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Teaching with digital biology: Opportunities from authentic sequences and 3D models

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Structured Abstract

Background: Swiss schools are required to develop students' digital competencies in each discipline (CIIP, 2018). However, teachers in Geneva, Switzerland aren't supplied with many official resources or recommendations to help them implement these requirements. This article presents a project that developed a theoretical framework referring to three types of digital education skills (DES): (DES A) new approaches to building or validating knowledge, (DES B) critical-thinking skills, (DES C) new didactic methods and elaborated proposals to help biology teachers comply with the requirements. Building and discussing models is a core scientific practice and can develop understanding of scientific phenomena and the nature of disciplinary knowledge (Schwarz et al., 2009). The digitisation of biology and affordable 3D printers make it possible to produce tangible models of most proteins mentioned in secondary biology education from freely available, authentic research data. This combination opens unprecedented opportunities for classroom activities, allowing students to (DES A) practice digital biology methods based on a discussion of solid evidence (DES A) and (DES B) support the development of critical thinking.

Purpose: This article first presents a theoretical perspective developed to reveal the learning potential of digital biology, focuses on its feasibility, and finally discusses the educational potential offered by scenarios, with some data from a proof-of-principle example. Based on how biology research nowadays builds knowledge and on research showing educational benefits of using authentic research data and 3D models (better questions, more discussion of models, enhancing motivation), this article presents technical step-based *course-of-action* scenarios (CoAscenarios) that were tested in classrooms, helping teachers and learners to access and use authentic data to address difficult learning issues such as evolution or the form–function problem, by manipulating authentic research data and physical, tangible models. With a focus on strengthening students' skills in building and validating knowledge using the new digital approaches (DES A), the CoAscenarios contribute to the ongoing change process rather than pedagogical guidelines, which come from educational authorities. They are designed to be used independently of teachers' methods. This article seeks to stimulate discussion of these opportunities and the challenges that many schools face.

Sample/setting: In a proof-of-principle example, we describe one possible use of selected CoAscenarios (Nos. 17, 20, 21) tested in three pilot classes in upper secondary school ($N = 48$ students in total, 2016-2019) and improved in over 20 in-service teacher training courses (since 2002). These activities, including hypothesis testing and discussions of data as evidence of evolution, are organised in the format of a classical hands-on school lab.

Design and Methods: The project (2019-2021) collected 25 classroom-tested CoAscenarios which are now presented on an open MediaWiki platform. As a proof-of-principle, we discuss three CoAscenarios: No. 17 concerning sequence data, and No. 20 and No. 21 concerning tangible models. In CoAscenario 17, students used authentic protein sequences to compare the degree of similarity of one protein each across different species, visualised as highlights on aligned sequences, and discussed this evidence of common origin and of divergence caused by mutations. Then, students observed areas of their protein sequence in which little or no change could be observed across species. They discussed how natural selection can explain this evidence. Using 3D-printed tangible models, they compared conserved parts of the sequence with areas of the model to test and improve their naïve mental models with regards to the learning goals. To this effect, teachers used CoAscenario 20, in which a table gives the protein name, a link to its sequence, biological information in the UniprotKB database, 3D structures in the Protein Data Base (PDB), a picture of the 3D-printed model, and ready-to-print files (.STL). CoAscenario 21 helps teachers convert 3D structures from the PDB to a 3D-printable format. Feedback about feasibility and usefulness was collected in questionnaires. This led to improvements

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being made to the platform. Data from student questionnaires were analysed for perceptions of these learning activities. We will also briefly present some results from a questionnaire used in a teacher training course.

Observations: Results from classroom observations: the students handled technical steps with more ease than expected, allowing discussions to focus on biological questions such as natural selection, mutation, how proteins fold, protein–substrate interactions, conservation of structures in evolution, how specific areas of the protein determine function and, in some cases, the limits of the lock-and-key model.

Conclusions: Results confirm the feasibility of such approaches and their alignment with the educational reforms of the discipline. Our results suggest that the choice made in the project to propose CoAscenarios expressed as technical steps frees the teacher to focus the lesson design on biological concepts, activities and discussion of the evidence found, rather than on the technical mastery of websites and platforms. Expected difficulties, such as drawing from different models for explanations, were confirmed. The use of authentic research data helped reveal conceptual gaps in student understanding and allowed teacher feedback that guided students towards better mental models. This should help dissemination at this early stage of adoption of digital biology. Results also open new educational strategies based on authentic data embodied in material objects and databases and suggest more research into the educational effects of 3D model use in different learning designs.

Keywords: *Models, evolution, 3D structure, bioinformatics, learning designs, authentic data, digital learning*

1 Introduction

Swiss schools are required by a federal action plan for digital education (CIIP, 2018) to introduce computer science as a discipline but also as an approach to the construction of knowledge in each of the school subjects. As for biology, this project, with its roots going back several years (Lombard, 2008; Lombard & Blatter, 2009) developed a conceptual framework that we will refer to here, organised around three types of discipline-specific digital education skills (hereafter DES): (DES A) new approaches to building or validating knowledge, (DES B) critical-thinking skills and (DES C) new didactic methods to teach classical biology. These skills were proposed to and considered by local think tanks (DIP, 2018; DIP, 2019).

While most efforts to comply with digital teaching seem to concentrate on (DES C), we argue that teachers need most support in (DES A) and (DES B), where some of the most innovative and effective opportunities can be developed. Section 2 develops how digitisation has deeply transformed biology research and discusses the educational implications. According to biology historian Morange (2008), the paradigm that dominated biology from the mid-20th century has subtly changed. Schools mostly refer to this previous molecular biology paradigm (Entress, 2022), in which questions are about the underlying mechanisms of biological processes, and their answers are expected as causal explanations in terms of molecular interactions (Morange, 2003).

Today, biology functions mainly under an information-control paradigm in which living phenomena are explored in terms of information-regulation processes and flows. Current research produces new knowledge mostly by digital treatment of this information, comparing information such as DNA, RNA, protein sequences between organelles, healthy or defective cells, tissues, individuals, species, each within ecosystems, along their development or in archaeological traces of evolution. The expression “digital biology” is recent and overlaps with bioinformatics. However, since authorities require school to integrate digital biology, this article refers to this expression.

Can education ignore the new ways by which knowledge is being produced and validated in research (DES A)? On that topic, the National Research Council (NRC) (2003) produced a report warning educators how profoundly the digital revolution has transformed biological research and recommending a comprehensive re-evaluation of undergraduate science education and a renewed discussion on the ways in which engineering and computer science are presented to students, including mastery of digital information and models. We have argued (Lombard, 2008) that schools cannot ignore this change. To this effect, we have been developing teacher training programmes since 2002, which have led to the project presented here.

