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Digital Learning Material for Model Building in Molecular Biology

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Building models to describe processes forms an essential part of molecular biology research. However, in molecular biology curricula little attention is generally being paid to the development of this skill. In order to provide students 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 that is based on expert analysis and historical data; they first 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, the biological implications of the extension 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 indeed facilitates model building in analogical situations and the students judged working with the case positively.

KEY WORDS: molecular biology; education; model building; computer.

INTRODUCTION

Building models of processes such that phenomena can be explained and predictions can be made, is at the heart of science. In molecular biology research, many models have been made such as for example, models for the regulation of gene expression under a range of various conditions and for different signal transduction pathways. In this context a model is a conceptual construction that should facilitate the explanation of phenomena and the making of predictions. Such a model can be qualitative as well as quantitative, even though thus far most models in molecular biology are qualitative. Qualitative models in molecular biology are often represented by some kind of figure (see for example Fig. 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 (Frazier *et al.*, 2003; Nurse, 2003). 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 that 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.

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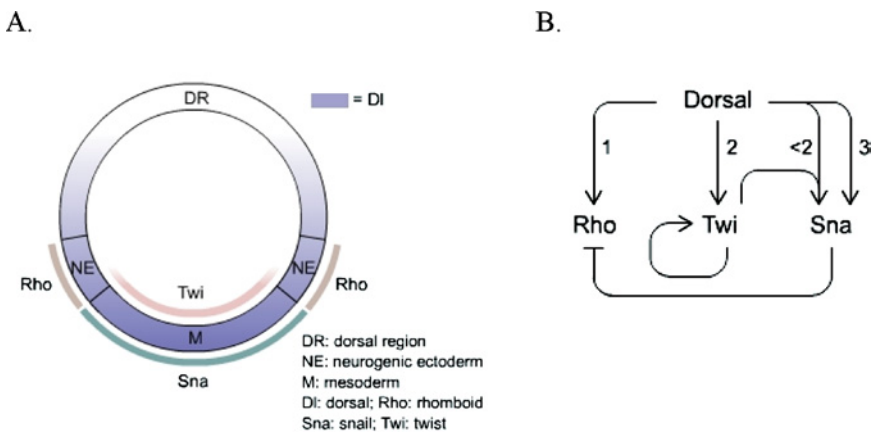


Fig. 1. Subdivision of the ventral part of the *Drosophila* embryo. A: expression pattern of four genes in schematic representation of a dorsal–ventral cross-section of the early *Drosophila* embryo; B: model of interactions between the four genes/proteins. Dl: *dorsal*, Rho: *rhomboid*, Sna: *snail*, Twi: *twist*, D: dorsal side, V: ventral side, →: transcriptional induction, ⊣: transcriptional repression, numbers indicate threshold concentrations.

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

MODEL BUILDING IN MOLECULAR BIOLOGY

We needed to have a good model building method that is suitable for students in order to get more direction for the structuring of the practice in model building (Janssen, 1999; Shulman and Quinlan, 1996). To get inspiration for such a method, we analyzed molecular biology experts while building a model and we used historical data on scientific discoveries in molecular biology.

For the expert analysis, six molecular biology researchers (three PhD students, one Post-Doc and two assistant professors) were asked to build a model based on a number of experimental data. This model is the same as the students eventually build 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, which forms the worm and later the adult fly. This pattern of different cell types 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 type. 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 characterizes the worm and later the adult fly. The model the experts (and students) had to make concerns the concentration dependent interpretation of a dorsal–ventral ("back-belly") morphogen gradient that is formed very early during *Drosophila* development. The genes that 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 Fig. 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 (Stathopoulos and Levine, 2002)).

The six molecular biology researchers were asked to think aloud while building the model and the whole process was audiotaped. Each scientist followed roughly a similar approach: he first tried

to understand the assignment and the experimental data. Thereby, most made a drawing in which the problem was visualized in an alternative manner. Then experimental results were interpreted and conclusions were drawn. At one stage they then tried to combine these conclusions into a model. When such a model was built indeed, it was then evaluated with the experimental data to some degree. The final models differed greatly in explanatory power. One scientist actually succeeded in building a model that was in agreement with all data. Two scientists got very close and built a model that could explain all but one experimental result. Two scientists built a model that was not capable of explaining the wild-type situation and that 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 that 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 by itself 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, looses 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 is indeed a lot of *dorsal* present, because I indeed concluded this from this [experiment 3]. *Snail* can . . . *dorsal* . . . but if there is indeed little *dorsal*, let's see, that goes here and if the *dorsal* . . . No, that's not true, what am I doing?

