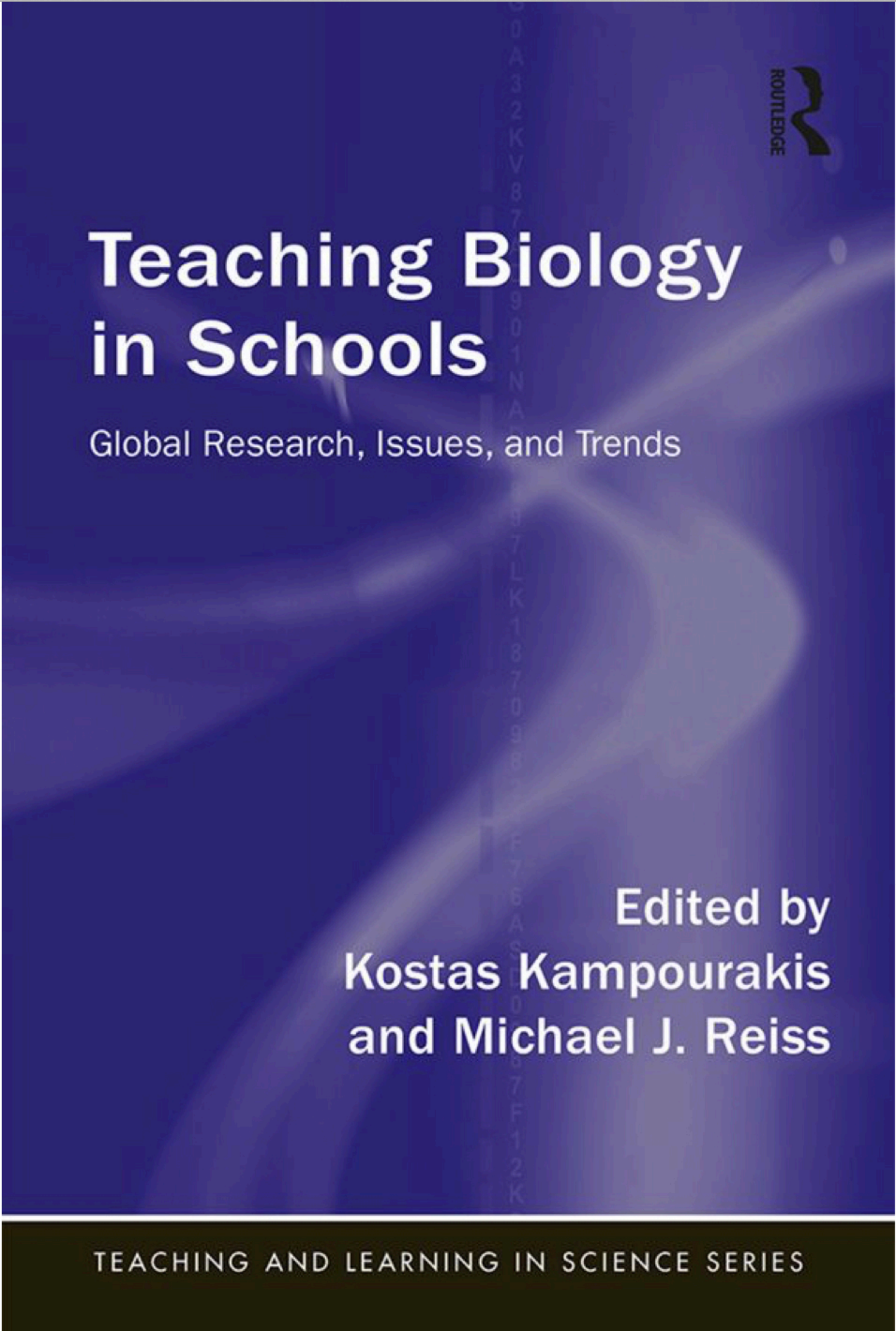
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4

Molecular Biology

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Introduction: What Is Molecular Biology?

The term 'molecular biology' suggests a sub-discipline of biology, such as ecology or genetics. However, molecular biology can better be described as a perspective that biologists use to explain the phenomena they are studying. This is visible in sub-disciplines such as molecular cell biology, molecular genetics and molecular evolution.