As the NRC (2003) insists, models are crucial to understand difficult learning issues in biology. Freely available research data offering sequences and 3D structures, and affordable 3D printers, now allow tangible 3D models to be produced from research data, and they provide educational opportunities. Some research suggests that digital molecular models can assist learning about and understanding protein structures and functions, so students using tangible models and hand gestures can express ideas that they could not initially put into words and ask better questions, and that, by using models, students can improve their understanding of how molecular structures relate to biochemical functions. We have previously found that comparing sequences can help students understand evolution mechanisms (Lombard, 2011a) and we have hypothesised that, similarly, 3D structures could help students relate form and function, using research data as evidence. This article – in the context of required educational reforms to include digital biology – aims to develop a theoretical perspective about the educational potential of freely available research data that digital biology offers, such as sequences and 3D structures.

After a brief review about models in science education, the use of tangible 3D models in biology will be discussed. We then present a discussion of research about using authentic research data (such as sequences), arguing in favour of their potential use in classrooms. The development of teacher acceptance as they discover new uses for these resources and according to their diverse teaching methods leads us to choices for structuring the projects’ deliverables.

While this is not an experimental design, the following question guides the argument in this article: can the proposed uses of authentic research data and tangible 3D models help teachers develop new activities addressing difficult learning subjects (evolution, protein folding, form–function...)?

This article’s goals are i) to develop a theoretical perspective and discuss the feasibility and educational potential offered by freely available digital-biology research data to help teachers address the required reform, ii) to discuss how our theoretical perspective was implemented in the project’s course-of-action scenarios (CoAscenarios) available on an online platform, including concrete examples of the use of sequences and tangible 3D models, and iii) what educational effects can be expected. This article aims to help teachers and authorities discuss the central place of digital biology and its pedagogical implications.

Furthermore, it addresses the following sub-questions: Can the proposed uses of authentic research data and tangible 3D models improve student engagement and involve students in more complex and relevant questions? Can they help students better use different models to reach understanding (i.e., make explanations and predictions) in biology?

We present a selection of 25 tested technical step-based scenarios available on an open platform addressing mostly (DES A), partly (DES B) and indirectly (DES C). We focus primarily on (DES A) by using sequences and research-generated structures converted into tangible 3D models.

The scenarios are structured as technical step-based CoAscenarios that help students develop up-to-date skills by manipulating authentic research data and physical, tangible models. They were chosen to be as pedagogically neutral as possible to allow their use in very different teaching approaches and to help teachers progressively adopt and adapt them into their teaching culture.

As proof of this principle and to illustrate the theoretical perspective, an exploratory study was conducted in a teacher training course and three pilot classes in upper secondary. Using sequences and 3D structures in open research databases allowed comparing protein sequences to find evidence of common origin and divergence and printed 3D protein models helped to relate form and function and provide evidence to discuss mechanisms of evolution. Results from classroom observations led to improvements in the CoAscenarios. Data from questionnaires addressing student perceptions of these learning activities were analysed to improve the CoAscenarios presented and to discuss educational implications for student guidance in activities and improve future learning designs.

2 Research Background

Local authorities (DIP, 2018) have defined general principles for digital education that include i) knowledge and skills needed to become competent, equal, responsible, empowered, active and protected digital citizens; ii) introducing digital tools when they present a clear added value pedagogically; and iii) teaching how to make use of, understand, and evaluate digital resources, as well as participate actively in a digital society. A reference document (DIP, 2018) mentions transversal digital skills that include i) information skills to identify and handle reliable and relevant information, in order to build knowledge independently; ii) technical and technological skills; iii) reflective skills allowing a critical, informed and responsible assessment of the societal impact of digital technologies; iv) skills to produce, distribute and receive content; and v) communication and collaborative skills to interact effectively and harmoniously with peers and teachers.

How this should be done in secondary biology-chemistry classes was still being debated as this project emerged. Additionally, there is not a large body of didactic research upon which teachers can rely to help them in this transition. The conceptual framework developed in this project – before digital education was required and these principles were defined – identifies three types of discipline-specific skills: DES A, DES B, DES C. This text refers to these categories and will focus mostly on new approaches to building or validating knowledge (DES A), and partly on critical thinking skills (DES B). During the project, most efforts in local schools and in projects mentioned in the literature that we were aware of seemed to concentrate on DES C (new didactic methods to teach usual biology), for example: Rasch and Schnotz (2009); Waight and Abd-El-Khalick (2011); Jong, Linn and Zacharia (2013); Roda-Segarra (2021); Bölek, De Jong and Henssen (2021). This literature is now so abundant that it has been integrated into general educational syntheses by Hattie and Yates (2013) and Taber (2019). Research on critical thinking skills is briefly discussed at the end of this section. In this article, we argue that most innovative and efficient opportunities relate to skills for new approaches to building or validating knowledge and critical thinking skills. Being new, DES B and DES C are among those aspects for which teachers need most support to realise their full potential.

Research on digitisation has deeply transformed biology research. Here, we discuss the educational implications of this transformation. In reference to new approaches to building or validating knowledge (DES A), awareness of a major change introduced by digitisation across biology goes back to the beginning of the 21st century. According to biology historian Morange (2008), the molecular paradigm that dominated biology from the mid-20th century onwards has subtly changed to a paradigm of information-control, in which living phenomena are explored in terms of information flow and the regulation of biological processes. According to Machluf and Yarden (2013), biology in the 21st century is expanding from a purely laboratory-based science to an information-aided one. They refer to bioinformatics, that they define as computerised databases used to store, organise, and index data and specialised tools to view and analyse data. In the educational context here, we include this under “digital biology”.

Based on Morange (2003), we define the molecular biology paradigm essentially as molecular causal explanations of underlying mechanisms, where answers are expected in terms of molecular interactions. In the information-control paradigm, however, answers are expressed in terms of information flow and control (e.g., DNA sequences \rightarrow RNA (cis-regulation) \rightarrow (trans-regulation) \rightarrow protein). Of course, information is stored in molecules, but the focus is on the information itself – the sequences – not on the medium, and research produces new knowledge mostly by digital treatment of this information, such as by comparing information in DNA, RNA or protein sequences between organelles, healthy or defective cells, tissues, individuals, or species, and along development or in archaeological traces of evolution. Current biology research clearly illustrates how these new ways of validating knowledge (DES A) are essentially what justifies publication. Often, this information is extracted from databases, and researchers might never have touched the specimens they are analysing. For example, Lemopoulos and Montoya-Burgos (2021) analysed the evolution of scales in more than 11 600 fish species without their hands ever smelling of fish. Even when a first step is converting these molecules (sequencing) to digital information, this step is not what justifies publication, but rather the digital comparison to other digital data. For example, the conclusion that Denisovans are different from modern humans and from Neanderthals that Krause et al. (2010) produced was based on DNA sequences from a small piece of bone digitally compared to numerous other sequences from databases. The molecular aspects of extracting and sequencing DNA represented a minor methodological part and the discussion of their hypotheses revolved around digital evidence and methods. In the wake of the Human Genome Project, Butler (2001) had warned about this change in *Nature* with an article entitled “Are you ready for the revolution?”.

