Digital Learning Material for Experimental Design and Model Building in Molecular Biology

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CONTENTS

SCOPE

Designing experimental approaches is a major cognitive skill in molecular biology research, and building models, including quantitative ones, is a cognitive skill which is rapidly gaining importance. Since molecular biology education at university level is aimed at educating future researchers, we consider it important that students already start developing these skills during their studies. In general, cognitive skills can be acquired by practicing them in the context in which they will be applied. At the start of this project, only part of the students had the opportunity to practice designing experimental approaches, whereas most students did not obtain any practice in building models at all.

A general pedagogical approach in which students practice cognitive skills in their context of application is the cognitive apprenticeship approach. In this approach, students receive coaching while working on authentic problems. As students gain more experience, this coaching gradually fades or the task becomes increasingly complex.

Digital learning material enables different degrees of coaching, which is needed to implement cognitive apprenticeship-style learning. There are also other benefits of using information and communication technology (ICT), particularly if learning material is designed to consist of fairly self-contained, internet based, independent modules. For example, it is possible to generate experimental results based on the design decisions made by a student; to have students carry out numerical simulations of a quantitative model; and to handle differences in prior knowledge and working pace among students. Even though digital learning material seems attractive to realize apprenticeship-style practice for experimental design and model building in molecular biology, there are hardly any design principles available yet to exploit the opportunities the computer offers for this purpose. Developmental research is a type of research which is aimed at developing design principles for the construction of educational interventions by concurrently constructing prototypes which illustrate their application.

In this project, developmental research is employed to develop design principles to construct digital learning materials for university-level molecular biology education, which enables students to practice the design of experimental approaches and the building of models. Concurrently, prototypes are constructed that illustrate the application of these guidelines.

In chapter 1 an introduction is given in which molecular biology research and molecular biology education are described. Existing pedagogical guidelines and developmental research as a research approach are discussed as well.

The main part of this thesis consists of chapters 2 through 6, which describe the development and evaluation of the digital cases. These chapters contain materials of articles published or in press (mostly unchanged) and are therefore structurally independent. Each chapter describes (a) case(s) with a different structure. Where appropriate, the degree of coaching is decreased within a case.

Chapter 2 and 3 describe cases in which students practice the design of experimental approaches. Chapter 2 focuses on dealing with differences in prior knowledge. In chapter 3 a case is described in which an approach is applied which allows for a precise mediation of specific learning goals. Four additional cases were developed with a similar structure, but with increasingly complex tasks and a gradual reduction of coaching.

Chapters 4, 5, and 6 describe cases in which students practice model building. Chapter 4 describes a case in which students are guided to build a model step by step. The model building cycle they follow was developed based on expert analysis and historical data.

Chapter 5 describes a case in which students are again guided to build a model step by step according to the same model building cycle as is described in chapter 4. However, this case contains an additional element, namely the use of numerical simulations to facilitate the building of the model. The chapter consists of two parts. In the first part, the design considerations are described with respect to the current developments in research in the molecular life sciences and our vision on how education should be innovated to deal with these developments. In the second part, more general pedagogic considerations are discussed and the case and its evaluation are described in detail.

Chapter 6 describes a case which contains another complexity for the students when compared to the case which is described in chapter 4. Students are no longer guided step by step, but have to organize their model building approach themselves.

Chapter 7, finally, summarizes and discusses the yield of the research performed.

For each chapter (paper) a specific demo-site was made. It is, however, also possible to access all cases discussed via a web page which was made for this thesis: http://mbedu.fbt.wur.nl/demo_thesis

CHAPTER 1

Introduction

In this project, developmental research is employed to develop design principles to construct digital learning materials for university-level molecular biology education, which enables students to practice the design of experimental approaches and the building of models. Concurrently, prototypes are constructed that illustrate the application of these guidelines.
In the following sections of the introduction we will motivate this aim and provide additional background information.

MOLECULAR BIOLOGY RESEARCH

Molecular biology is a discipline which evolved from biochemistry after the discovery of nucleic acids as the basis of genetic information. In the fifties and sixties, research was focused on the structures of the various nucleic acids as well as on the molecular mechanisms involved in the translation of information at the nucleic acid level into protein. During this period, research was especially focused on "simple" organisms like viruses and bacteria [1].
With the development of recombinant DNA technology, it became possible to change genes very precisely and to study the effects of these changes. It also became easier to study molecular mechanisms in multicellular organisms, such as mechanisms which control growth, differentiation and pattern formation. Such studies required the integration of different disciplines, such as genetics, biochemistry, cell biology and bioinformatics (molecular life science). Therefore, a plethora of experimental approaches is used in the molecular life sciences. Such experimental approaches often consist of several techniques. For example, specific transgenic organisms are often created and studied in order to elucidate the effect of specific genetic changes at the organism level. In order to create such transgenic organisms, several techniques need to be combined, such as techniques to enter foreign DNA into host cells, to determine whether the foreign DNA is indeed integrated in the host genome, to determine expression levels of different genes, etc. Designing experimental approaches by combining different techniques is therefore an important skill in the molecular life sciences.
Currently, we are in the functional genomics period and information of all proteins encoded by genomes is being obtained. Often the sets of genes involved in a specific process are known. Through the use of different experimental approaches, the interplay of the involved proteins in controlling such processes is elucidated. The different interactions are often

described in a qualitative model. Such a model depicts, for example, whether a certain protein induces or inhibits the expression of a specific gene; it does not give a quantitative relation between the concentration of the protein and the magnitude of its effect. Building qualitative models is therefore also an important skill in the molecular life sciences. A research topic where the identification of the genes involved has occurred relatively early, and where different qualitative models which include these genes have already been formulated based on additional functional experiments, concerns patterning during the early development of the fruit fly *Drosophila*.

With the development of various omics (genomics, transcriptomics, proteomics, metabolomics etc.) we will obtain information about all the components of a cell. A major new challenge in the molecular life sciences will now be to investigate by which mechanisms these individual components determine the properties of a module (ribosome, spliceosome etc.), organelle, organ, and organism. A growing community of researchers believes that this requires quantitative models as well as methods to analyze these models and their behavior, such as numerical simulations. The larger emphasis on quantitative models in particular, will also make the molecular life sciences more predictive instead of primarily descriptive in nature [1-4]. Building quantitative models is thus a skill which is rapidly gaining importance in the molecular life sciences. *Drosophila* development is also an example of a research area where an increased focus on quantitative models can be observed.

MOLECULAR BIOLOGY EDUCATION

Since designing experimental approaches is an important skill in research, and model building, including quantitative model building, is rapidly gaining importance, we believe that molecular life science students should acquire some experimental design and model building skills during their study. In general, in order to acquire cognitive skills, students need to practice these skills in the context in which they will be applied [5,6]. We restricted our analysis of the existing education to courses in molecular biology and looked at how much practice students obtain in experimental design and model building.

At the start of this project, undergraduate molecular biology education at Wageningen University consisted of lectures and practical courses. Furthermore, at the end of their

undergraduate phase, students usually participate in actual research in small groups during several weeks.

The design of experimental approaches is practiced to some extent during some of the lectures. However, it is usually difficult to activate more than only a part of the group, partly because students think about design questions at very different paces. Furthermore, different students may think about a design problem along different lines, which means that different students may require different kinds of feedback. Due to time considerations, and also to ensure that other students do not drift away from the subject, a lecture does not offer adequate possibilities to provide each student with such specific feedback. Thus, even though there is some practice in the design of experimental approaches, only part of the students actually benefit from this practice.

During most practical courses, students follow predetermined protocols, which introduce them to different techniques. Occasionally, students participate in some experimental design themselves. They calculate, for example, how a specific dilution can be made, draw up pipetting schemes etc. However, they do not participate in the design of the approach as a whole. In fact, students are often so preoccupied with the execution of individual operations, that they even fail to survey the approach they follow. Thus, even though students engage in some experimental design to specify the precise execution of single experimental steps during practical courses, they do not practice the design of experimental approaches as a whole.

When students participate in a research project for a short time at the end of their undergraduate phase, they naturally follow an experimental approach. However, given the short time span of this research, experiments need to be started relatively fast, which limits the students' involvement in the design of the experimental approach.

Thus, at the start of this project, only part of the students obtained some practice in designing experimental approaches. Many others did not actually practice it at all. It is therefore not surprising that lecturers and supervisors of MSc projects complained about students' poor experimental design skills.

For model building, the situation was even worse: the building of both qualitative and quantitative models as well as building quantitative models was mostly neglected during undergraduate education. Therefore, students could not be expected to possess good model building skills after having finished their studies.

The situation at Wageningen University described above appears to be representative of other universities. Much education still consists of traditional lectures and practical courses [7-10]. Furthermore, it is also acknowledged elsewhere that students have problems to determine which technique can be used to answer a particular question [11] and it is broadly considered to be a challenge to introduce more model building, especially the building of quantitative models, into life science education [8,12].

TOWARD A PEDAGOGICAL APPROACH

Cognitive apprenticeship

As was mentioned before, in order to acquire cognitive skills, students need to practise them in the context in which they will be applied [5,6]. A general pedagogical approach in which students practice cognitive skills in their context of application is the cognitive apprenticeship approach [13,14]. In this approach, students work on authentic problems. While working on these problems, coaching is offered to the students. As students gain more experience, this coaching gradually fades or the task becomes increasingly complex.

Working on authentic problems increases the probability that future similar problems can be solved easier by using analogies [15,16]. A solution to an analogous problem may, for example, only require some minor adjustments in order to solve a new problem. Even if the analogy is less strong, certain aspects of a formerly encountered solution may still be helpful to solve a new (sub)problem. In molecular biology research analogies are used extensively, as was shown by studies of lab meetings in molecular biology research laboratories [17,18]. When students design experimental approaches and build models, they can acquire a range of different potentially useful analogues. For experimental design, these include, for example, general experimental design strategies, the final experimental approach, single techniques which are used to address sub-questions, including reasons why alternatives are less suitable, and methods to interpret experimental results. For model building, these include, for example, general model building strategies, the final model which is designed, single elements of the final model which can also be part of models for different systems, alternative hypotheses to explain phenomena, general experimental approaches to test certain hypotheses, and methods to interpret experimental results with respect to a model. When designing experimental

approaches and building models, both the operational semantics and the symbols which are commonly employed, can be learnt as well. With regard to the design of the cases, the challenge is to chose the topic in such a way that it is representative not only with respect to the final experimental approach or model, but also with respect to the techniques used, the single elements in a model, etc.

Digital cases

Digital learning material enables us to realize different degrees of coaching, which is necessary for apprenticeship-style learning [13]. Digital learning material also has a number of other benefits with regard to the implementation of cognitive apprenticeship for experimental design and model building in molecular biology. Digital learning material can readily present, or even generate, experimental results. Interpreting such results is essential for students in order to build models and to evaluate whether they have designed their experimental approaches in a useful way. Furthermore, in order to introduce students to quantitative simulations, digital learning material naturally offers the opportunity to have students perform real simulations themselves. Moreover, digital learning material offers the possibility to present difficult aspects of certain molecular mechanisms with animations or simulations, which may support understanding of these mechanisms. Lastly, differences in prior knowledge among students can be overcome to some degree by making an adaptive system and/or by providing direct links to information which is required at a certain design stage.

If the digital learning material is designed to consist of fairly self-contained, independent, web-based modules, a number of additional requirements can be satisfied. First, if the material is delivered via the internet, it is relatively easy to include some practice in working with databases which contain sequence data and which are accessible via the internet. Using such databases is becoming increasingly important for the design of experimental approaches. Second, if the material is designed in such a way that it is self-contained and internet based, students can work at their own pace and can also work at home. This could enable a fairly large amount of flexibility with respect to differences in working pace among students. Third, if the material consists of independent modules, teachers or students themselves can make a

selection of modules which best suit their interests or expected level without actually having to use all cases. However, this does not imply that the modules do not have a preferred order based on their contribution to the acquisition of skills.

Thus, we decided to apply cognitive apprenticeship and develop digital cases in which students are coached to address authentic research questions by designing experimental approaches and building models. Each case forms a fairly self-contained, independent web-based module. In order to ensure that the cases are fairly self-contained, it is necessary to put a relatively strong emphasis on the implementation of different kinds of feedback. This feedback is necessary to help students draw proper conclusions about the usefulness of their decisions. It can also be useful to help them make subsequent decisions.

Coaching within cases

When coaching is implemented, one should make sure that students are challenged sufficiently, without being asked too much of. Moreover, the coaching should be aimed at engaging students in activities which enable them to learn to perform the task independently and relatively fast.

To our knowledge, there are no specific design principles available to structure coaching for practice of experimental design and model building in molecular biology on the computer at university level. Since it may be possible to extract design principles from existing digital learning material [19], we searched for such digital learning material. Several applications were found which focused on experimental design, including some visually very attractive ones (examples: [20-22]). However, they have students focus mainly on individual techniques and do not (or hardly ever) require them to combine techniques themselves. Actually, we did not encounter any material at university level which was explicitly aimed at designing whole experimental approaches for molecular biology. For model building in molecular biology at university level, we encountered material which stimulates students to make qualitative models for the action of different bacterial operons [23]. However, students have to use experiments which are more typical of biochemistry than of molecular biology. Furthermore, the material does not generate feedback to students (except for simulated experimental outcomes). It is therefore probably not self-contained and thus not suitable to extract design

principles for the implementation of coaching in self-contained learning material. To our knowledge, there are also no design principles available to realize practice in designing experimental approaches and building models for molecular biology at university level without the involvement of the computer.

In other areas of biology education, research has been performed in which design principles were developed to realize practice for research-like reasoning activities [24-27]. This research stresses the importance of analyzing discipline specific features of a scientific task. Furthermore, it is recommended to design instruction around key models in the discipline under study [25,26], which is in line with what was mentioned above about the selection of topics. However, the actual methods which were developed, do not seem to be very suitable for this project for a number of reasons: they concern disciplines (e.g. evolution) which, in contrast to molecular biology, do not lend themselves to easy experimental manipulation [24,25]; they stress the exploitation of prior knowledge instead of the use of experimental results [27]; they focus on a broader range of learning goals, including, for example, the acquisition of presentation skills [25,26]; and they do not concern the development of fairly self-contained digital learning materials [24-27].

When introducing students to quantitative models, we use computer simulations. At first sight, design principles from the field of scientific discovery learning with computer simulations might seem applicable. In scientific discovery learning with computer simulations, many students display floundering behavior unless some extra measures are taken. Combining simulations with various instructional support measures can help to overcome these problems [28]. These instructional support measures, however, are not aimed at learning how to use simulation as a scientific research method. In scientific discovery learning with computer simulations, students often have to infer, through experimentation, characteristics of the underlying model, which is unknown to the students[28,29]. This is different from the way scientists employ simulations, since they generally have access to the underlying model and often even built it themselves. Therefore, specific design principles to structure coaching for scientific discovery learning with computer simulations are of limited use to structure the coaching for practicing the use of simulations in the way molecular biology researchers can use them in their research.

Thus, there is a lack of specific design principles to structure the coaching of fairly self contained practice in the design of experimental approaches and the building of models for molecular biology. Developmental research is a type of research which is aimed at developing such design principles by concurrently constructing prototypes which illustrate their application [19,30-32].

DEVELOPMENTAL RESEARCH

In developmental (or development) research, the researcher develops an educational intervention experimentally [19,30-32]. An educational intervention can comprise products, programs, materials, procedures, scenarios, processes etc. Developmental research consists of an iterative process of designing, testing and adjusting an educational intervention. The product of developmental research consists of prototypes and design principles. The prototypes can serve as inspiration for other educators and the design principles should help others to develop comparable interventions. The ultimate aim of developmental research is not to test whether theory, when applied to practice, is a good predictor of events. Instead, the major knowledge to be gained is in the form of design principles, which have a heuristic nature and serve to support designers in their task. Developmental research avoids the problem that everybody has to invent their own wheel when putting general pedagogical theories into practice. On a fairly abstract level, developmental research reduces the uncertainty of decision making in designing and developing educational interventions [19,30-32].

The way developmental research is carried out depends on the exact situation. Actually, methodology is still being discussed in literature [19,30-32]. Here we have developed digital cases and explicated the most important design considerations. The material has been and will be tested in regular courses. During the tests, different data are collected. These include observations of supervisors, tracking data which indicate which answers students gave to questions in the cases, answers on evaluation forms which will be handed out, and answers to exam questions. During the second half of the project, audio-tapes of students working with the material are employed as well. These data are used to improve the material and to test whether learning goals have been achieved.

In summary, this research should lead to tried and tested learning material for experimental design and model building in molecular biology, principles for the design of such material, and more specific directions for further research.

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CHAPTER 2

Web based learning support for experimental design in molecular biology: dealing with differences in prior knowledge

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ABSTRACT

An important learning goal of a molecular biology curriculum is a certain level of proficiency in experimental design. Currently, students are confronted with experimental approaches in textbooks, in lectures and in the laboratory. However, most students do not reach a satisfactory level of competence in the design of experimental approaches. This paper describes the development of a web-based application which supports the acquisition of the relevant skills. The application consists of an activating part and a library part. In the activating part, the student is presented with a biological question which must be solved experimentally. Therefore, the student has to make a set of coherent choices, execute steps in an experiment, and interpret the experimental results. Furthermore, a DNA sequence has to be analyzed using web-accessible databases. The library consists of learning objects which present essential general information about techniques and biology. A test with a small group of students yielded very promising results. However, a test on a larger scale revealed that students may encounter problems if a large part of the information in the library is new to them, or if they hold misconceptions about this information. Therefore, additional learning material was developed which allows students to become acquainted with the general information in the library which they do not possess yet, or to discover their misconception respectively. In combination with a number of further improvements of the original case, this additional learning material solved the problems encountered, and the material is now successfully being used in a regular recombinant DNA course.

INTRODUCTION

The Food and Biotechnology (FBT) program aims at the creation of a rich body of digital learning material for university curricula which are related to food science and biotechnology. The FBT program was initiated at Wageningen University in September 2000. The program focuses on web based learning support for those learning goals where digital learning material is expected to have a clear added value. One of the FBT projects aims at the development of digital learning material for molecular biology. This paper describes the first stage of this project.

One of the important learning goals of a molecular biology curriculum is a certain level of proficiency in designing an experimental approach. This involves the application of different techniques. Students are usually capable of understanding how these different techniques work, but they have difficulty combining them in a useful way, and judging whether they are suitable to find an answer to a particular question. Moreover, students often do not realize that experiments are performed with biological systems. Consequently, they do not use their knowledge of biology when designing experimental approaches, even though this is essential for the design of a useful approach. This insufficient application of biological knowledge can also be observed during the analysis of experimental outcomes.

The above-mentioned problems in experimental design may be inherent in the current educational setting. At present, students are confronted with experimental approaches in textbooks, in lectures and in laboratory courses. However, each of these formats has its own drawbacks. Textbooks do describe many experiments and approaches, but this is not sufficient for students to learn to choose techniques and to schedule operations. One of the problems is that students usually focus on the mechanisms behind the techniques, thereby losing sight of the uses of such techniques. In a lecture, on the other hand, more weight can be put on the actual design of experimental approaches. However, it is very hard to involve more than a limited number of students individually in such a way. Furthermore, even the students who do get involved, can hardly obtain personal feedback, due to considerations the lecturer has to take of the other students as well as the time allotted for the lecture. Finally, in a laboratory course students have little freedom when they choose and schedule operations. Moreover, they easily become preoccupied with the practical skills they still lack and, as a result, they even lose the overview of the specific experimental approach which is being applied. Thus, the teaching of more general aspects of designing experiments is virtually impossible. The possibilities of computer based learning support may offer a solution to the above-mentioned problem. Apart from the well-known argument that computer based learning support makes it possible to activate each student individually and generate personal feedback, many of the experimental results in molecular biology experiments are photographs or sequences, and can thus be represented digitally. Moreover, the processing of results in molecular biology experiments requires computers and web access. Recently, many DNA and protein sequences have become available in web-accessible databases. In current molecular

biology research, using these databases is becoming increasingly important for the design of experimental approaches and the interpretation of experimental outcomes. Therefore, learning to use information from databases has been added as a new learning goal in undergraduate courses. For an effective use of the available data, database searches have to be performed, and the data have to be combined with biological knowledge and knowledge about molecular biology techniques.

Thus, web-based learning support should improve the following skills:

- designing a basic experimental approach by selecting and combining suitable techniques;
- performing a database search;
- integrating information from biology, techniques and database searches.

These skills can only be improved if sufficient general knowledge of techniques and biology can be applied. Therefore, students also need to be presented with knowledge they have not mastered yet. This new material has to complement the lectures. Furthermore, as the lectures may change from time to time, the material should consist of modules which can be combined flexibly. It should also be possible to use these modules independently from the lectures.

In this paper we describe the development of the first module, including its evaluation. The paper concludes with a discussion of the methods we applied to teach the above-mentioned skills .

THE STRUCTURE OF THE SITE

In order to offer students the opportunity to practice the necessary skills, they are offered a case (see demo site) in which they have to design an experimental approach to solve a real (but basic) biological problem. In this way, the theory is placed in the proper context. This may not only be favorable for retrieving the theory from memory in a similar context [1], but it also makes its relevance more apparent, which may motivate students [2]. Moreover, the general information which is needed to successfully go through the case becomes available to the students just when they need it. This just-in-time information presentation is, amongst others, recommended by the Four Component Instructional Design model [3], which gives guidelines for teaching complex cognitive skills. Some general information may be needed several times when going through the case. In order to have this information in one place, we constructed a

library (see demo site) which contains all the necessary general information. This library consists of independent, self-explanatory learning objects. This setup enables students to study only a selection of the learning objects, and no specific study order is required. However, if preferred, a student could also study all information in the library before starting with the case. Furthermore, the library ensures that students with varying amounts of prior knowledge of single techniques and biological aspects can, in principle, complete the case.

THE LIGHT INDUCTION CASE

In the light induction case, the student has to isolate a gene which is induced in plants upon light exposure, and analyze its DNA sequence. The student is guided through the case by multiple-choice questions to prevent him or her from becoming lost and frustrated. Sometimes, a choice between different techniques is offered. In this way, the student is stimulated to actively think about the possibilities of the techniques, which is essential for the design of an experimental approach.

After choosing a technique, the student is immediately confronted with the experimental result. This result has to be interpreted in order to find out whether applying the technique was useful or not. Thereby, it is essential to take biological aspects into account. This is illustrated by the screen dump from the demo site shown in figure 1. This shows the screen the student sees after choosing to analyze differences in mRNA concentrations on an RNA gel on which total RNA is loaded. This choice has led to a useless result because mRNA cannot be visualized with this method. This is partly due to the fact that mRNA, the RNA which needs to be studied, forms only a minor fraction of total RNA. Thus, it is necessary to use knowledge about biology to decide whether the technique is useful. The student will discover that the technique was not useful after selecting a band for analysis.

This format, in which students are confronted with a result that has to be interpreted, has several advantages. Firstly, it is probably easier for students to remember whether a technique is useful in a certain context or not, if they discover this themselves, rather than if someone simply tells them. Secondly, if students do not use their biological knowledge, they are automatically confronted with the consequence. This probably makes a stronger impression than if it is pointed out to them during a lecture. Thirdly, a picture of an experimental result implicitly

contains a lot of information about the precise use of a technique. By interpreting the results, students are stimulated to focus on and give meaning to these results. These include results of techniques which were not useful and which are usually not shown in a textbook. As people tend to have a good memory for meaningful interpretations of an image [1] and easily make inferences from them [4], the students are in this way again stimulated to remember the precise use of a technique. Sometimes it is also necessary to interpret the result in order to continue with the procedure.

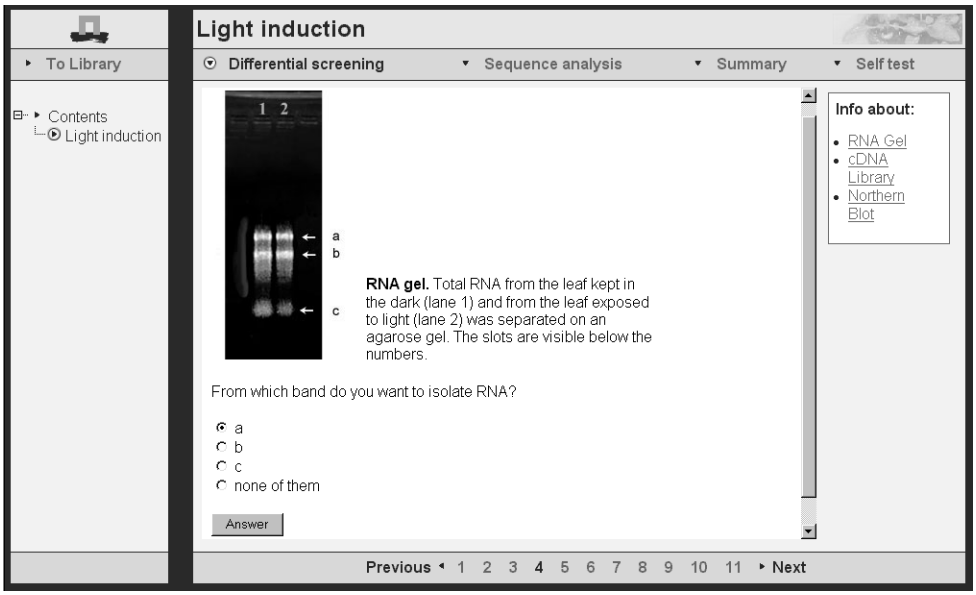

Figure 1. Screen dump of a screen a student sees after selecting a technique. In order to be able to interpret this result, the student needs to use his biological knowledge. Only after a correct interpretation of the result, will it become clear that this technique was not useful in this context.

The gene can eventually be obtained by applying a method which is called "differential screening". This method was chosen for several reasons. Firstly, the problem is an example of a very common research question in molecular biology. In many instances, genes which are specifically induced under certain conditions have to be identified. Even though differential screening is a relatively old method, it was chosen because it clearly illustrates the problems

involved. Moreover, more advanced methods are still largely based upon the same principles. Therefore, understanding the differential screening method may facilitate the understanding and proper application of technologically more advanced methods, based on an analogy process [1].
After isolating the desired gene, the DNA sequence of the gene has to be analyzed (see sequence analysis section on the demo site). The first sequence to be analyzed is not complete, as is usually the case in practice. Another reason why this partial sequence is offered, is that students have to discover for themselves that it is not complete. Therefore, experimental findings have to be combined with knowledge of biology. The student has to perform an additional experiment to obtain the complete sequence. This sequence has to be analyzed by performing a database search. In order to perform this search, it is again necessary to actively use biology knowledge as well as knowledge of the applied experimental techniques.
The interactive part of the case is followed by a summary. This summary contains overview pictures, as well as information which explains why applying a technique in the given context was useful or not. In principle, the summary contains all the necessary theoretical information. Thus, the interactive part should support the training of extra skills, whereas the theory can be found in the summary.
Finally, the student is presented with a number of multiple-choice questions, which serve as a self-test.

THE LIBRARY

The library contains general information which is needed to go through the case, so that the material can, in principle, be used by students with varying amounts of prior knowledge. The library contains information about techniques, database searches and processes which take place inside cells. As mentioned before, the library contains independent and self-explanatory learning objects.

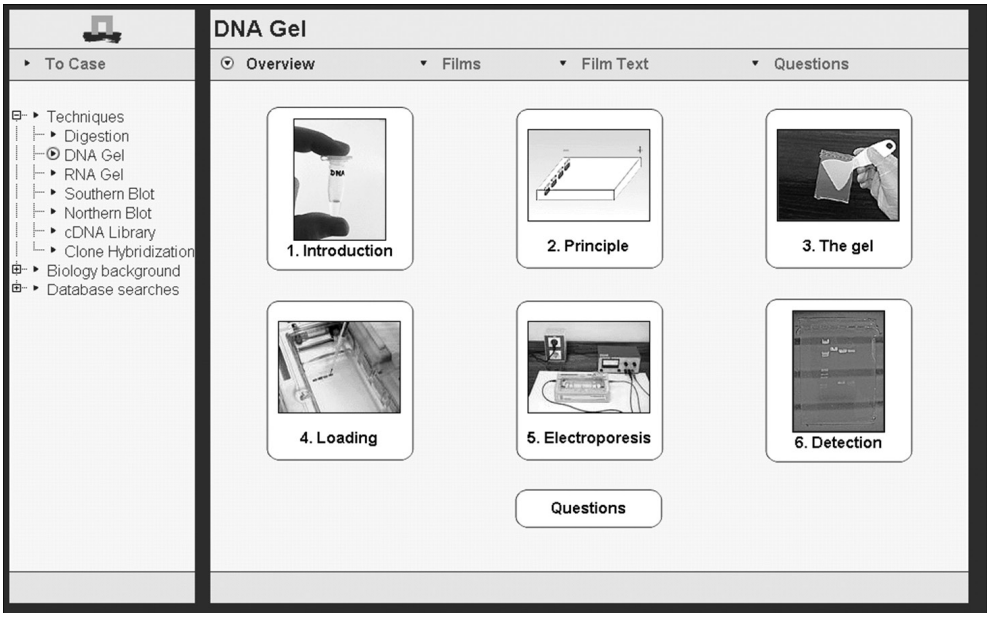

Figure 2. Typical introductory screen for a technique in the library. Pictures give an impression of the content of the movies. A student can click on a picture to start a movie. Questions are available as well.

