Students´ Learning of Molecular Modeling in Science Education

The case of computer-aided drug design against malaria disease

Chrissy van Enckevort | 3785688
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Utrecht University

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Supervisor:	*dr. G.T. (Gjalt) Prins (assistant professor)* *Freudenthal Institute for Science and Mathematics Education, Faculty of Science, Utrecht University, Utrecht, the Netherlands*

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Chrissy M.W. van Enckevort

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Abstract

Models are important tools used in the production, dissemination and acceptance of scientific knowledge (Dori & Barak, 2001, p. 62). The skills to learn with, about and to construct a model are important for understanding in science. Within science education, especially in chemistry education, molecular modeling (construction of a model) received a more extensive place in the curriculum. Despite the importance of this topic, little is known about teaching molecular modeling in chemistry or science education and also the amount of teaching materials is limited.

In this study, a design based experiment was performed to get an insight in students' learning of molecular modeling. Within the context of drug design for malaria disease, students had to complete a curriculum unit in which they had to model a molecular analog. 24 students worked in teams of three students during the intervention of the curriculum unit. It was investigated which insights and learning outcomes the design acquired for students in the process of molecular modeling. Also the affection of the students was measured. Data was collected by using a set of questionnaires, analyzing the recorded audiotapes and written answers and doing a group interview. The audiotapes and written answers were coded, scored and compared to a reference framework drafted in a hypothetical learning trajectory (HLT) to get an insight in the learning outcomes of the students. An inter-rater reliability check was included to ensure reliability. The questionnaires and the interviews were used to map the (improved) insights in molecular modeling and the affection of the students.

The outcomes of this study are promising for the future. Students show great affection for the curriculum unit and a clear insight is gained about the improvements which have to be implemented to improve students' learning about molecular modeling.

Keywords *Molecular modeling - Context-concept based - Design Based research – Drug Design*

Introduction

Models and modeling are considered integral parts of scientific literacy (Gobert & Buckley, 2000, p. 891). They are an intermediary between the abstract theory and the concrete actions of an experiment. Models help making predictions, guide inquiry, summarize data, justify outcomes and facilitate communication (Dori & Barak, 2001, p. 61). Gobert and Buckley (2000) described a model as a simplified representation of a system, which concentrates attention on a specific aspect of that system (p. 891). According to Dori and Kaberman (2012), a model is a representation of an object, event, process, or system (physical or computational), which interactively constructs the composition and structure of molecular phenomena (p. 71). Models can give a visualization of complex ideas, processes and systems (Dori & Barak, 2001, p. 61), a mental model is formed in the brain (Kozma & Russell, 1997, p. 950). A mental model is an idea of the mind (Gilbert, Boulter, & Elmer, 2000, p. 3-17). It is inaccessible for others because everyone constructs his one version of a model in the mind (Gilbert, 2005, p. 2). We construct mental models to display our understanding (Treagust, Cittleborough, & Thapelo, 2002, p. 357, p. 12). Mental models become expressed models when they are placed in a public domain. When the public domain, for example, a research group or a school class, agrees on this expressed model, the expressed model becomes a consensus model and will be used as a scientific model in the public domain (Gilbert, 2004, p. 117).

In science education, students should learn about models; what is a model and why are they useful. Second, students should learn with models, this to promote the understanding of a target system (Gobert & Buckley, 2000, p. 892). Besides learning about and with models, a third method is learning to construct models. The construction of a model takes place by integrating pieces of information about structure, function, behavior and causal mechanism. This approach aims on developing, adjusting and/or optimizing a model. By constructing a model, students get a better understanding of the wording of the model

(Prins, Bulte, Driel, & Pilot, 2009, p. 682). Models are important within science education and it is expected students are familiar with models. However, numerous studies revealed that students have difficulties working with and understanding models, there is a knowledge gap.

In chemistry education, different models, such as, mathematical models, chemical equations and iconic and symbolic models are used to represent molecules (Prins et al., 2009, p. 682). Models of molecules take a dominant position, probably because the focus of chemistry is on the molecular structure of substances (Dori & Kaberman, 2009, p. 601). Models of molecules enable students to do mental transformations and visualizations from a two dimensional to a three dimensional structure (Cody et al., 2012, p. 31). With the help of models, students can visualize molecules, give statements about possible interactions and are able to relate the structure of a molecule to the function (Kozma & Russell, 1997, p. 950). Recent technologies make it possible to use computerized modeling tools for constructing molecular models. With the help of these software tools a scale of possibilities for molecular modeling becomes available (Oda & Takahashi, 2009, p. 60; Sutch, Romero, Neamati, & Haworth, 2012, p. 46). Molecular modeling is therefore, a more and more popular topic within chemistry education. Some insights are gained about working with modeling tools in science and chemistry education but, there is still a lack of knowledge and especially materials to incorporate these scientific tools well in science and chemistry education (Kaberman & Dori, 2009, p. 599).

In this study, we aim at involving students in molecular modeling and getting an insight in students' conceptual understanding and learning of molecular modeling. Therefore, a curriculum unit based on the authentic practice of drug design is designed and enacted with a group of students. Within the authentic practice it is meant to mimic the real life context of drug design as realistic as possible.

Theoretical background

According to Dori and Kaberman (2012), the skill of molecular modeling can be defined as the understanding of spatial molecular structures and the ability to transfer between molecular representations and chemistry understanding level (p. 72). A general working definition for molecular modeling is defined in this study as a visualization of a molecule, shown in a three dimensional spatial structure which can help to see and understand possible (molecular) interactions and could help to relate the structure to the function of a molecule.

Molecular modeling in chemistry education

Molecular models aim to visualize the three dimensional structure of a molecule. In former times, students' involvement in molecular modeling in chemistry education was guided with various approaches. The ball and stick model, space filling model and the sphere cylinder model are the best known examples (Dori & Kaberman, 2012, p. 71). Students get a three dimensional visualization by building molecules with molecular kits consisting the before mentioned molecular models. The use of these kits has decreased over the last years. New and recent technology advancements have brought computerized molecular modeling (CMM) to a higher level. As mentioned, a lot of new software is developed to computational model molecules with all kinds of different purposes (Wu & Shah, 2004, p. 5). Possibilities range from visualizing a three dimensional molecule, to perform very complex calculations or simulations on large molecules. It is possible to visualize, rotate, manipulate and optimize molecules with computational molecular modeling, it gives, us humans, a better insight in molecules and their interactions (Oda & Takahashi, 2009, p. 52). With the help of molecular modeling, researchers are more capable to design, for example, new drugs or materials. Because the behavior of molecules is more specific predicted, a lot of money can be saved, only research is done into the most promising molecules. These molecules are further investigated to eventually develop a new drug which can fight severe diseases like cancer, AIDS or malaria.