Now this information (i.e., sequences) can be modified in a computer and used to direct the synthesis of DNA molecules that will help cure diseases, improve industrial processes, allow experiments, and that have even been introduced into cytoplasm to produce a synthetic organism which will live as directed by its new genome (Gibson et al. 2010).

This change to digital biology is even more evident in a more recent publication, wherein an artificial intelligence (AI) algorithm was hailed as *Science's* 2021 “Breakthrough of the Year: AI brings protein structures to all” (*Science* Editorial, 2021). Indeed, Jumper and colleagues (2021) developed an artificial intelligence software that could predict 3D protein structures. Until then, protein structures could be determined only through painstaking lab analyses, involving X-Ray crystallography, nuclear magnetic resonance, etc. They did this without any molecular procedures, instead drawing from protein sequences (UniProtKB¹ database) and structures (PDB² database). This new AI algorithm computed structures for nearly all known proteins (> 200 million, from bacteria to plants to vertebrates including mice, zebrafish, and humans).

All these examples reveal that biological research produces and validates knowledge in new ways (DES A). In a nutshell, we might say DNA is still at the centre of biology, but to understand the processes of life, researchers focus on the information it carries (not the chemistry), and the fluxes of this information or its regulations.

Databases store and share various forms of authentic research data (including DNA, protein sequences and 3D structures, the latter being relevant to this article). Most can be freely accessed by all, including schools.

The educational implications have been emphasised by the NRC in a large report (2003). It warns educators how profoundly the digital revolution has transformed biological research and recommends a comprehensive re-evaluation of undergraduate science education and a renewed discussion on the ways in which engineering and computer science are presented to students, including mastery of digital information and models. This led us to argue (Lombard, 2008) that high schools cannot ignore this change. This does not imply that digital biology should replace molecular biology in schools, but that it can help learn some difficult concepts and that it addresses some skills that authorities require schools to teach.

An important dimension of this project is the focus on models. Among others, the NRC (2003) and Schwarz and colleagues (2009) insist models are crucial to understanding difficult learning issues in biology. Here, we explore educational opportunities that might be created by freely available research data offering sequences and 3D structures, and affordable 3D printers now allowing tangible 3D models to be produced from research data. According to Levkovich and Yarden (2021), visualisation of proteins using digital molecular models can greatly assist both experts and students in learning about and understanding proteins' structures and functions. Levkovich and Yarden (2021) write that there does not seem to be a large body of didactical research on which to rely to design and guide teaching using 3D models. Nonetheless, Gregorcic, Planinsic and Etkina (2017) found that students relied heavily on nonverbal meaning-making resources, most notably hand gestures and resources in the surrounding environment to communicate ideas that they initially were not able to express using words alone. Howell et al. (2019) found strong learning gains with respect to students' ability to understand and relate molecular structures to biochemical function. We also found that comparison of sequences (Lombard & Blatter, 2009) could help students understand evolution mechanisms and hypothesise that tangible 3D models could help students relate form and function, using research data as evidence of evolution.

2.1 A few words on the use of models in science education

Acknowledging that scientific practice revolves around building and discussing models (Schwarz et al. 2009), we refer to the definition used by Schwarz et al. (2009): models are abstract, simplified representations of a system of phenomena that highlight its essential characteristics and can be used to generate explanations and predictions. For a given phenomenon, there are several models (Fig. 1 for examples): each has a different domain of validity and is relevant to different problems (Martinand, 1996). Therefore, there is no perfect “top model” (Lombard, 2011b), but different models that highlight some characteristics and can be used to predict or explain different aspects of the phenomenon; they are relevant for different problems. Figure 1 shows different representations of the same tRNA molecule. The top-left model (“cloverleaf”) is best suited to discuss how the complementarity in areas of the sequence determines the folding, giving rise to the cloverleaf name of this model and the 3' chemical affinity with the amino acid (a.a.) is explicit. The top-right model can help students understand the interactions of the codon and anticodon, on the ribosome and the a.a.-transferring (hence its name) role of tRNA; this model highlights the flow of information rather than the molecule's shapes. The bottom-left model shows how the tRNA folds in space (tertiary structure), and colour coding can help understand which parts of the cloverleaf model (insert) are folded into which area of the tertiary structure. Bottom right is a 3D-printed model from the project database which can be manipulated by students to understand its structure, and how it attaches to a.a. and codon. There is no one perfect model, but each highlights a few characteristics and can be used to predict or explain different aspects of the phenomena; they are relevant for different problems, as Martinand (1996) shows.

Here we will distinguish the mental representation of a phenomenon used by the teacher, the student, or the researcher, referred to as the mental model (henceforth M-model), and the concrete representations of these models (images, diagrams, objects, formulas, etc., abbreviated A-model) that Bereiter (2002) calls “conceptual artifacts”. These artifacts support discussion and allow confrontation with students', teachers' and researchers' M-models. These in turn can be referred to as A-models such as an image, a diagram, a text or a 3D object. Activities organised around an A-model

¹ UniprotKB is described as the reference for high-quality, comprehensive and freely accessible resource of protein sequence and functional information.

² Protein Data Base (PDB) contains experimentally determined 3D protein structures obtained by X-ray diffraction or cryo-electron-microscopy (Cryo-EM)

can help learners discuss their M-models and bring them closer to achieving the learning goals. This process of developing M-models is called “modelling” (Schwarz, et al. 2009). Learning to select which are the most relevant M-models and knowing when to use them in each context is a critical difficulty in learning science (Potvin, 2019).