Beside the similarities mentioned earlier, we also identified two striking differences between the three scientists who (nearly) built a fully explanatory model and the other three. The more successful group checked more precisely and more systematically whether the data were in agreement with the model indeed. Furthermore, 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 built at one stage a simple model that 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 that can explain the wild-type expression pattern, but not all experimental results, is easier than building the final model at once. This is due to the fact that such a simple model contains less elements and/or interactions among them and that less 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 an additional experimental result is subsequently analyzed, it is then possible to focus on just one specific part of the mechanism. Other experimental results and other parts of the mechanism can be ignored temporarily then. 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 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 keep 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 such coaching that they would build the model in a deductive way, in which they build a relatively simple model first and subsequently extend this model step by step. The more successful scientists started with different simple models. We chose 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 has to be explained eventually anyway, while a minimum number of data are used.

Beside expert analysis, we also used historical studies to get 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 (Resnik, 1995). 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 (Pauling and Corey, 1953). Watson and Crick also considered the biological role of DNA and proposed the now broadly accepted double helix structure 2 months later (Watson and Crick, 1953). With this structure, they could envision a simple mechanism by which DNA could be duplicated, such that cells can acquire the same genetic information upon cell division.

It is evidently only possible to take into account the biological implications during model building, 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 quite some 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 to be premature 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 are for example very frequently robust against temperature differences, this is probably very important for such organisms.

The eventual full model building cycle is outlined in Fig. 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.

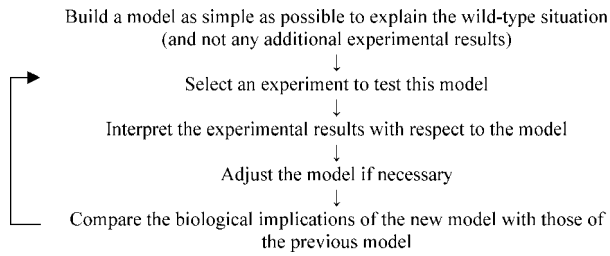


Fig. 2. The model building cycle that is followed in the case.

PEDAGOGICAL APPROACH

Executing the different model building steps as shown in Fig. 2 may be quite difficult for students, because the steps require reasoning in combination with using factual knowledge of general biological principles as well as of 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 their output. Reasoning is then required to decide whether or not the data are in 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 that are put on students for the execution of the individual model building steps, we decided to have students initially focus on executing them and to shield them initially from ordering the steps themselves. Thereby we wanted to apply a form of cognitive apprenticeship where students, while working on realistic problems, are strongly coached initially and this coaching gradually fades during the process (Bielaczyc and Collins, 1999; Collins *et al.*, 1989). 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 that 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 at home.

In this paper we describe the development and evaluation of the first digital case we designed in which 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 the students encounter 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 talks about it and, 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 that are mainly ordered according to the model building cycle in Fig. 2 and highlight the individual model building steps. By having the student actively think about the individual steps in a very precise way and by giving them sufficient feedback, the student 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 student automatically works according to the model building cycle as a whole. This is probably not sufficient for students to use the model building cycle independently, but being able to work passively with it, can form a first step to actually learn to use it independently (Collins *et al.*, 1989). The fact that the student spends some time in building the model and thereby reasons about different parts of the model, is likely to facilitate memorizing the eventual model considerably.

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* (Fig. 1). For the selection of the topic, we limited ourselves to well studied mechanisms in developmental biology, which can be understood relatively easily, such that it is not necessary to quantify the model and use mathematical analyses and/or computer simulations in order to elucidate the behavior of the model. 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 that were used to reveal the model, such as for example 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 I. 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 is 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. To improve the understanding of the student, if necessary, a simple animation was added (Fig. 3), thus employing the possibilities the computer offers for interactive representations. Then the student develops the first conceptually most basic model that could account for the wild-type situation. This model, however, requires molecular mechanisms that are not commonly found in cells and is therefore biologically unlikely. Therefore, two alternative models are built before selecting an experiment (Fig. 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 prevents the occurrence of potentially harmful intermediate cell types better.