The explanation of a technique consists of 2 to 6 movies, because of our previous positive experiences with these types of movies. Figure 2 gives a screen dump (see demo site) of the introduction page for the technique, which is labeled DNA gel. The page contains pictures which give an impression of the content of the movie. The student can click on a picture in order to start a movie. The movies do not take more than 2 minutes, and consist of spoken text supported by photographs, annotations and animations. As stated before, when designing experimental approaches, it is essential to know the different purposes of a technique. Therefore, this is stressed in the first movie. The second movie explains the principle of a technique. The explanation of some techniques also highlights specific steps of the technique in order to give the student an idea of its complexity and scale. A movie showing a typical experimental result is sometimes added as well, which makes it easier for the students to interpret results on their own afterwards. The script and the still images of each movie are available. Extensive experience with the use of movies at Wageningen University has shown

that some students prefer to view the text if the pace of the movie is too slow for them. The written text is also better for students who just want to scan through the theory quickly [5], for students whose mastery of the English language is insufficient to understand the audio, and also in situations when there is no sound available. Besides the movies, each learning object contains a few short questions to let the student internalize the newly acquired concepts. If the techniques are similar, the same movies are used to explain identical steps. If applicable, this is clearly indicated.

The learning object on the database search contains some text to explain the background, as well as a simple simulation. In this simulation a search can be performed in controlled circumstances. If the student follows the instructions given at the top of a page, he or she will stay within the simulation and receive new instructions. However, it is also possible to leave the simulation and find out what would happen if another strategy were followed. This learning object also contains a number of multiple-choice questions.

The learning objects which deal with the general information on biology contain schematic drawings, tables, etc. in which the most important information is summarized. These objects serve to refresh the student's memory, and are not meant to introduce new information.

INITIAL EVALUATION RESULTS

Initially, the material was evaluated with a group of 6 volunteers. This evaluation was carried out to identify ways to improve the site. By testing websites with a small number of users, most usability problems should become clear [6]. The results of this initial small-scale evaluation were very positive: the students highly appreciated working with the material and a comparison of the pre- and post-test revealed that the material was indeed instructive. The evaluation also yielded ideas for improvements. Most importantly, students had problems performing the database search. Therefore, the above-mentioned simulation was added to the library. Further minor improvements include the addition of a clarifying figure, the rephrasing of some of the feedback, and the removal of a number of spelling mistakes.

Subsequently, the material was used in a regular recombinant DNA course by 41 students. This evaluation yielded less positive results, possibly because in a regular setting students work with the material in a different way than in an evaluation setting, and also because some problems

only become apparent in larger groups, where there is less supervision per student. Answers on evaluation forms gave some indication that students were not convinced that they had learnt enough (Table 1). Indeed, only about 40% of the students answered the most important exam question about the material sufficiently well (Table 1), whereas usually roughly two thirds of the students answer exam questions sufficiently well. Based on process observations and analysis of the complete exam, a number of problems were identified. Firstly, the exam results showed that students still held relatively many fundamental misconceptions about individual techniques. The material may indeed not be suitable to eliminate misconceptions: students who hold misconceptions are usually not aware of them and therefore they may think that they already know the theory. As a consequence, they do not study the respective library objects. There also seemed to be some problems with students who had very limited prior knowledge of the general theory in the library. On the one hand, the supervisors had the impression that some of them studied the theory only superficially, possibly because studying a large amount of new theory is not very motivating, since it may give the feeling that it impedes progress through the case. On the other hand, even students who studied the theory thoroughly still had problems applying this knowledge in the case, probably because the theory itself is conceptually rather difficult, and its application in the case is not straightforward. Lastly, the steps which were taken in the case appeared to be too large for a part of the students.
Thus, evaluation in a regular course revealed that adjustments of the material were still necessary.

IMPLEMENTED CHANGES

As a result of the initial evaluations, a number of changes were implemented. Most importantly, an additional introductory element was developed, which was aimed at: a) eliminating students' misconceptions in prior knowledge if present; b) complementing students' prior knowledge of individual techniques if necessary; c) introducing them to basic cloning strategies. Even though this element is not a case in the sense that students address a certain question, we will still refer to it as the "basics case" here. It consists of two sections. In the first section, students have to answer a multiple-choice question about each of the techniques they should eventually be familiar with. These questions are formulated, based on

the conceptual mistakes which were encountered in the exams. If a student does not answer such a question correctly, he or she is stimulated to study the library object about the respective technique. Furthermore, he or she has to answer several additional questions about the same technique before being able to progress with the initial question about the next technique. If students answer such an initial question correctly, they can choose themselves whether they want to study the respective library part and answer the additional questions, or whether they want to continue with the next technique immediately. Thus, this section should eliminate the most common misconceptions and it should fill students' knowledge gaps of single techniques by having them focus specifically on those techniques which are not clear yet. In this way, students who already possess sufficient general knowledge of techniques should not become bored, since they can progress through this section very quickly, and even such a fast progression may still be useful to refresh their knowledge. In the second section of the basics case, students have to indicate which approaches can be used to address four different general cloning problems respectively. By introducing students to these basic cloning procedures, they should be better prepared to design the more sophisticated cloning strategy in the light induction case.

As a result of the initial evaluations, the light induction case itself was adjusted as well. This was done in such a way that students could progress in smaller thinking steps. Lastly, the case was offered later in the course, when students are already more familiar with experimental procedures in molecular biology in general.

SUBSEQUENT EVALUATION RESULTS

After the implementation of the changes described above, the material was used by a group of 22 regular students. The implemented changes seem to have been really useful. Answers on evaluation forms suggest that students were able to work better with the case. This was confirmed by the exam results, which are now satisfactory (Table 1). Supervisors also had the impression that students understood better what they were doing. Furthermore, they indicated that with the material it was easier to cope with the (sometimes large) differences in prior knowledge among students. In combination with the fact that the students liked working with

the material (average score of 4.3 on a 1 to 5 scale on the evaluation forms), we were satisfied with these evaluation results.

	Scores before adjustments	Scores after adjustments
Question of the evaluation form	Average, scale: 1 (disagree completely) - 5 (agree completely)	
By working with the "light induction" case the principle of differential screening became clear to me	3.4 (N=41)	4.1 (N=22)
Despite the fact that I managed to get through the "light induction" case, I did not understand what I was actually doing.	2.7 (N=41)	2.2 (N=22)
Exam Question*	Percentage of students who gave an answer that was good enough	
Plant pathogens like the fungus *Cladosporium fulvum* (causative agent of mildew disease) induce upon infection of tomato leaves the expression of a number of specific plant genes that play a role in the defence against the fungus. Describe in detail an experimental approach for isolating such tomato "defence-genes".	39% (15 out of 38 passed)	65% (13 out of 20 passed)

* This question is the one that was asked on the exam after students had used the adjusted material. The exam question which was given after students had used the original material, is basically the same, but another pathogen was mentioned.

Table 1. Comparison of evaluation results before and after the implementation of the basics case and other changes.

In order to obtain more insight into how students used the basics case, a number of questions concerning this issue were added to the evaluation form. The results are shown in Table 2. As can be concluded from these results, most students considered the basics case to be useful to refresh their knowledge of techniques, to fill gaps in their prior knowledge, and to better prepare themselves for working with the light induction case. Furthermore, two thirds of the students indicated that they discovered that they still did not fully comprehend some of the techniques which they thought they already understood earlier. This suggests that the basics case was also useful to eliminate misconceptions. Thus, even though the basics case has a very simple structure, it still appeared to be very useful to help overcome many of the earlier problems.

Evaluation Question	Number of students who disagree (1+2)	(3)	Number of students who agree (4+5)	Average score
For me, the "basics" case was useful to refresh my knowledge of cloning techniques	0	5	16	4.3
Without the "basics" case, it would have been much harder to go through the "light induction" case	5	0	17	4.0
Because of the "basics" case, I discovered that I still did not completely understand some of the techniques of which I thought I already understood them earlier.	5	2	14	3.7
For me, the "basics" case was useful to fill up gaps in my prior knowledge	3	4	15	3.9

Table 2. Use of the basics case for different students.

FINAL REMARKS

A web-based application which supports learning experimental design in molecular biology has been developed. After some adjustments in the original design, the web site is now successfully being used in the course "Gene Technology" at Wageningen University. Currently, the demo site is accessible worldwide for review.

The ultimate goal is that students be able to design experimental approaches in new, unfamiliar situations. The application confronts the students with situations and experimental results, which forces them to actively use their knowledge of biology while designing a new approach. It is expected that students will eventually become used to applying their knowledge while working with molecular biology techniques.

Learning how to design an experimental approach while addressing a new question in molecular biology, is supported by the website in three ways. Firstly, the differential screening method which students use in the case, can be used to address similar biological questions. Secondly, the differential screening method can also serve as a schema when designing an analogous, technically more advanced approach. Finally, the application forces the student to focus on the precise use of each technique in multiple ways. It is essential that the student becomes very much aware of the exact use of a technique. Thus, it should become easier to design new approaches using the same techniques. Moreover, students will probably gradually learn to focus more on the use of a technique when studying new ones in the future. This may even lead to a better performance for designing approaches which consist of these new techniques as well.

In addition to the above-described material, several additional cases are being developed, covering the production of transgenic organisms. The research is progressing towards a qualitative simulation environment which will present the consequences of a student's choice in terms of experimental results based on programmed rules. In the perception of the student, the number of different options will be almost unlimited. On the one hand, this offers the students a more realistic situation and more opportunities to test their own ideas, but on the other hand students could easily flounder and show unstructured behavior [7]. The main challenge for the future will thus be to embed the simulation of experiments in an environment which guides and supports the students.

ACKNOWLEDGEMENTS

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Demo site: http://mbedu.fbt.eitn.wau.nl/edmedia_demo

CHAPTER 3

Web Based Learning Support for Experimental Design in Molecular Biology: a Top-Down Approach

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ABSTRACT

The attainment of a certain competence level in experimental design is an important learning goal of a molecular biology curriculum. Currently, undergraduate students are confronted with experimental approaches in textbooks, lectures and in the laboratory courses. However, most students do not reach a satisfactory level of competence in the design of experimental set-ups. This paper describes the development of web-based cases which offer students the opportunity to practice their design skills while addressing realistic research questions. Even though this may seem obvious, we did not develop a virtual lab which is as realistic as possible. In such a lab, students automatically focus on issues beyond the scope of an undergraduate course, which may hamper the acquisition of the essential basic concepts. Instead, an approach was chosen in which students first have to design the overall procedure, before working out the individual steps. Especially during the first stage, students' control was limited, in order to shield them from practical complexities. The material was evaluated in a regular educational setting and it already fulfils most of the requirements we initially set. In the discussion, the developed format is compared with those used in other disciplines.

INTRODUCTION

In line with the Bologna declaration [1], Wageningen University converted its education to the BSc-MSc system. Therefore, educational programs had to be revised. We took this opportunity to reflect on a number of learning goals in the molecular biology curriculum. One of these goals is the attainment of a certain level of competence in designing an experimental approach. This implies the application of various techniques in order to address a specific research question. After finishing their undergraduate courses, our students usually know how different techniques work. However, they have difficulties selecting a set of appropriate techniques to solve a specific problem. Furthermore, working out techniques in more detail and tailoring them to specific situations, as well as combining different techniques, appears to be a problem. Lastly, students do not accurately use their knowledge of biology when designing an experimental approach. Thus, although our students do succeed in acquiring knowledge of different techniques as well as biology during their undergraduate courses, they

have difficulties in applying this knowledge actively for the design of experimental approaches.

The indicated problems in experimental design may be inherent in the traditional educational setting, in which students are confronted with experimental approaches in textbooks, lectures and laboratory courses. Each of these formats has its own drawbacks. Textbooks do describe many experiments and approaches, but this is not sufficient for students to learn how to choose techniques and how to schedule operations. One of the problems is that students usually focus on the technical details of techniques, thereby losing sight of the uses of such techniques. In a lecture, more weight can be put on the actual design of experimental approaches. It is, however, very hard to involve more than a limited number of students in such a way. Furthermore, even the students who do get involved, can hardly obtain personal feedback, due to considerations the lecturer has to take of the other students as well as of the time allotted for the lecture. In a laboratory course, finally, students have little freedom when choosing and scheduling operations, due to a range of practical limitations. In addition, carrying out poorly designed experiments may cause too much frustration. Another problem is that during a laboratory course, students easily become preoccupied with the practical skills they still lack. As a result, they even lose the overview of the specific experimental approach they are following. Thus, the teaching of more general aspects of designing experiments is virtually impossible. The possibilities of computer-based learning support may offer a solution to the above-mentioned problem. Apart from the well-known argument that computer-based learning support makes it possible to activate each student individually and generate personal feedback, many of the results of molecular biology experiments can be represented digitally. This offers, in principle, the opportunity to let students perform experiments virtually and show them the resulting experimental data. These experiments in particular include those that cannot be performed in real laboratory courses due to practical limitations as well as those that are badly designed. Trying out badly-designed experiments virtually can be very instructive and much less frustrating than performing them in a real lab. Posner and Rudnitsky also state that significant learning often occurs in a setting where it is safe to try [2].

In molecular biology research, a standard way to obtain information about the function of a gene, is through the creation of genetically modified organisms in which this gene is

overexpressed or disrupted. With the recent sequencing of several complete genomes, it is expected that the usage of this approach will increase even more in order to translate this DNA sequence information into functional information [3]. Therefore, we decided to create digital cases in which students have to design a procedure in order to create such genetically modified organisms. They also carry out the experiments virtually and interpret their results in order to design the subsequent steps of the approach.

This paper describes the development of these digital cases, including the requirements which have to be met, a description of the actual material as well as evaluation results. Eventually, we developed a format for the cases in which students have to design a procedure in a top-down fashion. In the discussion, this format is discussed further and it is compared with formats which are used to teach design in other fields.

REQUIREMENTS FOR THE DIGITAL CASES

In our regular course, the cases will be used to supplement lectures and a textbook [4]. We consider the material to be useful in this setting, provided that a number of requirements are met.

Firstly, the students should appreciate working with the material. Their opinion of the cases is assessed via evaluation forms. The material should be awarded an average score of at least 7.5 on a 1 - 10 scale. Furthermore, the students should perceive the material to be really instructive; they should enjoy working with the material, and should prefer working with it rather than getting additional explanations during lectures. In disagree-agree questions of this nature, they should award an average score of at least 4 on a 1-5 scale. Wageningen University assesses the students' perception of the quality of the courses, the course material, and the teachers on a regular basis with standard evaluation forms which consist of disagree-agree questions. An average appreciation of 3 on a 1-5 scale on these forms is considered satisfactory, and an average of 4 or more results in a letter of praise from the university. Therefore, we are satisfied when students give a score of 4 or more on a 1-5 scale.

Secondly, students should not only appreciate working with the material, they should also develop their experimental design skills by working with it. In order to obtain an indication of this, exam results are analyzed. In the exam, a number of questions are included which deal

with selecting and working out techniques for the creation of genetically modified organisms. The students should reach an average score of at least 7 (on a 1-10 scale) for these questions.
In addition to these requirements for the regular setting, the material should also meet another requirement. As the quality of learning material is partially determined by the extent to which the material is exposed to critique from peer reviewers and students, it is important that the material should be used not only in our regular educational setting, but also in several different educational settings in different places. In order to ensure this, the cases should form modules which are fairly independent from each other, so that a student or a teacher can select the cases he or she is interested in. Furthermore, the material should, in principle, be suitable for self-study, and it should be able to support students who have different degrees of prior knowledge. Finally, in order to ensure that the material can also be used at other universities, it is important that it is accessible worldwide.

FORMAT OF THE CASES: STUDENTS DESIGN AN EXPERIMENTAL APPROACH IN A TOP-DOWN FASHION

In order to simulate a real research situation, we initially wanted to create a virtual laboratory in which students would have the opportunity to perform a range of different experimental steps. In such a setting, a step can be carried out virtually after selecting it and designing it in more detail. By interpreting the experimental data, the students can find out whether they have made good decisions. In such a virtual lab, the students have to actively use their knowledge of techniques and of biology in a situation where they have a lot of control and ample opportunity to test their own ideas. However, after analyzing the students' task in such an environment in more detail, we concluded that this format is not really suitable for undergraduate students. In the described virtual lab, the students basically have to design at two different levels simultaneously: they have to design an overall procedure by assembling several experimental steps, and they also have to work out these individual steps in more detail, while making use of results from previous steps. Students should be capable of designing at this latter detailed level, while keeping track of the overall strategy. Moreover, it is very useful to practice this, because it requires active integration of knowledge of biology with knowledge about techniques. However, for the design of the overall procedure itself, the

situation is different. In molecular biology, procedures are not simply right or wrong. Instead, they can be placed on a scale of more or less useful. In order to judge the precise usefulness of an experimental procedure, knowledge of a range of practical issues such as efficiency, sensitivity and reliability is required. This knowledge is usually only acquired after extensive practical experience and this is beyond the scope of an undergraduate course. However, in the initially proposed virtual laboratory, students may have to compare different alternatives which are nearly equally useful, such that this practical knowledge is required to select one of them. This may distract students from the more important conceptual issues and it can lead to premature cognitive overload. Thus, such a virtual laboratory does not fully support the intended learning goals for undergraduate students, because students have too much control over the design of the overall procedure. Schwier and Misanchuk also caution that only those learners who are generally high achievers or who are knowledgeable about an area of study can benefit from a high degree of learner control [5]. In order to really focus on the learning goals for undergraduate students, another format had to be developed in which the students have less control over the design of the overall procedure. At the same time, however, the students should keep an overview of what they are doing, which implies that they should not simply follow instructions and carry out experiments without knowing why.

The fact that in this case it is actually only possible to work out individual steps in more detail once the whole procedure is known, inspired us to develop a format in which the student is first supported to design the overall procedure. Only after this procedure has been designed, can the students carry out the experiments virtually. Thus, students design the procedure in a top-down manner. Students' control can be different in both phases. By limiting students' control in the overall design phase, they can be shielded from unnecessary complexities. Moreover, as the overall procedure is designed before the student actually performs it, it is also possible to include additional support while the student is performing the experiments. It is possible, for example, to include questions which address the interpretation of specific aspects of an experimental result as well as questions which highlight the possibilities of alternative techniques. However, students design the procedure themselves, so they should be able to keep an overview, and not just follow the instructions blindly. In subsequent cases, students' control can gradually be increased at the two levels independently.

EXAMPLE: A CASE ABOUT THE CREATION OF A "SMART" MOUSE

One of the developed cases deals with the creation of a "smart" mouse and can be viewed on the demo site (http://mbedu.fbt.eitn.wau.nl/demo_jilr). Upon starting the case, the students receive a short introduction about memory formation and they are given the assignment to create a specific transgenic mouse in order to find out whether a certain protein is involved in learning. The subject in itself is not relevant: it merely serves to motivate the student. Furthermore, based on the Case Based Reasoning (CBR) theory [6] learning will be promoted by working out a realistic research question. After reading the introduction, the student can start designing the outline of the procedure. In this case, the students first have to answer several multiple-choice questions which support them in analyzing the assignment. Furthermore, they have to choose between two general overall procedures, after which the conceptual differences between these alternatives are highlighted. Then the students have to work out this general procedure further by selecting a number of experimental steps and putting them into order (see figure 1). Theoretically, about 10 million different procedures could be proposed, which means that it is impossible to simply scan each possibility and select the most useful one. The steps the students can select from are chosen in such a way that they should be able to design a procedure by actively using their background knowledge. In this way, they are shielded from a number of practical complexities. In this case, for example, the students do not get the option to work with second-generation offspring of the initially altered mouse (F2 mice). A part of these F2 mice are homozygous for the additional gene and working with them has some practical advantages. However, generating these mice requires additional time. By not offering the possibility to work with F2 mice, the students do not have to consider these practical issues and can focus on conceptually more important ones instead. Upon submission of the proposed procedure, the students receive feedback which depends on the procedure they propose and which gives hints to further improve the proposed procedure.

The feedback is generated by the program on the basis of a form of pattern matching. The student could, for example, propose to test the learning capabilities of a mouse after determining the expression levels of a receptor in the brain of the same mouse. The student then receives as feedback that this order is not useful, because it is necessary to obtain a sample of the brain for the determination of the expression and that, even if the mouse were to

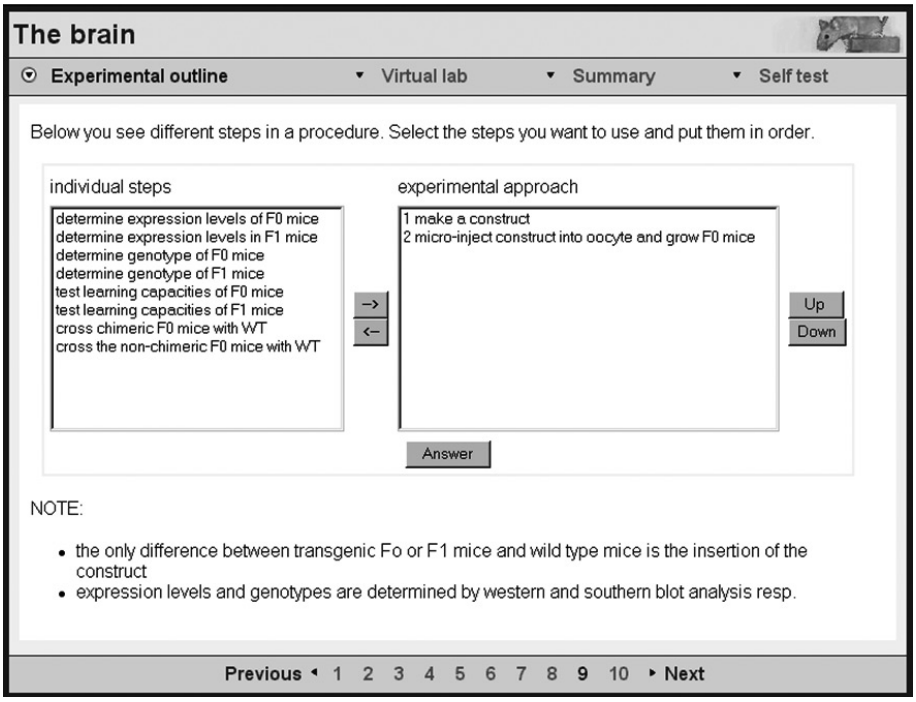


Figure 1. Screen dump of an assignment in which the student has to design a procedure by selecting and ordering different experimental steps. Upon answering, the student immediately receives feedback which is dependent on the proposed procedure.

survive this procedure, it would certainly influence its learning capabilities. This example also illustrates that the students should use their knowledge of biology: they should realize that gene expression levels differ from tissue to tissue. In this case, using the feedback eventually leads to the design of one single procedure. Because of the direct availability of feedback which is dependent on the student's answer, the procedure can be designed by students with varying levels of competence. Students with a relatively low level of competence for the skill will perform more iterations, thus receiving more hints and support.

Once the outline of the experimental procedure is designed, the student can perform the different steps virtually. Figure 2, for example, shows the experimental result of a southern blot analysis. In order to perform this analysis, the student had to select the restriction enzymes he or she wanted to use. The program then calculated the position of the bands and generated the experimental result. The student has to interpret this result by answering several

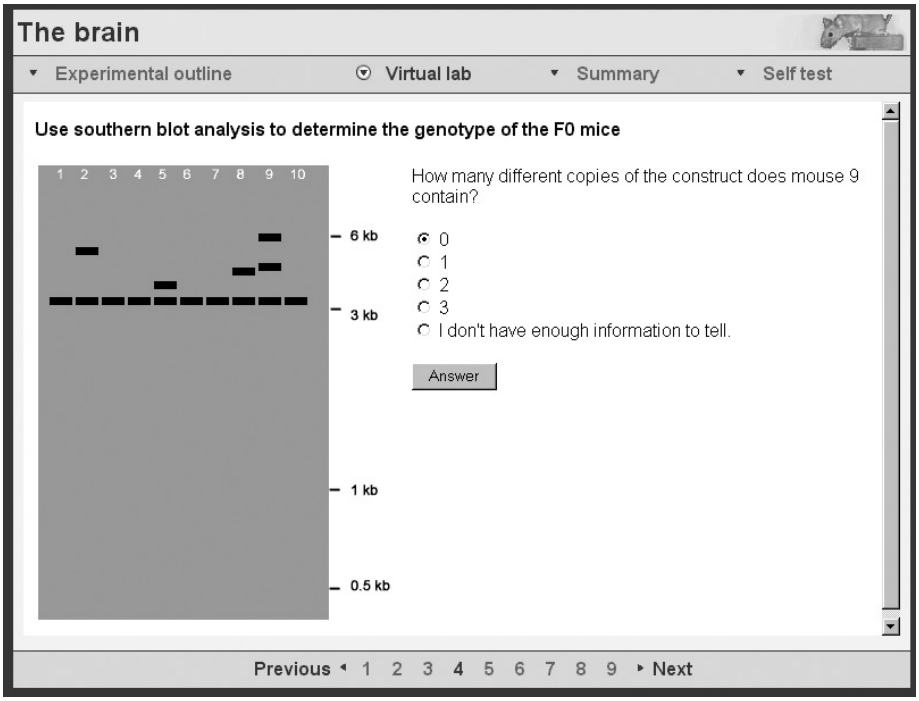


Figure 2. A question to help the student interpret his or her experimental result. After the student had selected a restriction enzyme combination, the southern blot on the left was generated. There are questions included in order to let the student find out whether he or she chose a useful restriction enzyme combination. In this case, different copies of the construct inserted in the mouse genome can be distinguished, which means that the combination was useful indeed.

questions. These questions also help the student in determining whether he or she chose a useful restriction enzyme combination. In the figure, the student has to determine how many copies of the added gene construct were inserted into the genome of the mouse. Therefore, he or she has to realize that the added gene is also already present in normal wild type mice, and that the presence of this wild type gene is responsible for (only) one band. This, in turn, is only possible if the student actively integrates knowledge of the southern blotting technique, of the overall procedure and of biology. In this case, the student chose a useful restriction enzyme combination, so that it is indeed possible to determine the copy number in mouse 9 (which is 2).

Instead of southern blot analysis, students often propose to use another technique, the polymerase chain reaction (PCR) technique, to determine the copy number. Therefore, upon completion of the southern blot analysis, the student is asked whether PCR could have been used instead. The student then finds out that this is not the case. Thus, in this way, the conceptual differences between southern blot analysis and PCR analysis are emphasized in a context in which these differences are relevant. After answering this question, the student can continue with the next experimental step. Should the student need the results of the southern blot analysis when performing one of the later experiments, he or she can easily access an overview which shows his or her personal results of the analysis. By performing all the virtual experiments, the student can discover that overproduction of the protein in mouse brains does indeed lead to improved learning and memory formation.

After finishing the virtual experiments, the student receives some additional information in which the case is briefly compared with the original research paper [7] the case was inspired on. This stresses the relevance of the technique for current research, which should further motivate the students, as being aware of the relevance of theory is an important motivational factor [8]. Moreover, some additional philosophical comments are given about the reasons why organisms do not naturally have higher levels of the studied protein in their brains. This should stimulate the student to think further about the content. Afterward, the student can view a summary, which shows his or her personal results. This also contains all the theory the student has to master, including information about alternative options the student did not necessarily select him or herself. This also serves to prevent disadvantaging students who went through the cases without making any mistakes, which is a potential problem that is also discussed by James [9]. The case is completed by a self-test with questions about the most important concepts which were dealt with in the case.

Some background information the student may need in order to go through the case, can be found in a separate library which can be accessed at any time. Providing learner-selectable information just-in-time, for example, is recommended by Jonassen [10].

EVALUATION

Evaluation of the material in the regular setting

The first two developed cases about genetically modified organisms were evaluated in our regular course. Nearly all the students had enough biology background knowledge and they had some practical experience with a number of basic techniques. As we previously received indications that the awareness of being a participant in a study makes students more motivated, we decided not to inform them about this, and the evaluation was carried out in a completely regular setting. Students only had to fill out an evaluation form at the end, which is not uncommon for them. A disadvantage of this approach is that the test situation is less controllable. In this case, for example, a number of students who worked with the material, did not answer the exam questions about it. In total, 41 students filled out the evaluation forms, and 35 students answered the exam questions about the creation of transgenic organisms.

The evaluation forms were used to assess the students' judgment of the material. The results are outlined in table 1. It must be noted that this overall judgment also includes a case with

Evaluation question	**Mark**	**Required**
	scale 1-10	
Give a mark (scale 1-10) for the computer part of the course	7.8	= 7.5
	1 (disagree) – 5 (agree)	
I liked working at the site.	4.1	= 4.0
I learned a lot from working at the site.	4.1	= 4.0
I prefer working at the site to additional lectures.	4.3	= 4.0

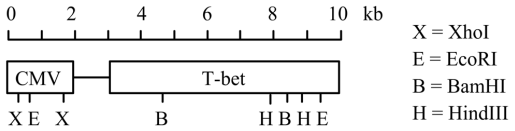
Table 1. Results from evaluation forms (n=40). The marks given by the students are compared with the marks which were required in advance. A statistical outliner (≥6 SD from the mean) was discarded. Including it would not alter the conclusions concerning the requirements.

another format, which has not been described in this paper. As we did not receive any indications that the students judged this additional case more positively than the ones described in this paper, we conclude that the design requirements concerning the judgment of the students were fulfilled.