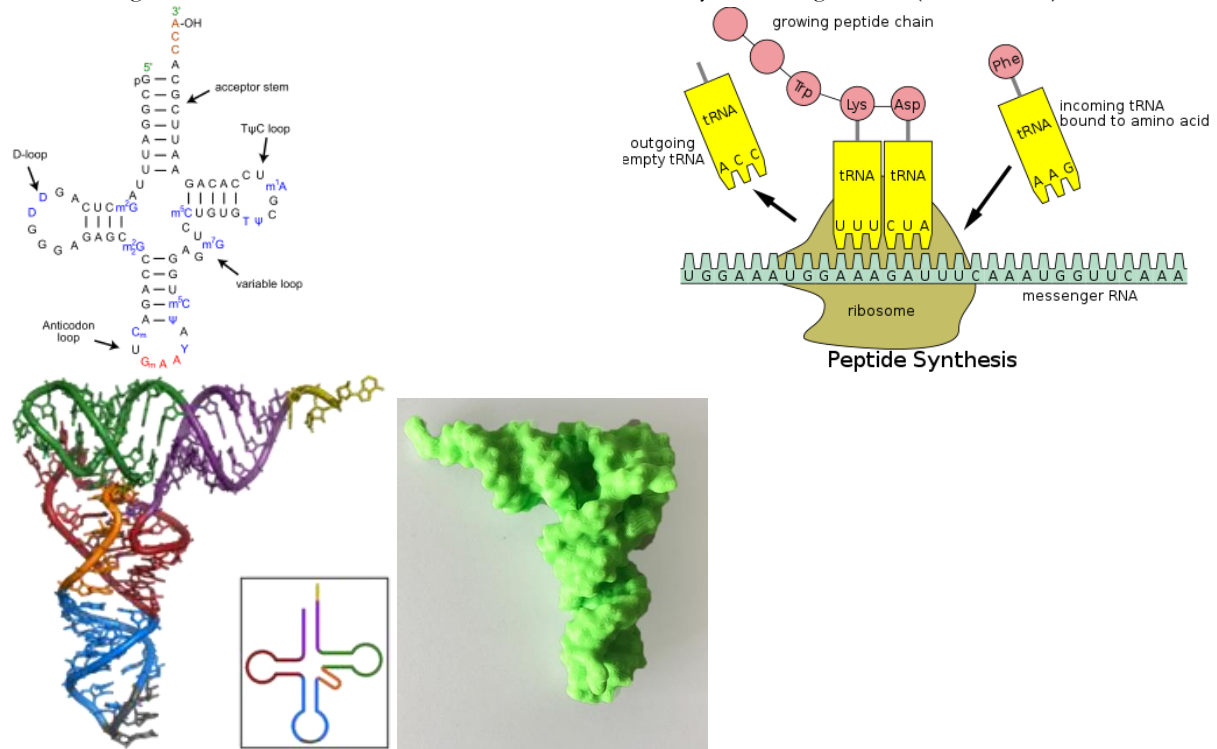


Fig. 1. Different representations (A-models) of tRNA from the Transfer RNA page on Wikipedia; bottom right is a 3D printed A-model (artifact) from the project’s database. Each of these models highlights different characteristics, and can be used to predict or explain other aspects of transcription; thus, they are relevant for different problems. Sources: Top left is licensed by Yikrazuul, top right by Boumphreyfr, bottom left by Yikrazuul, under (CC BY-SA 3.0). bottom right by Lombard F.

2.2 How might authentic data improve learning?

The A-models used in classrooms are often stereotypical representations of the diversity of biological structures. For example, animal cells are illustrated as spherical, with a nucleus in the middle (Fig. 2, left), while they in fact come in a great variety of forms and said type is not the most frequent; this oversimplification might confuse or hinder students’ understanding (Dahmani, Schneeberger & Kramer, 2009). Based on a large body of research (in French), Chevallard (1991) explains how knowledge is necessarily transformed as it is transposed (didactic transposition – DT) into school knowledge. During this process from research to publication to curricula, many characteristics specific to scientific knowledge are altered. These include loss of the context in which the knowledge was produced, the methods that produced it, its diversity, uncertainty and the limits of its validity; rather, it is presented as abstract, definitive and without context (for a discussion in English, see Lombard and Weiss (2018)).

The didactic model in Fig. 2 on the left presents “the animal cell” as simplified, definitive, without context, variations or limits. In that form, it easily leads to well-known exercises and classical assessments, and it is socially recognised. This is quite typical of the transposed knowledge that Chevallard (1991) predicts will be found in the classroom. Chevallard calls “monuments” knowledge that an educated person should know but that is disconnected from the reference knowledge it is supposed to represent. The opposite applies (Fig. 2, right) to a 3D printed A-model of an antibody molecule based on the authentic structure data in a research database (PDB): it is connected to current research, is specific (Immunoglobulin-g), hides less of its complexity, and is new to most teachers, authorities and parents. Here, activities need to be invented to develop their educational potential; as an example, Fig. 2 (right) illustrates an activity based on an A-model from this project, in which students explore (with beige magnetic antigens) in which area of the protein antigens interact with the antibodies (antigen-binding pocket).



Fig. 2. Left: a typical didactic A-model of an animal cell, printed in 3D from: www.thingiverse.com/thing:2485063. Right: a 3D-printed A-model from authentic research data of an antibody showing student exploration of interaction with an antigen (forces between a magnet in the antigen-binding pocket of the antibody and in the antigen A-model held by the student illustrate chemical interactions). Credit: Lombard, F.

The Cognition and Technology Group at Vanderbilt (1990) considered that true research data are more authentic than carefully selected, educationally polished data, in agreement with DT. Since research knowledge loses some of its scientific characteristics as it becomes school knowledge, its authenticity diminishes as it is transposed. This is not the only use of the term “authenticity”: according to Weiss and Müller (2015), in reference to PISA, it describes a close relationship to actual and real contexts. According to Yarden and Calvalho (2011) others refer to authenticity for activities outside of classroom and still others to activities analogous to those scientists practice, such as students posing questions and designing their own paths to solve them. Another definition by Doyle (2000) proposes child-centred, subject-centred, or situated authenticity. In a recent synthesis, Schriebl, Müller, and Robin (2022) propose three dimensions: real-world authenticity, disciplinary authenticity and, on the perpendicular dimension, personal authenticity. Referring to its etymology, the Greek *ἀθηντικός*, “authenticity” means to act on one’s own authority, which nicely qualifies original research knowledge, rather than that validated by schools’ or teachers’ authority. Here, we will refer to authenticity (of knowledge) in this sense: authenticity of knowledge is greatest in research data and primary literature and diminishes as it is transposed into textbook knowledge and classroom knowledge.