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. To evaluate the implications of model 2 the student had to answer three different questions, in which the implications were analyzed step by step. It was even possible to answer easier sub-questions instead. In order to provide the student enough challenge while analyzing the biological implications of model 4, there is only one question

Table I. Description of the Different Steps of the Case, Including the Model Building Cycle Step it (Mostly) Deals with

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, the simplification was used 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 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.

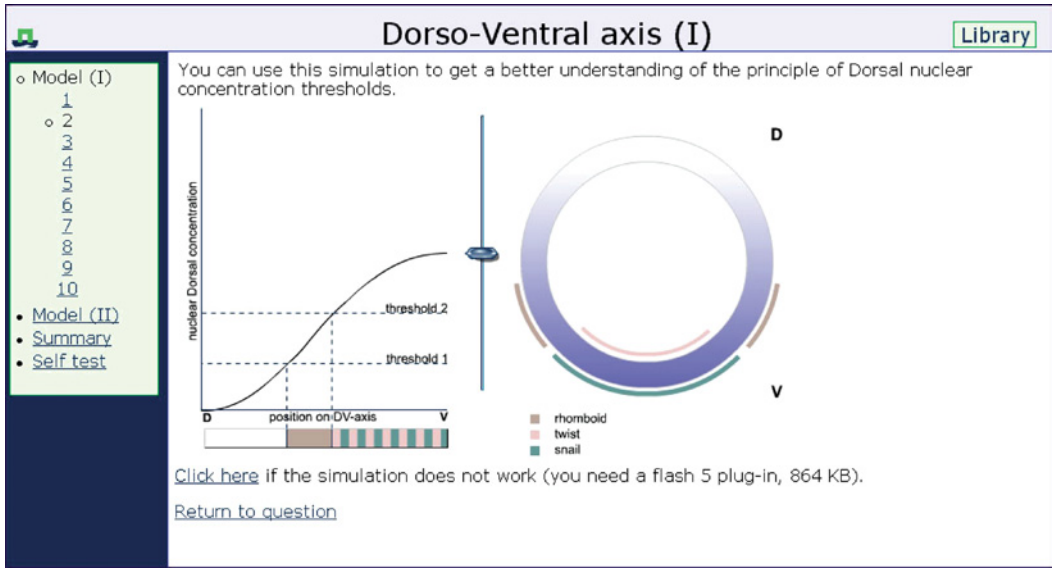


Fig. 3. The animation that was used to explain the concept that *Dorsal* is a morphogen, if necessary. The student can adjust the maximum concentration of *Dorsal*. The expression pattern of the other genes changes accordingly.

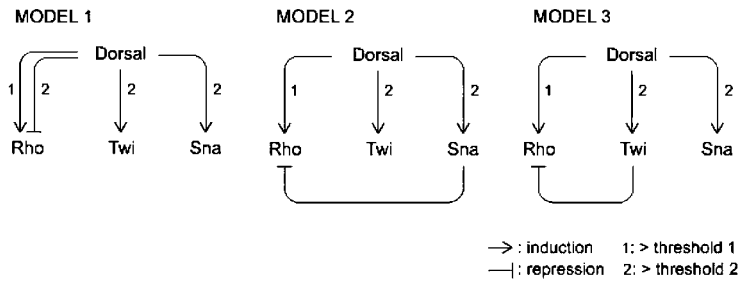


Fig. 4. The three models the students construct initially.

implemented in which the student needs to take several steps himself. 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.

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

Thus far, the simplification was made 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. The 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. The student also has to evaluate models then with respect to the biological implication of generating sharp boundaries. At the end literature sources and some additional background information is provided.