In order to obtain an indication of the level of competence attained by the students, the exam results were analyzed. The students scored very well on the part of their exams which dealt with the creation of transgenic organisms (table 2), and the requirements were indeed met for most of these questions. The students scored at least 7, except on question 3. This question indeed requires the application of a relatively difficult concept: the students have to realize that they have to make use of unknown restriction sites outside the construct. In both digital cases, students were confronted with a problem similar to the one they had to solve for exam question 3. In order to obtain more insight into the learning process, tracking data were analyzed. These tracking data indicate which pages were opened on which computer. Even though it is not known which students were working on which computers and whether they were simply guessing or not, these data may still give a rough indication of the process. When the concept had to be applied in the first case, on 15% of the computers, the first given answer was correct. In the second case, this happened on 29% of the computers. On the exam, 60% of all the given answers were good enough (worth a score of 6 or more). This suggests that every time the concept has to be applied, some more students actually grasp it. Students who did not master the concept after going through the cases may have given the right answer by coincidence, and may not have realized why their answer was correct. In order to improve the results in future, feedback will be included which explicitly states why the chosen approach is useful. Furthermore, in an additional case which was developed later, the students have to apply the concept again, which may also lead to better results. Thus, the students scored very well on their exams and the requirements concerning the exam results are nearly satisfied. We expect that the cases will fully meet the requirements for the regular setting once the proposed improvements are implemented.

Introduction

It is hypothesized that the T-bet protein is involved in regulating the balance between two types of T-helper cells and that a surplus of T-bet causes autoimmune diseases. To test this hypothesis, you decide to create a transgenic mouse in which the T-bet gene is overexpressed in the whole body. Therefore, you use the following construct (the CMV-promoter originates from the Cytomegalo virus).



Question	**Score**
1 Describe the procedure you would use to create the transgenic mouse.	8.6
2 How can southern blot analysis be used to distinguish the transgene from the endogenous T-bet gene? Indicate the position of the probe(s) you would use.	8.3
3 Which restriction enzyme(s) would you use to determine the number of integrated copies when southern blot analysis is used? Make also a drawing of the autoradiogram for control mice and transgenic mice that contain two copies of the transgene.	6.2
4 Is it possible to use PCR to distinguish transgenic and non-transgenic mice? If so, indicate the positions and orientations of the primers.	7.2
5 How do you determine whether T-bet is overexpressed in white blood cells?	7.7

Table 2. Average scores for a number of exam questions (n=35). The obtained scores are given on a scale of 1 to 10. A score of at least 7 was initially required for each question.

Usefulness of the material in different educational settings

In order to promote the usefulness of the material for different educational settings, a number of additional requirements had to be satisfied. Firstly, the cases had to form fairly independent modules. Therefore, there are no cross-references between the different cases. Furthermore, each case starts with an introduction and finishes with a self-test, thereby forming an independent learning unit. Moreover, even though subsequent cases are increasingly difficult because students are given increasingly more control, it is not assumed that students have actually gone through the previous cases. If necessary, students can still receive basic feedback and they can look up all the background information in the separate library. In order to facilitate the usage of this library, it is always easily accessible and if there is information in the library which may be helpful to solve a certain problem within a case, this is indicated, and a direct link toward the specific information is provided. Furthermore, the library has a very modular structure, so that it is relatively easy to study only a specific part of the theory. The cases also had to be suitable for self-study. The implemented feedback and the background information in the library are also useful for this purpose. Naturally, it is not always possible to predict whether the given information is sufficient or not. Therefore, students' questions during the tests are documented, and this information is used to make the site more self-explanatory. The included feedback and the library objects also make the material more suitable for students with varying degrees of prior knowledge. Often, the student's answer determines how basic the information in the subsequent feedback will be. In this way, students only receive the very basic information when they actually need it, so that those who do not show that they need it, do not get bothered with it. The practical aspect of the requirement that the cases should be useful in different universities, has lead to the decision to make the material completely web-based. Thus, the usefulness of the material for different educational settings was promoted in several ways.

So far, we have some preliminary indications that the material is indeed suitable for different educational settings. Firstly, the material was also used by 6 students who did not have the required biology background and who did not have any experience with molecular biology techniques. Despite their lack of prior knowledge, they gave the material an overall average score of 7.8 (on a 1-10 scale), and they indicated that the level of the material was good for

them. Secondly, some students used the material at home and managed to go through the cases without additional help from teachers. Thirdly, two students used a case about the creation of a salt-tolerant tomato plant to learn something about making transgenic plants, while they were participating in an elaborate advanced practical course. They studied the case in the laboratory during some waiting steps in their experiments. It would not have been possible for them to study this case separately, if the cases did not form independent modules. Thus, we have some indications that the material can be used in various situations. We plan to perform additional evaluations to yield more reliable data concerning the suitability of the material for different educational settings.

DISCUSSION

In order to improve the experimental design skills of students, a set of digital cases was developed. It was decided not to simulate a real lab as realistically as possible, because students are then automatically confronted with issues beyond the scope of an undergraduate course. Instead, a format was developed in which students first design the overall procedure, and work out the individual steps afterward. Thereby, students' control can be limited in both phases independently. Especially during the first phase, students' control was limited in order to shield them from certain practical complexities. An obvious disadvantage of this format is that students do not learn to take these practical factors into account. On the other hand, this format offers the advantage that it is possible to really focus on specific learning goals, so that students can learn the underlying concepts relatively fast. This, in turn, should form a good basis to further develop one's design skill later, to a level at which these practical complexities are taken into account as well.

Besides molecular biology, there are also other disciplines in which design essentially implies designing at an overall level and at sub levels simultaneously. Bridge, a tutorial environment for novice programmers [11], is an example of a program with a similar format to the one described in this paper, even though the subject matter and the design issues involved are very different. There are also other formats which are employed to learn design. They offer students different degrees of control. For an introductory course in process engineering, for example, a design environment was developed in which students have to design chains of unit

operations and where they have to adjust parameters for each operation [12]. In this environment, students' control is higher than in the environment described in the current paper. In order to ensure that the inexperienced students, for whom the material is intended, do indeed benefit from the environment, the students are given assignments which start at a relatively low level and become increasingly complicated. A format of another nature, the completion strategy, was developed for an introductory course in programming [13]. In the completion strategy, students have to complete well-designed, incomplete programs while making use of worked-out examples. In order to be able to complete the program, the student has to understand the given overall structure. Compared to the format described in this paper, the completion strategy obviously offers the student less control for designing the overall structure. However, it offers at least as much control for designing at sublevels. Not only does the preferred format depend on the precise level of the students and the specific learning goals, but it also depends on the nature of the subject. For example, we could not have used the format which was developed for process engineering, because the simplest procedure to create a genetically altered organism is already fairly complicated. On the other hand, if the outcome of a single step, for example, largely determines the nature of the next one, designing in a top-down manner is probably not possible, nor desirable.

Designing experimental approaches is a complex cognitive skill which students do not sufficiently master during their undergraduate years in the traditional educational setting. In order to tackle this problem, we developed highly interactive digital learning material which provides personal feedback and generates experimental results depending on the student's decisions. With this material, students can practice applying their theoretical background knowledge when designing experiments without investing large amounts of time. Because of the good experiences we have had thus far, we are also planning to use web-based learning materials to support other complex cognitive learning goals which are hard to achieve in the traditional classroom.

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Demo site: http://mbedu.fbt.eitn.wau.nl/demo_jilr

CHAPTER 4

Digital Learning Material for Model Building in Molecular Biology

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ABSTRACT

The building of models in order to describe processes, forms an essential part of molecular biology research. However, in molecular biology curricula, relatively little attention is paid to the development of this skill. In order to provide students with the opportunity to improve their model building skills, we decided to develop a number of digital cases about developmental biology. In these cases, the students are guided to build a model according to a method which is based on expert analysis and historical data: first, they build a simplified model based on the wild-type only, and then they extend this model step by step, based on experimental results. After each extension, its biological implications are evaluated. The first case was evaluated three times during a regular course at Wageningen University, The Netherlands, and once at the University of Zurich, Switzerland. The analysis of audiotapes revealed that students did indeed engage in the reasoning processes which are typical for model building. Furthermore, exam results seem to suggest that working with the case does indeed facilitate model building in analogical situations; and the students judged working with the case positively.

INTRODUCTION

Building models of processes in order to explain phenomena and make predictions, is at the heart of science. In molecular biology research, many models have been made, such as models for the regulation of gene expression under a range of different conditions, and models for different signal transduction pathways. In this context, a model is a conceptual construction which should facilitate the explanation of phenomena and the making of predictions. Such a model can be both qualitative and quantitative, even though thus far most models in molecular biology are qualitative. Qualitative models in molecular biology are often represented by some sort of figure (see for example figure 1) with an additional written description, whereas quantitative models are commonly represented by mathematical expressions. Recently, the rate at which data are acquired in molecular biology research has increased tremendously, and it is considered to be a great challenge to build models to account for these data [1,2]. Surprisingly, however, model building generally receives relatively little attention during a molecular life sciences curriculum. This is, for example,

illustrated by the fact that in curriculum recommendations by the American Society for Biochemistry and Molecular Biology (ASBMB) model building is currently not explicitly mentioned as one of the skills which biochemistry and molecular biology students should have obtained by the end of their undergraduate program (http://www.asbmb.org (>education >undergrad curriculum)). Given the importance of model building in research, we wanted to create an opportunity for undergraduate students to practice model building in order to improve their model building skills.

To this end, we have developed a number of digital cases in which students are coached to build a model on their own. Here we will describe the development and initial evaluations of the first case.

MODEL BUILDING IN MOLECULAR BIOLOGY

We needed a good model building method, suitable for students, in order for us to obtain more direction for the structuring of the practice in model building [3,4]. In order to find inspiration for such a method, we carefully observed molecular biology experts while they were building a model, in order to analyze how they do this. Furthermore, we used historical data on scientific discoveries in molecular biology.

For the expert analysis, 6 molecular biology researchers (3 PhD students, 1 Post-Doc and 2 assistant professors) were asked to build a model based on a number of experimental data. This model is the same as the one which was eventually built by the students in the first case. It deals with a process early in *Drosophila* development. *Drosophila* is a model organism for the study of development. Such studies are aimed at resolving the question as to how a single fertilized egg can develop into an organized spatial pattern consisting of different cell types. This pattern, which shapes the worm and later the adult fly, is formed step by step. In the fertilized egg, there are gradients of compounds present, which are called morphogens. By the concentration-dependent interpretation of these morphogen gradients, the embryo is subdivided into different domains. These domains differ from each other with respect to the expression of a (small) number of regulatory genes, which are involved in specifying cell types. In these domains, new morphogen gradients are often established such that the domains can be subdivided further. A series of such subdivisions, in combination with other

developmental processes such as cell division, cell growth, cell movement and cell death, leads to the establishment of an organized spatial pattern which shapes the worm and later the adult fly. The model which the experts (and students) had to make concerns the concentration dependent interpretation of a dorsal-ventral ("back-belly") morphogen gradient which is formed very early during *Drosophila* development. The genes which are crucial for the interpretation of the morphogen gradient were identified by screening for mutant flies in which the subdivision along the dorsal-ventral axis was disturbed. In figure 1 the expression patterns of the crucial genes in the wild-type situation (= normal situation, in which the embryo was not altered experimentally) are shown. It also shows a model describing how the morphogen gradient is interpreted (reviewed in [5]).

The 6 molecular biology researchers were asked to think aloud while building the model, and the whole process was audiotaped. Each scientist followed a roughly similar approach: he first tried to understand the assignment and the experimental data. Thereby, most of them made a drawing in which the problem was visualized in an alternative manner. Then experimental

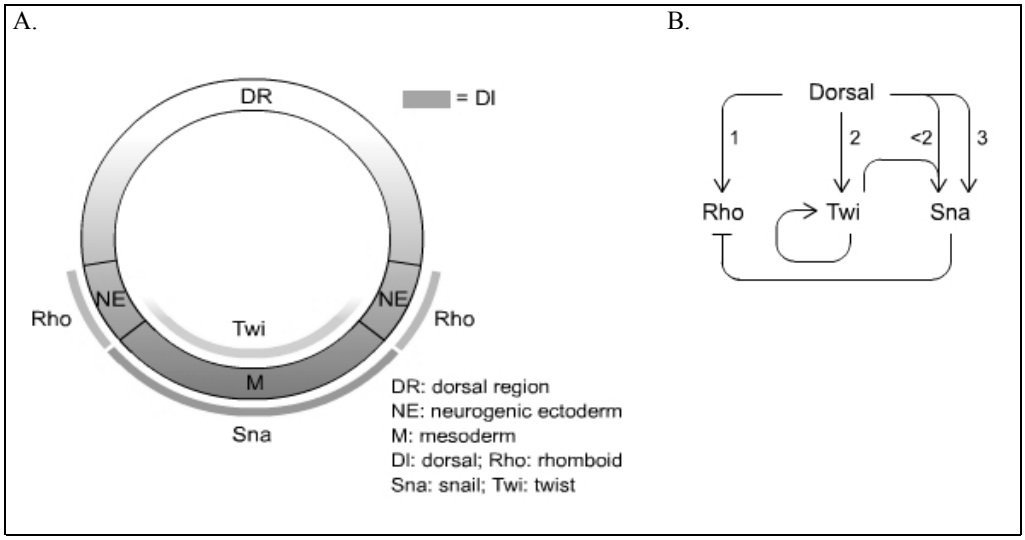


Figure 1. Subdivision of the ventral part of the *Drosophila* embryo

A: expression pattern of 4 genes in schematic representation of a dorsal-ventral cross-section of the early *Drosophila* embryo; B: model of interactions between the 4 genes/proteins. Dl = *dorsal*, Rho = *rhomboid*, Sna = *snail*, Twi = *twist*, D=dorsal side, V=ventral side, → = transcriptional induction, ⊣: transcriptional repression; numbers indicate threshold concentrations.

results were interpreted and conclusions were drawn. At one stage they subsequently tried to combine these conclusions into a model. Once such a model had been built, it was evaluated, to some degree, with the help of the experimental data. The final models differed greatly in explanatory power. One scientist actually succeeded in building a model which was in agreement with all the data. Two scientists came very close and built a model which could explain all but one experimental result. Two scientists built a model which was not capable of explaining the wild-type situation and which was not in agreement with at least two of the experimental results. One scientist did not manage to build a model at all and gave up. In order to identify factors which are important for the explanatory power of the final model, we analyzed the model building processes in more detail. Surprisingly, each scientist drew at least one false conclusion because of a reasoning mistake at one stage, but the number of false conclusions was not correlated with the quality of the final model. Furthermore, the scientists regularly did not manage to successfully complete a reasoning chain, but these problems in themselves were again not correlated with the quality of the final model. In the following fragment, for example, the scientist who eventually managed to build the most useful model, loses track of what he is doing and needs to start all over again (translated from Dutch):

"Then we have this one [experiment 4]... *snail* is induced by *dorsal*, but only if there really is a lot of *dorsal* present, because I did conclude this from this [experiment 3]. *Snail* can .. *dorsal*... but if there really is little *dorsal*, let's see, that goes here and if the *dorsal*... No, that's not true, what am I doing? ".

Besides the similarities mentioned above, we also identified two striking differences between the three scientists who (nearly) built a fully explanatory model and the other three. Firstly, the more successful group checked more precisely and more systematically whether the data were indeed in agreement with the model. Secondly, there was a marked difference in the progression of the models in both groups. In contrast to the less successful ones, the more successful scientists at one stage built a simple model which could explain the wild-type situation, but only a few other experimental data. This model was then adjusted and extended step by step, until the final model was built. In this way, the more successful group switched from an initially predominantly inductive approach to a more deductive approach. We think

the two differences are related to some extent, and explain them as follows: Building an initial, simple model which can explain the wild-type expression pattern, but not all the experimental results, is easier than building the final model at once. This is due to the fact that such a simple model contains fewer elements and/or fewer interactions among these elements. Furthermore, fewer data have to be taken into account while building it. Despite the fact that the initial model is simplified and does not take into account a number of experimental data, it can still explain the wild-type situation and give some overview of the interactions between different parts of the whole mechanism. When, subsequently, an additional experimental result is analyzed, it is possible to focus on just one specific part of the mechanism. While doing this, it is possible to temporarily ignore other experimental results and other parts of the mechanism. After changing a specific part of the mechanism, it is relatively easy to understand the consequences of this change with respect to the whole mechanism, as the initial simple model can serve as a template. This in turn makes it easier to evaluate whether the extended model is still in agreement with the previously analyzed data. The model can be extended further in this way until it is in agreement with all the available data. Thus, building a simple model first and adjusting it afterward is easier than building an elaborated model at once, which can even be so hard that people give up. Furthermore, it is easier to maintain an understanding of the model, which in turn facilitates checking whether the experimental data are indeed in agreement with the model.

As a result of this analysis, we decided to offer the students coaching in such a way that they would build the model using a deductive approach. Hereby, students are encouraged to first build a relatively simple model and to subsequently extend this model step by step. The more successful scientists started with different simple models. We decided to have students build an initial model based on the wild-type situation only. This ensures that the initial model can explain the wild-type situation, which eventually has to be explained anyway, while a minimum number of data are used.

Besides expert analysis, we also used historical studies to find inspiration for a good model building method. Such studies show that it can be very useful to take into account the biological implications of a model while building it [6]. This can even help to distinguish between alternative models in the absence of conclusive experimental data. This is, for example, illustrated by the discovery of the DNA structure. Based on X-ray data and theories

on chemical binding, Pauling and Corey published a triple helix structure in February 1953 [7]. Watson and Crick also considered the biological role of DNA and proposed the now broadly accepted double helix structure two months later [8]. With this structure, they were able to envision a simple mechanism by which DNA could be duplicated, such that cells can acquire the same genetic information upon cell division.

During model building, it is evidently only possible to take the biological implications into account, if one understands these implications and if one can evaluate models with respect to these implications. For the models the students build, these conditions may not be fulfilled, as it sometimes requires a considerable amount of reasoning to evaluate a model for a certain biological implication. It can, for example, be hard to analyze whether a model can yield a sharp boundary between two adjacent tissues or whether a model can yield potentially harmful intermediate cell types. Therefore, we considered it too early to let the students take the biological implications into account while building a new model. Instead, we wanted them to focus primarily on understanding the implications and evaluating models with respect to these implications. To this end, we extended the above described deductive approach with an additional step in which students have to evaluate the biological implications of each modification step. Systematically applying this method may also give insight into the importance of certain biological implications. If molecular mechanisms in poikilothermic ("cold-blooded") organisms, for example, are very frequently robust against temperature differences, this is probably very important for such organisms.

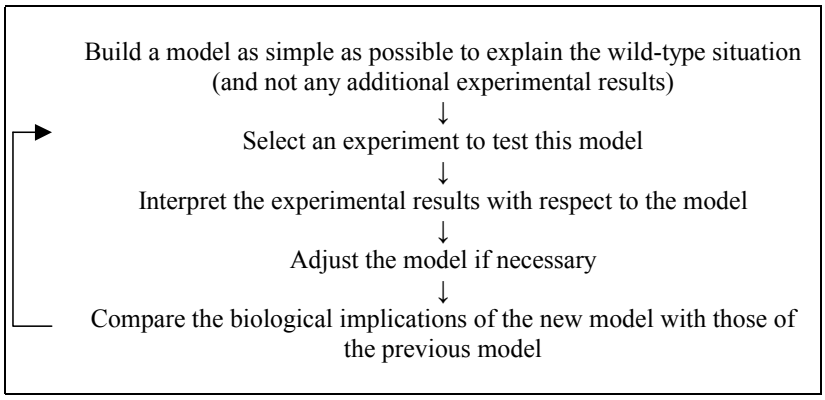


Figure 2. The model building cycle which is followed in the case.

The eventual full model building cycle is outlined in figure 2. Initially, a model based on the wild-type situation is built. This model is modified step by step, based on additional experimental data. After each modification, the biological implication of this modification is analyzed.

PEDAGOGICAL APPROACH

Executing the different model building steps as shown in figure 2 may be quite difficult for students, because the steps require the use of reasoning in combination with the application of factual knowledge of both general biological principles and specific types of experiments. In order to interpret the results of a promoter study, for example, it is necessary to have biological knowledge of genes and the role of their promoters, as well as knowledge of promoter studies, including the output of such studies. Reasoning is then required to decide whether or not the data are indeed in agreement with a certain model. The expert analysis revealed that even scientists who are very familiar with the type of experiments and models used, sometimes draw false conclusions because of reasoning mistakes. Considering the expected demands put on students for the execution of the individual model building steps, we decided to have students initially focus on executing them and to initially shield them from ordering the steps themselves. Thereby, we wanted to apply a form of cognitive apprenticeship in which students, while working on realistic problems, are strongly coached initially and where this coaching gradually fades during the process [9,10]. We considered the computer to be a useful medium to mediate this, because it can readily be used to provide feedback on students' personal decisions, without the requirement of intensive supervision. The computer can also be a useful tool to improve the understanding of a certain mechanism, as it offers the opportunity to provide an interactive visual representation of the mechanism which can be used to investigate its behavior. Moreover, if the material is delivered via the internet, it can easily be distributed and thus be accessed from home.

In this paper, we describe the development and evaluation of the first digital case we designed. In this case, the student is relatively strongly coached to build a model. Its most important learning goal concerns the execution of the individual model building steps in the situations encountered by the students in the case, as well as in analogical situations. Learning

the model building method as a whole does not form a learning goal of this case, but it could be a learning goal in later cases. Even though this is certainly not the main goal, students should also memorize the final model they build. This should facilitate them to read literature about it or to understand presentations about it. Furthermore, if they forget part of the model afterward again, they should still be able to quickly look up the details if necessary. The case is designed as a series of closed questions. These are mainly ordered according to the model building cycle in figure 2 and they highlight the individual model building steps. By having the students actively think about the individual steps in a very precise way, and by giving them sufficient feedback, they should not only be able to carry out the same steps again in the future, but they should also be able to carry out the steps in analogical situations. By answering the subsequent questions, the students automatically work according to the model building cycle as a whole. This is probably not sufficient to enable students to use the model building cycle independently. However, being guided to follow the cycle in the case, can form a first step to actually learn to use it independently [9]. The fact that the students spend some time building the model, thereby thinking about the different parts of the model, is likely to considerably facilitate memorizing the eventual model.

DESCRIPTION OF THE CASE

The case can be viewed at the demo site (http://mbedu.fbt.eitn.wau.nl/demo_jset). It deals with the subdivision of the dorso-ventral ("back-belly") axis of the fruit fly *Drosophila* (figure 1). For the selection of the topic, we limited ourselves to well-studied mechanisms in developmental biology which are relatively easy to understand, such that it is not necessary to quantify the model and use mathematical analyses and/or computer simulations in order to elucidate its behavior. The eventual subject was selected based on a number of arguments. Firstly, it illustrates a crucial feature in developmental biology, namely the previously mentioned subdivision of a part of an embryo into different domains by the concentration dependent interpretation of a morphogen gradient. Secondly, the selected process illustrates a number of recurrent mechanisms, such as regulation at gene expression level, the role of gradients and the presence of positive feedback. Thirdly, the experiments which were used to reveal the model, such as mutant studies, are very commonly used in developmental biology

research. Lastly, the selected mechanism illustrates a very common biological implication of molecular developmental mechanisms: its characteristics ensure the formation of a sharp boundary between adjacent regions (future tissues), such that the development of some kind of intermediate cell types, which are useless or can even be harmful for an organism, is prevented.

The structure of the case is outlined in Table 1. The case is subdivided into two parts, mainly to indicate to the student that a new design cycle starts after part I, and that this could, for example, be a suitable moment to take a short break. Part I starts with an introduction in which some background and the overall assignment to build a model are given. After reading this introduction, the student has to predict the phenotype of a mutant in which the levels of the morphogen *dorsal* are increased. This question was not added to check a hypothesis or model, but rather to test whether the student is familiar with the crucial concept of a morphogen. In order to improve the student's understanding, if necessary, a simple animation was added (figure 3), thus employing the possibilities the computer offers for interactive representations. Then, the student develops the first, conceptually most basic model which

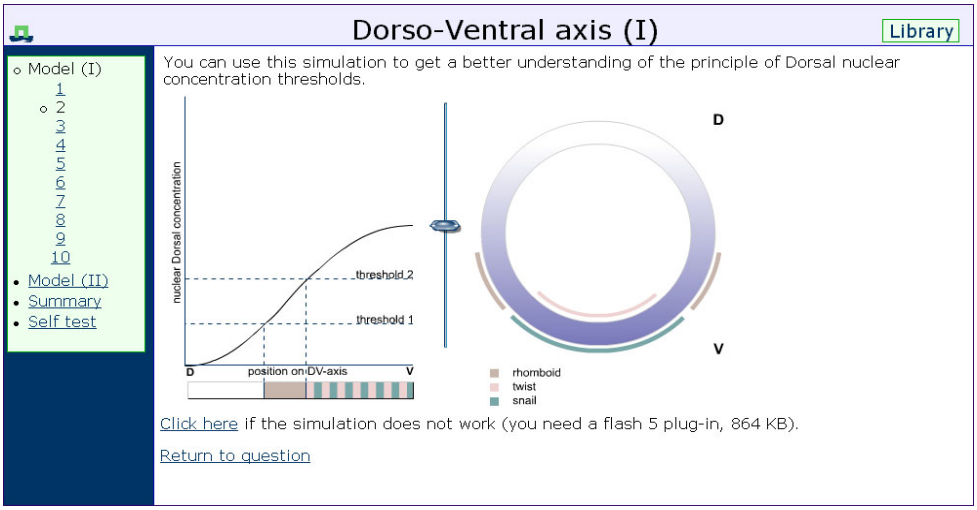


Figure 3. The animation which was used to explain, if necessary, the concept that *Dorsal* is a morphogen. The student can adjust the maximum concentration of *Dorsal*. The expression pattern of the other genes changes accordingly.

Part	Model building step	Step description
I-1	-	Introduction
I-2	-	Question to test whether the concept "morphogen" is clear
I-3	Build model for wt	The most basic model (model 1) is built.
I-4	Build model for wt	A second model is built, because model 1 is biologically unlikely
I-5	Build model for wt	A third model is built, which is conceptually very similar to model 2 and is as likely as model 2.
I-6	Select experiment	An experiment is selected to distinguish between models 1-3.
I-7	Interpret experiment	One of the three models (model 2) is selected based on the experimental result
I-8	Analyze biological implication	Model 1 and 2 are compared with respect to their robustness against changes in the concentration of the morphogen *dorsal*: there is no difference.
I-9	Analyze biological implication	The behavior of model 1 is predicted in case of a mutation in the promoter of the *snail* gene. This mutation can lead to the occurrence of an intermediate cell type.
I-10	Analyze biological implication	The behavior of model 2 is predicted in case of the same mutation. In this case, the mutation does not lead to the occurrence of an intermediate cell type. Thus, model 2 prevents the occurrence of intermediate cell types better than model 1.
II-1	Interpret result	A new result is shown which is not in agreement with model 2 and conclusions have to be drawn (model 2 needs to be adjusted).
II-2	Adjust model	Question about the nature of the adjustment: this is not yet known based on the available experimental data.
II-3	Select experiment	An experiment is selected to reveal how to adjust model 2.
II-4	Interpret result / adjust model	A conclusion is drawn based on the experimental result (model 4)
II-5	Analyze biological implications	The biological implications of this adjustment are analyzed: the extension does not change the robustness of the model against changes in *dorsal* concentration, but is prevents the occurrence of intermediate cell types even better than model 2.
II-6	Adjust model	The knowledge about the biological implication is used to formulate model 4 more precisely.
II-7	Analyze biological implication	Until this point, a simplification has been made in that there are *dorsal* threshold concentrations below which no gene expression is induced and above which maximum gene expression occurs. In reality, however, the boundary is not that sharp. This is explained and the implication for the sharpness of one of the boundaries is asked.
II-8	Analyze biological implication	Information is presented explaining that auto-activation of *twist* occurs. The consequence of this auto-activation with respect to the sharpness of the *twist* boundary is analyzed.
II-9	-	Some additional information is provided including a reference list.

Table 1. Description of the different parts of the case, together with the model building cycle step the part (mostly) deals with.

could account for the wild-type situation. This model, however, requires molecular mechanisms which are not commonly found in cells, and therefore it is biologically unlikely. Therefore, two alternative models are built before selecting an experiment (figure 4). Based on an experimental result, one of the three models (model 2) is then selected, and the biological implications of this model are analyzed. The models appear to be the same with respect to their robustness against changes in the morphogen concentration, but the second model better prevents the occurrence of potentially harmful intermediate cell types.