Within chemistry education these new possibilities with molecular modeling are also useful. Research has revealed that three dimensional visualization of molecules provides a better understanding for students. When students model the molecules by themselves the effect on the learning outcomes are even bigger (Dori & Kaberman, 2012, p. 88). Dori and Barak (2001), showed that students become more capable of defining and implementing new concepts, are better able to transfer between the chemistry understanding levels (macroscopic, microscopic and symbolic) and can explain answers when making use of a computational model next to a physical model (p. 70). According to Barak and Dori (2004) computerized molecular modeling (CMM) fosters the understanding of molecular three dimensional structures and the ability to draw spatial molecules (p. 130). With CMM students

gain new experiences in learning science, this has a positive impact on students' general conceptual understanding of what models are and the way models work (Treagust et al., 2002, p. 358).

In Israel, a case-based formative assessment was performed in which students were tested on their higher order thinking skills, one of these skills was molecular modeling (Kaberman & Dori, 2009, p. 598). Students knew the criteria of the experiment and teachers had followed a training program about how to teach students on their molecular modeling skills. The results showed that when using computerized media, students were more skillful in drawing computerized models spatially, understood what they were doing and made connections between the different chemistry understanding levels. Students still had difficulties in drawing spatial models but, there was a significant improvement in the ability to transfer between molecular formula and spatial models and vice versa. A CMM learning environment, contributed to improved modeling skill scores for students at all academic levels (Dori & Kaberman, 2012, p. 84).

The results of these outlined studies using CMM are promising. In this study however, we aim to involve students in a process of molecular modeling in which they relate the three dimensional structures with intermolecular interactions. Besides constructing a model, students have to reason about the three dimensional structures and molecular interactions involved within the model. To our knowledge, no research is conducted focused on designing efficient teaching approaches for this area of teaching molecular modeling (Gobert & Buckley, 2000, p. 891; Wu & Shah, 2004, p. 5). This study aims to contribute to the knowledge about learning and teaching molecular modeling. The definition of molecular modeling is defined in service of the context of drug design. This is therefore defined as the ability to construct a three dimensional molecular model which can be used to explain and relate molecular interactions to the properties of a molecule. With the molecular model, data has to be generated and in turn, the molecular model has to be used to explain this data.

Authentic practice of drug design

The development of new drugs is a time consuming process. As the timeline in Figure 1 shows, it takes about 8 years to introduce a new drug on the market. It takes a lot of time to select the most promising molecules and testing the potential drug on animals and later, in a clinical trial, on humans to make sure the drug works efficient and has limited side effects.

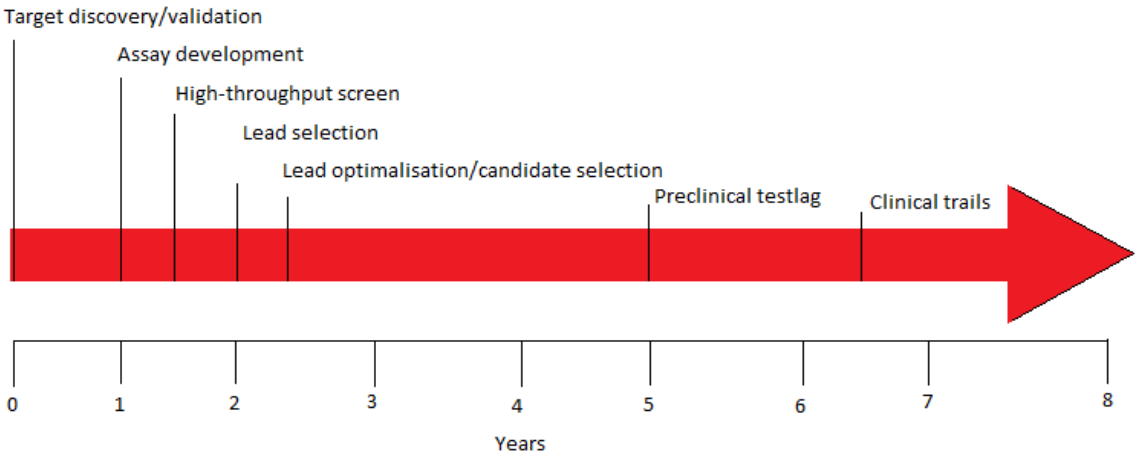


Figure 1: Timeline for drug development.

An element of the drug design cycle, lead optimalisation, is used as context in this study. Figure 2, is a schematic picture of what lead optimalisation is about. Lead optimalisation is a stage in the drug design cycle in which possible leads (= molecules) are selected which can attack the targets in the, in this case, malaria parasite. An important target in the malaria parasite is the DHFR enzyme, see Figure 3, an enzyme which is indirectly involved in the synthesis of DNA. Pyrimethamine, Figure 4, is a molecule which was able to block this DHFR enzyme. Due to changes in the three dimensional conformation of the malaria parasite, the DHFR enzyme changed in spatial structure. As a result of this, pyrimethamine is no longer able to bind effectively to the DHFR enzyme, the malaria parasite has become resistant to pyrimethamine (Rastelli et al., 2000, p. 1127). Development of a new drug is therefore needed in order to continue the fight against malaria disease.

With lead optimalisation thousands of molecules are tested on the parasitic and human DHFR enzyme. This is done by calculating the binding affinity between the molecule and the DHFR enzyme. The human DHFR enzyme is also included in this calculating step, because the new drug has to leave the human DHFR enzyme untouched, the human body still has to function normal. Blocking the human variant of the enzyme would kill the human cells.

Calculating the binding affinity of the different molecules at the binding site of the DHFR enzyme is done to compare different molecules and to be able to select the best working molecule. The binding affinity is a number which reflects the extent of binding between the binding site of the enzyme and the possible lead molecule. The binding site is formed by the amino acid to which the lead molecule binds. The calculations, also called dockings, are done with a software tool. The software tool measures which molecule in which conformation fits the best to the target. Based on these calculation a molecule can be rejected or selected for the next step in the cycle of drug design.