In an approach we might consider as circumventing DT, helping students develop their understanding using authentic research knowledge that has not undergone these transformations (or only partially) has been proposed by some researchers. According to Yarden and colleagues (2009), helping students come to grips with adapted or primary literature (APL) can promote the learning of both science content as well as science epistemology and introduce learners to contemporary scientific issues. Additionally, students often reported enjoying the activities and found them interesting and relevant. The students were more engaged and stressed the contrast between the authenticity of the activity or scientific articles and the traditional curriculum. These authors also found that APL promotes engagement, knowledge integration, inquiry thinking, discipline-specific epistemic beliefs, and increased comprehension of the subject matter among high-school students. Dorfman and Yarden (2021) found evidence for higher-level and more diverse thinking. Authenticity might not be only for older students; Yarden and colleagues (2015) propose a learning progression and mention that short and simple APL articles have been used in 6th and 8th grade (Shanahan, et al. 2009), allowing students to become familiar with the structure of scientific writing early in their education, which could prepare them to read more complex texts later. Referring to authenticity in 3D models, Gregorcic, Planinsic and Etkina (2017, p. 020104-2) found that “in their discussions the students relied heavily on nonverbal meaning-making resources, most notably hand gestures and resources in the surrounding environment [...]. They juxtaposed talk with gestures and resources in the environment to communicate ideas that they initially were not able to express using words alone”.

To sum up, this project was based on the premise that helping students to use the authentic research data that is now available (as much as their development allows) opens new educational opportunities and can reduce the effects of DT. For biology or science education, the literature on the educational effects of using tangible 3D A-models in science is still rare.

Hansen and colleagues (2020) reviewed 20 years of literature for the use of 3D printing in biological education and found only 13 articles investigating the benefits for student learning. For example, Howell and colleagues (2019) found strong learning gains with respect to students’ ability to understand molecular structures and relate them to biochemical function. Beltrame and colleagues (2017) propose that converting digital 3D molecular data into real objects enables information to be perceived through an expanded range of human senses, including direct stereoscopic vision, touch, and interaction. They also suggest that such tangible models facilitate new insights, enable hypothesis testing and serve as psychological or sensory anchors for conceptual information about the functions of biomolecules.

Printing physical, tangible artifacts of proteins is still rare in schools. “Although evidence suggests that handling physical models supports gains in student understanding of structure–function relationships, such models have not been widely implemented in biochemistry classrooms. [...] Three-dimensional (3D) printing represents an emerging cost-effective means of producing molecular models to help students investigate structure–function concepts.” (Howell, et

al. 2019, p. 303). These authors found that through interaction with these 3D learning A-models, students improved their skills at relating molecular structure to biochemical function, evaluating molecular dynamics considering structure–function relationships, and translating between two- and three-dimensional models. They suggest instructors can employ these modules in any context or course for which the content is relevant, including lectures, flipped classrooms, recitation or small-group tutoring.

Of course, research is at an early stage and these results are still tentative and only partly based on 3D models in biology, but they suggest authenticity, as we have defined it, can improve learning. To that effect, this project explores how authentic data and 3D A-models might support activities to improve student understanding of difficult subjects such as evolution or the form–function problem. For an example, see section 4.2.

Three-dimensional printing in education requires technical mastery of procedures that are not generally known to teachers. However, Schneider and colleagues (2017) present methods for digital manufacturing in education (not specifically science) and argue that it creates opportunities for teachers to create educational objects adapted to their own needs and teaching methods. Beltrame and colleagues (2016) propose step-by-step procedures to convert and print proteins, on which we built for CoAscenario 21.

Of course, printing tangible A-models is only a first step. Learning gains will depend on the activities and learning designs in which students are involved by teachers according to their teaching methods. As Rabardel (2003) shows, this is an iterative process: while the chosen tangible A-model first influences and constrains the potential educational uses, as teachers appropriate them, they develop their own uses, elaborate new potential and conceptualise the object in new ways – it becomes a new “instrument” according to Rabardel (2003). Therefore, the full educational potential of a new educational artifact appears only with time and iterations. For example, a 3D-printed protein artifact might first be used simply as a visual representation the teacher shows during a lecture. Then, as the teacher becomes more familiar with the object and seeks or imagines other uses for it, they might simply propose to students to manipulate these tangible A-models. Later, they might realise this manipulation needs to be guided to help learners formulate hypotheses about the link between structure and function. Later still, activities to compare protein sequences and 3D structures in different species might allow testing of hypotheses to help students improve M-models about evolution. The CoAscenarios offered in the project, being as pedagogically neutral as possible, will be used in very different manners and teaching methods and will progressively develop their full potential as teachers’ culture progressively includes them – they become “instruments” in the sense of Rabardel (2003).

2.3 Three-dimensional visualisation requires cognitive skills – and raises equality issues

Seeing a representation – however well thought-out it might be – does not guarantee it will be understood in the intended manner (Ainsworth, 1999), and student use of 3D A-models of proteins raises specific visualisation issues. According to Levkovich and Yarden (2021), there are three main means of displaying visual information using molecular A-models of proteins: (1) retrieving structure files from a databank and visualising them using a molecular viewer; (2) encouraging the haptic perception of protein structures using tactile molecular models in combination with visualisation of molecular models; and (3) using virtual reality or augmented reality in 3D.

In classrooms, 3D structures are typically only presented as pictures, either on paper or projected, and sometimes dynamically visualised on computer screens where the visual system of learners is expected to infer the 3D structure by interacting with the image produced on the screen. This requires complex knowledge: for Levkovich and Yarden (2021) it involves content knowledge of protein structure and function, procedural knowledge of visualising molecular A-models, procedural knowledge of using software or applet features, and epistemic knowledge of molecular M-models. Indeed, the cognitive skills that are central to visual literacy in biochemistry are complex; Levkovich and Yarden (2021) identify eight: decode, evaluate, interpret, spatially manipulate, construct, translate between M-models, translate across levels of organisation and complexity, and visualise relative size. These skills are probably not equally mastered by all students, but, according to Koone (2022), tangible A-models can alleviate the cognitive load and even help students with impaired spatial visualisation.

While 3D models of molecular interactions are the basis of several chapters in teaching biology (biosynthesis of proteins: tertiary and quaternary structure; enzymatic action, hormonal receptors and neurotransmitters, antibodies–antigens, etc.) students are most often confronted with “flat” 2D A-models: images in books, screens or projections that they cannot manipulate. While teachers are comfortable linking this 2D representation of a volume to physiological M-models to predict and explain biological phenomena and students can generally reproduce the illustration or diagram (A-model) seen in class, the latter are not all able to predict or explain a slightly different situation (Millar, 2009), suggesting they have not developed an efficient M-model or did not bring it to mind in that context (Hammer, et al., 2005). This problem is dubbed by Lemke (1990) the “classroom game” – where students frame activities in science classes as the production of answers for the teacher or for tests, rather than as making new sense of the natural world. With Millar (2009), both show the importance of real engagement of students with activities.

According to Howell et al. (2019), understanding the relationship between molecular structure and function is an important goal in life sciences education. How structure results from sequence is also at the core of understanding evolution.