In the second part of the case the student is presented with an experimental outcome which contradicts model 2. In order to adjust model 2, new experiments need to be performed. The adjusted model (model 4) is then analyzed with respect to its biological implications. These implications are very similar to those of model 2. In order to evaluate the implications of model 2, the students have to answer three different questions, in which the implications are analyzed step by step. It is even possible to answer easier sub-questions instead. In order to provide the students with enough challenge while they are analyzing the biological implications of model 4, there is only one question in which they need to take not just one, but several steps themselves. Furthermore, the answers are formulated more abstractly. This illustrates that, even if closed questions are used, it is still possible to modify the degree of coaching.

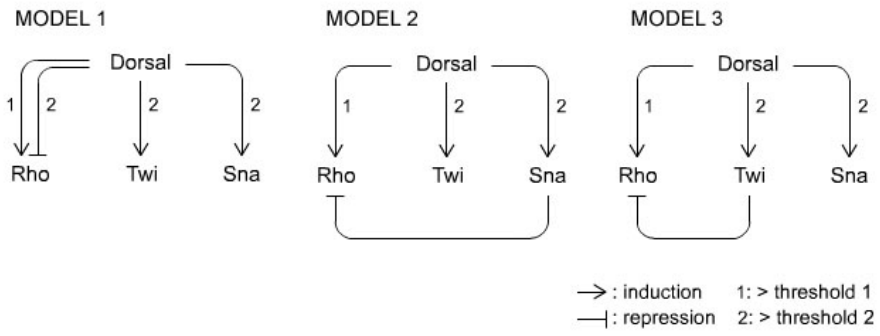


Figure 4. The three models initially constructed by the students.

After analyzing the biological implications of model 4, these same implications are used to formulate model 4 more precisely. Thus, here a first little step is made to actually take the biological implications into account while building a model. We expected this to be possible, because at this stage the student have already worked with this particular implication twice before.

Thus far a simplification has been made in that thresholds are absolute: below the threshold no expression occurs and above it high expression occurs. However, in reality, there can be concentrations at which intermediate levels of expression are found, such that expression borders do not have to be sharp, but can be blurry instead. This simplification is made because the concept of morphogens may be new to some students, and this concept can most easily be understood in terms of absolute thresholds. Therefore, only at the end of the second part of the case, when the student already has some experience with thinking in thresholds, nuances about the sharpness of boundaries are provided. At this stage, the student also has to evaluate models with respect to the biological implication of generating sharp boundaries. At the end, literature sources and some additional background information is provided.

Besides the model building part, the case also contains a summary and a self-test.

EXPERIENCES WITH USAGE BY STUDENTS

Set-up

The material was used three times during a regular course with third year students at Wageningen University. It was used by 6, 8 and 32 students respectively, while supervision was present. Attendance was not obligatory, but the theory was part of the theory the students had to learn for the exam of the complete course on development. Students could work alone or in pairs, depending on their own preference. In order to obtain more information about the way the students use the case, tracking data were collected which reveal the answers that were given, and two groups of students were recorded on audiotape each time. In order to obtain an indication as to how much the students learnt from working with the case, questions about it were added to the exam of the whole course. Lastly, in order to obtain information about the students' opinion of the case, an evaluation form was handed out after the case had been completed. After using the case for the first time, some rather small changes were

implemented, such as replacing some text parts with figures. Even though these changes did influence some of the evaluation results, the overall results were quite similar.
The material was also used by 13 third year students at the university of Zurich. Students mostly worked in pairs. They also filled out an evaluation form and were given exam questions about the case.
As the results were comparable each time, we will discuss the pooled results here. It should be noted, however, that we did not give identical exam questions in consecutive courses, because students use exam questions of previous courses to prepare for their own exam. Therefore, we will only discuss the exam results of the last group of 32 Dutch students.

Process description

The case was developed to give the students an opportunity to build a model on their own in the presence of coaching. In order to obtain an impression of whether the case can indeed engage students in active model building and the rather sophisticated reasoning processes involved, the audiotapes were analyzed. Here, we will give some citations which illustrate the reasoning the students went through during the different stages of the model building cycle: building the initial model, selecting an experiment, interpreting an experimental result, adjusting a model, and analyzing the biological implications of a model. The fragments in this paragraph were all translated from Dutch.
In the following fragment, two students are building a part of the first basic model (question I-3 of the case). They find an explanation for the fact that *rhomboid* is expressed at intermediate *dorsal* concentrations (between threshold 1 and 2), but not at high *dorsal* concentrations (above threshold 2).

MN: But there it grows [*rhomboid* is transcribed], doesn't it, there in between, between [threshold] 1 and 2, because below 1, you don't have anything yet.
MG: I believe *rhomboid*, that it is just already there, even though, oh no
MN: No, it is not there yet. It is made between [threshold] 1 and 2
MG: It is produced and then it gets bigger and then, if it is too big, then, it gets smaller [student sounds doubtful].

MN: Between [threshold] 1 and 2 it [*rhomboid*] is being made, so it simply has to be a +.
MG: Yeah.. [student still sounds doubtful]

In order to make sure they really understand it, they then decide to go back to check the animation which explains the concept of morphogens and their thresholds (figure 3). A little later they come back to the same part of the model:

MG: Oh, wait, I already get it! This binds... In the beginning [at low concentrations of the morphogen *dorsal*] it [*dorsal*] only binds the rho affinity [he probably means: the promoter site of *rhomboid* with high affinity], which ensures that induction occurs.
MN: Because there is only little [*dorsal*] present.
MG: And when it [*dorsal*] is at the second thingy [threshold], it [*dorsal*] also binds to these [low affinity *dorsal* binding sites in the promoter of *rhomboid* which cause transcriptional repression if *dorsal* binds to them] and it [*rhomboid*] does not become available anymore.

In the following fragment, students evaluate three different experimental approaches with respect to their usefulness for distinguishing between two alternative models (question II-3 of the case). The experimental outcome must reveal whether *twist* is sufficient for induction of *snail* expression or whether *dorsal* is required as well.

JS: What do you think?
JR: If we use B [the construct in experiment 3], we can check whether *twist* can do it [induce *snail* expression] by itself.
JS: I also think that this one [construct B in experiment 3] is possible because with this one [construct A in experiment 2] you cannot do anything, then you only know whether *dorsal* can do it [induce *snail* expression by itself] and we do not want to know that.
JR: No, we want to know whether *twist* can do it [induce *snail* expression] by itself or in combination with *dorsal*. And the first [experiment] is...?
JS: yeah, decrease whole *dorsal*, so that there is not any *dorsal* any more, but yes, then *twist* is not produced either and then you cannot check what influence it has on *snail*.
JR: So then it would be this one [experiment 3]

At one stage of the case, students are presented with an experimental result which is not in agreement with their former model (question II-1 of the case). The students try to explain what they see and consider two alternative explanations. Then they make a start in adjusting the former model by identifying the part of the model which needs to be adjusted:

MG: If there is no *twist*, then [the expression domain of] *snail* gets smaller and *rho* gets larger, so *twist* has a positive influence on *snail.*
MN: and a negative one on *rho*
MG: eh no, *twist* has a positive influence on *snail* and *snail* has a negative influence on *rho* ..
MN: yes, that's also possible
MG: ..so if this one [*twist*] is not present, then this one [expression domain of *snail*] gets less big and this one [expression domain of *rho*] gets bigger
MN: so then something must get in between there [in the previous model]... so that is wrong [a part of the previous model].

In the following fragment, the biological implications of model 2 versus model 1 need to be analyzed (Question I-8 of the case). In this case, both models react identically to an increase in the concentration of *dorsal*, because it does not matter whether *dorsal* or *snail* represses *rhomboid* expression in the region where *dorsal* has a concentration which is higher than threshold 2. Therefore an altered robustness against changes in d*orsal* concentration is not a biological implication of model 2.

IK: *Snail* also only starts suppressing [rhomboind expression] after this point [where the *dorsal* concentration reaches threshold 2], so I think it [position of the *rhomboid* expression domain] stays the same, whether it [*rhomboid* expression] is repressed by *snail* or by *dorsal* at a concentration of [threshold] 2.
MR: OK, yeah, exactly, because it is under that threshold [he probably means: *rhomboid* expression occurs when threshold 2 is not yet reached].

The above fragments illustrate reasoning related to the model building steps as outlined in figure 2. In these fragments, students eventually draw the right conclusions based on proper reasoning. This occurred fairly often with all six groups which were audiotaped. However, sometimes they also made reasoning mistakes and used the feedback to understand their mistakes. In some groups, students did not reason aloud before answering some of the questions. They simply asked each other which answer they would choose and if they both had the same answer, they would check it. In these instances it is of course not possible to assess their reasoning. Lastly, one group sometimes chose an answer after discussing it only superficially. We have the impression that there were a few students, who were not audiotaped, who checked the answers even faster. This can, of course, have a negative influence on their learning outcomes. However, the overall impression was that, while going through the case, students went through a lot of reasoning processes which are typical of the different stages of the model building process.

Especially after the case was used for the first time, the audiotapes in combination with the tracking data were also used to further improve the case by identifying unclear points.

Learning outcomes

In order to obtain some insight into how much the students learnt from going through the case, the exam results were analyzed. As was mentioned before, the results of the last group of 32 Dutch students will mainly be discussed here. The other groups had slightly different exam questions. The overall results were similar. The exam questions which are discussed here are shown in Table 2.

The first exam question tests whether students have passive factual knowledge of the mechanism involved. This question was needed in order to be able to ask the subsequent questions.

The second question tests whether students can propose experiments with which they can distinguish between similar models. This is a crucial step in model building. In order to answer this question, students should be familiar with different experimental approaches, and they have to be able to activate this knowledge while answering the question. Furthermore, they have to be able to evaluate the usefulness of different experimental approaches in order

to distinguish between different models. As the question shows analogy to tests which they had to perform in the case, this question tests whether students are capable of applying their model building skills in an analogous situation.

The third question tests whether students can describe why the model yields a very sharp boundary between two adjacent domains. This was part of the case and the question is therefore included to check whether students can indeed give an explanation of this biological implication of the model. In order to take this biological implication into account while building models, it is evidently essential that new models can be evaluated with respect to this characteristic as well. Therefore, students have to evaluate whether the other models are also capable of yielding a sharp boundary between two adjacent domains in question 4.

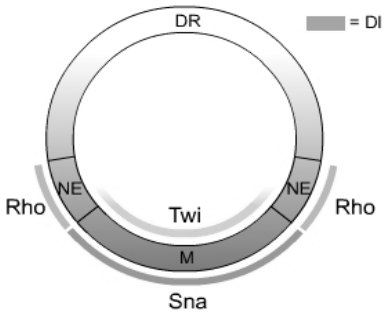
The exam results are given in Table 2. Almost all students (30 out of 32) passed this part of the exam (they scored an average of at least 5.5 on a 1 to 10 scale for the 4 questions). This is a relatively high number of passes, as in general only roughly two thirds of the students pass an exam. As can be seen in Table 2, students by far had the best score on the first question, which was to be expected, as answering it requires just a little factual knowledge. On the third question, the scores were the lowest. When analyzing the results, we found that two different conceptual mistakes were repetitively made when students answered question 3. Therefore, we are planning to add an additional self-test question in which students will be confronted with this misconception, if present. Given the fact that question 2 and 4 require relatively much reasoning, we were satisfied with these results.

The last three questions could, in principle, be answered based on reasoning and relatively little general knowledge of biology. During the previous evaluations, there were 5 students in total who did not go through the case, but who did enlist for the course and did take the exam. They scored 3.2, 2.0 and 2.4 on average for questions which are similar to question 2, 3 and 4 in Table 2 respectively. These results should not directly be compared with the results of students who went through the case, because these 5 students may, for example, have been less motivated than the others. However, this still strongly suggests that it is very difficult to answer the exam questions based on reasoning and knowledge of biology only.

Thus, the exam results suggest that going through the case facilitates answering questions in which modeling steps have to be taken which are analogous to the ones which have to be taken in the case.

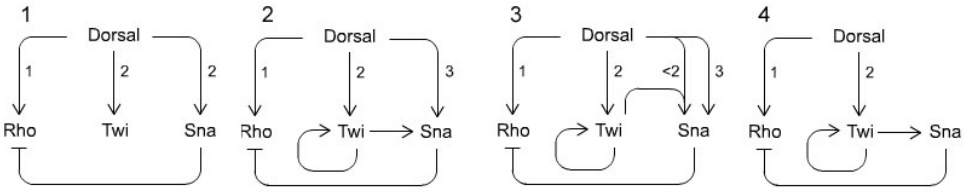
Introduction

The figure shows the expression patterns of a number of genes at the dorsal-ventral axis during the early development of a *Drosophila* embryo.



DR: dorsal region
NE: neurogenic ectoderm
M: mesoderm
DI: dorsal; Rho: rhomboid
Sna: snail; Twi: twist

Each of the following 4 models describes a gene network which can, in principle, form the above expression pattern.



	Question	Score (n=32)
1	Which of the above models describes the biological system best (no explanation needed)?	10
2	Describe how experiments can be used to eliminate the other models.	6.6
3	The border between the *rhomboid* expression domain and the *snail* expression domain is very sharp. Explain why this is the case. (use graphs!)	6.1
4	Which other model (or models) of the above models describe(s) a system that generates a comparably sharp border between the *rhomboid* expression domain and the *snail* expression domain (explain)?	7.0

Table 2. Average scores on a 1 to 10 scale for a number of exam questions by students who worked with the case while supervision was present.

Students' opinion

In order to assess the students' opinion of the case, an evaluation form was handed out after they had worked with it. In total 49 out of 59 forms were returned. Three of the questions are shown in Table 3. As can be seen in the table, the students judged the material positively (4.0 on a 1-5 scale), liked working with the case (4.1 on a 1-5 scale) and thought they had learnt a lot from it (4.0 on a 1-5 scale). Wageningen University assesses the students' perception of the quality of courses, course material and teachers on a regular basis with standard evaluation forms. An average appreciation of 3 on a scale of 1 to 5 on these forms is considered satisfactory, and an average of 4 or more results in a letter of praise from the university. Thus, the students really seemed to appreciate working with the case.

Evaluation question	**Score (n=49)**
	scale: 1- 5
Give your overall impression of the case (encircle the mark).	4.0
	1 (disagree) – 5 (agree)
I liked working with the case	4.1
I learnt a lot from working with the case	4.0

Table 3. Results from three questions on the evaluation form.

On the evaluation forms, there were also a number of open questions, where students were asked to give their general impression of working with the case, and also to compare working with the case to following a lecture. Nearly all students gave answers saying that they were activated, that they really got to understand it, that they would remember it better, etc. This, for example, is illustrated by the following citation:

"When you work on the case yourself, you understand it better than when you only listen to someone telling it. You learn better when you work with the material yourself."

Other advantages of working with the case mentioned by several students were that they could work at their own pace, that they could also work with it at home, and that it gives an impression of how models are built in research. Disadvantages mentioned by several students were that it can be tiring to work behind the computer (especially when reading English texts); that they sometimes had to spend a lot of time answering a single question; and that it was sometimes appealing to look at the feedback before really thinking about it. Two advantages of lectures were mentioned several times. Firstly, during lectures there are often interesting extensions of the theory. Furthermore, it requires less time to discus a model. Thus, the answers on the evaluation form confirm that in general students are really activated. They also suggest that cases and lectures could complement each other well, because they have different strong points.

As mentioned before, the main learning goals of the case include performing the individual steps of the model building cycle which is outlined in figure 2, and not being able to use this cycle themselves. However, in order to obtain some idea as to whether students could still recall the overall approach they followed, a question which asked for this general approach was added to the evaluation form. Most students indicated that they started with a simple model and that they extended this model stepwise. When asked to give advantages of this approach compared to an approach where experimental data are given all at once and where the final model has to be built directly based on these data, most students indicated that the latter approach would be too complex and that they would not be able "to see the wood through the trees" any more. Thus, even though learning the design cycle as a whole was not a learning goal and students were not stimulated to actively think about it while working with the case, students could still recall the general approach when asked, and they could mention an important advantage of this approach.

DISCUSSION

The case described in this paper was developed in order to give students the opportunity to practice model building in molecular biology and thereby improve their model building skills. In the case, the student is guided to build a fairly complicated model by going through subsequent model building cycles. Audiotapes revealed that the case was indeed able to

activate the students to go through the reasoning processes which are typical for the different stages of model building. Furthermore, exam results suggested that working with the case facilitates answering questions in which modeling steps have to be taken which are analogous to the ones that have to be taken in the case. The exam results also show that student acquired at least some passive knowledge of the eventual model. If acquiring factual knowledge is the sole goal, studying a book or listening to a lecture may be more efficient, because then students do not use their cognitive resources to analyze results, compare different models, etc [11,12]. Some students did indeed mention that mechanisms can be memorized more efficiently during traditional lecture courses.

In the case, students automatically follow the design cycle in figure 2. When asked for it on an evaluation form, most of them were able to reproduce the general approach followed and give an advantage of this approach. We expect, however, that this will not be sufficient for them to use the method independently. Therefore, we are currently developing an educational case in which students are much less guided while building a model, and in which they have to organize their model building process themselves. Based on this experience, they are then encouraged to evaluate model building methods. Such a problem-posing approach is, for example, proposed by Lijnse [13].

While designing the case, the model building cycle outlined in figure 2 was very helpful as a guideline to think up and order the subsequent questions. This design cycle was developed based on observations of experts who were building the same model we wanted the students to build, as well as on historical data about scientific discoveries in biology. The design cycle may also be useful to build models for other (molecular) biology mechanisms. However, there are also modeling problems for which this approach is not useful. If, for example, in theory there are innumerable equivalent models which can explain the wild-type situation, it is not useful to continue to build a model without additional data. Instead, it is much more useful to start collecting experimental data in order to uncover the underlying mechanisms. We are also planning to have students evaluate these kinds of issues after building a model all by themselves.

We used the computer to implement practice in model building for molecular biology. An important reason for this was the possibility the computer offers to guide students and to give them direct feedback on their individual choices. In this way floundering and waiting can be

avoided, such that students can build and analyze a rather complicated molecular biology model in less than two hours. The computer also offers the opportunity for interactive representation of certain concepts, which we indeed exploited in one of the questions in the case. Furthermore, the fact that the case is basically a self-contained module which is delivered via the Internet, should enable its usage in a variety of settings. Indeed, we have some preliminary results which indicate that students can use it for self-study without any supervision, even though they seem to learn a little more when supervision is present. In addition, it was also relatively easy to use it at the University of Zurich. We hope the case will be used at other universities as well, and that we will be able to improve it further based on the additional evaluation outcomes.

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CHAPTER 5A

Biology by numbers: introducing quantitation into life science education

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Driven by the massive datasets that are generated by "omics" research, the molecular life sciences are entering a new phase. This phase is characterised by a shift in focus from individual genes and their products to networks and whole systems [1-3]. For a thorough analysis of the behaviour of networks and their underlying principles, quantitative tools are often necessary. Numerical simulations can, for example, be used to explore the behaviour of a network when the values of different parameters are varied, and, in turn, mathematical analysis can help to understand a particular biological phenomenon [2].

The successful application of quantitative tools in the molecular life sciences requires a good understanding of these tools and sufficient knowledge of the biological system under study. This can be achieved by collaboration between quantitatively trained scientists such as physicists on the one hand and biologists on the other. However, cultural differences hamper such collaboration [1]: even at the undergraduate level, students in the different disciplines speak very different languages [4].

A more productive approach is therefore to prepare students better for the quantitative nature of the molecular life sciences by integrating quantitative thinking and biology in the life science curriculum. This can be achieved in various ways. For example, a curriculum could be developed in which mathematics, the physical sciences, and biology are introduced together [4]. However, we recommend that quantitative thinking also be included throughout the curriculum in the biology courses themselves, covering topics such as cell biology, developmental biology, and biochemistry. We consider this important because it will help to show students how quantitative tools can be used to address various cutting edge questions in biology.

A MODELLING MODULE IN DEVELOPMENTAL BIOLOGY

As an example of the integration of quantitative teaching and cutting edge biology, we have implemented an educational module in which numerical simulations are used in an existing course on developmental biology (http://mbedu.fbt.eitn.wau.nl/demo_plos). Some of the features of this module and the thinking that led to its development are quite general, and so we present the module here as a case study in the hope that this might inspire and guide others to create similar resources.

First, we wanted to illustrate to students the value of using numerical simulations to study a developmental process. Therefore, a pattern-forming mechanism was selected that can initially be rather hard to understand: the generation of the morphogen gradient formed by the extracellular signalling molecule decapentaplegic (Dpp) early during Drosophila embryogenesis [5]. The generation of this gradient results from the fact that key proteins are synthesized in different embryonic regions, from the formation of complexes of these proteins, and from the different diffusion rates of these complexes and their components, as well as from the specific degradation of some components. Students are guided through the creation of a model for Dpp gradient formation based on a set of experimental data. At several stages, students can perform simulations in a separate simulation environment. Students use simulations, for example, to check whether a number of core interactions is sufficient to yield the most important characteristics of the wild-type gradient.

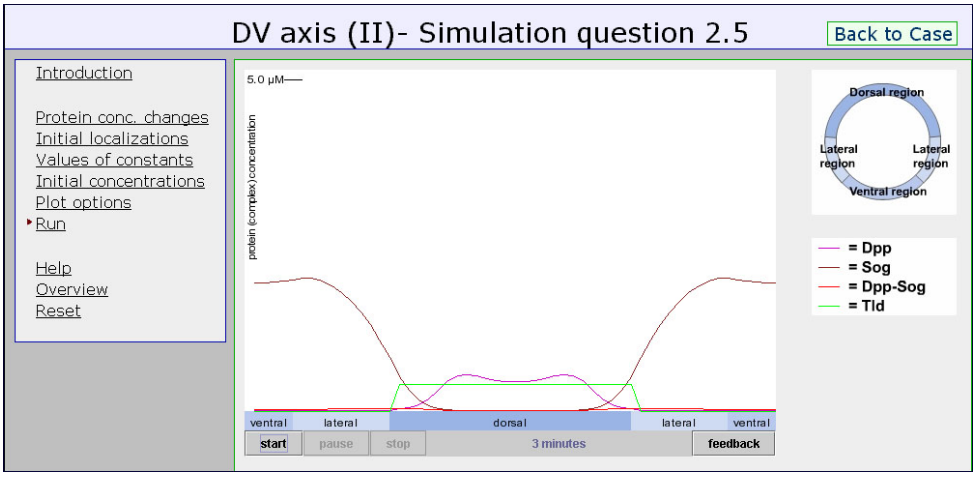

Figure 1. A simulation that students can perform. After several minutes, Dpp forms one peak in the center of the dorsal region, as in the wild type. The various elements of the quantitative model can be entered under "protein conc. changes", "initial localizations", "values of constants", and "initial concentrations". The numerical simulation itself shows the dynamic behavior of the designed quantitative model.

Second, we designed the simulation environment in such a way that biology students with their existing mathematical background can build quantitative models and run numerical simulations themselves. In this environment (Figure 1), students do not have to program anything, or set up differential equations, themselves. Instead, they indicate which processes occur at the molecular level, and the program then shows how each of these processes is translated into a term in a differential equation. In Figure 2, for example, the program adds a diffusion term to a differential equation if the student indicates that diffusion occurs. Besides setting up the equations in this way, students specify the initial localisations and concentrations of the different proteins, as well as the constants that are used in the differential equations.

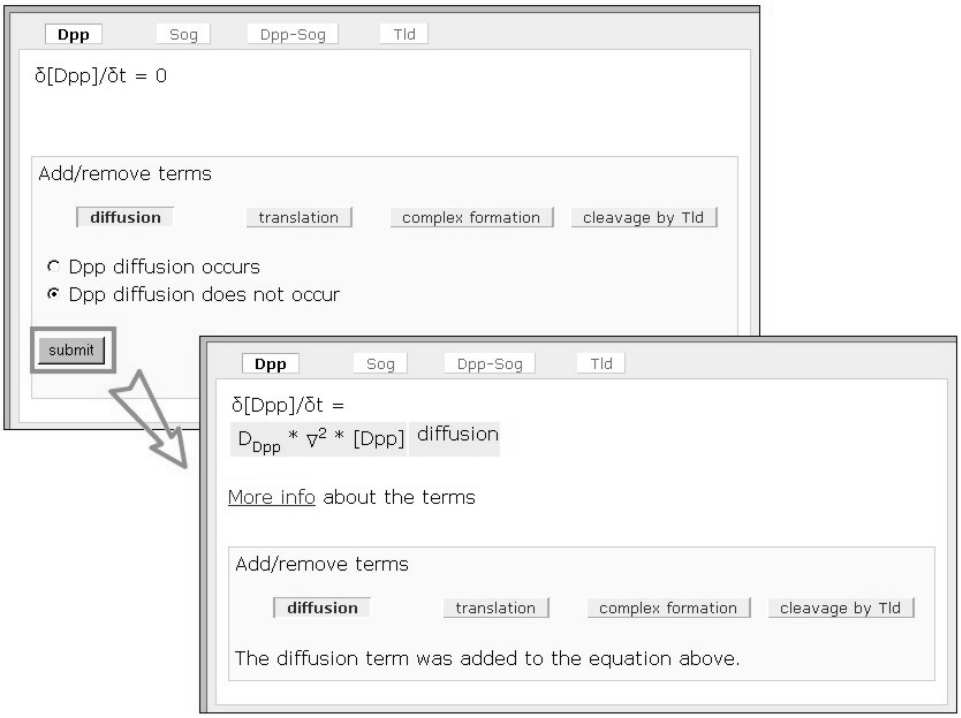

Figure 2. Illustration of how students can set up differential equations. If a student indicates that Dpp diffusion occurs, a diffusion term is added to the differential equation that describes the changes in Dpp concentration.

Third, we wanted to make sure that students would use the simulation environment effectively. Therefore, a clear goal is formulated when students enter the simulation environment. For example, they are asked to make a model that generates a Dpp gradient that fulfils a number of specific criteria, or simulates certain mutants. After running a simulation, students can view feedback that helps them draw conclusions or consider the next step to be taken. If a student's model, for example, generates a gradient that is too shallow, the student has to indicate which change in the model he expects to be useful for generating a steeper gradient. The student then receives an intuitive explanation of the usefulness of the given suggestion. If an increase in the synthesis of one of the proteins, Short gastrulation, is proposed, for example, feedback is given that this could indeed be useful, since there would then be more Short gastrulation available to transport Dpp, such that the gradient can become steeper. In this way, the student is stimulated to carefully consider each step and is provided with sufficient support to decide which is a useful step to follow. In addition, with this type of feedback, explanations are given that relate quantitative changes in the model to qualitative changes in its behaviour, which should increase the student's understanding of the behaviour of the biological model.

We consider it important that students, while using the module, are not distracted too much by quantitative issues from the actual biological principles and facts. These have to be mastered in order to obtain a strong biological background. If students want to learn more advanced quantitative skills, they can still follow courses that are specifically aimed at this aspect.

THE FUTURE

Quantitative analysis is already gaining importance in molecular life sciences. Therefore, it is desirable that curriculum changes are implemented in the short term. This poses challenges to faculties, especially to those whose members do not have much, if any, experience with the application of quantitative tools in their own research. Therefore, it may be useful to initially focus on the development of learning materials that are rather self-contained, such that their application requires relatively little competence in quantitative analysis from the teaching staff. If these materials are openly available they can be incorporated rapidly into existing

courses, such that even the current generation of students may be better prepared to integrate quantitative thinking and biology in their future research.

ACKNOWLEDGMENTS

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CHAPTER 5B

Introducing molecular life science students to model building using computer simulations

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ABSTRACT

Computer simulations can facilitate the building of models of natural phenomena in research, for example in the molecular life sciences. In order to introduce molecular life science students to using computer simulations for model building, a digital case was developed in which students build a model of a pattern formation process in developmental biology with the help of a combination of experimental data and computer simulations. For the development of a pedagogical approach, we used a number of design principles with respect to a suitable model building method and also with respect to increasing the students' understanding of (biological) systems. The case was then developed along the lines of this approach. Additional software components have been developed to provide sufficient feedback and support for students when working with the simulations. The case has been evaluated in three third year undergraduate courses, both at Wageningen University in the Netherlands and at the University of Zurich in Switzerland. Students appreciated working with the case and most exam questions about the contents of the case were answered relatively well.

INTRODUCTION

Computer simulations can play an important role in science education. They are, for example, well-suited for a form of discovery learning [1], where the main task of the learner is to infer, through experimentation, characteristics of the model underlying the simulation, which is unknown to the learner. Scientific discovery learning with computer simulations can lead to more "intuitive" knowledge than expository teaching, and it can lead to the mastery of discovery skills (see refs in [1]). However, with this kind of scientific discovery learning using computer simulations, students do not learn how computer simulations can be applied in actual research in order to facilitate the building of models of natural phenomena.