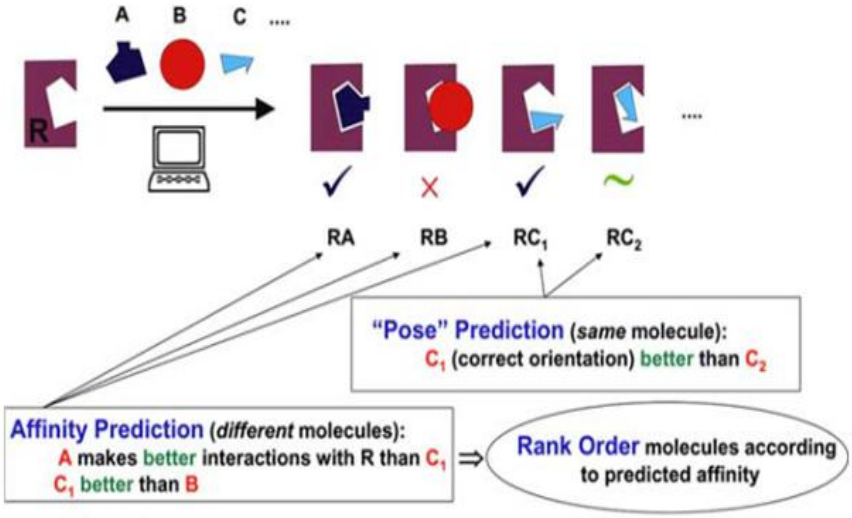


Figure 2: Schematic picture of lead optimalisation (Kroemer, 2007, p. 313)

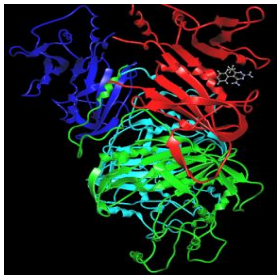
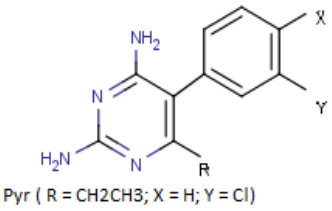


Figure 3: DHFR enzyme



Pyr (R = CH2CH3; X = H; Y = Cl)

Figure 4: Pyrimethamine

Design principles for the construction of the curriculum unit

There are three main design principles taken in consideration in this study.

First, is the stepwise building of the curriculum unit according to a six staged general process for modeling, developed by Webb (1994). The study of Webb was aimed on conceptualizing the process of modeling and revealed that students apply a general procedure for modeling. This six staged general process Webb developed and generically tested is shown in Figure 5. This figure shows the model with a translation to the designed curriculum unit. This general process was the starting point for the structure of the curriculum unit and anchor points were drawn for each step of the modeling process. The arrows show the relation between the different phases of the process and the real world. The arrows between the levels show possible feedback between different levels.

Second point is the use of a context, the process of drug design. Chosen is to design a context based curriculum unit, in which the students learn to model in a practical way. This bottom up method is different from the traditional theoretical and abstract way of teaching, because the students have to learn molecular modeling by bring the concepts in practice, not by instruction of a teacher. In this study the context of malaria disease is chosen, it is tried to mimic the process of lead optimalisation as precise as possible for the students. It is likely that other authentic practices like catalysis or material development could be used as a meaningful context too.

Last point it the use of an ICT component, which has to be functionally applied. From the intervention of the curriculum unit, it should become clear if the ICT component is functional applied at all points in the curriculum unit. If not, adjustments should be made.

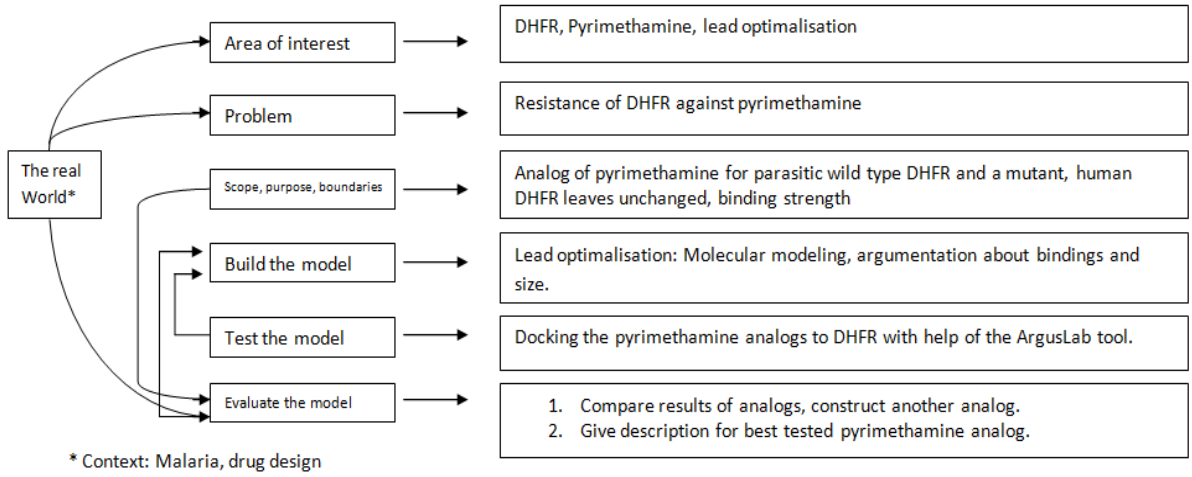


Figure 5: General process of Webb (1994) applied on the curriculum unit.

Scope and research questions

Molecular modeling is an important topic within science education. The importance of the topic is even more increased with the introduction of the context-concept based chemistry education. Since 2007 the chemistry education in the Netherlands is, mandated by the government, renewed. With the context-concept approach as a starting point, a new view on chemistry education was developed. The goal of this development was to create a curriculum which is more relevant for students, less overloaded and more consistent (Kuiper, Folmer, Ottevanger & Bruning, 2011, p. 5). The end terms, elaborated in the syllabus, describe the skills students have to master. The syllabus for chemistry is divided into eight domains (A-G). These domains are in turn divided in sub-domains. The syllabus for 2015-2016 (Bertona et al., 2012, p. 1-38), the school year in which the first vwo context-concept based chemistry education exam is performed by Dutch students, includes four sub-domains which refer to molecular modeling, A7, B1, B2 and D4 (Bertona et al., 2012, p., 10, 15, 16, 35). It is described students have to be able to construct a model, explain properties of a molecule with help of models, work with molecular models en do molecular modeling by themselves.

As mentioned, there is a lack of teaching materials which cover the molecular modeling topic. In order to provide more teaching material, a curriculum unit is developed and tested in this study. The curriculum unit is intended for students who attend chemistry classes at 5vwo in the Netherlands. Because there is limited knowledge about teaching this topic, the curriculum unit was designed with help of experienced teachers, experts on education and experts in the field of drug design. This to make sure a curriculum unit was developed which is, contextually and conceptually, well constructed and fitting to the new chemistry education approach.