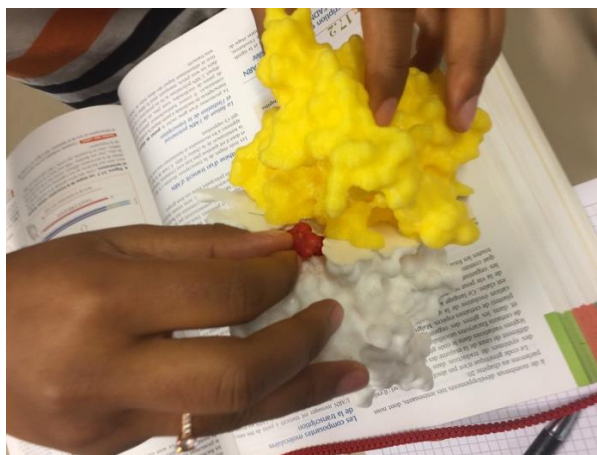


Fig. 3. Manipulating tangible objects can help understand how structure determines function. In this example, ibuprofen (red) blocks the enzyme Cox1 (top half yellow, lower half white) by attaching to the active site.

Tangible A-models could be used to highlight different biological properties of proteins, such as spatial interactions, different areas (reactional site, transmembrane, DNA binding, etc.). Comparing authentic sequences and manipulating proteins could help students address difficult learning questions (drug–target protein interactions (see Fig. 3 for an example), antibodies and antigen-binding site, different forms of the protein cystic fibrosis transmembrane conductance regulator (CFTR)³ and cystic fibrosis, different spike proteins and affinity with human ACE2 receptor, etc.). Based on this theory, this project explored how new approaches to building or validating knowledge in research (DES A) can be used in schools to improve learning, specifically using authentic research data, sequences and structures to print tangible 3D A-models.

We will now briefly discuss digital biology and critical thinking skills (CT) (DES B), Jiménez-Aleixandre and Puig (2022) stress the importance of educating critical citizens in a world that challenges the boundaries between truth, fiction, and deliberate misinformation – that we refer to as “post-truth”, not only for a better understanding of science. Biology education is a privileged context for the development of the critical thinking needed to sustain democracy in a time of crisis. For example, Quitadamo and Kurtz (2007) highlight the potential of engaging students in computer-supported writing to develop CT. In the late 20th century, Facione (1990) argued that a proper domain-specific understanding of methods is needed for CT. Higgins (2014) discusses critical-thinking skills for 21st-century education, and shows that some skills are not new, but others, such as the capability to manage large quantities of digital information relevant for decision making, raise new challenges for education. For Jiménez-Aleixandre and Puig (2012), CT must include the ability to evaluate knowledge on the basis of available evidence. These CoAscenarios help students access such evidence that digital biology now offers. We have argued (Lombard, 2008) that this major change offers new opportunities but also that teachers first need a good understanding of this new biology before they can help learners develop the CT now required to address this change. This is why CT is not explicitly addressed in the proof-of-principle example discussed in section 4.2, but as teachers become more fluent with digital biology, these CoAscenarios could be used in learning designs to develop these CT skills. Also, research at Geneva University proposed and discussed a design to develop critical thinking skills to discuss recent research in this new biology (neurosciences) that were tested in local schools, and proposed assessment methods (Lombard, Schneider, Merminod & Weiss, 2020).

We will now discuss the learning activities produced and collected during the project, addressing new approaches to building or validating knowledge (DES A) and partly critical-thinking skills (DES B), tested in upper secondary biology classes, and organised them in a repository in a form allowing their use under various teaching methods.

3 Methods

This project has its roots in 2002, when collaborations with Dr Marie-Claude Blatter of the Swiss Institute for Bioinformatics led to over 20 in-service teacher training courses. With digital biology integration now required by the curriculum, this project (running between 2019 and 2021) collected from teachers (including Author 1) various uses of digital biology in classes, which were organised and rewritten as technical step-based CoAscenarios that follow the following structure (see Appendix 1).

1. Title: expressed as a verb describing what the CoAscenario produces (e.g., “Determine the 3D structure of a relevant protein”)
2. Procedure: the main part, consisting of steps to extract data from the database in order to answer a biological question
3. Possible insertions into curricula

³ Malformed CFTR proteins cause cystic fibrosis

4. Concepts and pedagogical scenarios in which it could be integrated; possible questions for students
5. References

At this preliminary stage of the introduction of digital biology teaching, this project focused on delivering technical step-based CoAscenarios written as lab working protocols, while the implementation in classes, detailed assignments, tone and tasks are left to teachers. Nonetheless, when available, examples of possible insertion in curricula and sample student productions were added.



Scenarios were not organised as pedagogical guidelines: first, because of the very different methods chosen by different teachers and the diversity of possible instrumentations (Rabardel, 2003) while teachers appropriate the artifacts; second, because they would need to be validated by commissions and authorities, which is an ongoing process.

During the project, these CoAscenarios were demonstrated to teachers for comments and improvement. They were then transferred to an open access wiki platform using the same technology as Wikipedia, ensuring long-term access and update.⁴

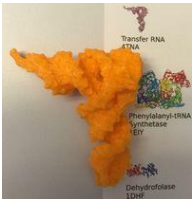


The project produced 25 CoAscenarios (technical steps) that were tested in classrooms and presented in teacher training. Some of the CoAscenarios address (DES B) questions (such as learning to find evidence to discuss possible fake news), however, this is not the focus of this article, and the examples proposed address mainly (DES A). We present here CoAscenarios 17, 20 and 21 describing how to find the protein sequences and 3D structures of 20 proteins and nucleic acids selected for relevance to biology-chemistry secondary classes, and how to convert them to tangible 3D-printed A-models. Before the project, these CoAscenarios were tested in three pilot classes in upper secondary school ($N = 48$ students in total, 2016-2019) as will be described in section 4.2.

To simplify choice, CoAscenario 20 presents a table relating protein name, link to sequence, biological information in UniProtKB database, 3D structures in PDB, picture of 3D printed A-model and ready-to-print format (.STL). Current printers have a limited printing size, so except for Cox1 and the corresponding drug molecules, all A-models were printed at the optimal size for the printer rather than at a given scale. See an extract in Table 1 and full CoAscenarios in supplementary material. A detailed description of one possible use is given in section 4.2.

Tab. 1: Simplified table presenting a selection of proteins and data offered.