The molecular life sciences constitute a research area in which computer simulations, as well as other quantitative methods, are rapidly gaining importance [2-4]. Numerical simulations, for example, can be employed to discover novel biological principles [5]. In order to better prepare molecular life science students for quantitative research, curriculum adjustments are required which are aimed at a better integration of biology and quantitative thinking [6,7]. For

the integration of quantitative thinking into existing biology courses, it is important that the added value of quantitative thinking for biology research is illustrated, and that no more mathematical knowledge is required than the current molecular life science students already have. Furthermore, students should be supported to work with the quantitative methods efficiently, such that they do not get distracted too much from the biology [8].

One example where numerical simulations have been employed in research in order to discover novel biological principles, constitutes a pattern formation process early during the development of the fruit fly *Drosophila*: the formation of a gradient of the protein Decapentaplegic (Dpp) [5]. According to this model, a stable, dynamic Dpp gradient emerges from processes at the molecular level in combination with a specific distribution of the molecules among different regions of the embryo, prior to the gradient formation. Diffusion rate differences between free Dpp and a complex of Dpp and another protein, Short gastrulation (Sog), are particularly essential for the formation of the Dpp gradient [5].

It is worthwhile that undergraduate students who follow courses in developmental biology become acquainted with this model for a number of reasons. Firstly, protein gradients play a crucial role in development, and therefore it is important that students are introduced to mechanisms for the formation of a gradient. Secondly, diffusion rate differences are crucial in the model, and diffusion rate differences are also predicted to be important in other pattern forming processes [9,10]. Thirdly, the Dpp gradient formation illustrates that interactions and properties at the molecular level can contribute to an emerging pattern at the embryo level, thus showing that emergent behavior can be important in developmental biology. Lastly, the gradient forming mechanism is robust against concentration fluctuations of most of the participating proteins. This is an important biological implication of the model, since it enables embryos to develop normally, even if the protein levels are not tightly controlled.

This paper describes the development and evaluation of a digital case in which students are engaged in building a model for the Dpp gradient formation with the help of computer simulations.

DESIGN PRINCIPLES

The learning material is aimed at achieving a number of learning goals. Upon working with the material, students should be aware of the added value of simulations for research. Furthermore, they have to know how certain biological models can be converted into a set of (partial) differential equations, from a conceptual point of view (see Figure 3). They need to know, for example, that interactions among molecules can be represented by specific terms in (partial) differential equations, but they do not have to be able to formulate such terms themselves. Furthermore, they do not have to be able to program anything themselves either. Since experimental results are essential for model building, students should also be able to employ experimental results to test certain aspects of a model. Lastly, after working with the learning material, students should understand the mechanism by which the Dpp gradient is formed. By this we mean that they should be able to describe, in their own words, how the gradient is formed under wild-type (normal) conditions, as well as explain the behavior of the biological system under different experimental conditions.

In research, a rather simple model to describe the formation of the Dpp gradient was published initially [11]. Later, however, it was shown that this simple model was seriously flawed [12]. It then took three years before the current, conceptually different model was published [5]. This shows that the formulation of this new model was certainly not trivial. Compared to researchers, students have little experience with the interpretation of experimental data and the building of models. Therefore, in order to offer students the opportunity to actively participate in building a model of the gradient formation, we found it necessary to offer considerable support. A pedagogical model for such support is the cognitive apprenticeship model [13]. In order to structure this support, a pedagogical approach was developed based on a number of design principles with respect to a suitable general model building method and with respect to increasing the students' understanding of complex biological mechanisms. These design principles will be discussed in this section.

Previously, a digital case had been designed in which students have to build a qualitative model for another pattern forming process during *Drosophila* development [14]. In that case, students are guided through a model building method in which they first build a model which is as simple as possible in order to explain the wild-type situation. Other data are temporarily ignored. This simple model is then modified step by step, in order to explain additional

experimental data, which are selectively presented to the students. After each modification step, the biological implication of the modification is analyzed. Students evaluate, for example, whether the newer model can generate sharper boundaries between adjacent regions, which is important to ensure that during the further development of the organism, distinct tissues are formed and the formation of some kind of intermediate tissues is prevented. There were a number of reasons for using this approach. The general structure, in which a simple model is modified step by step, was chosen because expert analysis suggested that scientists who use such an approach developed models which could explain more data than scientists who attempted to build the complete model directly [14]. The step of evaluating the biological implications was added because historical studies have shown that it can be very useful to take the biological implications of a model into account while building it [15]. The model building method was successful in guiding us towards the design of a digital case which activates students by letting them go through reasoning processes that are typical for model building. This indeed seems to improve students' model building skills [14].

In order to obtain an indication as to whether this model building method could also serve as a design principle for guiding students to model the formation of the Dpp gradient, we analyzed the model building stages which took place in actual research. As was mentioned before, a rather simple model was used initially to explain the Dpp gradient formation [11]. After it was shown that this model was not valid [12], a new model [5] was developed in two stages. First, a core model which could explain the major characteristics of the gradient was developed. Subsequently, this model was extended. The extended model was used to study further properties of the network [5]. Thus, in actual research, the model also went through different stages of increasing complexity before the latest version was built. Furthermore, the principle underlying the initial model which was rejected afterwards, is still used to explain other biological patterning mechanisms (see e.g. [16]). Therefore, it is an additional advantage if students are introduced to this principle as well. As a design principle, we thus wanted students to follow a model building cycle in which they first build a simple model, which is subsequently modified step by step (or even conceptually changed). After each modification step, the biological implications of the adjustment are analyzed.

In order to help students understand the specific model, a number of design principles are employed which were formulated by White and Frederiksen in the context of helping students

understand basic electricity with computer simulations [17-19]. Firstly, before focusing on quantitative models, students should focus on qualitative models. Secondly, students should be confronted with a progression of models. Subsequent models can, for example, show a progression with respect to their degree of elaboration. Lastly, students should make conceptual links from models with a lower level of abstraction to those with a higher level of abstraction, by running a simulation of the model and reflect on emergent behaviors [17-19]. For the specific biological system, this could be converted into a design guideline to stimulate students to reflect on the effect of changes in binding affinity, diffusion rates and synthesis rates on the properties of the emergent gradient. Besides, in the model building cycle described above, different models are evaluated with respect to their biological implications. This should further help students to understand the different models.

Introducing biological implications could actually be seen as introducing an additional level of understanding: the first level of understanding reflects the different molecular properties, whereas the second level reflects the properties of the emergent gradient at embryo level. The additional third level reflects the effects of these properties on the further development of an organism in its biological context. If the formation of the gradient, for example, is robust against changes in the values of a range of parameters, then the gradient formation could proceed similarly under different temperatures. This is an important feature for poikilothermic ("cold-blooded") organisms, such as the fruit fly, which do not maintain a constant body temperature.

PEDAGOGICAL APPROACH

The design principles for different sorts of support described above served as a basis to develop the pedagogical approach as outlined in Figure 1. Students are guided to follow the model building cycle in a general model building part, and whenever numerical simulations are useful to carry out a certain step of the cycle, they can enter a separate simulation environment in which they are supported to build quantitative models and run simulation experiments.

Students use the simulation environment for two (related) purposes. Firstly, they use simulations to check whether a qualitative model which they built in the general model

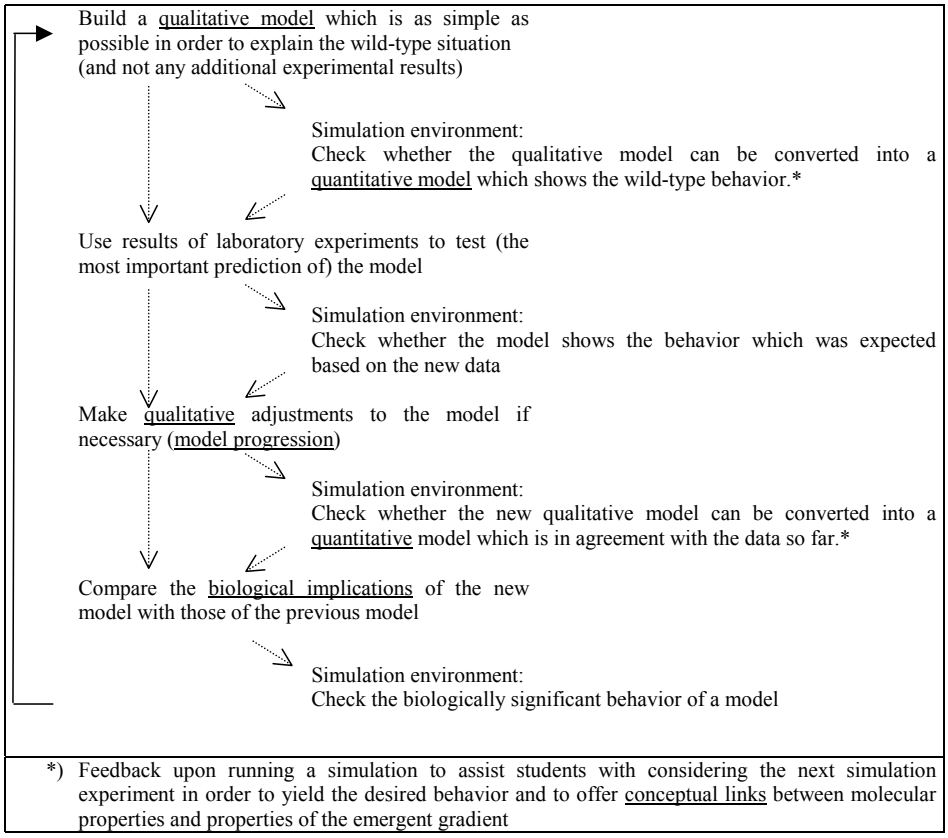

Figure 1. General pedagogical approach. Quantitative simulations are only employed if qualitative reasoning is insufficient. Four design principles with respect to understanding the biological model are integrated in the approach (underlined): the progression of models, the introduction of qualitative models prior to quantitative ones, the offering of conceptual links from lower-level to higher-level models, and the analysis of the biological implications of the model.

building part can be converted into a quantitative model which indeed shows the desired behavior. In this way, they can verify that the qualitative model does not contradict the data concerning the behavior of the biological system. It is, of course, particularly useful to do this if qualitative reasoning is not adequate to assess the behavior of a qualitative model. If there are not enough data to formulate the quantitative model directly (which is often the case in biological research), assumptions, such as certain parameter values, are made about the

missing data, and these assumptions can then guide the formulation of future experiments. As a result of a large parameter space, the simulation environment allows for a vast number of different models. This implies that building a quantitative model which is in agreement with certain data, may require a lot of simulation experiments if a model is simply modified randomly until it is in agreement with the data. In order to ensure that students consider in advance which modification is likely to be an improvement of the model, students receive feedback immediately after each modification. This feedback helps the student to recognize the relationship between the quantitative model, which is based on the properties and interactions of the single proteins and protein complexes, and also on the emergent properties of the gradient formation, which can be viewed by running the simulation. The second use of the simulation environment, which is related to the use described above, is to check whether a quantitative model can explain new experimental data. Furthermore, properties of the quantitative model can be studied. It can, for example, be determined whether the model is robust against changes in its parameter values.
This approach ensures that students follow the model building cycle which was considered useful, and that the added value of using computer simulations to build models is illustrated. Furthermore, it is an application of the design principles to help students understand the biological system (see underlined features in Figure 1).

DESCRIPTION OF THE DIGITAL CASE

The digital learning material can be viewed at http://mbedu.fbt.wur.nl/demo_jcmst. The general pedagogical approach was used as a template to design the material. The material thus consists of a general model building part and a simulation environment. Both parts will be discussed in this section.

General model building part

In the general model building part, students are guided to develop a model for the formation of the Dpp gradient. Dpp is initially uniformly distributed and forms a gradient afterward. This gradient is formed as a result of complex formation between proteins, specific cleavage

of protein complexes, differences in diffusion rates among different components, and different initial localization of the participating proteins [5]. In particular, the diffusion rate of free Dpp is lower than that of a complex between Dpp and Sog.

In order to have the students work with numerical simulations themselves, it is evidently necessary to use the computer. It was also decided to use the computer to mediate the other stages of the model building, because it offers the possibility to provide feedback on students' personal decisions without the requirement of intensive supervision. Furthermore, the material is web-based, such that it can easily be distributed and thus accessed at home.

The structure of the general model building part is outlined in Table 1. At the beginning, students can already view a list with experimental data which will eventually be used to build the model. Situations in which there is already a large number of data available, but no models yet to account for them, are likely to occur increasingly often in future research, as a result of the large increase in the rate at which data are generated, and the high accessibility of these data in web-based databases.

Students essentially go through the model building cycle in Figure 1 three times. Sometimes steps which were not considered instructive enough are taken over by the computer. For example, when testing whether their third model is in agreement with the experimental results which are available to them, students initially have to run simulations in order to mimic experimental manipulations themselves, such that they learn how to do this. For example, they can mimic the situation in a homozygous loss-of-function mutant of a certain protein by setting the concentration and production of this protein to zero and running the model. After they have done this a few times, they are presented with previously generated simulation results in order to save time (Figure 2) and prevent rather useless repetitions.

The general model building part is followed by a summary and a self-test.

	Model building step	Description of step
part I		
1-2	-	Introduction
3	Formulate qualitative model I in order to explain the wild-type situation	Students are stimulated to formulate a simple source-sink model for the Dpp gradient formation.
4	Access simulation environment: Build quantitative model I, based on qualitative model I	Students translate the simple qualitative source-sink model into a quantitative model in order to get acquainted with the simulation environment.
5	Test main prediction model I	Select experimental results which can provide information about main prediction model I
6	Test main prediction model I	Interpret selected experimental results: main prediction is contradicted by one of the results.
7	Test main prediction model I	Interpretation of an additional experimental result to confirm need for rejection of model I.
part II		
1-4	Formulate qualitative model II	In several steps a new qualitative model is built in which diffusion differences are crucial.
5	Access simulation environment: Build quantitative model II based on qualitative model II	Since it is hard to assess through qualitative reasoning whether the new qualitative model can indeed generate the observed gradient, students translate this model into a quantitative model.
6	Test main prediction model II	Select experimental results which can provide information about main prediction model II: such a result is not available yet. Extend present model first before performing experiment.
7	Access simulation environment: Evaluate biological implications of model I	Students test whether model I describes a system which is robust against halving protein concentrations: this is not the case.
8	Access simulation environment: Evaluate biological implications of model II	Students test whether model II describes a system which is robust against halving protein concentrations: it does, as predicted by the data.
9	Evaluate biological implications of model II	Reasons for robustness of model II are given.
part III		
1-4	Formulate qualitative model III	Students analyze experimental results in order to implement additional proteins in their model.
5	Access simulation environment: Build quantitative model III based on qualitative model III	Since model III does not differ conceptually from model II students, do not build the quantitative model themselves, but perform a test with a preprogrammed quantitative model instead.
6-12	Test model III (also: with simulation environment)	All available experimental data are systematically checked with respect to model III. Simulations and/or previously generated simulation results are used several times to facilitate this.
13	-	Additional information: includes speculation about biological implication of last extension of model

Table 1. Description of the general model building part. For every step, it is indicated which part of the general model building cycle is dealt with.

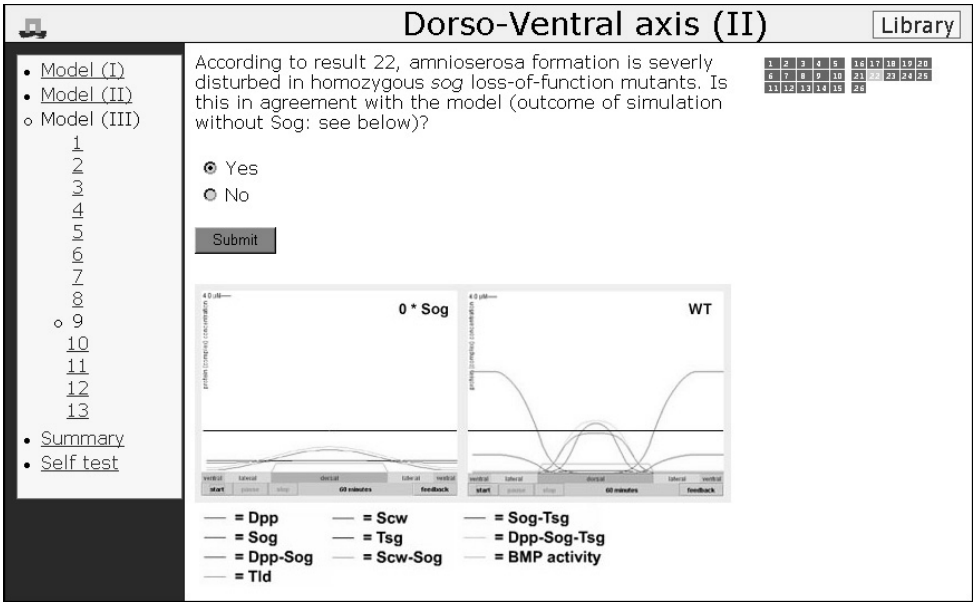

Figure 2. Screen dump which shows an example of how students can evaluate the third model with the help of previously generated simulation results.

Simulation Environment

The simulation environment implements various sorts of feedback and support. This helps students to use the simulation environment efficiently with their current mathematical background, and it ensures that the students themselves do not have to do any programming. Furthermore, it can promote the understanding of the models themselves.

Upon entering the simulation environment from the general model building part, students receive a specific assignment. They have to build a model which can generate a gradient with specific characteristics, or they have to perform certain tests. Having a clear goal should contribute to using the simulation environment efficiently.

Students also obtain support with the building of the quantitative model itself. In order to determine the initial localizations of the proteins, students have to select a schematic figure of the embryo in which the desired region is indicated. If this localization is biologically not feasible, students are informed about this and have to select another initial localization.

Students are also supported while setting up the partial differential equations. When students, for example, indicate that Dpp diffusion occurs, the program shows a diffusion term in the equation which describes the Dpp concentration changes over time (Figure 3). In this way, students can view the actual mathematical formulation, and see their choices reflected in it. However, they do not have to give this formulation themselves, such that very little prior knowledge of differential equations is required.

It is possible to assign a wide range of values to the different parameters. In order to give students some direction, standard values are given by default (Figure 4). However, it is still necessary to change several values and, if students wish to, they can change all of them.

When students want to run a simulation of the model, the program first checks whether the model is self-consistent. If, for example, the differential equation for Dpp shows a term for Dpp-Sog complex formation, this term also has to exist in the differential equations for both

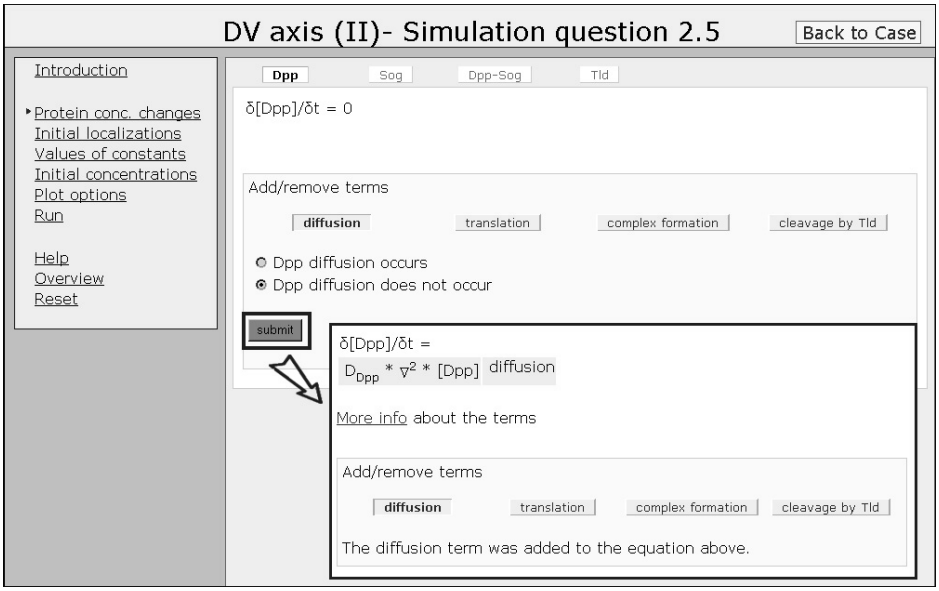

Figure 3. Setting up partial differential equations in the simulation environment. Initially the Dpp concentration does not change over time. If students indicate that diffusion occurs, the diffusion term is added to the differential equation which describes the changes in Dpp concentration over time.

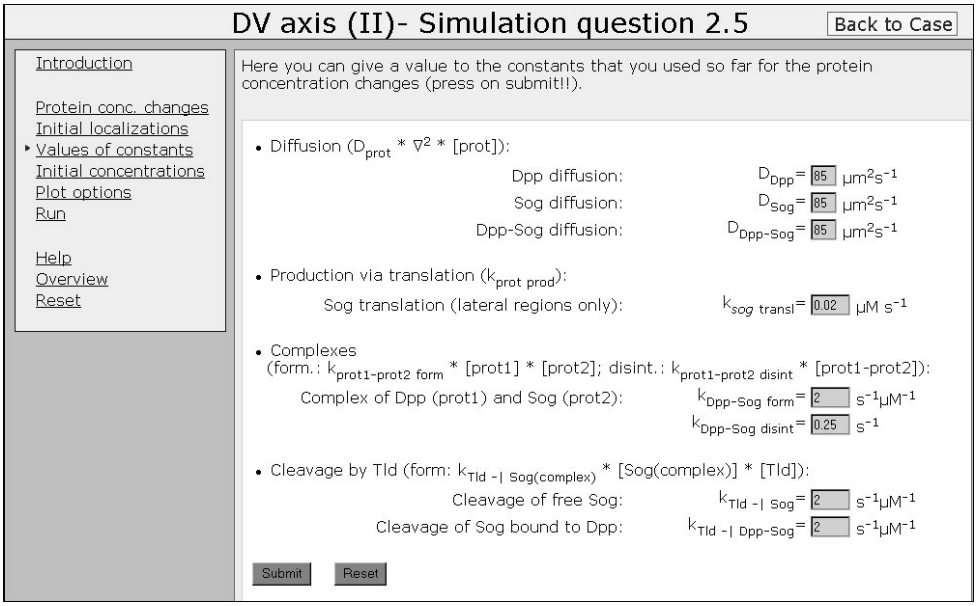

Figure 4. Giving values to constants in the differential equations. A wide range of different values can be entered. In order to give students some direction, standard values are already given.

Sog and the Dpp-Sog complex. If this is not the case, students receive feedback on how to make their model consistent. In addition, if the students have to use the simulation environment to perform specific tests, the program first checks whether the quantitative model is suitable to carry out such a test. If not, students are given information on how to change their model. For example, in order to test the robustness of a model against halving the amount of Sog, the initial Sog concentration as well as the Sog production need to be halved. If students only halve the initial concentration, they receive feedback to the effect that they need to reduce the production as well.

Upon running a quantitative simulation, students receive feedback which helps them to draw conclusions and/or consider the next steps to be taken. As an example, Figure 5 depicts a series of screen dumps of the feedback students receive while building the second quantitative model. First, the simulation result of the student is evaluated with respect to the requirements the gradient has to fulfill. In this case, the gradient is not sufficiently steep. Then, the students are asked to propose a modification to their model in order to yield a steeper gradient. In this

case, an increase in Sog production is suggested. The subsequent feedback informs the students whether this could be a useful modification or not, based on qualitative arguments. In this example, increasing the Sog production could be useful, because it would make more Sog available to transport Dpp, which could result in a steeper gradient. Such an argumentation should help students gain a better understanding of the model, since it couples biological aspects with characteristics of the quantitative model and its behavior. When the requirements are met and/or the tests are performed, and valid conclusions are drawn by the students, they can exit the simulation environment and return to the general model building part.

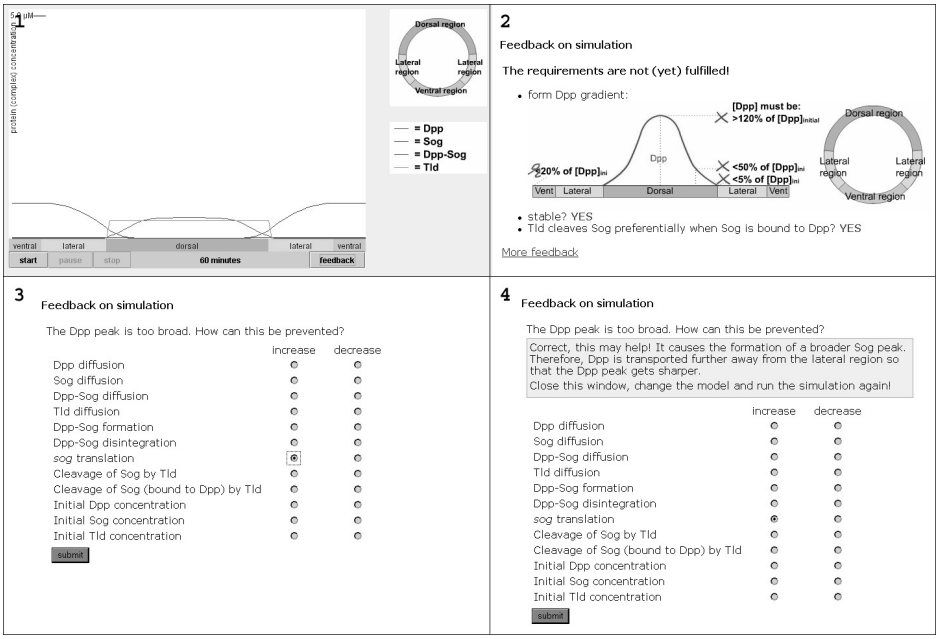

Figure 5. Four consecutive fragments of screen dumps which show an example of the feedback the students receive upon running a simulation. The first screen dump shows the simulation result. When pressing "feedback", students can view whether the resulting gradient satisfies the requirements. In this case (screen dump 2), the requirements are not satisfied. In order to obtain support to improve the model, students can ask for more feedback. They can then propose a change to their model (screen dump 3). After submitting it, they can read a qualitative argument as to whether this change is a potential improvement or not (screen dump 4).

EVALUATION

Set-up

The material was used three times during regular third year undergraduate courses on developmental biology. It was first used by 15 Dutch students at Wageningen University. After that, it was used by 13 Swiss students at the University of Zurich, and the third time, it was used by 31 Dutch students, again at Wageningen University. Each time, a number of data were collected. In order to assess the students' opinion, an evaluation form was handed out at the end of the sessions. As mentioned before, after working with the case, the students should be aware of the added value of simulations for research. In order to assess the students' ideas on this issue, a question about this added value was included in the evaluation form. Upon working with the case, students should also know how certain biological models can be converted into a set of (partial) differential equations from a conceptual point of view, and they should also be able to use experimental results in the context of model building. Furthermore, they should understand how the Dpp gradient is formed. These aspects were tested by a number of exam questions which were included in the exams of the complete courses on developmental biology.
After students had used the case for the first time, a number of significant improvements were implemented, in order to enable students to work with the case more efficiently. As a result, the time it took to go through the case was reduced from two sessions of 3-4 hours to two sessions of 2-3 hours. These improvements will be discussed first. After the case had been used for the second time, we implemented only some minor improvements which did not change the overall results of the subsequent evaluation. Therefore, the results of the second and third evaluation were pooled, and these combined results will be discussed below.

Improvements after initial evaluation

After the material had been used for the first time, a number of improvements were implemented. Most of them concerned the simulation environment. It appeared to be possible to build a model which did not yet yield the desired gradient, but which could not be improved with the feedback given, since this would require assigning values to parameters which were outside the range the environment permits. Since at this stage the model almost fulfills the requirements, and the most important features are already implemented, students should already have gained enough understanding of the model. Therefore, the feedback was adjusted such that if the proposed changes are not sufficient, students can load a

preprogrammed model which does fulfill the requirements. Another improvement concerned the addition of a tutorial which can be used when students enter the simulation environment for the first time. The tutorial contains some questions about setting up partial differential equations, and a short general explanation about using the simulation environment. It was added because it cost the students quite some time to become used to the simulation environment and to obtain an idea of how the partial differential equations were used during the simulations. Furthermore, exam results showed that relatively many students did not manage to fully grasp the concept of differential equations and could not clearly distinguish between setting up differential equations and solving them. There were also some technical improvements which were implemented in order to limit the processing capacity required by a simulation experiment. Apart from the above improvements to the simulation environment, there were also some relatively small improvements to the general model building part. Most importantly, a more idealized version of an experimental result was added, which can help students with the interpretation of a less idealized result.

Results of subsequent evaluations

Here, the pooled results of the second and third evaluations are discussed. In order to assess the students' general opinion of working with the case, answers on the evaluation forms were analyzed (35 out of 44 forms were returned). Table 2 shows that the overall impression of the case was 4.1 on a scale of 1 to 5. Furthermore, students liked working with the case (4.0 on a 1-5 scale), and they thought it to be instructive (4.1 on a 1-5 scale). At Wageningen University, courses are systematically evaluated with similar questions. An average appreciation of 4.0 or higher is given to about 20% of the courses. Considering the fact that at least part of the students did not have any affinity at all with quantitative thinking and mathematical language, we were very satisfied with these results.