The goal of this explorative design study is to get an insight in student´ learning of molecular modeling by testing and optimizing a curriculum unit. This curriculum unit could, in the future, be introduced to chemistry teachers in the Netherlands. Testing the curriculum unit in the design experiment should give an insight in students' reasoning about three dimensional structures and intermolecular forces. In the curriculum unit, students are meaningful involved in molecular modeling within the context of drug design against malaria. Within the design study, it is aimed to gain knowledge about designing materials for learning molecular modeling. In order to obtain these new insights, two research questions are addressed:

1. What are the learning outcomes regarding molecular modeling of the students participating the designed curriculum unit, `Molecular modeling, drug development against malaria`?
2. To what extend do students gain insights into the process of molecular modeling with emphasis on three design principles?

Method

In this section the participants, research setting, tools, data collection and data analysis are described.

The method used in this study is design based research. Design based research consists usually of a series of steps to produce new theories and practices that can impact a naturalistic teaching setting (Barab & Squire, 2004, p. 2). Design experiments aim on a greater result in understanding of a learning ecology. A challenging aspect of this kind of research is to prove theoretical insights that underpin a design or the other way around. This underpinning is valuable because, showing the usefulness of a theory in practice can strengthen a theory (Barab & Squire, 2004, p. 8). By designing the elements of an ecology and predicting how these elements function together, learning is supported. The outcomes of a design based research are often local and empirical and therefore hard to replicate in the exact same way. Uncertainty are therefore often reduced by including a predicting element (Cobb, Confrey, DiSessa, Lehrer & Schauble, 2003, p. 9; Akker, 1999, p. 2, 5).

The predictive element is implemented by drawing a hypothesized learning trajectory (HLT). In a HLT, the expected learning activities and outcomes of the students are described. In this study, the HLT is based on the six staged general process for modeling developed by Webb (1994). In the HLT the activities of the curriculum unit are linked to the phases of the process of modeling, see Appendix 2. Next to that, learning outcomes are formulated for every phase and scored in a later stage of the study.

Curriculum unit

The designed curriculum unit is named; ´Molecular modeling, drug development against malaria disease'. In this context based curriculum unit, students take the role as researcher with the task to design a new potential drug against malaria disease. The modeling approach in the curriculum unit is based on the authentic modeling approach used in drug design; lead optimalisation. It is supposed that students get motivated by the real life context. In a previous study from Sanders (2012), research was conducted with the help of experts, teachers and students to validate a first outline of the curriculum unit. With the results of this study the design has been further elaborated by expert teachers. A curriculum unit of six chapters was constructed. Appendix 1 shows a schematic version of the curriculum unit, with a short outline of the activities the students have to perform.

Students first get introduced to the malaria context and are guided step by step to the main assignment, lead optimalisation of pyrimethamine. Students learn about concepts related to drug design, get an insight in the binding site for the malaria drug and the amino acids involved in this binding site. Also the students are introduced to pyrimethamine (Figure 4), the substance for which the malaria parasite has become resistant. With help of the molecular modeling software tool ArgusLab[1] the molecules

[1] www.arguslab.com

are visualized and calculations are conducted. ArgusLab was chosen as a software tool because it is easy to use, has variable capabilities and is free available (Oda & Takahashi, 2009, p. 52).

After the introduction, the students start with the main assignment; designing a new analog of pyrimethamine, which fits better to the DHFR binding site and has more binding affinity. Students perform this optimalisation by changing three functional groups of pyrimethamine, X, Y and R, see Figure 4. When the students finished this activity, the curriculum unit links back to the broad scope of the project to evaluate and recap the learning process and new concepts.

In order to get an answer to the above mentioned research question, a small pilot was conducted in which students performed the curriculum unit.

Participants

Twenty-four, 11th grade students, from three schools in the Netherlands conducted the curriculum unit, each receiving a small financial compensation for their contribution. The group of students consisted of 11 girls and 13 boys in the age between 16 and 18.

Their average grade for chemistry was 7,4 (scale from 1 – 10), generally they liked chemistry and find it not that hard. About half of the participating students considers a chemistry related study. Their reasons to participate to the pilot were; broadening their knowledge and get an insight in drug development and the working of molecules. They expected the curriculum unit would be fun, interesting and renewing.

The intervention of the curriculum unit was done by an experienced teacher. He was well prepared and guided and also involved in the development of the curriculum unit.

Research setting

The students were for the first time introduced to the curriculum unit at their own school. During an intake, the course of the experiment was explained. After that, a questionnaire[2] was conducted to reveal the prior knowledge of the students, a baseline measurement. After the first questionnaire, the students got a homework task, the first two chapters of the curriculum unit. A week after that, the students came to the Freudenthal Institute at Utrecht University, to perform the remaining part of the curriculum unit and handed in the homework task.

The students started with a second questionnaire in which questions were asked about the homework part, molecular modeling and their further expectations of the curriculum unit. After that, a classical introduction and recap was done. Here the homework task was discussed and a preview of the day was given. The remaining part of the day, the students worked, with some breaks, on the curriculum unit. The curriculum unit was performed in eight teams of three students. The teams were compiled by mixing gender, schools and average scores in chemistry.

During the day, their conversations were recorded in combination with their movements on the computer (Camtasia files) and observations were done. The observations were done to get an insight in troubles when performing the curriculum unit, faults in the curriculum unit, problems with the software tool ArgusLab and to get a quick view on the learning process the teams went through. When possible, problems were solved right away and also notes were made to be able to adjust the changes in the curriculum unit in a later stage.

At the end of the day students handed in their work, a last questionnaire was conducted and a group interview was taken. In this questionnaire but also in the group interview, questions about their affection and questions about the content of the curriculum unit were requested.

Data analysis

The collected data was analyzed to get an insight in the way of thinking and the molecular modeling approaches of the students. Figure 7 shows a timeline with the order in which the data collection occurred.

To make a generally tendency visible, the set of questionnaires were analyzed by summarizing the answers the students gave individually. Especially the expected change in the interpretation of the concept molecular modeling was analyzed. Also their affection with the topic of drug design and their recommendations were mapped. Table 1 shows the question of the questionnaires which were analyzed. The first column shows in which questionnaire or questionnaires the analyzed question was asked, the second column depicts the question which was analyzed.

[2] Protocols of the data resources are elaborated in the next section.

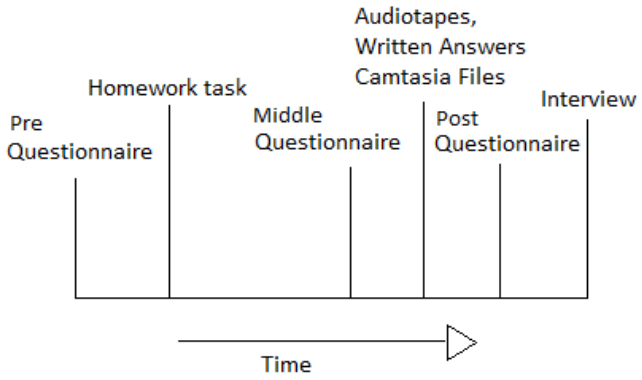


Figure 7: Data collection timeline

Table 1: Analyzed questions from the questionnaires.