Selected Protein name	UniProtKB Entry	PDB Entry	Picture of protein A-model	Ready-to-print STL files
Human haemoglobin	HBB_HUMAN HBA_HUMAN	1a00 4hhb* 2hhb	 Haemoglobin (2x2 subunits red, 4x heme white)	Hemoglobin.stl Heme group.stl
Human insulin	INS_HUMAN	2hiu* 1ben	 Insulin	InsulinReady2print.stl
Human nucleosome	H4_HUMAN	5b40	 Nucleosome (histone + 1 DNA loop only)	5B40_histone-protein-only.stl DNA-filament-2-circles.stl
Immunoglobulin IgG (mouse)	GCAA_MOUSE IGH1M_MOUSE	1igt* 1igy	 ImmunoglobulinG	IgG1-ready-2-print.stl.zip With pockets for magnets to simulate affinity in antigen-binding pockets

⁴ https://edutechwiki.unige.ch/fr/Bioinformatique_-_opportunités_pour_l'enseignement

tRNA	Not a protein!	4tna		4TNA-ready2print.stl
CFTR Causes cystic fibrosis when defective	CFTR_HUMAN P13569	5uak	 CFTR normal-form	CFTR-ready-to-print.stl
CRISPR-Cas9	Q99ZW2	5F9R	 Cas9 protein with zips for DNA and guide RNA	Cas9-ready-to-print.stl cas9-crispr-printed-with-DNAzip-small.JPG

Data were collected during a teacher training course (one afternoon), ($N = 12$ teachers, upper secondary level). We extracted evidence of teachers' perceptions through an anonymous online questionnaire that authorities administered at the end of teacher training (Satiscore©, designed for authorities to evaluate training programmes and not specifically for research). Questions included:

- Were the documents of good quality?
- Were the theory and practice balanced?
- Did the methods used enhance your learning?
- Did you meet your objectives?
- Did you develop new skills?
- Will you transpose new knowledge and skills into your practice?

While these data helped improve the CoAscenarios and offered qualitative evidence, statistical analysis would not make sense because of the small number of participants. These courses also raised awareness among teachers of the new ways in which biology research produces knowledge (DES A) and contributed to spreading the platform.

4 Observations

4.1 Pilot study (teacher training)

First, teachers were introduced to CoAscenario 17 and used it to choose a protein and compare the degree of similarity of proteins across different species, using research data from UniProtKB. Then, they visualised this similarity as highlights on aligned sequences. They then discussed this evidence of common origin and divergence. They compared this pattern across the different proteins chosen and observed the degree of similarity between a selection of species for each protein. Next, they used CoAscenario 20 to select proteins deemed relevant to their teaching. Finally, CoAscenario 21 guided them to convert the PDB structures to a 3D printer-compatible format (.STL), using the open-source software Chimera (Fig. 4). This was also used for adjustments such as removing irrelevant molecules or selecting nucleic or amino acids to print separately (e.g., CRISPR/Cas9 as an enzyme and the DNA on which it acts, Fig. 4). Teachers with no particular computer skills all succeeded in the technical stages, and the discussion focused on the uses in class. Responses at the end of the training indicate their interest and satisfaction, but only a few planned to introduce these practices in their classes at that time (before it became a requirement).



Fig. 4. From authentic data (PDB Structure, left) to 3D printing (middle) to tangible objects (right) – CRISPR-Cas9 with black zips representing DNA and guide RNA in this example.

4.2 Sample use in upper-secondary biology courses

This proof-of-principle example shows one possible implementation but should not be viewed as validation of the whole project. However, it illustrates how various forms of authentic data and A-models might be used in activities to express, confront and improve students' M-models. We present here a combination of the CoAscenarios 17, 20 and 21 that appeared most convincing to teachers who tried it in the pilot study (section 4.1). It addresses a difficult learning issue: student-available activities to understand evolution are badly needed.

The main steps in order of performance are outlined here:

A) Students working in pairs chose from a list of proteins relevant to their course or to their everyday life – still using CoAscenario 17 for technical procedure – then found its amino acid (a.a.) sequence in the UniProtKB database. They were asked to confirm whether all the different proteins studied by the class were indeed made from the same 20 a.a.

B) To compare the degree of similarity of proteins across different species, each group chose in the same database – still using CoAscenario 17 – their protein from different species, including human, mouse, rat, chimpanzee, cow, horse, a commonly studied fish (*Danio rerio*) and a few others at their leisure.

In order to visualise the similarities of these proteins and find evidence of common origin and divergence – using CoAscenario 17 – they used the alignment tool in UniProt. Once the alignment appeared, they selected an option to highlight the degree of similarity of a.a. across the selected species (Fig. 5).

C) They were instructed to observe this overall picture on all the computers of the class to see if a large degree of similarity across species could be found for all proteins. In computer classrooms, all screens are usually positioned such that they can be seen from the centre of the room.

D) The students focused on human and chimpanzee, and each group observed whether the proteins for these two species were very similar, but different for other species. The exercise was repeated for mouse–rat. A discussion was organised around the question: can these results be explained other than by common origin and divergence caused by mutations across time since the last common ancestor?

E) To study how conserved areas can be evidence of selection, students were asked to observe areas of their protein in which little or no change could be observed across species (Fig. 5, left).

Then, a second discussion was organised around the question: concerning these areas of your protein where little or no change in sequence was observed for all these species, can you find any other possible explanation than this: “individuals with mutations in this area have not been able to reproduce (or less) and their genes not transmitted”?

The discussion led to predictions linking conserved sequence to function and 3D structure.

F) In a further lab implemented in one class – using CoAscenario 20 – students searched for the corresponding 3D structure in PDB, converted it to a .STL file – using CoAscenario 21 – and transferred it to the teacher in order to have it printed as a 3D A-model of their protein (Fig. 5, bottom right). In two class, the proteins were provided.

G) Finally, to confront their naïve M-models and predictions from E), students compared the conserved parts of the a.a. sequence and the structure of the A-model (using a tool in PDB that highlights areas of protein structure in relation to the selected part of sequence and vice versa).

Printing different areas of the A-model with different colours (3D printers capable of this are getting increasingly affordable) could be an interesting improvement. The latest class discussed the example of the spike protein of SARS-CoV-2: some areas in which it has most mutated could be identified in the sequence and shown on the protein A-model.

While the data available do not allow definitive answers, they contribute to guide further exploration using the theory developed here and suggest teaching strategies to help students develop M-models and digital biology skills with authentic activities embodied in material objects.

The project delivered 25 tested technical-step CoAscenarios on an open platform addressing new approaches to building or validating knowledge and critical thinking. We have discussed here a selection that explores the educational potential of authentic data from freely accessible databases and research tools such as sequences and comparison tools, as well as 3D structures printed as tangible models.

The CoAscenarios are structured as lab working protocols detailing steps to extract data from the database to answer a question, but are as pedagogically neutral as possible to allow their use in very different teaching methods.