Morange has suggested that molecular biology should not be considered as a sub-discipline of biology, but as a specific level of explanation (Morange, 2000). All biological sub-disciplines include molecular explanations of phenomena on the cell, organism or population levels. In biological research, these explanations have created deeper insights into these phenomena without making research on higher levels obsolete. Phenomena studied by molecular biologists therefore almost always refer to phenomena on cellular and higher levels of organization, of which the molecular level is the lowest level of explanation. An example is the interaction of proteins in a muscle fiber, explaining the phenomenon of muscle contraction on the cellular and organ level.

The same counts for molecular biology in biology education; here too, molecular biology can be described as the lowest level of explanation. The part molecular biology plays in biology education is therefore about asking and answering 'how questions' when studying phenomena at the cellular level (van

Mil et al., 2016). This also means that molecular biology is biology and not chemistry. Although the molecular phenomena follow the laws of chemistry and physics, the questions that drive molecular biological research are biological ones. These questions ask for the functions of molecules on cellular and higher levels, and for the structures of molecules explaining mechanisms in the cell. Nevertheless, without the input of chemists and physicists, these explanations would not have been developed, because they depend on understanding the chemical interactions about biological molecules. Molecular biology is therefore a field where many disciplines meet (Huang, 2000).

Molecular biology provides unity in biological phenomena. One of the first steps in this process was that molecules found in organisms could be synthetized in the lab, and therefore did not have any special properties and were not a separate kind of chemistry. The universality of the building blocks of cells, of the genetic code and of many metabolic pathways made us aware of the extent to which all organisms are related. Even more importantly, many molecular explanations could fully explain the mechanisms causing the phenomena on higher levels. This meant the end of hypotheses on 'vital forces' and led to the materialistic stance that denies the existence of "any kind of stuff in the world other than the stuff described by physics and chemistry" (Dupré, 2009, p. 33). For these reasons, molecular biology has transformed biology into a more coherent scientific discipline.

In this chapter, we include traditional biochemistry contents in our description of molecular biology. The distinction between molecular biology and biochemistry is not clear. Courses in biochemistry tend to focus more on the chemistry of molecules in the cell, such as enzyme kinetics and redox potentials, whereas courses in molecular biology focus more on gene and protein function in the cell, but most textbooks on either biochemistry or molecular biology will cover both aspects.

Why Teach Molecular Biology?

Based on the curriculum emphases formulated by Roberts (1982), several types of arguments can be furnished to teach molecular biology, such as everyday engagement with science, societal decision-making and correct explanations.

First, many concepts and terms in molecular biology like DNA, proteins and

enzymes are commonplace in everyday language. These terms are mentioned in movies and on the news; they can be found on the labels of consumable products and are discussed by health providers. We are supposed to understand information on processes such as enzymatic breakdown and diffusion, and information on dangerous or healthy substances acting at the cellular level.

Second, on a societal level, issues such as environmental pollution, malnutrition, drug abuse and development of new therapies or biofuels involve the mentioning of molecules, either of specific substances such as carbon dioxide and glucose or of groups of molecules indicated as stimulants, nutrients or antigens. As for everyday situations, making informed decisions on these issues requires a level of 'molecular literacy', because a deficient understanding of molecules might hinder comprehension of the issue. For example, the idea that molecules from organisms are 'more natural' and therefore healthier than synthetic substances might lead to wrong conclusions. A functional molecular literacy includes not only 'knowledge in science' but also 'knowledge about science': the ways molecular biological knowledge is generated and applied in societal contexts (Tibell & Rundgren, 2010).

Third, regarding the role of molecular biology education in the formulation of correct explanations, an understanding of molecular phenomena is fundamental to understanding key processes on higher levels, and is essential for all life science studies. As Duncan and Reiser (2007, p. 939) stated, "understanding genetic phenomena entails understanding how mechanisms and interactions at the molecular (genes, proteins) and microlevels (cells) bring about effects at the macrolevel (organism, population)". Furthermore, knowledge of molecular biology integrates knowledge of biology with knowledge of the other sciences.

What Should We Teach About Molecular Biology?