The design of the case was aimed at illustrating the added value of using numerical simulations in research to students. In order to obtain an impression of the students' ideas about this added value upon working with the case, an open question about the added value was included on the evaluation forms. 13 Students commented that simulations can facilitate the model building process, because it can make complex networks more comprehensive.

Evaluation question	**Score (n=35)**
Give your overall impression of the case (encircle the mark).	scale 1-5 4.1
I liked working with the case I learnt a lot from working with the case	1 (disagree) – 5 (agree) 4.0 4.1

Table 2. Results from three questions on the evaluation form.

Furthermore, 8 students indicated that using simulations can be helpful to formulate good hypotheses, and that therefore laboratory experiments can be designed more effectively. 9 Students did not mention hypotheses, but remarked more generally that simulations could reduce laboratory work and save time and/or money. Finally, 3 students mentioned a reduction in experiments with animals and 3 students did not give any advantage. Thus, most students could indeed give an advantage of using simulations in research upon working with the case.

In order to obtain an impression of the other learning outcomes, exam results were analyzed (41 out of 44 students took this regular exam). The questions about the contents of the case, and the average scores are shown in Table 3. The first question tests whether students have enough factual knowledge of the model. Furthermore, since the students have to describe the roles of its components, the first question also tests whether they have enough understanding of the mechanism to describe the behavior of the model in qualitative terms. The second question tests whether students understand the behavior of the model sufficiently well to explain why it is robust against a certain experimental manipulation, which is a biologically important feature of the model. The third question tests whether students can actively think up an experiment, even though they did not have to do this in the case, where they only had to interpret its results. The last question tests whether students grasped the basics of translating a qualitative model into a set of partial differential equations. In general, students score about 6-7 on a scale of 1-10 for exams. Thus, the students scored relatively high on all questions except the question about the robustness of the model. In the case, students are presented with an explanation of the cause of this robustness. In order to stimulate students to think about this robustness more actively, this explanation will be replaced by a question in the future.

<table>
<tr><th colspan="2">Question</th><th>Score (n=41)</th></tr>
<tr><td>1</td><td>Scw, Sog, Tld and Tsg are involved in the formation of a Dpp activity gradient in the dorsal part of a Drosophila embryo. Indicate for each of these proteins what its role is in this process.</td><td>7.2</td></tr>
<tr><td>2</td><td>Explain why the formation of the Dpp activity gradient is robust against halving the Sog concentration.</td><td>4.7</td></tr>
<tr><td>3</td><td>Describe an experiment, which can be used to determine whether Sog and Tsg are necessary for Dpp diffusion.</td><td>8.2</td></tr>
<tr><td>4</td><td>Assume you want to simulate the following system:
• B and C diffuse, whereas A and D are immobile.
• A and B can bind and the resulting AB complex can disintegrate again into A and B.
• (AB) and C can bind and the resulting ABC complex can disintegrate again into (AB) and C.
• Both (AB) and (ABC) diffuse.
• D can cleave (AB), thereby releasing A and inactive B fragments.
Set up a differential equation, which describes the concentration changes of A in time (δ[A]/δt). Make thereby a selection from the terms below and make sure you use the correct signs (+ or -) in the equation.

<table><tr><td>Diffusion:</td><td>Complex disintegration:</td></tr><tr><td>$D_A * \nabla^2 * [A]$</td><td>$k_{AB\ disint} * [AB]$</td></tr><tr><td></td><td>$k_{ABC\ distint} * [ABC]$</td></tr><tr><td>Complex formation :</td><td></td></tr><tr><td>$k_{AB\ form} * [A] * [B]$</td><td>Cleavage by D:</td></tr><tr><td>$k_{ABC\ form} * [A] * [B] * [C]$</td><td>$k_{cl} * [D]$</td></tr><tr><td>$k_{ABC\ form} * [AB] * [C]$</td><td>$k_{cl} * [D] * [AB]$</td></tr><tr><td></td><td>$k_{cl} * [D] * [ABC]$</td></tr></table>
δ[A]/δt = ...</td><td>7.7</td></tr>
</table>

Table 3. Average scores on a 1 to 10 scale for exam questions based on the case contents.

DISCUSSION

In this paper a digital case was described in which students develop a model of a biological process with help of experimental results and computer simulations. The students appreciated working with it, despite the use of potentially demotivating mathematical language. The case was developed in order to make students aware of the added value of numerical simulations in the molecular life sciences. Answers on evaluation forms indicated that most students could indeed name a benefit of working with such simulations. Students also had to learn the basic principles of how a biological model can be translated into a quantitative model with partial

differential equations. Furthermore, they had to be able to employ molecular biology experiments for the building of a model and they had to understand the actual biological model. Again, answers on exam questions indicated that most students did indeed attain these goals.

In the digital case, students use computer simulations in a fundamentally different way than is often done for scientific discovery learning with computer simulations [1], where the main task of the learner is to infer the characteristics of the for the learner unknown model underlying the simulation (hereafter called "the unknown preprogrammed model"). The learners' basic actions are changing values of input variables and observing the resulting changes in values of output variables. The outcomes of computer simulation experiments of the learners thus serve as imitations of laboratory observations that need to be accounted for by the model the learner is building. Once the learner built a model, he can make predictions based on his model and use additional simulation experiments to test these predictions. However, he does not perform computer simulation experiments with his own model to check whether it indeed behaves the same as the unknown preprogrammed model. In the digital case described here, learners are supported to build a model that can account for real laboratory observations, instead of simulation experiments that serve as imitations of laboratory observations. Once the learner built a qualitative model, he uses this as basis to build a quantitative model. The learner then performs simulation experiments with his own quantitative model to check whether it can account for the laboratory observations, since qualitative reasoning is insufficient for this purpose. Thus, in the type of scientific discovery learning where learners infer the characteristics of an unknown model underlying the simulation, learners do not use computer simulations like researchers would use them: researchers do not have to infer the characteristics of an unknown model underlying a simulation, because they generally simply have access to models underlying simulations and often even built the models themselves. In the digital case described here in contrast, learners use computer simulations like researchers can use them: to support the building of a model that can account for the experimental observations by exploiting the simulations to assess the behavior of a system based on the characteristics of its components when this cannot be achieved with qualitative reasoning.

In the case, students worked with a simulation environment in which parameters could sometimes be altered over a relatively large range. Offering a relatively large parameter space can cause the generation of feedback on specific models to be rather challenging. When building model II for example, more than 10^{20} different combinations of parameter values can be entered. In order to give useful specific feedback despite this large number of possible combinations, the fact was exploited that these combinations can only yield a limited number of qualitatively different behaviors. The feedback was generated based on such qualitative behavior. However, since the set of partial differential equations cannot be solved analytically to our knowledge, the exact rules that determine the qualitative behavior are not clear. Moreover, it is not feasible to systematically scan the whole parameter space for the different behaviors that are generated, since this would require more than 10^{14} computer years if each simulation takes about one minute. In order to be able to generate useful feedback despite these difficulties, we generated feedback based on our own qualitative understanding of the model, that was acquired by much "playing around" with the simulations. Even though it cannot be guaranteed that the implemented feedback is appropriate for each model the students can theoretically build, in practice it appears to be sufficient for the vast majority of models the students actually make. As a byproduct of generating the feedback as described above, our own understanding of the dynamics of the model improved and this in turn enabled us to formulate a new model for another patterning process during *Drosophila* development [20].

In order to structure the case as a whole, a pedagogical approach was developed which combined design principles with respect to the understanding of a complex biological system and with respect to a suitable model building approach.

Three of the principles that were used to help students to understand the biological system were originally developed to help students to understand basic electricity [17-19]. They concern the offering of a progression of models, the introduction of quantitative models after qualitative ones and the making of conceptual links from lower-level models to higher-level models. When these principles were originally developed and applied, increasing the understanding of basic electricity was the main goal. Here, these principles were integrated into an approach that was not only aimed at increasing the understanding of a mechanism, but

that also engages students in the scientific process of acquiring such understanding in an actual research situation.

In the described case, students are guided to build a model step by step. In actual research, such guidance is not present. Therefore we are planning to develop a digital case in future where students are not guided step by step, but have much more freedom to organize their model building process themselves.

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CHAPTER 6

Digital learning material for student-directed model building in molecular biology

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ABSTRACT

The building of models in order to explain data and make predictions, constitutes an important goal in molecular biology research. In order to give students the opportunity to practice such model building, two digital cases had previously been developed in which students are guided to build a model step by step. In this paper, the development and initial evaluation of a third digital case is described. It concerns the selection of bristles during *Drosophila* development. In order to mimic a real research situation in a more realistic way, students are given much more freedom while building their models, and can thus follow their own model building approach. At the same time, however, students are provided with a sufficient amount of support, in order to ensure that they can build their models without the requirement of intensive supervision.

INTRODUCTION

Many science courses are taught as sets of facts, rather than by explaining how the material was discovered or developed over time [1]. This implies that students rarely have the opportunity to practice model building themselves. However, this constitutes a major scientific goal of science. In order to enable students to practice model building for molecular biology, we had previously developed two digital cases in which students have to build models based on experimental data [2,3]. In these cases, students are guided through the model building process step by step, which means that they do not have to consider the overall approach they are following. However, in a real research setting, there is generally much less guidance than in the previously developed cases. Therefore, we also wanted to create a situation in which students are not guided step by step, but in which they have much more freedom and have no choice but to consider the general approach they are following. This is in line with the cognitive apprenticeship approach, in which students are guided to solve an authentic problem. As students gain more experience, this guidance gradually fades [4]. In order to avoid the need for intensive supervision, we again decided to use the computer and create a digital case in which students are given a certain amount of support, while still having enough freedom to organize the model building task themselves. This case is independent of the previously designed cases. However, having worked with the older cases

gives students some experience with the interpretation of experimental data and model building, which may be helpful to work with the new case. In this paper we describe the development and initial evaluation of this digital case.

CASE DESIGN

Below, we will describe the different parts of the case and present the most important design considerations. The case can be viewed at the demo site [5], and its structure is outlined in Figure 1.

In the introduction, the biological problem is presented to the students. The topic we chose was a pattern formation process which takes place late in the development of the fruit fly *Drosophila*: the selection of cells which will eventually develop into bristles [6]. The epidermis contains two cell types: those with a bristle ("hair") and those without. The cells which form a bristle become surrounded by epidermal cells which do not have a hair. At an early developmental stage, the cells are equal and all have the potential to develop into one of the two cell types. Small differences (noise) between cells initiate this pattern formation. A cell which obtains a slight increase in the concentration of a molecule which can cause a

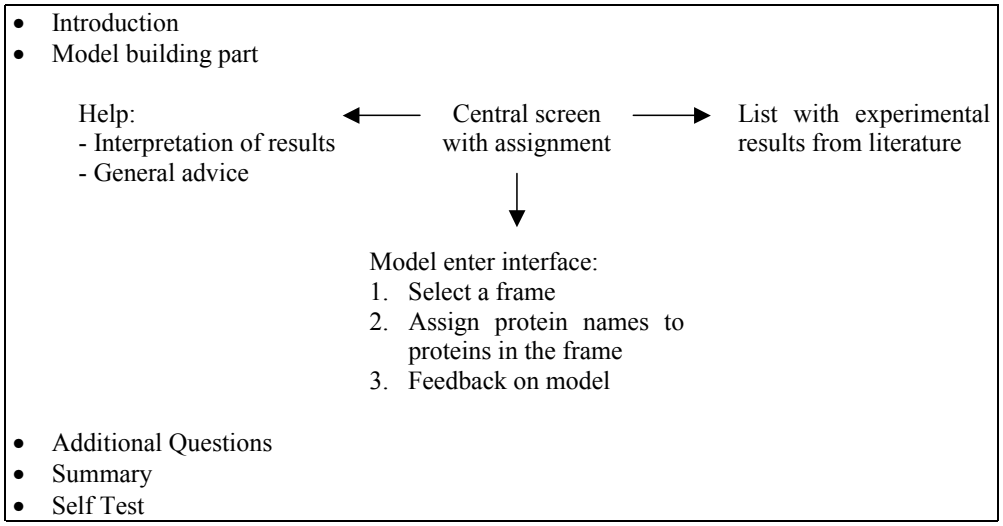

Figure 1. Structure of the case

bristle fate, will suppress the bristle fate in the surrounding cells, which subsequently causes the bristle fate in the central cell to increase even more. The surrounding cells will, in turn, affect all their surrounding cells, which allows patterning in the epidermis to spread. Thus, a random event is translated into a regular pattern. This is a more general principle in the development of organisms. It is, for example, considered to be the basis for the formation of stripes on the skin of zebras. We selected the *Drosophila* bristle formation because all the genes which are essential for this patterning have been identified, and all the biochemical functions of the encoded proteins are known as well. This set of genes seems to represent an evolutionary conserved module, because it is also essential for comparable pattern formation processes during other stages of *Drosophila* development, and also in other organisms [7].

In the model building part, students have to build a model based on a list with experimental results from literature, which can be accessed. They are stimulated to make a model with pen and paper first, since this is often the way it is done in research. As we wanted to provide

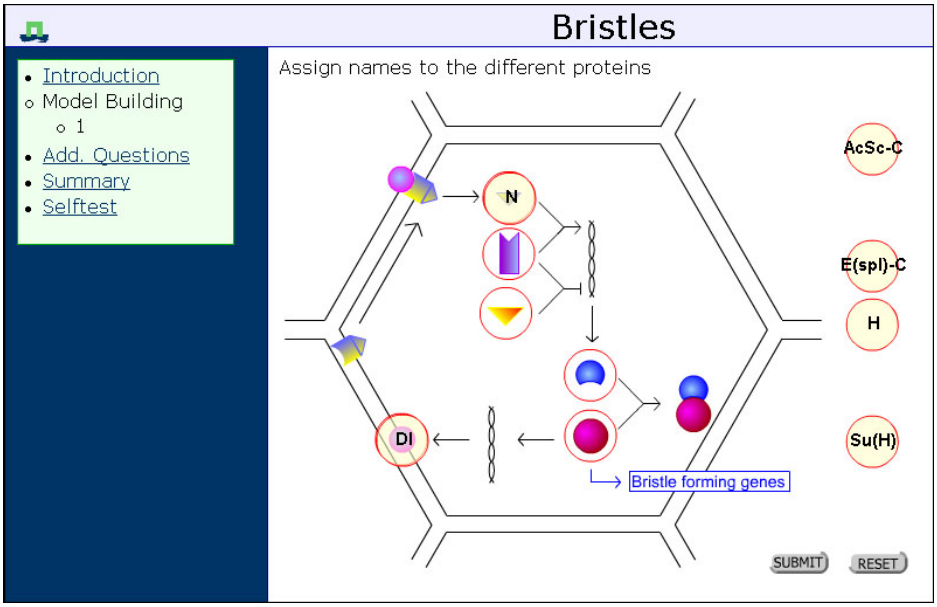

Figure 2. Screen dump of a model submission step: protein names are assigned to protein symbols by dragging and dropping.

students with feedback on the model they propose, it was necessary to design an interface which students can use to enter the model they drew on paper. The students can enter a model in two steps. First, they have to select one of twelve frames. A frame consists of symbols for different proteins with interactions among them, but without any protein names (an example can be seen in Figure 2). The interactions which can be found in the frame are those which are present in all cells prior to differentiation. In the second step, protein names can be assigned to the different protein symbols by dragging and dropping (Figure 2). With this relatively simple interface, it is still possible to enter more than 8000 different models. If students devise a model which is not included in this set of models, they can ask a supervisor for feedback.

Upon entering their model, the students receive feedback. If the students build a model which cannot, even in theory, account for the observed wild-type pattern in which a bristle cell is surrounded by epithelium cells, they will obtain feedback which explains why this is not possible. Subsequently, students are presented with a number of simplified models, which only contain proteins A and B. Here, students have to indicate whether these models could

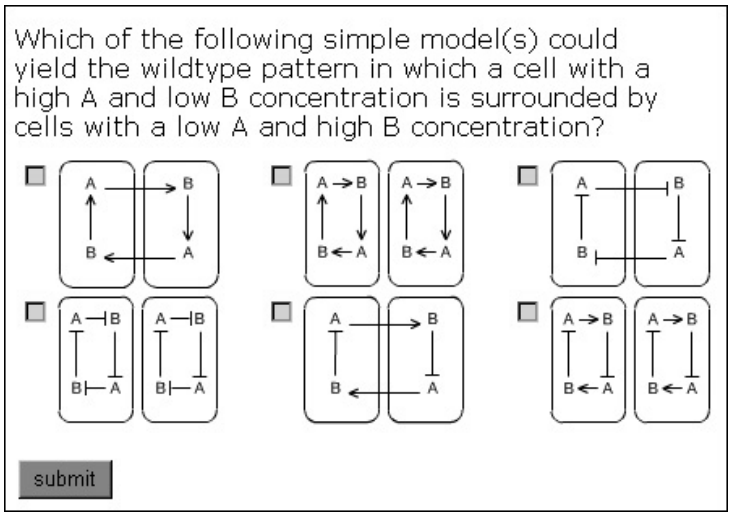

Figure 3. Screen dump with simplified models which students can select if they chose a frame which cannot account for the wild-type pattern formation.

theoretically account for a pattern in which a cell of one type is surrounded by cells of another type (Figure 3). By mapping their model onto such a simplified model, they should be able to avoid the building of a model which cannot account for the observed wild-type pattern afterward. If the students enter a model which can account for the wild-type pattern, but which is contradicted by one or more other experimental results, a number of experimental results are given, and the students have to indicate for each result whether or not it is in agreement with the model they proposed. This should help them to further improve their model. Thus, the feedback on the proposed model is given in such a way that it encourages students to find ways to improve the model on their own.

Besides giving feedback on the proposed model, we also wanted to offer students help during their model building process in such a way that they were less likely to become stuck. Therefore, we integrated a help function which can be accessed from the model building section. It offers two different kinds of help. Firstly, students can obtain help with the interpretation of the experimental results, which require the most reasoning steps. Upon selection of a result, a multiple choice question is given with different interpretations of the result, so that students first have to think about the interpretation on their own. Secondly, students can obtain some general advice on how to deal with the problem. They are stimulated to use a simplified model as a basis for a more elaborate model, and to start with the interpretation of experimental results which unambiguously show direct interactions among specific proteins.

After having built a model which can account for all the experimental data in the list with the results from literature, students move on to the additional questions section. The questions in this section are aimed at increasing the students' understanding of the pattern forming properties of their model and its biologically important features. The model ensures, for example, that two adjacent cells cannot both develop into bristles cells, which would make the epidermis too vulnerable. The case ends with a summary and a self test.

EVALUATION RESULTS

The case about bristle selection was used in a third year course on molecular developmental biology by 33 Dutch students, who had all worked with the two previously designed cases [2,3]. Even though the prior experience of the students was not completely identical, most students followed general courses on cell physiology, cell biology, biochemistry, and molecular biology earlier during their studies. 23 Students worked with the case while two supervisors were present, whereas the other 10 students worked with it at home because of scheduling reasons. The students who went through the case while supervision was present, mostly worked in pairs. While students were working with the case, tracking data were collected, which can be used to determine which models the students entered. Furthermore, evaluation forms were handed out afterward, and a question about the contents of the case was included in the exam at the end of the course on molecular developmental biology.

The students' general opinion of the case was assessed by means of evaluation forms (22 were retrieved). As shown in table 1, students gave the case a high overall rating (4.1 on a 1-5 scale), they liked working with it (4.2 on a 1-5 scale), and they thought they had learnt a lot from working with it (4.2 on a 1-5 scale). At Wageningen University, courses are systematically evaluated. Approximately 10% of the courses score lower than 3, about 70% score between 3 and 4, and about 20% score 4 or higher. Therefore, we were satisfied with these results.

Evaluation question	**Score**
	scale 1-5
Give your overall impression of the case (encircle the mark).	4.1
	1 (disagree) – 5 (agree)
I liked working with the case	4.2
I learnt a lot from working with the case	4.2

Table 1. Results of three questions on the evaluation form (n=22).

The main goal of the case was to offer students enough freedom, so that they can follow their own model building approach. In order to determine which approach students followed while building the model, and to verify that the case was indeed open enough to allow for different

approaches, a question about the approach which the students followed was included in the evaluation form as well. Most students started with the analysis of the experimental results in the library, wrote down their conclusions, and built a model based on these conclusions. It was found that there were differences in the precise order in which the experimental results were analyzed and in the way in which students organized their notes. After building their model, the students checked which of the given frames matched their model best, and subsequently positioned the proteins in this frame. If their first model was not in agreement with all the literature results, they used the feedback to further improve their model. Two students started with a simplified model which can explain the patterning that is observed in the wild-type, and extended this model with the help of the literature results. There were also some students who followed an approach which heavily relied on the structure of the case. Two students followed an approach which was aimed at systematically eliminating all the alternative models which can be entered in the case. Furthermore, there were a few students who submitted a model at a very early stage and used the feedback to improve this model step by step. In contrast to the others, these students probably submitted their first model based on guessing. They probably did not use trial and error while improving their model, since this requires considerably more time than improving the model based on reasoning. Thus, students indeed followed different approaches, most of which could, to a certain extent, also be applied in an real research setting, because they were independent of the specific structure of the case (with the exception of the feedback at the end).

During the design of the case, support was implemented in order to avoid the requirement of intensive supervision, while at the same time preserving the students' freedom to organize their model building task on their own. While using the case, 23 students and 2 supervisors were present, even though one supervisor would have been sufficient in this situation. The supervisors helped students when they became stuck, which can happen because the case does not guide students through the model building process step by step. When students became stuck, they usually overlooked one or more experimental results. Supervisors also answered a number of specific questions, and afterward they discussed the case in detail with a small group of students who deemed this useful. The case was also used by 10 students at home. Their judgement of the case could not be assessed separately, because the evaluation forms were anonymous. However, their exam scores were even slightly better than those of the

others (data not shown). In view of the above we conclude that the case already offered sufficient support for practical purposes. Nevertheless, based on the tracking data, the answers on the evaluation forms, and also on the informal talks with individual students, we are still planning to further improve the support given in this case. Firstly, tracking data have shown that students sometimes repeatedly selected frames which cannot explain the wild-type pattern formation. When students select such a frame, they are given feedback which explains why the frame cannot account for the wild-type pattern, and they have to select a simplified model which can explain this pattern. Students should then map an elaborate model onto this simplified model to check whether the elaborate model can indeed explain the wild-type pattern formation. Apparently, students do not always succeed in mapping the elaborate model onto the simplified one. Therefore, an additional question will be added in which students have to indicate which of the given frames can be simplified into the basic model that can yield the desired pattern. Secondly, a number of students indicated that they had some difficulties with the translation of their own model into a model which can be entered in the case. They suggested facilitating this process by adding a list with explanations of the symbols used, and by printing out the list with frames, so that they could first fill in the names of the proteins on paper. Therefore, we are indeed planning to add a list with symbols to the help section, and to hand out a printed list of frames in future.

Apart from testing the main goals of the case, we also included some questions about the whole course in the exam. This was done for several reasons: to test whether students had enough factual knowledge of the model for bristle selection; to check whether they understood the underlying pattern mechanism and implications of the model for the structure of the epidermis; and to test whether they were able to interpret an experimental result. Approximately 70% of the students had sufficient factual knowledge of the model. Usually, about two thirds of the students pass an exam, which is why we were satisfied with this result. However, only about 50% of the students performed sufficiently well on the other parts of the test. Therefore, the case will be improved in several ways. In order to better clarify the underlying pattern forming mechanism, an extra question will be added to the "additional questions" section. Furthermore, we realized that it is not necessary to interpret all the experimental results in order to build the final model. Therefore, we have decided to include a number of additional questions in the self-test. These questions will focus on the

interpretation of the results which require the most reasoning steps. The aim of this is to make sure that all students interpret these results at least once. Even though the exam question about a biological implication of the model was not answered satisfactorily either, the case will not be adjusted with respect to this feature: the case already contains a question which is similar to the one that was given on the exam.

DISCUSSION

Even though building models for molecular processes is an important aim in molecular biology research, there is still very little learning material available which gives molecular biology students the opportunity to practice the building of such models. In this paper the development and initial evaluation of a digital case is described in which students have to not only build a model, but also control this process on their own. It was found that students were indeed able to build their model according to their own approach. The fact that the students were able to use their own approach implies that the case indeed supports student directed model building. Furthermore, students appreciated working with the case and liked the challenge. The case contains support to avoid the requirement of intensive supervision. During our evaluation, one supervisor would have been sufficient for 23 students and 10 students even worked with the case at home. This led us to the conclusion that this group was indeed able to use the case with relatively little supervision, given the nature of the model building task.

The students who participated in the evaluation, had worked with two other cases before, which may have facilitated their working with the present case, as the previous cases had given them some training in the interpretation of experimental results and the building of models. Furthermore, students became acquainted with the symbols which are used to represent inhibition and stimulation. The present case does not require any factual knowledge of the specific models the students built in the previous cases. Therefore, the present case can also be used independently of the other cases if students have already acquired sufficient model building skills in another way. Furthermore, working with the case requires some prior knowledge about common regulatory mechanisms. Students need to know for example that transcription factors can induce or repress transcription of certain genes, that protein activity

can be modified by other proteins, that receptors in the cell membrane can confer signals upon ligand binding etc. It is also preferable that students have some knowledge of experiments that are generally used to elucidate signaling pathways to prevent an overload of new information.

Even though students were given a lot of freedom while working with the case described herein, there are still a number of differences with a real research setting. First, all the data which were given to the students were simplified and unambiguous. Furthermore, the data set was sufficiently complete to base a model on. Despite these simplifications, we still believe that the experience with the case can be useful for students in their further research. Not only is the nature of the experiments involved similar, but students also obtain at least some experience in deciding which experimental results should best be studied first, in organizing their notes, etc.

While building the model, most students followed an approach in which they first drew conclusions about individual interactions among proteins from a set of data. These interactions were then combined in their final model. With such an approach it is possible to build the model without thinking about its functioning. This could explain, for example, why the underlying pattern mechanism in the case requires more attention than expected in order for students to answer related exam questions correctly. A few students followed an approach in which they started with a very basic model which could account for the *in vivo* pattern forming behavior. They then mapped additional experimental data onto this model. It can, however, be a challenge to map more elaborate models onto simple models, which also seemed to be difficult for some of the students. This is why we have decided to include additional help with this mapping. In future, we intend to have students discuss advantages and disadvantages of different model building approaches, after having worked with the case described herein. Subsequently, we also aim to link these discussions to recent developments in molecular biology research. This research area faces the challenge of building models based on the massive data sets which were generated in "omics" research [8,9]. Discussions about different approaches which can be chosen to build these models, are of topical interest [8].

Thus far, we have only integrated model building in courses on developmental biology. However, we consider it to be important to also integrate some model building into other courses in which other types of experiments play a central role and other molecular

mechanisms are relevant. As a result, students would not only have to memorize existing models, but would also become aware of the different kinds of experimental data behind certain models. Furthermore, students would also acquire the skills needed to build such models on their own.

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CHAPTER 7

Concluding remarks

Designing experimental approaches and building models are important skills in molecular biology research. However, at the start of this PhD project, undergraduate university students hardly practiced experimental design, and did not practice model building at all. A pedagogical approach which offers students such practice is the cognitive apprenticeship approach [1], where students are coached to address authentic problems. The use of information and communication technology (ICT) is one way to implement such coaching. This project was aimed at constructing prototypes which illustrate how digital learning material can be used in order to realize university-level practice in designing experimental approaches and building models in molecular biology. Furthermore, it was aimed at developing principles to design such digital learning material.
In this section, the material which was developed will be reflected on first. Subsequently, we will discuss the most important design principles which were employed to develop the material. Finally, suggestions for future research will be given.

REFLECTION ON THE CASES

In this thesis, the development of a number of digital cases was described in which students practice experimental design and model building skills in molecular biology. The chapters describe cases with different structures. The cases can be viewed at the web-site belonging to this thesis [2]. Most cases were developed during several cycles of design, evaluation and adjustment. Ideas for improvements were obtained from observations of supervisors, remarks on evaluation forms, answers on exams, and tracking data, partly in combination with audio-tapes.
The cases were aimed at the acquisition of experimental design and model building skills in molecular biology. In the cases, students are supported both to design experimental approaches and to build models themselves. This should facilitate the design of new approaches and models, based on analogy. In order to assess whether students can indeed solve analogous problems after working with the cases, a number of exam questions were given.
In the exam questions on experimental design, students were asked to design an experimental approach which is analogous to an approach they designed in a case. The questions on model

building tested whether students could perform model building steps in situations which are analogous to the ones they encountered in the case: students were asked to design and/or interpret experiments in order to test certain features of a model, and to analyze the biological implications of the models they built in the case, or of analogous models. The questions on model building also tested whether students possessed factual knowledge of the model which they had built in a case. For more details about these questions, we refer to the respective chapters. The exam questions were generally answered satisfactorily, with the exception of the questions about the "Bristles" case which did not test factual knowledge. This case was evaluated only once. Since then, the case has been adjusted and future evaluations will have to show whether these adjustments are indeed sufficient. Most students who answered the exam questions had worked with the cases before. However, there were also a few students who took the exam, despite the fact that they had not worked with the cases. These students had very poor exam results. Even though more data are required for firm conclusions, these results suggest that working with the cases indeed facilitated the solving of analogous problems. It can therefore be argued that the cases are indeed useful to support the acquisition of experimental design and model building skills.