Questionnaire	Question
Pre Middle Post	1. What kind of associations do you have with Molecular modeling. In what kind of situations is molecular modeling applied? Write as accurate as possible your ideas/associations are with molecular modeling down.
Pre	2. Which type of bindings between molecules do you know? Name all these types and give a short description.
Middle	3. Explain in your own words what lead optimalisation is about
Post	4. Which concepts from the molecular chemistry do you need to explain lead optimalisation?
Post	5. What have you learned about molecular modeling in this curriculum unit?

The audio taped data, Camtasia files and written answers were used for scoring the aimed learning outcomes of the teams in the HLT. The audio taped data were used as the primary data resource and the written answers were used as secondary data resource. An outline of the HLT is given in Appendix 2. The HLT was divided in different phases, based on the model of Webb (Figure 5) and related to the activities in the curriculum unit. Each phase contains statements of expected learning outcomes. The audio data of four teams were completely analyzed. Only four teams were analyzed because of the size of the study. Two teams from which good results were expected and two teams from which less results were expected were analyzed. These teams were selected by analyzing the joint plan of action (activity 4, see appendix 1) which the teams drafted after they were introduced to the main assignment of the curriculum unit. In this plan of action the teams had to draft a rude plan for the remaining part of the curriculum unit. In order to take the whole range of results in consideration, those two teams that drafted a plan of action with the highest and lowest quality were selected for the analysis of the data.

A scoring system from zero to six was used in order to determine to which extend the expected learning outcomes were obtained by a team. The number zero was given when no quality judgment was possible. The number one was scored when a component was not reached by the students and a six was scored when a component was fully reached by the students. To make sure the coding was reliable, an inter-rater reliability check was conducted. First an introduction was given and the scoring was practiced with two of the four teams. After that, the remaining two teams were scored individually by the inter rater. 24 items of two teams, scored by two people were used in the two-way random effect model to calculate the interclass correlation coefficient. This internal consistency was defined by calculating the Cronbach's alpha coefficient. A Cronbach's alpha coefficient of 0,942 proves an excellent internal consistency.

After scoring the learning outcomes, each teams got an average score per phase. Based on this average score a quality rating per phase was given. When 75% of the teams had a score of a four or higher, a phase was rated as successful. This 75% is based on the 80% norm which is often applied in research. Because of the four teams involved in this study this was downscaled to 75%, three of the four teams had to score a score of 4 or higher.

Finally, the group interview was performed as a control for the affection of the students to the curriculum unit and to get the most important direct feedback. This semi-structured interview had only one prepared question. The students were asked what they liked the most about the curriculum unit and which point in the curriculum unit really needs improvement. The interviews took a few minutes and were recorded. The tapes were analyzed by collecting all the tips and tops the students gave.

To summarize, Table 2 shows which data was used for which research question. The data from the teams; the audiotapes and the written answers were used for answering the first research question. The set of questionnaires of the individual students and the interviews were used for answering the second research question.

Table 2: Research questions linked to the collected data .

Research question	**Data**
1. What are the learning outcomes regarding molecular modeling of the students participating the designed curriculum unit, `Molecular modeling, drug development against malaria`?	Audio tapes Camtasia Files Written answers
2. To what extend do students gain insights into the process of molecular modeling by means of involving students in drug design?	Set of questionnaire Interview

Findings

In this section the findings are presented. During the intervention of the curriculum unit, observations were done. From these observations it became clear that students run through a learning process performing the curriculum unit. This was the starting point for analyzing the collected data. The findings are described in order of the three design principles, as described on page six.

First, the quality of the modeling stages will be discussed. With the HLT as a reference framework, it is revealed which insights students have gained about molecular modeling by performing the curriculum unit. For a specification of the activities in the curriculum unit, Appendix 1 can be accessed. The complete HLT can be found in Appendix 2.

The first phase focused on identifying the area of interest, mainly done in activity six of the curriculum unit. Overall, the students performed a good job in this phase. However, the teams have difficulties with verbalizing the new concepts in this chapter. Apparently, students are not familiar enough with the new concepts in order to use them. Competitive inhibition, binding site and active site are three important concepts in this chapter which are often not verbalized by the students. A finding which could explain this, is that the students often skip the theoretical written parts of the curriculum unit. Frequently, the students started immediately with the activities, which were performed satisfactorily by the students.

In sub question c and d regarding activity six (Appendix 1), the teams had to place the amino acids in the binding site in a cube to get a three dimensional visualization, every team succeeded. The teams have shown notion that the binding site of the wild type and mutant are different from each other. All the teams found the binding site of DHFR and draw it spatial in the cube on the answering sheet. The teams who performed a better job, already looked into the functional groups of the amino acids in the binding site. Other teams just drew what they saw and did not discuss about it any further. Typical statements in this part of the curriculum unit are:

- Student in team 3: "*Cysteine has switched from place"*
  The student has said this when the team were talking about the difference between the binding site of the wild type DHFR and the mutant DHFR.

- Student in team 3: "*This one has to be placed in the front, the other one in the middle and that one in the back. Proline has to be placed in the back of the corner."*
  The student has said this when the team were discussing where the amino acids in the binding site had to be placed in the cube.

- Student in team 2: *"Molecular interactions, let us see, I see hydrogen bonds anyway, -OH is always hydrogen bonds. They can form hydrogen bonds because of the –OH groups in the carboxylic acids. "*
  The student has said this when they had to answer sub question b, which is about molecular interactions the amino acids in the binding site of DHFR can form.

The second phase of the curriculum unit was about identifying the problem. This stage turned out to be quite difficult for the teams. The questions that were asked, demanded a keen insight into the problem, the students really had to reason and talk to each other to be able to answer the questions. The teams regularly expressed their questions on the audio tapes:

- Student in team 1: "*But it is negative, then it is more, right? Probably, the more negative the better, I do not get it. Let us ask it to the teacher."*
  A student asked why the binding energy is a negative number and what the meaning is of this number.

- Students in team 8: *"Is it me or is the more negative the binding energy the better." "That is what I thought."*
  Students in team 8 talking about the binding energy. They came to the conclusion that the more negative the binding energy, the better the binding between pyrimethamine and the binding site. An explanation is missing, they just assume this because all the students in the team think the same about it. They do not ask the teacher about this.