The fact that molecular biology concepts are discussed over different topics in biology education makes it difficult to decide which elements are essential in a molecular biology curriculum. Rather than learning the molecular details of dissimilation, protein synthesis and cellular transport, for a better understanding students should learn the mechanisms and entities that underlie these processes. Howitt et al. (2008) argued that molecular biology

education should contribute to the development of big ideas in this domain and have developed a concept inventory for molecular biology that captures these ideas. In their proposition, the most basic concept is that of equilibrium, with which other concepts are linked, such as regulation, information and communication, energy and organization, compartmentalization, catalysis, self-assembly and molecular evolution. Based on what was mentioned earlier about what molecular biology is and why it should be taught, we offer a small set of core concepts for a molecular biology curriculum.

a. *Molecules are the only components of which organisms are built.*
   All organisms are made of molecules and only of molecules. The molecules of living organisms can be synthetized and are made of the same atoms as the universe. However, the molecular composition of organisms differs from the inorganic environment in the composition and size of the molecules, largely consisting of only a few elements (C, H, O, N). Most of the molecules are dissolved in an aqueous internal environment that is separated from the external environment and can therefore create specific conditions for reactions and electrochemical gradients.
b. *Cellular activities can in principle be explained by interactions of molecules, in particular proteins.*
   Students need some basic knowledge about how activities and interactions of biomolecules are grounded in physical and chemical changes. Fundamentally, they need to understand the constant movement and collision of molecules in a cell. For some simple phenomena, such as diffusion, this already explains the respective phenomenon sufficiently. For other phenomena, more complex interactions have to be understood. Molecular properties such as being 'energy rich' or 'poisonous' exist only through the interaction with other molecules. Without a proton acceptor such as oxygen, glucose would not be 'energy rich', and without a receptor that can be blocked, a substance has no poisonous effect. Phospholipids form double layers only through their interaction with water molecules.
c. *Interactions between molecules in the cell depend on a limited set of characteristics.*

Molecules differ in size, polarity, charge, stability and binding properties, which explain their interactions and activities. Van Mil et al. (2016) provided a simplified account for the interactions and activities of biomolecules based on a combination of intelligible changes: colliding, binding and changing shape. Despite its limitations, this account makes clear that a limited set of basic changes can form the basis for very complex structures and functions in cells.

d. *Relating cellular structures and functions to the properties and interactions of their molecular constituents offers a deeper understanding of 'how it works'.*
Some examples of structure-function relations are:

- Properties of DNA afford key features like coding and accurate replication—functions needed for the information repository of the cell.
- Proteins' three-dimensional shapes and chemical properties (charge, hydrophobicity) afford and constrain the kinds of functions they can carry out.
- Size and charge influence permeability of molecules through membranes.
- Many interactions entail a 'lock-and-key' process (enzymatic reactions, signal transmitting, drug effects, hormonal influence, immune reactions).
- The polarity in phospholipids explains the formation of layers in an aqueous environment.

e. *There are several levels between cells and molecules.*
Subcellular structures such as chromosomes and ribosomes are known and can be made visible with high-powered microscopes. However, a cell has many other phenomena between individual molecules and the whole cell. Many molecular modules can be distinguished in a cell, regulating hormonal influence in the cell or chromosome separation during mitosis. These are temporary complexes and therefore often not visible, but they consist of closely and specifically cooperating molecular structures. Furthermore, in a

cell different compartments with different conditions exist.

f. *Interactions between molecular and higher levels go both ways.* The statement that molecular processes form the 'lowest level of explanation' does not mean that molecular explanations are the most fundamental explanations or that organisms are fully governed by molecular processes. Interactions between molecular processes and higher-level processes go both ways. Not only do molecular interactions explain the mechanisms of cellular processes, but processes on organismal and cellular levels influence at the molecular level which genes are expressed, which hormones are released or which cells will divide or die.

In the next section, we focus on protein interactions. These can explain a whole range of cellular phenomena, as there are different functions that proteins carry out in and out of the cell, such as serving as structural components, transport, catalysis, signaling, receiving signals, etc. Proteins are thus a central explanatory element of molecular biology explanations and illustrate all of the points mentioned above.

What Is Difficult to Learn About Molecular Biology?