Beside 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. Presence 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 get more information about the way the students use the case, tracking data were collected that reveal the answers that were given and two groups of students were recorded on audiotape each time. To get an indication about how much the students learnt from working with the case, questions about it were added to the exam of the whole course. Lastly, to obtain information about the students' opinion of the case, an evaluation form was handed out after the case was completed. After using the case for the first time, some rather small changes were implemented like replacing some text parts with figures. Even though these changes did influence some of the evaluation results, overall the 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 made exam questions.

As the results were comparable each time, we will discuss the pooled results here. However, we did not give identical exam questions in consecutive courses, because students use exam questions of previous courses to prepare themselves 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 themselves in the presence of coaching. To get 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 that 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 and 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 (about 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 [it sounds doubting].
MN: Between [threshold] 1 and 2 it [*rhomboid*] is being made, so it simply has to be a +.
MG: Yeah.. [it still sounds doubting]

In order to make sure they really understand it, they then decide to go back to check the animation that explained the concept of morphogens and their thresholds (Fig. 3). Somewhat 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* that 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 to distinguish 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*, than [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 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, which is concerned with the model building steps as outlined in Fig. 2. In these fragments, students eventually draw the right conclusions based on proper reasoning. This occurred fairly often with all six groups that were audiotaped. However, sometimes they also made reasoning mistakes and used the feedback to understand their mistakes. Some groups did not reason aloud before answering some of the questions. They simply asked each other what they would choose and when they would both choose the same answer, they would check that answer. 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 students went through a lot of reasoning processes which are typical of different stages of the model building process while going through the case.

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

Learning Outcomes

To get 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 that are discussed here are shown in Table II.

The first exam question tests whether students have passive factual knowledge of the mechanism involved and was needed 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. To answer this question, students should be familiar with different experimental approaches, they have to be able to activate this knowledge while answering the question and they have to be able to evaluate the usefulness of different experimental approaches for the distinction between different models. As the question shows analogy to tests they had to perform in the case, this question tests whether students are capable of applying their model building skills in an analogous situation.

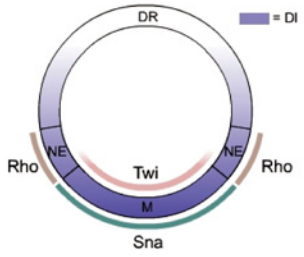
The third question tests whether students can describe why the model yields a very sharp boundary between two adjacent domains. This was part of the case and the question is therefore entered to check whether students can indeed give an explanation of this biological implication of the model. In order 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 II. Almost all students (30 out of 32) passed this part of the exam (they scored at least 5.5 on average on a scale of 1–10 for the four questions). This is relatively many, as in general only roughly two thirds of the students pass for an exam. As can be seen in Table II, students scored the best by far on the first question, which can be expected as answering it requires just a little factual knowledge. On the third question the scores were lowest. When analyzing the results, we found that two different conceptual mistakes were repetitively made when answering question 3. Therefore, we are planning to add an additional self-test question in which students will be confronted with this misunderstanding if present. Given the fact that question 2 and 4 require relatively

Table II. Average Scores on Scale 1–10 for a Number of Exam Questions by Students Who Worked With the Case While Supervision was Present

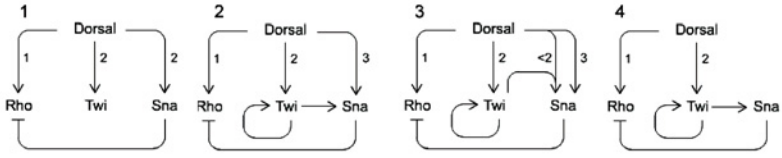
Introduction

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 that 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 the other experiments can be used eliminated with experiments.	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

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 in total five students who did not go through the case, but did enlist for the course and did make the exam. They scored 3.2, 2.0 and 2.4 on average for questions that are similar to question 2, 3 and 4 in Table II respectively. These results may not directly be compared with the results of students who did go through the case because these students may have been less motivated than the others for example. 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 that are analogous to the ones that have to be taken in the case.