The students seem to understand that the new analog has to leave human DHFR untouched. Also, they come to the conclusion that the more negative the binding energy, the stronger the binding is. Students cannot explain this however, a few teams asked the teacher for an explanation.

Learning goals that were not succeeded by most teams were about the connection between DHFR and pyrimethamine. It is not clear for the teams why the DHFR enzyme became resistant for pyrimethamine. Also, they do not really have the notion of what ArgusLab does when docking a protein with a lead and the natural working of DHFR in the human body is not clear for the students.

The third phase is about defining the scope, boundaries and purpose of the curriculum unit. Students have to think about their next steps on forehand. The teams had to design the first analog they wanted to test and give an argumentation. All teams did understood that the notion that the new analog has to bind better to the parasitic DHFR then to the human DHFR. Most teams had gained an insight with help of the previous activities and took this as a starting point for designing the first analog but, the teams had some difficulties with the argumentation. They recognize molecular interactions but they do have difficulties with putting into words why they choose a certain analog. Notable is that the teams often focus on one or two molecular interactions, not all molecular interactions were taken into account, see Table 3. All the teams look into hydrogen bonds and one or two other interactions, sterical hindrance, hydrophobic interactions or polarity.

In the last phase students were really going to model, test and revise a new analog. All the teams started with an analog which was somehow argued. Three teams chose a strategy for designing an analog in which they focused on mainly one molecular interaction, even if they mentioned two or more in the previous phase. Based on the docking results they try another possible analog, their strategy is a trial and error strategy. These teams have a limited notion of the molecular interactions involved, the teams get stuck and do not know how to go further this is followed by a negative impact on their motivation. The team, team 2, which takes more molecular interactions in consideration, does a better job and does have a more structured strategy for designing the new analog. Every analog they docked worked a little better, this had a positive impact on their motivation and their results in the end.

Reasoning why they choose a certain analog is difficult for the teams. But, all the teams do perform a consequent comparison of the binding energy of the analog to the human and the parasitic DHFR. They understand what is meant by the assignment and how to proceed the process.

Table 3: Best modeled analog of the analyzed teams.

Team	- X group	- Y group	- R group	Interaction(s)	Binding energy (Kcal/mol)
1	$-CH_3$	$-CH_3$	$-(CH_2)_4-NH-NH_2$	Polarity Hydrogen bonds	Wild type: - 11,36 Mutant: - 11, 32 Human: - 9,89
2	$-CH_2-CH_2-CH_3$	$-CH_2-CH_2-Cl$	$-(CH_2)_3-NH_2$	Polarity Hydrogen bonds Sterical hindrance	Wild type: - 12,09 Mutant: - 11,49 Human: - 5,85
3	-S	$-(CH_2)_3-CH_3$	$-CH_2-CH_3$	Hydrophobicity Hydrogen bonds	Wild type: - 9.82 Mutant: - Human: -
8	$-CH_3$	$-CH_3$	$-NH_2$	Hydrophobicity Hydrogen bonds	Wild type: - 11,94 Mutant: - 11,21 Human: - 10,39

Table 4 shows the overall scores of the teams per phase. As expected, team 1 and team 2 did a good job and scored on average 4 to 5 points out of 6. Team 3 and team 8 had more difficulties performing the curriculum unit and scored an average of 3 points out of 6.

The students in the ´better´ teams do not score better on chemistry in school. In fact, on average, the teams with less scores show higher average grades compared to team 1 and 2. It can be stated that, the average scores of the students in team 1 and 2, are a proof of principle. These outcomes show that the outline of the curriculum unit is well constructed.

Table 4: Overall scores of the teams per phase of the HLT. The phases are according to the structure of modeling process, described by Webb (2004).

Team:	**1**	**2**	**3**	**8**
Stages in Modeling				
1. Identify the area	ND*	++	+	+-
2. Define the problem	+	+	--	+-
3. Decide scope, boundaries and purpose	+	++	+-	-
4. Build, test and evaluate the model	++	+++	--	+-

* No data available to give a rating

As mentioned, a norm of 75% was applied when the learning outcomes of the teams per phases were scored, taking in consideration the four teams which were analyzed. 75% of the teams succeed when, three or more teams scored a + or higher on a certain phase. From Table 4 it becomes visible that all the phases need some improvement, not one of the phases reaches this 75% norm. When looking at the teams separately, the teams which were selected on their good results (team 1 and 2) did a good job during all the phases of molecular modeling when performing the curriculum unit. The two teams which were selected since they had some troubles performing the curriculum unit (team 3 and 8) indeed scored less compared to the other two teams.

Context

Analysis of the whole set of questionnaires revealed that students got a better insight in molecular modeling. Typical associations with molecular modeling in the pre questionnaire were:

- About half of the involved students gave a wrong description. Adjustment of DNA, dividing of cells, enlargement of molecules are quoted in the questionnaire.
- Some students have a good idea of molecular modeling. Spheres and rods are mentioned, adjustment of molecules, designing of molecules.
- Sometimes molecular modeling is linked to drug development.

In the post questionnaire typical associations with molecular modeling were:

- Molecular modeling is an adjustment of molecules/proteins/enzymes, on microscopic level, sometimes linked to the use of a computer.
- Often linked to drug development.
- Sometimes a definition of lead optimalisation was given.

The big difference between the questionnaire before and after performing the curriculum unit is the number of correct explanations of the students. Also the descriptions are more specific and often the context of the curriculum unit is taken into account when describing molecular modeling.

It was found from the post questionnaire and the interview, that the curriculum unit might be more difficult for the students. Especially the activities at the beginning of the curriculum unit were too easy and not challenging enough. Students made clear that searching information on the internet is too easy for them. It also became clear that students would like to have more classical instruction parts, especially for the teams who had some troubles with designing a new analog. Some advices for designing a new analog would be helpful. Finally, a tip which was given many times was the need of more theoretical background in the curriculum unit.

Students were positive about the distribution of theory and practice, whereby a lot of practice is included in the curriculum unit. The freedom which students have when they are designing the new analog is also positively received. The students also mention often that the curriculum unit is interesting and informative for everyone.

When looking specific to the set of questionnaires and comparing the results of the students in the teams who performed the best, the worst job and the remaining students, it is noted that the students in the two best teams have a good individual understanding of molecular modeling. Also the students in team 8 have a quite well understanding. Two students in team 3 have

difficulties with the theoretical part of the posttest, but the remaining student has a good understanding of molecular modeling. The students in the teams from which the audiotapes were not analyzed, give a definition of molecular modeling which can be a bit more specific. Most of them understood the core of the concept. When placing them between the teams with good performance and worst performance they are placed a little bit to the right from the middle.