Obviously, one should not expect students to be expert experimental designers or modelers after some practice with the cases. This would require much more practice, especially with different kinds of problems. Furthermore, the cases offer substantial coaching, and this coaching needs to fade further. Actually, for the “Bristles” case (Chapter 6) there is already relatively little coaching present. Moreover, the cases focus on conceptual issues. All sorts of practical issues, such as reliability, availability of laboratory equipment, time requirements and costs are not included, while of course also being important in an actual research setting. Despite these considerations, we still expect that, with respect to the design of experimental approaches, working with the cases can provide a good basis to further develop this skill in a real research setting. It would of course also be helpful if students followed some practical courses during their study as well, such that they would already be familiar with some of the practical issues involved. For model building, the developed cases serve as an introduction. In order to enable more efficient learning in a real research setting, additional education may be required. In the cases, students evaluate the biological implications of a model after each modification. They do not take such implications into account in advance, because we

expected that it would be too hard for students to take such implications into account without some prior practice with the evaluation of biological implications. In order to increase the students' awareness of the potential of considering biological implications at an earlier stage, we hold the view that it would be useful to have them participate in a modeling process where this really makes a large difference. Another aspect which may require some elaboration during further education concerns the method of model building. In the "Bristles" case (described in Chapter 6), students are challenged to control their model building process themselves, and thus also choose a model building method themselves. In order to gain more from these experiences, a more elaborate reflection on the methods followed will be required. Lastly, in the "Dorsal-ventral axis II" case (described in Chapter 5), students are introduced to numerical simulations. In principle, this should be useful to facilitate the communication with more quantitatively schooled scientists should these students ever want to use such simulations in their later research. In order to use quantitative simulations all by themselves, however, more elaborate training would be required.

The cases are web-based and were designed in such a way that they are rather self-contained, thus requiring little human supervision. Furthermore, they can, in principle, be used independently of one another. During the project, this format made it possible to select different cases for different courses; to change the order in which students work with some of the cases, such that better connections with the lectures could be made; and, to a certain degree, it offered possibilities for self-study. This last option was important in order to deal with scheduling problems, and to review the cases at home to study for exams. Furthermore, the possibility for self-study was very useful to cope with differences in working pace. The time needed to go through a case varied largely among students, even if they had a very similar background. Students who did not manage to finish a case while supervision was present could, in principle, continue working with it at home, enabling them to stay in the course. Even though the cases are rather self-contained, students were always offered the possibility to work under supervision. In general, one supervisor was sufficient for twenty to fifty students.

The supervisors had several roles. Firstly, they coped with any technical problems. Secondly, they provided interested students with information which was not part of the actual subject matter. Thirdly, their presence helped motivate students to work seriously with the cases.

Lastly, they answered questions if students encountered any problems with the content while working with the case. With regard to this last point, it should be noted that, after several rounds of evaluations, the vast majority of regular students hardly encountered any such problems. During most of the evaluations described in this thesis, the main developer was one of the supervisors. By now, all cases have also been used without the presence of the developer. Even though this needs to be studied more systematically, evaluation results seem to be similar thus far, suggesting that a successful use of the material does not depend on the presence of the developer. The format of web-based, rather self-contained, independent modules also made it relatively easy to use some of the cases at another university: namely the University of Zurich, Switzerland. As the cases were easily accessible via the internet, a selection of cases could be made which best fit with the existing courses, and demands on supervisors were relatively low.

While developing the material, we also aimed to make the material suitable for groups which are heterogeneous with respect to prior knowledge. This was achieved not only by making the cases rather self-contained and thus allowing for different working paces, but also because the required prior knowledge was minimized. Ideally, students should be familiar with different experimental techniques before working with the experimental design cases. However, if this knowledge is not present, it can still be acquired by studying the library and by working with the "Basics case" (Chapter 2), which helps students select the parts of the library they still have to study. For model building, it is desirable for students to have followed some undergraduate (molecular) biology courses and that they are not unfamiliar with experimental approaches used in molecular biology research. The exact level of prior knowledge does not seem to be very important. The model building cases were used in three different third year courses, two at Wageningen University and one at the University of Zurich. Even though these students had followed different kinds of courses earlier in their studies, problems caused by lack of prior knowledge were not encountered with Dutch or Swiss students. Both the experimental design cases and the model building cases were also used by international students who were studying at Wageningen University. The variation in prior knowledge is larger among these students than among the Dutch students. Despite these differences, a large part of these students was able to work with the cases, even though some of them needed a considerable amount of time to work with the material and required quite some supervision.

Thus, it seems that the cases are indeed relatively suitable for heterogeneous groups with respect to prior knowledge.

REFLECTION ON THE DESIGN PRINCIPLES EMPLOYED

While developing the cases, a plethora of design decisions had to be taken. As noted in the introduction, we first decided to develop cases in which students engage in cognitive apprenticeship learning: they practice experimental design and model building by addressing authentic research questions while coaching is offered. These cases should form web-based, rather self-contained cases which can, in principle, be used independently of each other. In order to realize this, design principles needed to be made explicit. The design principles take the form of heuristics. Applying them can facilitate the design of the cases, but it does not guarantee success [3]. In this section we will give an overview of the different design principles for realizing practice in experimental design and model building in the form of digital cases. First, the design principles will be given, then examples of their application in the developed material will be described and reasons for their development will be discussed. Finally some of the design principles will be discussed further. Some of these design principles have not been described in the previous chapters, because of focus and space considerations. The principles are ordered according to the different stages of case design. It should be noted, however, that this order is not always followed strictly during the design process. The stages concern the selection of a topic, the structuring of the case into different sections, the structuring of the whole-task practice section(s) of the case, the presentation of information, and the implementation of student-computer interaction.

Topic Selection

Topic selection for experimental design

1. Select an experimental approach which is representative for a class of approaches which is widely used in research;
2. Select an experimental approach which consists of techniques that are frequently used in research;

3. Select a concrete authentic research question which illustrates the application of the experimental approach, and which is expected to motivate students.

In this project, for example, we followed the above design principles to develop five cases in which students create different kinds of transgenic organisms. Three of these cases illustrate the application of transgenic organisms in research. The research topics are derived from literature and include the molecular basis of intelligence, asthma, and the regulation of body weight. The other two cases illustrate the application of transgenic organisms in agriculture. The topics include the creation of salt tolerant tomatoes which can grow in otherwise almost infertile soil, and the creation of tomatoes which are resistant against certain pathogenic bacteria, thus decreasing the need for pesticides.
In general, problem solving can be facilitated by using analogy [4,5]. By applying the above design principles, it is more likely that, when students encounter problems in their later research, they will be able to solve them (partly) based on analogy to the problems they encountered in the cases.

Topic selection for model building

Select models which:

1. represent systems that often occur in biology, for example in different organisms;
2. illustrate more general regulatory principles in biology;
3. introduce many different classes of proteins, interactions, and other biological "building blocks";
4. include frequently reoccurring biological implications;
5. are based on experimental approaches that are generally applied in the respective research fields.

In this project, three pattern forming mechanisms during *Drosophila* development were selected according to the above design principles. Each mechanism shows much homology to mechanisms which are active during similar developmental stages in other organisms. One of the mechanisms chosen (bristles selection, see Chapter 6) is even active during different

stages of development in a single organism. The mechanisms illustrate different general regulatory principles, such as the functioning of feedback loops, the occurrence of emergent behavior, lateral inhibition, exploitation of random differences in gene expression rate among different cells, etc. A range of different biological "building blocks" is introduced, including regulation of transcription, regulation of protein activity by protein-protein interaction, regulation of protein activity by mediating intracellular localization, mediation of direct cell-to-cell communication by membrane bound receptors and substrates, and pattern formation resulting from differences in mobility. In addition, each mechanism illustrates how sharp borders between adjacent regions can be achieved robustly, which is a biologically significant implication shared by many developmental processes. Lastly, the models are based on generally applied experimental approaches, such as the creation of different kinds of transgenic organisms (mutants), approaches to visualize the localization of mRNA and proteins, protein-protein binding and promoter binding assays, etc. as well as combinations of these approaches.

As for the design principles to select a topic for experimental design, the above design principles should help students build future models based on analogy. For example, if students are guided to build a model in which differences in diffusion rate are essential for pattern formation, they may think of this "building block" in future when other, better-known "building blocks", such as regulation at transcriptional or protein activity level, are insufficient to account for the observed pattern formation.

Sections within a case

1. Divide the case into a part where students are involved in whole task practice, a summary and a self-test;
2. Start the whole task practice section(s) with the biological question and the precise assignment. Finish by providing some additional information about the original article, relevance, etc.
3. Make sure that the summary contains sufficient information, so that students who accidentally gave only correct answers and thus received little feedback, still obtain all the relevant information.

Each case with whole task practice which was developed during this project, contains this structure. An alternative to focusing on the global whole task practice is practicing local sub-skills separately first. Focusing on whole task practice is recommended within the cognitive apprenticeship approach in order to allow students to make sense of the sub-tasks they are carrying out, and to give them a goal to strive toward as they take on and integrate more and more of the sub-tasks. Furthermore, it can improve the students' ability to monitor their own progress. In addition, since it promotes an understanding of the purpose of various sub-skills, it can help clarify the conditions under which these are applicable, their entailments, their relationships to other processes, and so on [1].
The application of the design principles described above also appeared to be practical because the resulting structure of the cases was clear to students. Furthermore, the structure contributed to making each case an independent module.

Design principles to structure whole task practice

The chapters in this thesis describe the design of whole task practice according to different design principles. The design principles to structure whole task practice were developed with the paradigm of a cognitive apprenticeship approach, with web-based, rather self-contained and independent cases in mind. In particular, making sure that the cases are rather self-contained, influenced the nature of the assignments which can be given, and the learning goals which can be obtained. For example, we did not include assignments where students have to find information sources on the Internet or elsewhere themselves, since we considered it to be too difficult to automatically generate sufficient useful feedback with the computer for such assignments. In this section, all the different design principles which were used to structure whole task practice will be discussed, with the exception of the design principles which were used to structure the "Light Induction" case (Chapter 2). The final structure of this case relied rather heavily on specific experiences with students, and the principle used give little support for the structuring of new cases.

Designing experimental approaches

1. Coach students to design an experimental approach by having them design the overall approach first. The single experimental steps should be designed and performed afterward.

This design principle was employed in the experimental design cases where students design an approach to create a transgenic organism (Chapter 3). Such an approach consists of different experimental steps, such as a step where "foreign" DNA is inserted into a genome, a step where cells are selected which integrated the foreign DNA into their genome at the desired location, etc. In the case, students are first guided to design a sequence of such experimental steps. They also focus on advantages and disadvantages of alternative approaches. Only after completing this overall design, do they design the first experimental step in more detail. Then they carry it out virtually and continue with the next step until the approach is completed.
An alternative to the design principle presented here, would be to create a more open virtual laboratory in which students can perform a range of different experimental steps. Immediately after a step has been selected, it can be designed in more detail and performed virtually. However, applying the above principle supports the learning goals for an undergraduate course better than such a virtual laboratory. When using such a virtual laboratory, students may have to compare different experimental approaches which can all be useful in theory, but which have different implications in practice. Analyzing such practical implications does not fall within the scope of an undergraduate course. Actually, in the virtual laboratory, learning goals which could be achieved at the level of the overall approach influence those that could be achieved at the level of individual experimental steps, and vice versa. For example, if students have to consider an alternative way to make transgenic mice, which involves embryonic stem cells, it is necessary to increase the freedom students have to design a construct by including selection markers, which are necessary to select the desired embryonic stem cells. Alternatively, if students have to become acquainted with PCR, for example, this technique needs to be added to the virtual library, and this increases the number of different sequences of experimental steps which can be designed. By applying the design principle

given above, the design at the overall level and the level of individual steps are much less dependent on one another, which makes it possible to set learning goals for the design of both levels independently.

More generally, the ability to put relatively little stress on design at the lower level can particularly be favorable in a university setting. Designing at the lower level generally involves relatively many recurrent skills which can relatively easily be acquired in a professional setting. More stress can then be put on designing at the higher level, which can be much more difficult to learn in a professional setting. In this way, once they have completed their studies, students can develop sufficient competence in a rather large range of different professional settings in relatively little time. .

Building qualitative models with much coaching

1. Guide students to build a model according to the following model building cycle: First, a simplified model is built to explain the wild-type situation. Parts of this model are then tested and adjusted, based on additional data. After each adjustment, the biological implication of this adjustment is analyzed.

This model building cycle was employed in the “DV-axis I” case (Chapter 4).

An alternative to this design principle would be to analyze all the available data first, and to integrate all the conclusions into a model afterward. Which method is preferable may depend on the nature of the model in question. In order to determine this for the model which students build in the "DV-axis I" case, we had several molecular biology researchers build the model, based on a set of data. In this case, researchers who started with a model which could account for the wild-type phenotype, but not for all the additional data, eventually managed to build a model which could account for more data than the researchers who combined all the conclusions in a final model at once. We decided to have students start with a model which can account for the wild-type phenotype only, since this constitutes the simplest model which can still theoretically account for the phenomenon is should represent. The step of analyzing the biological implications of the adjustment of a model was added because historical studies show that model building can be facilitated if such implications are taken into account [6].

However, since the analysis of the biological implications can be rather challenging for certain models, students perform this analysis after building or adjusting a model, and not before. If feasible, it would actually be preferable for students to already take the biological implications into account while building or adjusting a model.
The design principle described above could be implemented with technically simple, closed questions.
Not only was the model building cycle practical to have students focus on specific aspects of building models, it was also useful to have students understand the model they were building. Two factors may have played an important role. Firstly, the analysis of the biological implications of each subsequent adjustment of the model, stimulates the students to go beyond viewing the model as a collection of gene names and arrows, and to consider its properties in their biological context. Secondly, the progression of models, which each describe the whole process but become increasingly elaborate, seemed to facilitate the understanding of the final model (even though more studies are required to confirm this). A progression of models is actually more commonly used to help students understand a topic (see e.g. [7-9]).

Building qualitative models with little coaching

1. Stimulate students to first build a model with pen and paper, based on a list of experimental results, and to enter this model in the computer afterward.
2. Provide a separate section which students can consult for support while building their model. Include general advice on how to tackle the problem, help with the interpretation of individual experimental results, and help with the entering of the model into the computer.
3. Provide students with feedback (questions) on their model which can help them to further improve it.
4. Provide students with additional questions about the behavior of the model and its biological implications after they have completed building their model.

These design principles were employed in the “Bristles” case (Chapter 6). In comparison with the "DV-axis I" case (Chapter 4) and the "DV-axis II" case (Chapter 5), students receive much

less coaching. This is in line with the cognitive apprenticeship approach, where students receive less coaching as they gain experience [1]. The students are stimulated to build a model with pen and paper first (design principle 1) in order to make the process resemble a research situation, and to ensure that their model building process is not influenced by the interface where students can enter their model. The students are thus provided with a lot of freedom. In case they encounter a problem with the building of their model, design principle 2 ensures they can still receive some coaching. The students can select the coaching they need themselves. Design principle 3 should activate students to improve the model themselves, such that they learn more from their mistakes. Design principle 4 should ensure that students view the model as a representation of a biological system with a certain behavior which has consequences for the organism. Furthermore, this last principle should also ensure that students do not view the model simply as a collection of protein names and symbols which represent the different interactions among them.

An important implementation feature of these design principles is the interface where students can enter their model. This interface will be discussed under "Implementing student-computer interaction".

A condition for applying the above design principles is that students should have sufficient knowledge of possible biological interactions and experimental techniques, and that they should have sufficient experience with the interpretation of such techniques.

Introduction to building quantitative models

1. Support students to follow the same model building cycle as for qualitative models: First, a simplified model is built to explain the wild-type situation. Parts of this model are then tested and adjusted based on additional data. After each adjustment, the biological implication of this adjustment is analyzed.
2. Coach students to build qualitative models first. If it is not clear whether a qualitative model can indeed account for certain experimental data, support students to build a quantitative model based on this qualitative model in a separate simulation environment.

3. Provide students with feedback on how to further improve their quantitative model, preferably by having students propose a subsequent step themselves. Make sure that the feedback makes the relationships between the characteristics of the quantitative model and its qualitative emergent behavior explicit.
4. Also support students to use the simulation environment during other model building steps which are hard to carry out based on qualitative reasoning alone.

These design principles were used in the “DV-axis II” case (Chapter 5). The model building cycle which is proposed (principle 1) is the same as for building qualitative models, since it was successfully used in the "DV-axis I" case (see also 7.2.3.2). Principle 2 ensures that quantitative models are preceded by qualitative models. The qualitative models should help students understand the biological mechanism by making connections with their intuitive knowledge [9]. Furthermore, qualitative models are useful in grounding quantitative understanding and they can serve in their own right for solving problems [10]. Principle 2 also ensures that a benefit of computer simulations in research is illustrated. For example, in the DV-axis II case, students find that qualitative reasoning is not sufficient to determine whether a limited set of different kinds of processes at the molecular level can lead to the pattern observed at the embryo level. By representing these molecular processes in a quantitative model, and by simulating this model numerically, they find that this limited set of molecular processes is indeed theoretically already sufficient to yield the pattern observed. Students thus experience that using computer simulations can be essential for the formulation of good hypotheses. Principle 3 should help students to understand the biological model, since it stimulates them to make conceptual links between the biological model at the level of the molecular processes, and its emergent behavior at the embryo level. A similar principle has been shown to be important for students with respect to their understanding of theory and their ability to solve problems in another field, i.e. basic electricity [11]. Principle 4, finally, is also aimed at illustrating the added value of computer simulations for research.
In order to implement the design principles, it is necessary to include an environment where students can perform simulation experiments. Under "implementation of student-computer interaction" the environment which was designed for this case is described.

Providing information

The following design principles concern the decision steps in the decision tree shown in Figure 1, as well as their implementation.

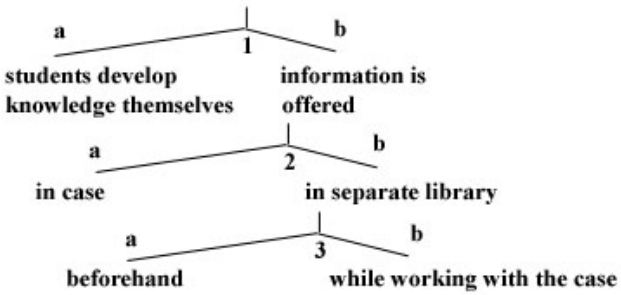

Figure 1. Decision tree for providing information

1a. Aim to have students develop knowledge about the final experimental approach or the final model on their own as much as possible. The same applies for knowledge about the solution of sub-problems, such as knowledge of which technique can best be used to test a feature of a model, and knowledge of the biological implications of different intermediate models.

b. Provide students with information about the specific research problem (including any experimental results from literature they need to use), general information about biology and experimental techniques, and information which helps students with steps that require so much reasoning that it can be too demanding for students to perform them all by themselves.

2a. Integrate information in the case itself if this information is very case-specific or fragmentary. This includes information about the specific research problem and information to help students with their reasoning.

b. Present information in a separate library if the information is rather general and could also be used for other cases. This includes information about biology and about experimental techniques. Aim to design the library in a modular way, such that it is

possible to study a certain part of the library without studying other parts. The library can also be used to present case-specific information which students need to consult several times while working with a case. This may include a list of experimental results from the literature which students receive at the beginning of the case and which they need to use while building a model.

3a. Stimulate students to study beforehand those parts of the library of which they have little prior knowledge or hold misconceptions. This can be achieved as follows: Offer students questions about the different modules of the library, based on common misconceptions which are identified by using exam results of previous cohorts of students. If students answer such a question correctly, make sure that they can continue with a question about another module in the library. If not, stimulate them to study the specific module in the library and have them answer additional questions about the same module.

b. Also stimulate students to use the information in the library just-in-time (JIT) while going through the case. This can be achieved by providing direct access from the case to the relevant parts of the library.

These principles were applied in all the cases. The cases about experimental design contain the most elaborate library. It contains explanations about single techniques, partly with movies, and it gives some general molecular biology information. Two of the cases about model building contain a limited library with experimental results from literature.

The first design principle is aimed at stimulating students to take part in the reasoning processes which are typical for the research task they engage in. The amount of information which is presented needs to be such that students are sufficiently challenged, but still able to perform the task. The size of the steps the students have to perform themselves can be determined as follows: First, the reasoning which is required for a certain step needs to be made explicit. Then, it can be estimated whether students have sufficient prior knowledge to carry out such reasoning, and whether the inference chain is not too long for students who haven't gone through a similar inference chain before. If the inference chain is too long, additional information can be given to support students with their reasoning. Alternatively, a question can be divided into sub-questions. The nature and order of these sub-questions

actually provides more implicit information about how the original question can be answered. However, even if the reasoning required is made explicit, it can still be hard to estimate whether a certain step size is suitable for students. Therefore, it is useful to perform tests with students as well, including small, informal ones during the very early stages of the design of a case.

The second design principle should ensure that information which is used repeatedly, is presented in one location. In this way, students can easily find the information. Furthermore, they can quickly see whether they have already studied the information before. Lastly, for the designer of the case it is clear which assumptions about knowledge of the theory can be made, since this theory is located at one place in the library.

Principle 3a stimulates students to study beforehand those parts of the library of which they have little prior knowledge. This is proposed for motivational reasons. If students have little prior knowledge of the information in a part of the library, it may require quite some time to study this information. It can be demotivating for students to study large amounts of information while going through a case, because they can get the impression that they are not coming any closer to solving the problem they are working on in the case. Principle 3a also proposes to stimulate students to study beforehand information of which they hold misconceptions. If students hold misconceptions about a topic, they are, almost inherently, not aware of this. Therefore, they may consider it to be superfluous to study the part of the library which presents the correct information. This can particularly be a problem if it is possible for students to progress through a case without being confronted with the misconceptions they hold. Lastly, principle 3a proposes a way to make sure that students only study those parts of the library of which they have little prior knowledge or hold misconceptions. In this project, this principle was applied in the "Basics case". Even though the format of the "Basics case" is very simple, adding it had a rather large effect on how students worked with one of the experimental design cases, namely the "Light Induction" case (Chapter 2). After introducing the "Basics case" and some other changes, the students' perceived understanding of the approach they designed in the "Light Induction" case increased, and the percentage of students who passed an exam question about it almost doubled. The necessity of explicitly dealing with differences in prior knowledge can also be illustrated by the observation that the

time students needed to go through the "Basics case" varied considerably, namely from less than half-an-hour to more than a day.

Principle 3b recommends that all information (also) be available JIT to students. An advantage of JIT presentation [12] is that students can go through the case even though they did not fully master the information which is needed to achieve this beforehand. Even if students studied some part of the theory not long before working with the case, it is still possible that they forgot some aspects of it again.

Vockell and Schwarz proposed a similar way to deal with misconceptions [13], which has, for example, been implemented in the Biology Project [14].

There is no unequivocal answer to the question of whether certain information can best be studied before or during a learning task [15]. In general, considerations of cognitive load [16,17] play an important role in such discussions: if studying the information imposes high cognitive load, it can best be studied beforehand; otherwise it can best be studied just-in-time [15,18]. However, the cognitive load which is imposed by certain information depends on prior knowledge [17]. Therefore, students with differences in prior knowledge may benefit from a different timing of information presentation. By applying the third design principle, students with low prior knowledge are indeed stimulated to study more information in advance. Thus, design principle three ensures a good student-specific balance between JIT information presentation and studying information beforehand.

Implementing student-computer interaction

If general design principles to structure the whole-task practice are available, the case can be structured according to these principles. In this phase of the case design, possibilities and limitations of the computer become more important. A very common way to implement student-computer interaction is to use multiple-choice questions and other relatively simple closed questions. In this project, such questions were used repeatedly, since they can be implemented very easily and still activate students to focus on certain concepts. A disadvantage of such questions is that students can develop an approach in which they evaluate each given option, which is usually not possible in an actual research situation, where there is typically not a limited set of given options. Furthermore, it offers students only

very limited possibilities to communicate their own ideas. In principle, numerous different interfaces can be programmed which allow for more open questions and more variation in students' input. Since we aimed at creating rather self-contained learning material, it became quite a challenge to implement sufficient feedback when students can give a high number of different inputs. Many different kinds of student-computer interactions were implemented in this project. It was particularly challenging to design student-computer interactions with sufficient input possibilities for students, in combination with sufficient support for the whole-task practice parts of the cases. Here, we will give design principles which can help to ensure that students are able to design experimental approaches, design and interpret individual experimental steps, build qualitative models with different degrees of coaching, and build quantitative models, each with sufficient feedback.

Ensuring that students can design an overall experimental approach

1. Have students select and order experimental steps, in order to enable them to propose an overall experimental approach.
2. Test whether the proposed approach has a certain characteristic. If it does not, provide students with feedback; if it does, test for the next characteristic.
3. Organize the feedback in such a way that students receive feedback on the most basic mistakes first, and on the less fundamental mistakes after that. If applicable, finish with feedback on how to optimize the proposed approach.

These design principles were applied in all the cases where students design an experimental approach (Chapters 2 and 3). The experimental steps constitute, for example, the making of a construct, the injection of the construct into an oocyte, the determination of the genotype of F0 mice, etc. In order to give feedback, it is often first checked whether the proposed approach contains a number of absolutely essential experimental steps, and does not contain any steps which should not be included. If "make a construct" is missing for example, students receive feedback that it is necessary to make a construct in order to create a transgenic organism. Next, it is often checked whether the proposed order is possible from a logical point of view. For example, a construct must be made before injecting it into an oocyte

and not vice versa. Again, students receive feedback if they propose a non-logical order. Often, it is possible to design alternative experimental approaches, which differ from one another with respect to the way the construct is entered into cells, and further experimental steps which depend on this. After the tests which ensure that students propose a logically consistent approach, it is usually tested whether the proposed alternative is indeed applicable. Next, it is often checked whether the proposed experimental steps are indeed sufficient to draw conclusions, and finally it is sometimes checked whether the exact arrangement of some of the experimental steps is the most practical one.

The first design principle enables students to propose a large number of different approaches (e.g. about 1.3 billion different approaches if twelve different experimental steps are offered). In contrast to multiple-choice questions, for example, it is not possible for students to simply scan each of the different possibilities. By carefully selecting a set of experimental steps which will be offered to the students, the learning goals can be mediated in a rather precise way.

Because of the potentially large number of different approaches which can be proposed, formulating feedback for each possible approach individually is not feasible. By applying the second design principle, it is possible to cover a large group of different approaches with a single test and corresponding feedback. For example, by testing whether a construct is made before injecting it into an oocyte and not vice versa, up to about half a billion possible answers can be covered if twelve different experimental steps are offered.

The third design principle makes it possible for students to receive feedback on the different reasoning mistakes they made. Furthermore, since the design principle ensures that students improve their approach as a whole step by step, students can become aware of the benefits of certain approaches as a whole. These advantages are not achieved by a commonly used, much more direct way to cover all options, i.e. by testing whether the first step proposed is the first step in the optimal solution, by subsequently testing whether the second step proposed is the second step in the optimal solution, etc.

An implication of offering feedback according to the third design principle is that students who design the desired sequence at once obtain considerably less feedback than those who initially design a sequence which still needs much improvement. Even though this may be

advantageous, it should also be taken into account that students who design the desired sequence at once might miss out on information they could benefit from.
The above design principles were initially designed to enable students to propose an overall experimental approach, but similar principles have been used for other purposes: most importantly to enable students to propose a DNA construct which consists of several genetic elements.

Ensuring that students can design, perform virtually and interpret single experiments.

1. Have students make authentic experimental design decisions; generate experimental results based on these decisions; and support students in drawing the proper conclusions, based on the generated experimental results.
2. As designer, do not produce images of all possible experimental results in advance. Instead, formulate rules with which the experimental results can be generated.
3. Also employ rules in order to give feedback. It can be practical to base these rules on the experimental result, which is generated by the computer, instead of basing it on the input of the students directly.

These design principles have been applied in the experimental design cases (Chapters 2 and 3). For example, in the "Body Weight" case, students have to check with southern blot analysis whether the cells they used integrated the DNA construct they designed in the desired position in their genome. Students have to make design decisions which are similar to those that have to be taken in a laboratory: They have to make a selection from the restriction enzymes and the probes, based on a picture of the wild-type gene and the construct they designed. In these pictures sites where restriction enzymes can cut the DNA and different possible positions for a probe are indicated. Taking into account that students can design several different constructs, 640 different combinations of design decisions can be entered, many of which lead to different results on the southern blot. The sizes of the fragments which will be visible on the southern blot, are calculated based on data on the sites where restriction enzymes can digest a certain DNA fragment, on the position of the selected probe, on the DNA fragments which are present in the student's construct, and on the location where the

construct is integrated in the host cells in different samples. These calculated sizes are then used to generate the image of the southern blot. The sizes of the fragments can give information about whether some of the students' design decisions were useful: if the different fragments have the same size, the southern blot cannot distinguish between different options and is therefore not useful. This information is used to offer students feedback in the form of a question in which they have to indicate which conclusion they draw.
The first design principle should ensure that design decisions in an actual research setting are mimicked, such that students develop thinking strategies which can also be applied in such a setting. The second design principle prevents the need to produce many different images by hand, which would require a considerable amount of time. In the example given above, only two images (one of an empty blot and one of a "band") needed to be made by hand, instead of hundreds. The third design principle prevents the need for the designer to reason about each possible combination of decisions separately in order to give feedback. In the example above, considering all 640 different possible student inputs separately would be rather cumbersome. Instead, since the number of different bands in certain lanes of the southern blot can give all the information needed about the usefulness of the student's design decisions, it was sufficient to consider 6 different combinations of numbers of bands.