There are several aspects of molecular biology phenomena that make them challenging to learn. Molecular biology phenomena occur at spatial scales that are very small (enzymes can be as small as 10 nm) and occur at very high speeds (100 or so reactions per second for some enzymes). These invisible and fast phenomena are intractable for students, making reasoning about them challenging. Compounding the intangible nature of molecular biology entities and processes, such as proteins and the many functions they carry out, is the lack of attention to these entities and processes in instruction (Duncan & Reiser, 2007; Marbach-Ad, 2001). Unlike the more extensive focus on genes and DNA, there is much less attention to proteins and their biological role in biology textbooks and instruction at the secondary level (Thörne & Gericke, 2014; van Mil et al., 2013). Thus, even though they are important entities in molecular biology, proteins remain relatively invisible to students throughout their schooling.

Aside from being invisible, molecular biology phenomena are also difficult to

understand because they comprise several levels of organization that are ontologically distinct: physical and informational (Duncan & Reiser, 2007). Physical levels include cells, organelles, protein complexes, DNA molecules and other molecules. Interactions within and across these levels result in phenotypes at the level of the cell (and consequently tissue, organ and organism levels). The information level in this system consists of genes, which do reside in a physical molecule (DNA). However, their role in the system can be conceived as being ontologically distinct from the other physical entities as they provide instructions for making proteins. Thus, the information and physical levels intersect at the protein level (rather than the organelle or cell levels, which in contrast are not directly coded by the information level). Understanding how this informational level interacts and intersects with the physical levels is not trivial for learners. Students, especially in the secondary grades (middle and high school), tend to think that genes code directly for the actual phenotype we can observe (e.g. structures and functions at the organ and organism levels) and may even conflate genes and traits (Lewis & Kattmann, 2004).

Venville and Treagust (1998) showed that students progress through a trajectory for conceptual change related to the concept of gene from an initial view of genes as passive particles associated with traits to a view of genes as informational (containing information for 'whole' traits) to the most advanced view of genes as containing productive instructions for proteins. The use of the word productive here denotes the idea that the instructions lead to the formation of a physical product (protein). The shift from conceptualizing genes as all-inclusive instructions (blueprint) to viewing them as productive instructions for proteins is a critical one in this progression (Shea & Duncan, 2013). Such a shift motivates the need for proteins as the mediating mechanisms between the informational level of genes and the subsequent (physical) organization levels, e.g. the cell level and beyond. Students who conceive of the genetic information more broadly as a blueprint for everything about us do not see a need for any mediating mechanisms; they essentially circumvent the protein level by asserting that genes code directly for whatever organismal structure or function for which they are trying to account (Duncan & Reiser, 2007).

Reasoning about protein function, and cellular processes more generally,

poses additional challenges in that these processes are often complex and emergent. The notion that complex structures like the clathrin cage shown in Figure 4.1 can self-assemble through random interactions in the cell seems counterintuitive and perplexing to students. However, through the interaction of specific adaptor proteins that facilitate the assembly of the clathrin monomers into a cage, under the right pH conditions and in the presence of the adaptor proteins these molecules can assemble into a cage in a test tube. Research on students' understanding of complex systems has shown that students struggle to conceive of complex structures and behaviors at the aggregate level as emerging from simple interactions at lower organization levels (Jacobson, 2001; Wilensky & Resnick, 1999).

High school and even college students do not readily conceive of how protein-based mechanisms can give rise to complex functions like sensing and transmitting signals, controlling gene expression, movement, etc. (Duncan & Reiser, 2007; van Mil et al., 2013). On the one hand, students struggle to envision how simple proteins can carry out complex functions; yet, on the other hand, they tend to imbue molecular and cellular structures with goals and intentional behaviors (Dreyfus & Jungwirth, 1990) or extrapolate functions from organs and organ systems onto molecular and cellular entities (Flores et al., 2003). These tendencies can engender anthropomorphic explanations of molecular processes—for example, assuming that molecules move directionally and intentionally (e.g. substrates move towards meeting their enzymes), rather than randomly (Stieff & Wilensky, 2003). Representing the movement of molecules is in some ways an issue of reasoning about chemical interactions. Similarly, students tend to assume that the properties of the whole are the same as the properties of the molecules—for example, that the molecules of a blue substance are blue themselves. Thus, students' understandings of chemistry also impact their ability to reason about molecular biology entities and processes.