ICT

The use of an ICT component, the software tool ArgusLab, seems to have to right impact. Introduction to ArgusLab was done step by step and guided with a detailed manual. The teams had to follow the steps in the manual precise to get the proper settings. The teams managed this quite well. The teacher was accessed when ArgusLab was not working according to the manual. Often this was due to the teams, by missing a line in the protocol. A few teams had troubles with ArgusLab, the software got stuck quite often by those teams, unsaved data were lost at this point.

By performing the curriculum unit, the students learned, step by step, more possibilities of ArgusLab. The steps had to be executed a few times because three enzymes were taken in consideration. Because of this, the students got a certain routine which gave confidence in working with ArgusLab.

Conclusions and Discussion

In this section the interpretation and the following conclusions of the results are outlined.

RQ1: *What are the learning outcomes regarding molecular modeling of the students participating the designed curriculum unit, `Molecular modeling, drug development against malaria`?*

It can be concluded that the learning outcomes of the students during this first pilot are promising. With the HLT as a reference framework, it became clear which learning outcomes were gained by the students and where there were troubles. Based on a plan of action, drafted by the teams at the beginning of the intervention, four teams were selected. From these four teams all the data was analyzed. The quality of the results were as expected. This plan of action, as a reference point, seems to be a good indicator for the remaining part of the curriculum unit. By choosing the most and less promising teams to analyze, the whole range of results is taken in consideration in this study.

Based on the findings in this study none of the phases of the curriculum unit reached the 75% norm. Indeed some adjustments have to be implemented, which are included under the heading reflection on the design principles in this section. It has to be taken into account that the four teams from which the data still has to be analyzed probably will range between the extreme results in this study. This because the best and worst performing teams were analyzed. Probably the overall results are of better quality as the results drawn in this study. So, further analysis of the other 4 teams has to be conducted to give the exact learning outcomes and a more precise indication of the quality of the curriculum unit. However, based on this study a clear insight is gained, adjustments can be made, the learning process of the students has become visible and targets for a new intervention can be set.

The set of questionnaires showed an improved image of molecular modeling and a great affection of the students with the context of drug design. When the curriculum unit is edited according to the recommendations in this paper, the findings during the intervention of the pilot and a teacher manual is designed, the curriculum unit could be further implemented.

RQ2: *To what extend do students gain insights into the process of molecular modeling with emphasis on three design principles?*

Reflection on the design principles

With the HLT as a reference framework it became clear what the students had learned performing the curriculum unit. Students are able to carry out the curriculum unit in teams in an independent manner. But, when looking phase by phase through the curriculum unit, some improvements are needed and recommended.

In the first phase, students barely made the new learned concepts explicit. The exact reason is not clear but it could be the fact that most teams immediately started with the activities and skipped the theoretical introduction of the chapter. This part is very important since the concepts are introduced and further explained. It could also be possible that the activities do not ask specific enough about these concepts. Revising the activities in this phase to get more focus on the important concepts is a possibility for improving the learning outcomes in this chapter. Another option is to give a more explicit instruction to the

students for reading the theoretical parts in this phase and also the rest of the curriculum unit.

Strong point about this part of the curriculum unit is the manner in which students discover the software tool ArgusLab in combination with exploring the binding site of the DHFR protein. The phase is build up, step by step so all students can follow the practical steps described in the curriculum unit.

The second phase is about identifying the problem. The teams really have to deepen into the theoretical facts behind the interaction between DHFR and pyrimethamine and DHFR and dihydrofolate. All teams have difficulties with formulating this. Next to that, the point that the malaria parasite became resistant due to a change in three dimensional conformations is missed by all the teams. Looking back to the curriculum unit, this is a point which does not become clear from the written text or activities. At this point, the curriculum unit has to be revised. There are different possibilities like adding an activity, an article, an extra theoretical part or a classical instruction to explain this important point to the students. A second improvement in the phase is needed within the docking part. It is questioned if students really have the notion what they do when performing a docking in ArgusLab. Adding a sub question in an activity would force the students to think about this.

During the third phase the students make a plan of action for the following activity. Students have to think about how their new analog is going to look like. The teams succeed but an improvement should be made. Students often look into only one molecular interaction, it is strived that students take more molecular interactions in consideration. If students get more explicit instructed to look at more than one interaction this should improve. It is the recommended to design a teacher manual in which this notion, other mentioned notions but also possible answers to the questions in the activities are included. When students are taking more molecular interactions in consideration, they have more options for designing the new analog, learn to bring more interactions into practice and have a better chance for succeeding in modeling a new analog.

Phase 4 in which the actual analog is designed, is a phase in which the teams get the space to design a new analog. This works well for the teams who understand what is expected and have a good notion of the molecular interactions involved. Teams how have a limited notion of these molecular interactions get stuck at a certain point. To make sure these teams also stay on the right track and motivated some guidance can be necessary at this point in the curriculum unit.

Strengths and limitations

Testing the curriculum unit in a small pilot showed a great affection of the students to the context and the structure of the curriculum unit. The set of questionnaires (pre, middle and post), but also the audiotapes, revealed that the students liked the curriculum unit and really enjoyed to perform the activities. Great affection raises the motivation of students which in turn could lead to learning outcomes above expectations. Besides the affection of the students, the curriculum unit is context based which fits in the educational innovations of the past and future years. It is a new way of learning about a chemistry subject, by working with a molecular modeling program, ArgubLab in this case. Coming to ArgusLab, the first limitation of the curriculum unit has to be stated. The program works not completely sufficient and a more specific manual for saving the files is needed in order to limit the troubles with ArgusLab. Another limitation is the small scale pilot itself. The participants are not a random reflection of the average chemistry student on secondary schools in the Netherlands. The students volunteered for performing the curriculum unit and got a small financial compensation in return. The affection for chemistry and results at school of these students were higher than the average student how attends chemistry in the Netherlands. Despite the fact that the students were not randomly chosen and the intervention was done under perfect conditions, performing the curriculum unit in this first pilot, gave a good insight in the curriculum unit, the learning outcomes of the students and the developments which have to be implemented for a successful further implementation of the curriculum unit.

Outlook

The curriculum unit itself has to be improved by the comments of the students and the outcomes of the analysis of the data, described in this paper. Also, a teacher manual with instructions and possible answers should be developed so a wider implementation of the curriculum unit could be possible in the near future.

Concerning molecular modeling, this study shows that students indeed are able to do argumentations on why they choose for a certain molecular model or a certain functional group. They are able to bring their knowledge about molecular interactions into practice and use it in

the context of drug design against malaria disease. It is expected that learning to model in another context has the same learning effect, the effect on the affection of the students cannot be predicted.