Ensuring that students can build a qualitative model

1. First have students draw a model with pen and paper, based on a list of experimental results from literature.
2. Have students enter their model by selecting a frame, and by positioning proteins in this frame with dragging and dropping afterward.
3. When generating feedback, first check whether the selected frame can yield the wild-type behavior. If not, provide a simple closed question which activates students to consider which kind of frames can yield the observed behavior.
4. Check whether the remaining models are in agreement with a set of experimental results. If the students' model is not in agreement with some of the results, provide a multiple answer question in which students have to indicate which experimental results contradict their model. As designer, do not consider for each of these models

whether they are in agreement with the set of results. Instead, formulate requirements which a model has to fulfill for it to be in agreement with a certain result. Choose the set of experimental results in such a way that the results allow for clear and unambiguous conclusions and in such a way that students cannot enter any models which are in agreement with this limited set of experimental results, but not with one of the other results given.

These design principles are applied in the "bristles" case (Chapter 6).
The first design principle aims to stimulate students to build a model in a way it is often done in research, and it ensures that students are not restricted by the interface with which they have to enter their model.
The second design principle ensures that students can enter quite some different models. In the bristles case, for example, students have to select one of twelve frames and position 6 proteins in a frame, such that they can enter a total of approximately 8600 different models. Despite this high number of possible models, it is still possible that students come up with a model which cannot be submitted. If so, students are required to ask a supervisor if they want to receive feedback on their own specific model, which they may not always do. An alternative would be to enable students to make their model on the computer with different proteins and genes, different interactions among them, and different intracellular localizations as building blocks. This would be attractive, since it allows for the entering of many more different models. However, we expect that it would require much more time for the designer to develop and implement such a format, especially if the aim were to implement specific feedback as well.
The first two principles imply that, before entering their model, students need to convert their representation of their model into the representation which is used in the case. This may make them aware that different ways of representation are possible.
The third design principle stresses how important it is that a model can, at least theoretically, account for the phenomenon it should represent. Furthermore, the principle can facilitate the giving of feedback. For the “Bristles” case, it was sufficient to consider the frames in order to test whether the model can yield the wild-type pattern, in which a cell of one cell type is

surrounded by cells of another cell type. Since 7 out of 12 frames cannot yield the wild-type pattern, this test covers approximately 5000 different models.
The fourth design principle stimulates students to evaluate their model in a way that can also be used in research. By formulating requirements which a model has to fulfill for it to be in agreement with a certain result, it is not necessary to consider each model separately. For example, if it can be concluded from a certain experimental result that protein A and B physically interact, these proteins must be positioned in the frame, such that they do indeed physically interact. The possible positions for each frame can be given without considering any proteins on any of the other positions. Therefore, a limited number of tests are sufficient to check whether a large number of different models is in agreement with a certain experimental result. In the "Bristles" case, about 10 tests are sufficient, on average, to determine for each of the remaining 3600 different models whether or not they are in agreement with a certain experimental result. Selecting the set of experimental results which are used in the feedback question in the way that is suggested by the fourth design principle, further facilitates the development of this feedback question.

Ensuring that students can build and numerically simulate a quantitative model

1. Give students the following support while they build and simulate the model.
   - Give students a clear assignment once they have entered the simulation environment;
   - Support students with the formulation of differential equations: Have students indicate which biological processes influence the concentration of a certain protein (e.g. complex formation with another protein). Let the program subsequently show the terms for these different processes in the (partial) differential equation which describes the concentration changes of this protein over time;
   - Support students to enter the initial localizations of proteins or other biological players, by having them choose between the pictures of the biological systems, where different regions are marked;
   - Provide default values for different parameters, in order to give students some direction in their search for suitable parameter values;

- When students want to run a simulation, first have the program check whether the student's model is mathematically consistent. Give feedback on how to change the model if this is not the case;
- Give students feedback which helps them to consider the next step to be taken or to draw certain conclusions, after they have run a simulation.

2. If students have to build a certain model, provide a feedback question in which students have to propose how they will improve their model. Explain to students why the proposed change is useful or not in such a way that biological aspects are coupled with characteristics of the quantitative model and its behavior. Implement such feedback questions based on the qualitative behavior of the model.

In the simulation environment described in Chapter 5, these design principles are applied. The first design principle ensures that students can use the simulation environment with only very limited mathematical knowledge and without any knowledge of programming. Furthermore, it ensures that students are guided to work with the simulations efficiently. In this way, students are not distracted too much from the biology, and they learn how simulations can be employed in an efficient way.

The second design principle should help students develop a better mental picture of the relations between the biological processes, the characteristics of the quantitative model in terms of differential equations, and the behavior of the model. Furthermore, it should prevent the more generally observed problem that students operate simulations without thinking enough about the process [19].

If students can enter many different combinations of parameter values, and if the model is not solvable analytically, the implementation of an adequate feedback question can be very challenging. By basing the implementation of the feedback question on the qualitative behavior of a quantitative model, the feedback question can still be implemented insofar as the different qualitative behaviors are known. The following example illustrates this. In the simulation environment described in chapter 5, students can enter models which, to our knowledge, cannot be solved analytically, such that the exact rules which determine the behavior of the models are not clear. Furthermore, students have to assign values to 11 different parameters, and given the range of values the interface allows them to enter, they can

enter more than 10^{20} different combinations of parameter values. It is not feasible to run all possible simulations while implementing the feedback question, since this would take more than 10^{14} computer years if each simulation experiment takes about one minute. Nevertheless, the number of qualitatively different behaviors seems to be limited. Examples of qualitative behaviors are that one single peak of the protein Dpp can be formed in the dorsal part of the embryo, that two peaks can be formed in the dorsal part of the embryo, or that one peak can be formed in the dorsal part of the embryo and one in the ventral part, etc. In order to give the feedback question, it is not only necessary to know the different kinds of qualitative behaviors the model can show, but also to understand how this qualitative behavior is affected by changes in parameter values. This understanding can be obtained by changing different parameter values when the model shows a certain qualitative behavior, by thinking up qualitative explanations for the observed effects, and by assessing the value of the explanations by testing whether they can be used to predict the behavior of other models correctly. The obtained understanding can then be used to implement the feedback question. For example, if a student's quantitative model forms a single Dpp concentration peak in the dorsal part of the embryo which is lower than the peak measured in real experiments, and the student proposes to increase the concentration of the protein Sog, then feedback can be given which indicates that an increased Sog concentration may indeed lead to the desired formation of a steeper peak, since more Sog is available then to transport Dpp to the dorsal part of the embryo. Thus, by testing the qualitative behavior of a quantitative model, it is possible to implement the suggested feedback questions. A problem is that it cannot be guaranteed that all different possible models are covered. However, by testing the simulation environment with many students, it becomes likely that the models which are most commonly built by students, are covered. Actually, the costs of implementing this principle turned out to be rather high. In this case, the costs were balanced by increased understanding of the dynamics of the system in terms of a new model for another patterning process during *Drosophila* development [20]. This was thus an example of a situation where educational activities served as a stimulant to view the topic from an alternative perspective, which directly affected research.

It is seen as a general problem that students tend to operate simulations without thinking enough about the process. A general design guideline in literature to prevent this, is to impose

"costs" or burdens on actions in order to stimulate reflection at key times. Costs may include key press / move limits, time constraints, manipulation of alternate representations of an object, or deliberately cumbersome procedures [19]. The feedback questions suggested above form an alternative to stimulate reflection.

FURTHER RESEARCH

In this section, suggestions for further research will be given with respect to the cases developed in this project, as well as with respect to the explicated design principles. Finally, we will plead for more developmental research on molecular biology education at university level.

The cases which were developed during this thesis could be used for future research in four ways. Firstly, the cases could be evaluated in other educational settings, e.g. at other universities. The fact that the cases are web-accessible and rather self-contained should facilitate such evaluations. These evaluations could also yield additional ideas to further improve the cases with respect to their suitability for different educational settings. Actually, the evaluations performed at the University of Zurich already form a first step in this direction.

Secondly, if the cases also appear to be successful in a larger variety of educational settings, large scale evaluations could be initiated, for example on the learning effects of the cases. Actually, such larger scale evaluations often follow successful smaller scale evaluations in developmental research [3].

Thirdly, it is conceivable that the implementation of the cases also affects learning outcomes on themes which do not directly concern the cases. For example, when students are presented with a new technique, they may more carefully evaluate which kind of research questions can be addressed with this technique. Therefore, it could be interesting to study the influence of the cases on other education programs. For example, a lecturer who used the experimental design cases in his course, noted that students' scores on questions which do not directly concern the cases, improved by about 20%. It would be worthwhile to see whether this observation could be confirmed with more systematic studies.

Fourthly, partly related to the above point, the cases could also be used as a tool for more fundamental research on problem solving. Much work on problem solving has involved the use of puzzles in very artificial domains [21,22]. Research has also been carried out on the nature of expert problem solving in knowledge rich domains, including molecular biology [23,24]. Studying precisely what subjects learn from working with the cases, gives the opportunity to gain more insight into how such expertise can be developed.

The design principles explicated in this chapter should facilitate the development of new cases on experimental design and model building in molecular biology. The design principles should, in principle, also be applicable in the design of digital learning material for other experimental molecular life sciences which are hypothesis driven and not purely descriptive in nature. These include such large research areas as cell biology, genetics, and physiology. In order to assess whether the design principles can indeed be applied for the above purposes, additional studies are required. These include an evaluation of the usability of the principles for designers (i.e. as a component of process evaluation) as well as an evaluation of the resulting cases (i.e. as a component of product evaluation).

Even though the design principles described in this thesis can be useful for the future development of other cases which focus on experimental design and model building in part of the life sciences, additional design principles will need to be developed as well.

Firstly, design principles are needed for topics where the developed principles are not suitable. In particular, students can only be guided to design an experimental approach by designing the overall approach first and designing individual steps in detail afterward, if a subsequent step in an approach does not strongly depend on the results of a previous step. If the outcome of a step strongly influences which step can best be taken afterward, it may be more useful to create an environment where students can select an experimental step, design it in detail, carry it out, and select a subsequent experimental step depending on the obtained results. More concrete design principles need to be developed for the implementation of such an environment. Furthermore, having students build a model by starting with a simplified one, which is then adjusted step by step based on additional experimental results, is not always desirable or even feasible either. In certain cases, it may, for example, be more suitable to have students interpret all the results before they start building the model. For such an approach, additional design principles are needed as well.

Secondly, in this project, design principles were formulated for the introduction of students to quantitative models in molecular biology which form a set of reaction-diffusion equations, and to numerical simulations as a way to assess the behavior of such models. Given the increasing importance of quantitative thinking in the molecular life sciences, we hold the view that students should also be introduced to different kinds of quantitative models, such as cellular automata [25,26] and visco-elastic systems [27,28], and to alternatives ways of analyzing the behavior of quantitative models in other biology courses. When integrating quantitative thinking into biology courses, it is possible to apply the general design principles described in chapter 5a, in order to achieve this. These principles state, amongst other things, that the use of a quantitative tool for biological research should be illustrated clearly, that the current mathematical knowledge of the biologically oriented students should be sufficient to follow the education, and that students should be coached to work with the quantitative tools effectively, such that they are not distracted too much from the biological aspects. In order to structure education more concretely, some of the more specific design principles developed may also be used, but it is likely that new design principles will be needed as well.

Thirdly, additional design principles need to be formulated in order to ensure that students learn to use strategies to structure their experimental design and model building tasks themselves. In most of the material which was developed during this project, students follow a strategy while participating in whole task practice, but the strategy they follow is determined by the learning material. In order to achieve that students are be able to apply such strategies themselves, they need to be conscious of the strategy they followed. This can be achieved in two different ways. Within the cognitive apprenticeship approach, it is advised to have students make the strategies they followed explicit, and to have them discuss advantages and disadvantages [1]. In this project, students had the opportunity to do this, though in a limited way, when they answered some of the questions on evaluation forms (for the cases described in Chapters 4 and 5). However, more elaboration would be needed here. Instead of offering students strategies and having them analyze these strategies afterward, a problem posing approach can be applied [29]. There, students are stimulated to solve authentic problems which they may not be able to solve yet, because they lack suitable strategies. The learning of these strategies is then dictated by the questions which arose while students tried to solve the authentic problem. Actually, the "Bristles" case (Chapter 6) could also be used in such a

problem posing approach, since it challenges students to solve an authentic problem by applying their own model building strategies.

Another facet which requires additional research, concerns the actual process of implementing the design principles. Such an implementation requires advanced knowledge of the subject matter as well as programming skills. Senior researchers usually possess most of the content knowledge, and because of their research, they tend to stay informed about new developments. This is particularly important in the molecular life sciences, which still yields many new insights, including such fundamental ones that even basic text books need to be updated regularly. However, such researchers usually have little, if any, experience with programming Internet sites. The task of actually developing digital learning materials should therefore not be allocated exclusively to them. Thus, it is necessary to define subtasks and ways of communication between the researchers and other experts. This can especially be rather challenging if many elaborate student-computer interactions need to be implemented, which is necessary in order to apply the design principles that were made explicit in this project. When addressing this problem in further research, partial solutions which have been formulated for other disciplines [30] could be made use of. Furthermore, the application of the design principles may also be facilitated if standard editing facilities are available for advanced closed questions which allow subject matter specific aspects to be entered without requiring any knowledge of programming. Such editing facilities could, for example, be developed for the question where students have to select and order experimental steps. Actually, based on the experiences gained within this project and other similar projects at Wageningen University, a larger project has been initiated on the design and implementation of advanced closed questions [31].

In this PhD project, developmental research was used as a research method. Developmental research and related research types are slowly gaining importance in order to realize innovations in molecular biology education at university level. In the United States, for example, the National Science Foundation finances "proof-of-concept" projects [32]. The expected outcomes of such projects consist of a prototype which addresses a nationally recognized need and is based upon sound, effective pedagogy; a pilot test of this prototype; a report of the results of this evaluation; and a dissemination of the prototype to the professional community. If "proof-of-concept" projects are successful, there are also supplementary funds

available for full-scale development projects. In this way, developmental research has become part of a strategy to realize educational innovations at large scale. We plead in general for more developmental research in molecular biology education, such that faculty members are supported to innovate their education and, in turn, students can be better prepared for their future research.

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NEDERLANDSE SAMENVATTING

Digitaal leermateriaal voor experimenteel ontwerp en modelontwikkeling in de moleculaire biologie.

Het ontwerpen van experimentele benaderingen is een belangrijke vaardigheid binnen moleculair biologisch onderzoek en het opstellen van zowel kwalitatieve als kwantitatieve modellen wordt in hoog tempo belangrijker. Aangezien universitair onderwijs in de moleculaire biologie erop gericht is onderzoekers op te leiden, vinden we het belangrijk dat studenten tijdens hun studie al een begin maken met de ontwikkeling van bovenstaande vaardigheden. In het algemeen kunnen cognitieve vaardigheden aangeleerd worden door ze te oefenen in de context waarin ze later zullen worden toegepast. Aan het begin van dit promotietraject kreeg slechts een deel van de studenten enige oefening in het ontwerpen van experimentele benaderingen; aan het opstellen van modellen werd zelfs nagenoeg geen aandacht besteed.

Een algemene onderwijskundige benadering waarbij studenten cognitieve vaardigheden in context oefenen, is de „cognitive apprenticeship“ benadering die geïnspireerd is op de klassieke meester-gezel relatie. Bij deze benadering worden studenten begeleid en ondersteund terwijl ze werken aan authentieke problemen. Naarmate de studenten meer ervaring hebben, krijgen ze minder begeleiding of krijgen ze complexere opdrachten. Het oefenen van experimenteel ontwerp en modelontwikkeling kan ertoe leiden dat toekomstige, vergelijkbare, taken gemakkelijker uitgevoerd kunnen worden door gebruik te maken van analogie.

Informatie en communicatie technologie (ICT) kan gebruikt worden om verschillende graden van ondersteuning te realiseren, in overeenstemming met de cognitive apprenticeship benadering. Het gebruik van ICT heeft ook een aantal andere voordelen, vooral wanneer digitaal leermateriaal ontworpen wordt in de vorm van internetgebaseerde modules die onafhankelijk van elkaar gebruikt kunnen worden en die in principe ook geschikt zijn voor zelfstudie. Het is bijvoorbeeld mogelijk om experimentele resultaten te genereren op grond van de ontwerpkeuzes van de student, om studenten numerieke simulaties uit te laten voeren van een kwantitatief model en om verschillen in voorkennis en snelheid van werken tussen

studenten op te vangen. Hoewel het aantrekkelijk lijkt om digitaal leermateriaal te ontwikkelen op basis van het cognitive apprenticeship paradigma voor het leren van eerdergenoemde vaardigheden, zijn er hiervoor nauwelijks ontwerpprincipes beschikbaar.
Ontwikkelingsonderzoek is een type onderzoek dat gericht is op het ontwikkelen van ontwerpprincipes voor het vervaardigen van onderwijsinterventies door gelijktijdig prototypes te ontwikkeling die de toepassing van deze principes illustreren.
In dit project wordt ontwikkelingsonderzoek toegepast om ontwerpprincipes op te stellen voor het maken van digitaal leermateriaal op universitair niveau, waarmee studenten het ontwerpen van experimentele benaderingen en het bouwen van modellen in de moleculaire biologie kunnen oefenen. Tegelijkertijd worden prototypes ontwikkeld die de toepassing van deze ontwerpprincipes illustreren.
Het hoofdgedeelte van dit proefschrift beschrijft de ontwikkeling van verschillende digitale cases, inclusief de overwegingen die bij de ontwikkeling een grote rol speelden en inclusief evaluatieresultaten. In de hoofdstukken 2 en 3 worden cases beschreven waarin studenten een experimentele benadering ontwerpen en in de hoofdstukken 4, 5 en 6 worden cases beschreven waarin studenten een model opstellen.
In de „Light Induction“ case (H2) ontwerpen studenten een bepaalde cloneringsbenadering stap voor stap. Om dit te kunnen doen, is kennis van verschillende cloneringstechnieken vereist. Deze technieken worden uitgelegd in een aparte digitale „library“ (bibliotheek). De case bevat directe links naar de relevante delen van de library, zodat studenten informatie in de library kunnen raadplegen op het moment dat ze deze informatie ook nodig hebben. Deze „just-in-time“ benadering bleek echter niet voldoende. Om de studenten te stimuleren om stukken uit de library te bestuderen waarover ze nog weinig voorkennis bezitten of waarover misconcepties bestaan, is de „Basics case“ ontwikkeld. Op grond van conceptuele fouten die in antwoorden op examenvragen geïdentificeerd zijn, is voor iedere techniek een meerkeuzevraag opgesteld. Wanneer een student een vraag niet goed beantwoordt, wordt hij gestimuleerd om het betreffende deel van de library te bestuderen en wordt hem een aantal andere vragen over dezelfde techniek gesteld. Wanneer de student de vraag wel goed beantwoordt, dan kan hij meteen doorgaan met een vraag over een volgende techniek. De leerresultaten van een tweede groep studenten die deze module eerst hadden bestudeerd waren

aanzienlijk beter dan de leerresultaten van de groep studenten die geen toegang hadden tot deze module.

In „The Brain“ case (H3) ontwerpen studenten een experimentele benadering om een transgene muis te maken. Uitgangspunt hierbij was om de studenten meer vrijheid te geven dan bij de „Light Induction“ case. Uiteindelijk is gekozen voor een opzet waarbij studenten eerst de grote lijnen van de benadering ontwerpen en daarna de individuele experimentele stappen verder uitwerken. Met deze opzet was het mogelijk om heel precies gewenste leerdoelen na te streven. Een belangrijk onderdeel bij het ontwerpen van de grote lijnen is het maken van een selectie uit een aantal experimentele stappen en het op volgorde zetten van deze stappen. Dit biedt de student de mogelijkheid om een groot aantal verschillende benaderingen voor te stellen (bijvoorbeeld ongeveer 10 miljoen wanneer 10 verschillende stappen aangeboden worden). Door op bepaalde karakteristieken van de benaderingen te testen, is het toch mogelijk op al deze opties nuttige feedback te geven. Bij het uitwerken en uitvoeren van digitale experimenten zijn er situaties waarin de studenten een groot aantal keuzes maken. Door de computer de resultaten te laten berekenen en op grond van deze resultaten afbeeldingen te laten genereren, kunnen studenten de resultaten van hun persoonlijke ontwerpkeuzes zien, zonder dat hiervoor veel tijd geïnvesteerd moest worden tijdens het ontwerpen van de case. Naast „The Brain“ case, is er een viertal andere cases ontwikkeld met dezelfde algemene opbouw.

In de „DV axis I“ case (H4) wordt de student begeleid om stap voor stap een model op te stellen voor een patroonvormingsmechanisme vroeg in de ontwikkeling van de fruitvlieg *Drosophila*. Eerst ontwerpt de student een zo eenvoudig mogelijk model om het wild-type expressie patroon van een aantal genen te kunnen verklaren. Dit model wordt stap voor stap aangepast op grond van nieuwe experimentele resultaten. Na iedere aanpassingsstap wordt de student gestimuleerd de biologische implicaties voor het embryo als geheel te analyseren. Voor deze benadering was gekozen op grond van expertanalyse en historische studies. De benadering kon met behulp van technisch relatief eenvoudige gesloten vragen geïmplementeerd worden.

In de „DV axis II“ case (H5) wordt de student begeleid om stap voor stap een model op te stellen voor een ander patroonvormingsmechanisme vroeg in de ontwikkeling van de fruitvlieg *Drosophila*. Bij stappen die moeilijk uit te voeren zijn zonder additionele

hulpmiddelen, gebruiken studenten numerieke simulaties in een aparte simulatie-omgeving. Zo gebruiken ze computersimulaties bijvoorbeeld om na te gaan of een beperkt aantal interacties op moleculair niveau al verantwoordelijk kan zijn voor de belangrijkste kenmerken van het waargenomen patroon op embryoniveau. Om ervoor te zorgen dat de simulatie-omgeving ook gebruikt kan worden door studenten zonder programmeer- en modelleerervaring en met slechts een beperkte voorkennis van wiskunde, bevat de simulatie-omgeving diverse vormen van ondersteuning voor het opstellen van het kwantitatieve model en voor het verder verbeteren van dat model in aansluiting op simulatie-experimenten met dat model. Vooral het implementeren van laatstgenoemde ondersteuning was een uitdaging, omdat het wiskundige model voor zover ons bekend niet analytisch oplosbaar is en studenten meer dan 10^{20} verschillende combinaties van parameterwaarden konden invoeren. Het bleek niettemin mogelijk voldoende ondersteuning te geven door te testen op de ons bekende kwalitatieve gedragingen van het kwantitatieve model. De uiteindelijke ondersteuning helpt studenten niet alleen efficiënt met de simulatie-omgeving te werken, het helpt ze ook bij het verklaren van de invloed van veranderingen in het kwantitatieve model, dat processen op moleculair niveau beschrijft, op het kwalitatieve gedrag van dit model, dat processen op embryoniveau beschrijft.

In de „Bristles“ case (H6) krijgt de student veel meer vrijheid bij het ontwikkelen van zijn model dan bij de voorgaande twee cases: de student wordt niet meer stap voor stap door het modelleerproces geleid, maar moet nu zelf het proces vormgeven. In de case wordt de student gestimuleerd om op grond van een lijst met experimentele resultaten uit de literatuur eerst een model met pen en papier te maken. Dit model kan hij vervolgens invoeren in twee stappen. Eerst moet een schermkader geselecteerd worden waarin verschillende symbolen voor verschillende soorten eiwitten en interacties staan. Vervolgens moeten eiwitnamen naar de verschillende posities in het gekozen kader gesleept worden. Op deze manier kunnen ongeveer 8600 verschillende modellen ingevoerd worden. Bij de feedback wordt eerst getest of de student een model gekozen heeft dat überhaupt het wild-type gedrag kan verklaren. Zo niet, dan krijgt de student hier vragen over. Als het gekozen model het wild-type gedrag wel kan verklaren, dan wordt getest of het model in overeenstemming is met de andere experimentele resultaten. Zo niet, dan moet de student van een aantal experimentele

experimenten aangeven of ze al dan niet in overeenstemming zijn met het voorgestelde model.

Alle ontwikkelde cases zijn geëvalueerd tijdens reguliere cursussen aan Wageningen Universiteit. Daarnaast is een tweetal cases ook aan de Universiteit van Zürich in Zwitserland geëvalueerd. De cases werden goed gewaardeerd door de studenten. Om een indruk te krijgen of de studenten ook over voldoende vaardigheden beschikten na het werken met de cases, werden examenvragen over de cases geïntegreerd in de examens over de vakken waarin de cases gebruikt werden. De meeste resultaten waren bevredigend of zelfs behoorlijk goed. Een uitzondering vormen de resultaten van een aantal vragen over de „Bristles case". Daarom is deze case sindsdien nog aangepast en toekomstige evaluaties zullen moeten uitwijzen of deze aanpassingen afdoende zijn.

In de algemene discussie aan het einde van het proefschrift wordt ingegaan op de opbrengst van dit onderzoek, namelijk de beproefde cases (prototypes) en de principes voor het ontwerp van zulke cases. Bij het bespreken van de cases wordt teruggekomen op de leerdoelen en op het feit dat de cases ontworpen zijn als onafhankelijke webgebaseerde modules die in principe ook geschikt zijn voor zelfstudie. Daarnaast wordt de geschiktheid van de cases voor groepen met relatief grote verschillen in voorkennis, bediscussieerd. Bij het bespreken van de ontwerpprincipes wordt een overzicht gegeven van deze principes en van de gedachten erachter. De ontwerpprincipes hebben betrekking op de verschillende stadia van het ontwikkelen van een case: de selectie van een onderwerp, het maken van een hoofdindeling binnen een case, het structuren van gedeelte van de case waarin studenten daadwerkelijk een authentiek probleem aanpakken, het verstrekken van verschillende soorten informatie aan de studenten en het implementeren van student-computer interacties.

Tot slot wordt een aantal suggesties voor toekomstig onderzoek gegeven met betrekking tot het gebruik en verder ontwikkelen van de cases en van de ontwerpprincipes. Daarnaast wordt een pleidooi gegeven voor meer ontwikkelingsonderzoek om innovaties binnen het onderwijs in de moleculaire levenswetenschappen te kunnen realiseren.

NAWOORD

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CURRICULUM VITAE

Hubertina Maria (Tinri) Wilmsen werd geboren op 4 oktober 1976 te Malden. In 1994 behaalde zij het VWO diploma aan het Stedelijk Gymnasium te Nijmegen. Van 1994 tot 1999 studeerde zij moleculaire wetenschappen aan de Wageningen Universiteit. Tijdens haar studie deed ze afstudeervakken bij de vakgroep moleculaire biologie aan de Wageningen Universiteit onder begeleiding van Dr. H. Franssen en Prof. T. Bisseling en bij de vakgroep biochemie aan de medische faculteit van de Katholieke Universiteit Nijmegen onder begeleiding van Dr. A. Zimmerman en Prof. J. Veerkamp. Daarnaast deed ze een stage bij de "division of endocrinology and metabolism", University of California San Diego (UCSD), onder begeleiding van Dr. T. Ciaraldi en Prof. R. Henry.

Na het behalen van het ingenieursdiploma in september 1999, begeleidde zij het practicum "algemene en fysische chemie" en assisteerde zij bij de ontwikkeling van digitaal leermateriaal voor moleculaire biologie, beide aan de Wageningen Universiteit. In januari 2000 ging zij terug naar San Diego en rondde daar haar eerder begonnen onderzoeksproject af. Daarnaast werkte ze bij de "division of biological sciences" aan de UCSD in de groep van Prof. G. Wienhausen aan de ontwikkeling van on-line colleges. In september 2000 keerde ze terug als AIO bij de vakgroep moleculaire biologie aan de Wageningen Universiteit, waar zij het onderzoek uitvoerde dat beschreven is in dit proefschrift.

Op 16 augustus 2002 trouwde zij met Christof Aegerter en op 30 september 2004 kregen ze een zoon, Nico. Sinds juli 2005 werkt ze in deeltijd aan het zoölogische instituut van de Universiteit van Zürich in de groep van Prof. E. Hafen. Daar doet ze theoretisch onderzoek naar de ontwikkeling van *Drosophila*.

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