Students' Opinion

To assess the students' opinion of the case, an evaluation form was handed out after they worked with it. In total 49 out of 59 forms were returned. Three of the questions are shown in Table III. As can be seen in the table, the students judged the material positively (4.0 on scale 1–5), liked working with the case (4.1 on scale 1–5) and thought they learnt a lot from it (4.0 on scale 1–5). 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 1–5 on these forms is considered satisfactory and an average of 4

Table III. Results from three Questions on the Evaluation Form

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

or more results in a letter of praise from the university. Thus, the students really seemed to appreciate working with the case.

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 to compare working with the case with following a lecture. Nearly all students made such remarks as that they were activated, they really got to understand it, they would remember it better etc. This is for example 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 on 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 that were mentioned by several students were that it can be tiring to work behind the computer (especially when reading English text), that they sometimes had to spend a lot of time on 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 Fig. 2 and not being able to use this cycle themselves. However, in order to obtain some idea about whether students could still recall the overall approach they followed, a question was added to the evaluation form that asked for this general approach. 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 at once and 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 that was 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 could indeed activate the students to go through the reasoning processes that 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 that are analogous to the ones that have to be taken in the case. The exam results also show that student acquired at least passive knowledge of the eventual model. If acquiring factual knowledge would be the sole goal, studying a book or listening to a lecture may be more efficient, because students do not use their cognitive resources then to analyze results, compare different models etc (Sweller, 1988, 1994). 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 Fig. 2. When asked for it on an evaluation form, most of them could 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 education in which students are much less guided while building a model and have to organize their model building

process themselves. Based on these experiences, they are then encouraged to evaluate model building methods. Such a problem posing approach is for example proposed by Leijnse (2004).

While designing the case, the model building cycle as outlined in Fig. 2 was very helpful as 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 as we wanted the students to build as well as on historical data on 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 there are theoretically for example innumerable equivalent models possible to 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 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 could be prevented, 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 that students can use it for self-study without any presence of supervision, even though students seems to learn somewhat 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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REFERENCES

Bielaczyc, K., and Collins, A. (1999). Learning communities in classrooms: A reconceptualization of educational practice. In Reigeluth, C. M. (Eds.), *Instructional-Design Theories and Models. A New Paradigm of Instructional Theory*, Lawrence Erlbaum Associates, Mahwah, NJ, pp. 269–293.

Collins, A., Brown, J. S., and Newman, S. E. (1989). Cognitive apprenticeship: Teaching the crafts of reading, writing, and mathematics. In Resnick, L. R. (Eds.), *Knowing, Learning and Instruction: Essays in Honor of Robert Glaser*, Lawrence Erlbaum Associates, Hillsdale, pp. 453–494.

Frazier, M. E., Johnson, G. M., Thomassen, D. G., Oliver, C. E., and Patrinos, A. (2003). Realizing the potential of the genome revolution: the genomes to life program. *Science* 300: 290–293.

Janssen, F. J. J. M. (1999). *Learning Biology by Designing – Exemplified and Tested for the Topic of Immunology in Secondary Education (Thesis in Dutch with a Summary in English)*, PhD Thesis, Univerity of Utrecht.

Lijnse, P. L. (2004). Didactical structures as an outcome of research on teaching-learning sequences? *International Journal of Science Education* 26: 537–554.

Nurse, P. (2003). Understanding cells. *Nature* 242: 883.

Pauling, L., and Corey, R. B. (1953). A proposed structure for the nucleic acids. *Proc. Natl. Acad. Sci.* 39: 84–97.

Resnik, D. (1995). Functional language and biological discovery. *Journal of General Philosophy of Science* 2: 119–134.

Shulman, L. S., and Quinlan, K. M. (1996). The comparative psychology of school subjects. In Berliner, D. C., and Calfee, R. C. (Eds.), *Handbook of Educational Psychology*, Simon & Schuster MacMillan, New York, pp. 399–422.

Stathopoulos, A., and Levine, M. (2002). Dorsal gradient networks in the Drosophila embryo. *Developmental Biology* 246: 57–67.

Sweller, J. (1988). Cognitive load during problem solving: effects on learning. *Cognitive Science* 12: 257–285.

Sweller, J. (1994). Cognitive load theory, learning difficulty and instructional design. *Learning and Instruction* 4: 295–312.

Watson, J. D., and Crick, F. H. (1953). Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 171: 737–738.