By performing the curriculum unit, the students bring their knowledge about molecular interactions into practice. They design a new analog for pyrimethamine. As Oda and Takahashi (2009) already stated, molecular modeling gives students a better insight in molecular interactions (p. 2). Visualization of the binding site gave students leads for designing the analog. Which is in accordance with earlier research of Barak and Dori and Cody et al., they showed the importance of visualization for students (p. 134; p. 29). The extra step of argumentation, included in the curriculum unit, turned out to be difficult but, gives an extra dimension and challenge for the students.

Teaching molecular modeling with this curriculum unit is promising for the future. The independent and explorative way of working is something that the students like and is stimulated by educational researchers. The results of this study have shown that, with some guidance, the students run through a learning process in which they get a notion of molecular modeling in the context of drug design.

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A**ppendix 1: The hypothetical learning trajectory**

Table 5: Outline of the activities in the curriculum unit; Molecular modeling, drug development against malaria.

Main aim	**Important concepts**	**Notions students should get from the activities**
Preparing activity	Protein structures Primary, secondary, tertiary and quaternary	**Activity 5:** Introduction to ArgusLab Insight in the four protein structures
Phase 1: Area of interest Exploring the 3D structure of the binding site	Enzyme and substrate Binding site and active site Competitive inhibition Functional groups DHFR	**Activity 6:** a) The catalytic centre of pyrimethamine is the same as the active site of the enzyme, this is called competitive inhibition. b) Functional groups in the binding site c) Looking into the binding site of wild type DHFR with ArgusLab d) Looking into the binding site of the mutant DHFR with ArgusLab e) Comparison of the binding sites.
Preparing activity	Building molecular Binding site Pyrimethamine	**Activity 7:** Introduction to building molecular in ArgusLab. Predicting which parasitic DHFR will bind best to pyrimethamine
Phase 2: defining the problem The parasite has become resistant for pyrimethamine, blocks the working of parasitic DHFR not anymore	Molecular interactions Hydrogen bonds, hydrophobic interactions and electrostatic attraction Sterical hindrance Antifolates Binding energy	**Activity 8:** a) Docking of wild type DHFR to pyrimethamine b) Docking of mutant DHFR to pyrimethamine Comparison of the binding energy between the two parasitic DHFR. **Activity 9:** a) Give an explanation for the fact that a drug may not interact with the human form of the enzyme. b) Docking human DHFR to pyrimethamine c) Question about why human DHFR still should interact with dihydrofolate en how this could be calculated in ArgusLab
Phase 3: Scope, boundaries and purpose	Functional groups Molecular interactions	**Activity 10:** Developing a strategy for designing a new analog of pyrimethamine.

Phase 4: Building, testing and evaluating the model Designing and docking a new analog of pyrimethamine		**Activity 11:** - Designing a new analog of pyrimethamine by changing three functional groups. - Give an argumentation for choosing certain functional groups. - Comparison of binding to parasitic and human DHFR.

Appendix 2: Hypothetical learning trajectory

	Activity					
Prior conceptual & procedural Modeling knowledge	4	To what extend do students have a broad outlook on the modelling stages described below? Do they mention relevant concepts and/or modeling activities as described below?				
	5	Supportive activity (instruction ArgusLab, structure of enzymes primair, secondair, tertiair, quartenair	**Team 2**	**Team 1**	**Team 3**	**Team 8**
1. Area of interest	6	1. The bindingsite is always equal to the active site: competitive inhibition	6	0	4	2
		2. The lead molecuul binds to the bindingsite	1	0	1	1
3D structure of active site (= binding site)	Students show	3. The amino acids form the bindingsite for the binding of pyrimethamine to DHFR, so also the active site	4	0	1	1
	notions of:	4.The conformation of the amino acids in the binding site in the mutant and the wildtype differ from each other	4	5	4	4
		also the 3D orientation.	-	-	-	-
		5. This amino acid has to be placed further to the left/right/back/front in the cube	5	0	6	1
		6. Students have attention for/notice/draw functional groups to the amino acids. Optionally the call some moleculair interactions	5	3	4	3
	7	Supportive activity (instruction ArgusLab, building pyrimethamine)				
2. Problem	8 and 9	7. Parasitair DHFR has resistence for pyrimethamine: this due to changes in the 3D structure of the binding site	1	3	1	1
		8. Pyrimethamine should leave humane DHFR untouched	6	5	3	6
		9. The more negative the binding energy, the stronger the binding	6	6	1	5
The parasite is resistent for pyrimethamine.	Students show	10. The binding energy is a negative number because, breaking bonds costs energy	4	4	1	1
Pyrimethamine blocks working of	notions of:	11. Pyrimethamine binds in a certain conformation (= pose) the best to the bindingsite in DHFR, ArgusLab does the calculation = docking	3	3	1	4
parasitair DHFR not anymore		12. Humane DHFR still has to make interaction with dihydrofolate in the presence of the pyrimethamine analog.	4	4	1	1
		13. The fit (= key-lock principle) of pyrimethamine in the bindingssite of parasitaire DHFR could be better	1	1	1	2
3. Scope, bounderies, purpose	10	14. The analog has to be a bigger molecule than pyrimethamine, sterical hindrance	6	3	1	1
WT, mutant and humane DHFR		15. Polair/apolair i.c.w. interaction or binding (elekstrostatic interactions)	6	5	1	1
Analog of pyrimethamine	Students show	16. hydrofobic/hydrofilic i.c.w. interaction or binding (hydrofobic interactions)	1	1	5	4
The highest (lowest) possible bindingenergy	notions of:	17. Compared to humane DHFR, the analog needs to bind better to parasitair DHFR	5	4	6	5
		18. Hydrogen bonds NH e/o SH bonds	6	6	4	1
4. Building the model	11	19. I would change group X, Y, R to pyrimethamine in .... because	6	4	1	3
5. Test the model		20. This analog of pyrimethamine works better/wors than pyrimethamine itself, so...	6	5	1	3
6. Evaluate the model	Students show	21. Given the present functional groups in the binding site, I would change pyrimethamine this way...	6	3	1	1
	notions of:	22. Applied strategy by the students:	-	-	-	-
Analog of pyrimethamine		A. Structured manner of working. Directed changes of groups to pyrimethamine with an argumentation based on	6	-	-	-
		moleculair interactions and/or sterical hindrance	-	-	-	-
		B. Trial and error strategy: non structured approach. Relatively random designing and docking an analog.	-	-	-	-
Designing and docking		No/little attention is payed to moleculair interactions and/or sterical hindrance	-	-	-	-
		C .Mix of A and B	-	5	4	4
		23. Periodic comparison of the docking results of humane DHFR	6	6	1	4
		4. The resultats of the docking mean that pyrimethamine has to change further this way	5	5	1	4