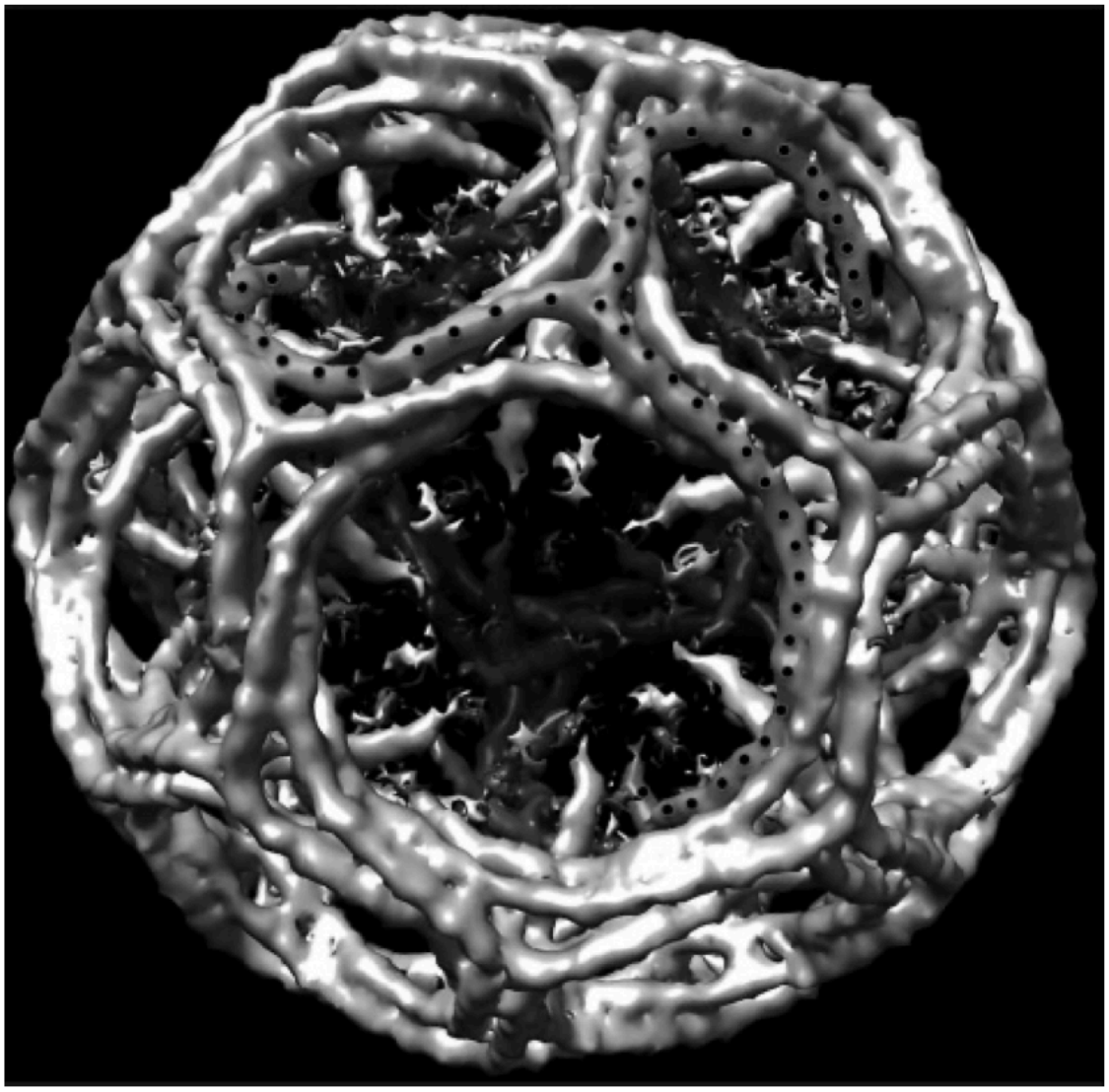

Figure 4.1 Clathrin cage composed of many clathrin proteins, with single clathrin protein, indicated with black dots on the image

In summary, reasoning about molecular biology phenomena presents several challenges to students given their ontologically distinct levels, unfamiliar entities and the emergent nature of their structures and processes. In the next section, we discuss some of the instructional implications that stem from these difficulties in terms of how and when we should teach molecular biology ideas.

