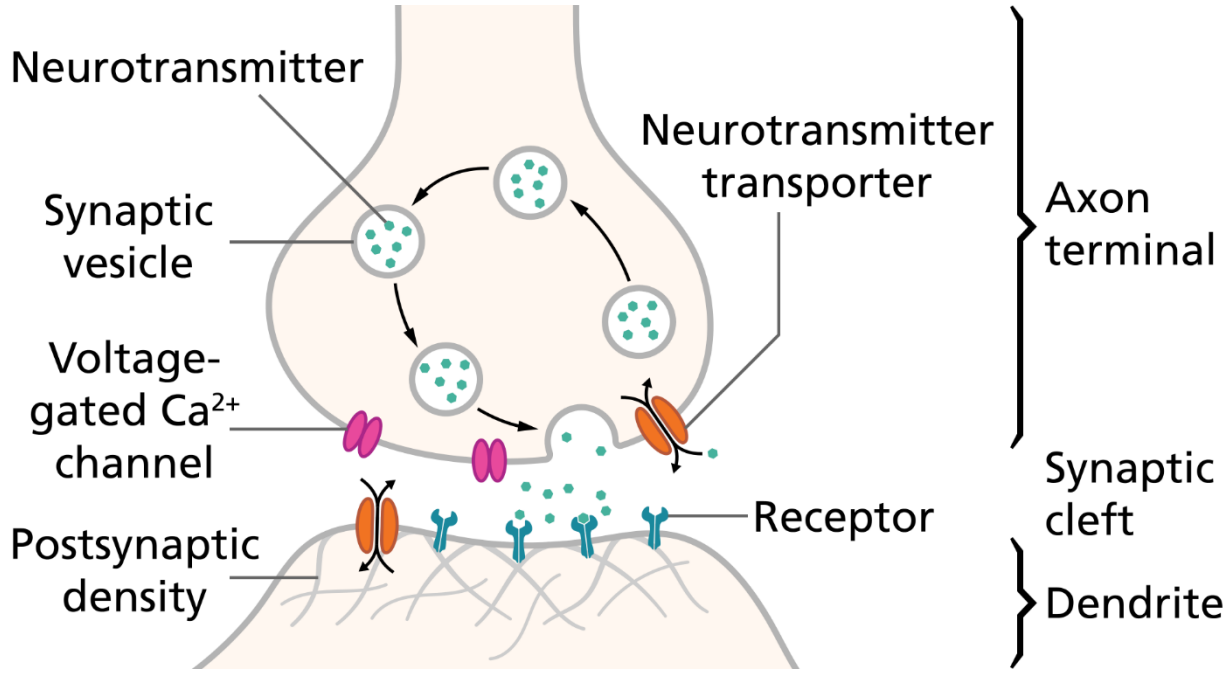

Figure 2: A synapse permitting signal transmission from one neuron (at the top) to another one (at the bottom). The synapse includes such entities as the axon of the transmitting neuron, neurotransmitters, and receptors in the wall of the receiving neuron. (Image licensed by Thomas Splettstoesser under Creative Commons Attribution-Share Alike 4.0 International)