A proof-of-principle implementation in biology classes and in training courses with experienced teachers confirmed the tools' technical ease-of-use and the feasibility of their operationalisation in the classroom. They pave the way to new pedagogical strategies that ground learning of authentic practices in the use of material objects: A-models whose confrontation with sequence data helped students develop complex M-models (folding of proteins, lock-and-key model, protein–substrate, conservation of structures in evolution, selection in sequences, etc.). The observations carried out with these CoAscenarios in classrooms also confirmed pedagogical alignment with the educational reforms required: teaching how to use, understand and evaluate information and engage in and create in a digital society (DIP, 2018).

Our results highlight that framing the activities in terms of models and modelling processes (Schwarz, 2009) might not be easy, but it is well aligned with the interdisciplinary “maths and natural sciences” focus on models in the curriculum (CIIP, 2010).

Because these A-models are based on authentic research data, they might reveal the limits of usual classroom artifacts and interfere with certain school practices and students' expectations based on transposed knowledge presented as definitive – as Chevallard (1991) explains. Indeed, these pilot studies have shown that confrontation with authentic data reveals some limits of the models presented in class. This was visible, for example, when discussing the A-model of CFTR protein: students asked about the shape of the defective version that causes cystic fibrosis (as defective proteins are short-lived; their structure could not be established experimentally, it is not in the PDB database and therefore cannot be printed).

In another case, we found that as students manipulated A-models (e.g., spike protein and ACE-2 receptor, aspirin and Cox1) the shapes did not seem to fit as expected, which revealed the limits of Fisher's (1894) lock-and-key model as frequently used in class. This model only considers the shapes and the interlockings, but binding between a protein and its target (substrate, drug or other substance) depends on many other factors such as surface rigidity, charge, etc. (Sowdhamini, 1995). While this lock-and-key model can make sense in the classroom as a first step, it could limit progress towards a broader understanding of the molecular interactions of living organisms if models are understood as simply “true” as DT suggests is generally the case.

We have seen that scientific models can be relevant for some problems but cannot be simply true or false (Martinand, 1996). Schwarz and colleagues (2009) consider that a central goal of science education is helping students move from understanding models as illustrations of reality towards an artifact useful for discussing explanations that can help develop their understanding (Schwarz et al., 2009, p. 640). Indeed, our results suggest manipulating 3D-printed A-models can help towards this goal. In line with Gregorcic, Planinsic and Etkina (2017), we found tangible A-models can support discussion by students to improve their M-models towards a scientific approach to exploration of new phenomena.

Furthermore, in line with Hattie (2008) showing that students are motivated by knowledge gaps but put off by knowledge chasms, these CoAscenarios were shown in our example study to help students discover gaps in their understanding at times when help from the teacher is available, and when help can transform chasms into gaps that can be filled with the resources available.

The research background also led to a clear emphasis on authenticity – in the sense of activities using data from research rather than carefully selected, educationally polished data. Of course, authentic data are complex, and learners need help to learn how to handle them, but the world students will face is complex, and this is needed to address the official requirement of developing knowledge and skills needed to become competent, equal, responsible, empowered, active and protected digital citizens (DIP, 2018). The intention behind this choice was also to engage students in activities that develop deeper biological understanding, rather than the “classroom game” (Lemke, 1990), by using diverse A-models, to discuss complex ideas relating to their M-models (Gregorcic, Planinsic & Etkina, 2017). While these pilot study results suggest that using authentic research data can to some extent circumvent classic DT, Chevallard's claim that DT is inevitable and necessary puts into question its generalisability and calls for more research.

Since the goal of this project is to offer a structured repository of CoAscenarios, not to prove that the proof-of-principle use is better than a reference intervention, the exploratory study's limits such as the small number of subjects, a questionably representative sample, and so on, do not fundamentally question the project's relevance.

Proposing concrete CoAscenarios and possible uses of tangible 3D A-models that can be integrated into various teaching methods without clashing could help teachers with the required transition. Teacher training courses based on these CoAscenarios and tangible objects can help overcome conceptual obstacles or difficulties recognised by teachers seems to improve acceptance, and might be a first step towards higher-level learning objectives.

Concerning critical thinking skills (DES B), we have shown how these scenarios can help develop the domain-specific understanding of methods that is needed for CT (Facione, 1990), as they give access to evidence that digital biology

now offers to evaluate knowledge (Jiménez-Aleixandre and Puig, 2012). However, our teacher training programmes suggest that teachers first need a good understanding of this new biology before they focus classroom activities on CT learning goals. This suggests that as teachers become more familiar with digital biology, they might progressively use and adapt (Rabardel, 2003) these CoAscenarios to develop higher-level objectives such as CT skills. A design to develop critical thinking skills about recent neuroscience research tested in local schools suggests this sequence is necessary (that were tested in local schools, and proposed assessment methods (Lombard et al., 2020)). Jiménez-Aleixandre and Puig (2022) insist on developing designs and didactics focused on CT learning goals, such as educating critical citizens to face the post-truth world. Our results prudently suggest these CoAscenarios offer a reassuring step for teachers to engage in this exploration.

Finally, this project describes a theoretical perspective that can be used to guide future instruction, a repository of technical step-based CoAscenarios and concrete examples of 3D A-models to help teachers and authorities discuss the central place of digital biology and its educational implications. These CoAscenarios pave new roads to discuss integration into curricula of in-school use of digital tools for learning, thereby actively developing user skills among students and teachers (CIIP, 2018) which are required in Swiss schools. The recommendations of the NRC (2003) suggest many schools worldwide must address this change, too. This article offers a theoretical perspective: classroom-tested CoAscenarios that could stimulate discussion and could possibly be translated and adapted to diverse educational contexts. Their discussion might help to realise the potential opportunities and challenges discussed by Hansen et al. (2020), Beltrame et al. (2017), Howell et al. (2019), Koone (2022), and others.

Furthermore, our results and theoretical perspective agree with Hansen et al. (2020): more research is needed on the didactics of the transposition of digital biology, and experiments for exploring the use of new learning artifacts, such as 3D-printed models of proteins in classrooms, to model and develop deeper knowledge. On a final note, we do not suggest that molecular biology in schools should be replaced by digital biology, but that it can help to teach some difficult concepts – when it presents a clear pedagogical added value as general principles of local authorities require (DIP, 2018), and that these CoAscenarios are a contribution to help students understand, evaluate, engage and create in a digital society as this same document (DIP, 2018) requires – as probably is the case in many other educational systems.

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7 Supplementary Materials

Sample CoAscenarios (translated) 17 and 20: see attached PDF files.

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