Recommendations for Teaching Molecular Biology

How Should We Teach Molecular Biology?

One of the core implications is that students need to become a lot more familiar with the functions and interactions of proteins in biological processes. Students need to develop a toolkit of protein functions that they can use to reason generatively about molecular processes, both familiar and novel ones. Such a toolkit will allow students to provide plausible protein-based explanations of molecular processes. In addition, students need to come to view molecular interactions as occurring through random collisions that lead to binding of molecules and ultimately to conformation changes in these molecules that afford specific functions (van Mil et al., 2016). Combining the notion of a protein-function toolkit with a framework for understanding the nature of protein interactions (colliding, binding, changing shape) is likely to yield deeper and more powerful understandings of molecular biology processes. In particular, it should support students in generatively developing explanations of phenomena that are novel and unfamiliar to them. These explanations may not be accurate (in the sense of postulating the actual mechanism involved), but they should be plausible in that they postulate a biologically viable and sensible mechanism. Given the educational goals of producing scientifically literate citizens as well as future scientists, being able to explain and reason about novel phenomena is an important achievement for students.

We also advocate for focusing on proteins first before teaching about DNA and the central dogma. As we noted earlier, students who learn about DNA as a 'blueprint' do not see a need for a mediating mechanism and thus do not view proteins as having a central role in mediating the effects of genes. In fact, even learning the details of the central dogma and how genes are translated to proteins does not ensure the subsequent understanding that proteins are therefore involved in all genetic phenomena in one way or another (Marbach-Ad & Stavy, 2000). Attending to protein structure and function and the roles proteins (and protein complexes) play in and out of cells first prompts the need for instructions for making these entities. Learning about genes and DNA is thus better motivated after the role of proteins has been established.

Our emphasis on protein-based mechanisms and developing plausible

explanations of molecular processes implies that instruction should engage students in figuring out molecular biology phenomena. Inquiry-based approaches to science instruction in which students engage in the exploration, investigation and explanation of phenomena are well suited for achieving the goals we posited. The choice of phenomena for investigation, however, needs to be well thought-out. We argue that in order to help students develop a toolkit of protein functions and understanding protein interactions, it is helpful to select phenomena in which proteins carry out functions with analogues in the macro-world. For example, protein functions such as channels, receptors, some structural proteins ('stretchy' muscle proteins) and transporters are simpler to reason about, as students are familiar with structures and functions in their everyday worlds that are analogous to protein functions (doors are similar to channels, transporters are similar to bicycles, muscle proteins are like rubber bands, etc.). While enzymes play a critical role in biology, and are often used as examples in instruction, they are not as accessible to students as there is no real analogue to speeding up reactions in their everyday worlds. Moreover, the structure of enzymes (unlike structures of channels or muscle proteins) does not suggest their function; one cannot see why a specific change in the structure will result in the enzyme not working beyond invoking the lock and key model. It seems to us that proteins other than enzymes may be a better entry point to understanding protein structure and function relationships and the variety of roles proteins play in cells. For example, as noted earlier students can readily reason about membrane channel proteins (viewing them as analogous to selective 'doors' in the membrane), and the topic of cell transport is usually one that is taught fairly early on in middle school biology. In terms of a channel protein context, a compelling phenomenon is lead poisoning, as lead enters the cell by mimicking calcium and is actively transported into the cell through the calcium channel. In fact, in order for students to develop a robust understanding of the myriad of functions proteins carry out, they should study a variety of proteins and related phenomena.

Students' investigations of molecular biology can be bolstered by viewing animations and using interactive simulations (Rotbain et al., 2006; Rotbain et al., 2008). Such simulations make visible the invisible and can illustrate molecular interactions in terms of the random nature of collisions and the importance of direct binding and conformational changes. However,

understanding visualizations depends on domain knowledge and familiarity with symbolism (Kozma, 2003). In addition, students sometimes treat visualizations as realistic depictions of phenomena rather than abstract models (Harrison & Treagust, 1996). Therefore, it is important to attend to students' capacity to process and understand the visualizations used and support them in making sense of what they are seeing and manipulating.

Agent-based modeling environments (such as NetLogo below) can also help students understand emergent interactions. There are several useful software simulations and animations that can support student learning, including the Molecular Workbench simulations from Concord Consortium (http://mw.concord.org/modeler/); NetLogo simulations, particularly for related chemistry ideas (https://ccl.northwestern.edu/netlogo/); and the genetics science learning center, which has various activities and animation for multiple topics in molecular genetics and cell biology (http://learn.genetics.utah.edu/).

When Should We Teach Molecular Biology?

The last issue we wish to discuss is how we can build students' understanding of molecular biology over time and across grades using the learning progressions approach. Learning progressions (LPs) are theoretical models of learning over time. LPs in science education are organized around a few core disciplinary ideas and practices and describe the development of students' understandings as intermediate steps or levels between initial and final states (Corcoran et al., 2009; Smith, et al., 2006). Descriptions of these levels are extensively grounded in research on student learning in the domain, and progress along the levels is mediated by targeted instruction and curriculum. It is important to note that LPs by their very nature are hypothetical; they are conjectural models of learning over time that need to be empirically validated. Currently there are no LPs in molecular biology; however, there are several in genetics that deal with molecular genetics concepts relevant to molecular biology (Duncan et al., 2009; Elmesky, 2013; Roseman et al., 2006; Todd & Kenyon, 2016).

A core proposal of these progressions is that students should begin learning about proteins and their functions earlier in their schooling, rather than waiting to introduce these ideas only in high school. Research on this

progression has shown that even middle school students (age 12–14) can reason about protein structure and function and develop protein-based explanations (Shea & Duncan, 2013). At this stage, students are expected to understand that genes contain instructions for making proteins (but not for how proteins themselves are synthesized, for which other proteins are required). Thus, students can begin to reason about the ways in which changing the instructions (mutations) might affect a protein's general structure and consequently its ability to function. At this stage, proteins are seen as little machines that can carry out functions and are part of structures in the cell. Their structure is only discussed in general terms as 'being stretchy', traversing the cell membrane, having an opening that allows specific molecules to pass through, etc. Teaching about the amino acid composition and other chemical properties of proteins is not really necessary at this level.

Building on these early understandings of proteins as little machines that can do the work of the cell, high school level molecular biology instruction can then delve into the central dogma and how the genetic code is actually 'read' by cellular machinery to produce proteins. At the high school level, students' ideas about the nature of specific genetic mutations (missense, nonsense, frameshift, etc.) can be deepened and connected to the actual composition and structure of proteins in terms of amino acid sequence and three-dimensional structure. In simple form, the idea that the regulation of gene expression is something that is controlled in the cell is also within the grasp of high school students. Phenomena like tanning in humans and ripening in fruit can be discussed as mechanisms in which an external signal can trigger, in a protein-mediated way, the expression of genes that result in the making of new types of proteins in the cell that confer new functions or structures (resulting in new phenotypes). We would argue that more complex concepts like metabolic pathways, signaling pathways and transcription regulation in development (e.g. homeobox genes) are best addressed in either advanced high school courses or in post-secondary classes.

We also wish to point out and emphasize that teaching students the details of processes such as transcription and translation in protein synthesis, stages of meiosis, structure of DNA, Krebs cycle, etc. does not guarantee an understanding of the bigger ideas (Duncan, 2007). Rather, such a focus tends to result in students 'missing the forest for the trees' because their fragmented

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may encounter throughout their lives.

In this chapter, we have taken a stab at identifying these ideas, as well as when and how to teach them, given known learning challenges in this domain. One of our key messages is that we need to refocus biology education on powerful frameworks that can help students understand key molecular mechanisms, such as protein interactions, rather than the specific details of molecular structures and pathways. Engaging students in inquiry and sense-making using these frameworks to explore a variety of meaningful molecular biology phenomena is more likely to engender students who appreciate molecular biology and can successfully engage in personal and civic decision making in their everyday encounters with molecular biology.

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