Molecular modelling for pre-academic chemistry education

Opinions of experts, teachers and students on an initial curriculum unit sketch

Gerret Sanders, Gjalt T. Prins

In science education, students should come to understand the nature of models and modelling. Students often have trouble understanding advanced features of modelling. It is not a trivial task to design learning materials resolving these learning difficulties. In this study we designed a curriculum unit sketch for learning molecular modelling for pre-academic chemistry education, a type of modelling which uses software tools to calculate molecular properties. We focused primarily on the *process* of modelling and used the scientific practice of malaria drug design as a context for learning. The design of the curriculum unit sketch was guided by five criteria: Scientific soundness & authenticity, Student engagement, Student knowledge base, Software usability, and Feasibility. Experts, a teacher and students were interviewed to assess to what extent the design criteria were fulfilled. All of the respondents considered the curriculum unit sketch a good basis for further design of teaching material. For each criterion, there was further room for improvement. For instance, the 'Scientific soundness & authenticity' criterion can be further improved by making parts of the sketch have a larger focus on drug resistance. Nevertheless, this study shows that a pre-academic molecular modelling curriculum unit can potentially be designed to be both usable in class and engaging to students.

Introduction

Models are an important tool used in the production, dissemination and acceptance of scientific knowledge. They are generally seen as a connection between scientific theory and the world as experienced (Prins, Bulte, Van Driel & Pilot, 2009).

The learning of models and modelling is regarded as an integral part of scientific literacy (Justi & Gilbert, 2002). As Grosslight, Unger, Jay & Smith (1991) have shown, this learning is not a trivial matter. Students generally think of models as 'copies of reality' or 'scale models' (Taber, 2010) and have trouble understanding more advanced features of models and modelling, such as the purpose of creating a model, a model as a representation of an idea and the notion that models can be tested and changed during the development of ideas.

To increase student understanding of these more advanced features, it has been suggested to focus on the process of modelling and the use of models in education (Gilbert, 2004). Instead of providing students with ready-made models, students should become involved in a modelling process (Gilbert, 2004), in which their understanding contributes to the development of their models, and testing of their models contributes to evolving understanding (Prins, Bulte, Van Driel & Pilot, 2008).

It has been argued that real scientific practices can be adapted for designing teaching-learning materials, in which modelling can be embedded (Edelson, 1998). In this paper, such real scientific practices will be denoted 'contexts'. Naturally, there are many of these real scientific practices

available, some of which are suitable to use as a context in science education. It is advisable to involve students in multiple contexts, ensuring they encounter and experience different modelling processes.

In this paper we will focus on the contexts that employ *molecular modelling*. Molecular modelling (MM) is an important approach in different domains of scientific research, such as in drug design (Höltje, Sippl, Rognan & Folkers, 2008), polymer chemistry (Rutledge & Theodorou, 1998), crystal chemistry (Myerson, 1999), catalysis (Van Daelen, 1996) and inorganic chemistry (Comba & Hambley, 1995). It is expected that MM's importance will grow in future decades with the improvement of computer tools and increase in computing power. Additionally, the use of computerised models in education improves students' model perception and improves awareness of the role of models (Barnea, 2000; Justi & Gilbert, 2002). In our opinion, it is worthwhile to involve students in secondary science education in a modelling approach with such widespread impact and significance.

Since MM is relatively new in the science curriculum, there are no ready-to-use educational materials available for Dutch high school education. Moreover, designing such materials is not a trivial task, because of the wide range of definitions of MM and the challenges of designing feasible, high quality educational materials based on a scientific practice. The purpose of this research study is to make a first step towards designing curriculum materials for learning MM for secondary chemistry education. This will be done by adapting a context into a first sketch of a curriculum unit. This sketch will then be evaluated by experts on MM, experienced chemistry teachers and students.

Molecular modelling in science and education

In this section, first MM within scientific practices will be defined. Secondly, current uses of MM in both university level and pre-academic education are described.

Molecular modelling in scientific practice

In scientific practice, any MM approach usually consists of a number of steps. The first step is establishing a preliminary model of the molecule, which includes the correct stoichiometry and connectivity. This preliminary model is based on experimental results or a mathematical approach. This model is run through an algorithm that takes into account all forces between atoms, in order to get a good estimate of the molecule's actual geometry. Many different approaches and computer tools exist for these kinds of calculations (Barnea, 2000; Comba & Hambley, 1995). The resulting 'molecular model' can be used to predict properties of the molecule. These include microscopic properties, such as forces involved in conformational changes of the molecule and intermolecular forces (e.g. Dileep, Tintu, Vinod, Saliha & Sadavisan, 2011), and resulting macroscopic properties such as solubility, boiling point or effect on living cells.

For this study, we define a molecular model as a computer-based model of a molecular structure, which can be used to predict properties of the molecule. Molecular modelling is the process of obtaining such a model and using it to predict these properties.

Molecular modelling in science education

A limited number of empirical studies have been conducted on MM in chemistry education, both at university and pre-academic level. This section gives an overview of these studies, in order to show the current state of MM in science education and to identify potentially suitable learning materials

and contexts for this study. Importantly, students need to be involved in the modelling *process* and materials need to use a scientific practice as a context.

First, we will discuss studies in which MM educational materials that focus on the *molecular structure* are described. Secondly, we will discuss studies which describe MM educational materials that relate the molecular structure to *molecular properties*.

Molecular structure

MM can be used as a 'learning tool' for students to learn about the molecular structure of a molecule they synthesised in a laboratory practical (Pernaa & Aksela, 2011). The following studies in pre-academic education use MM as a teaching aid to learn about molecular structure.

Pre-academic

Cody *et al.* (2012) described lesson materials focussing on the topic of stereo-isomerism, a specific aspect of molecular structure, through specially prepared interactive PDF (Portable Document Format) files. Molecular models within the PDF files could be rotated, translated and zoomed. Students only need a PDF reader, while designers need additional software to create these PDF files. This study did not use a scientific practice as a context. While user-friendly PDF files make classroom implementation easy, students are not able to build molecular models themselves.

Linenberger, Cole & Sarkar (2011) described high school lesson materials that focus on understanding Lewis structures and the general geometry of molecules through MM. VSEPR (valence shell electron pair repulsion) theory is introduced within these materials. Mostly, small and relatively simple molecules are modelled. Students do the modelling themselves in the classroom, using commercial software. The materials do not seem to use a scientific practice as a context.

While Linenberger *et al*.'s (2011) design involved students in the modelling process, neither this study, nor the study by Cody *et al.* (2012) used a context. This is understandable, as it may be difficult to find a scientific practice that focuses on molecular structure only.

Molecular properties

In several designs, the calculated structure is used by students to predict microscopic and, in some cases, macroscopic properties. We first describe pre-academic education studies in which this activity is embedded. Second, university education studies are discussed.

Pre-academic

Gledhill *et al.* (2006) described teaching materials about the use of MM in designing malaria medicines. The malaria drug design context as explained to students is available on a website (E-Malaria Project, 2005). The course focused on protein-ligand binding. For practical reasons, tri- and tetrapeptides were used as ligands. Students would design these oligopeptides themselves and submit them for a 'docking' calculation. They needed no prior knowledge other than basic biochemistry. However, the paper mainly described the design and creation of a custom software system to use with the lesson materials. The article did not describe in detail how the materials were actually used in class.

Several interrelated studies were done in Israel. The educational materials used in these studies were designed for high school chemistry. The materials had the common goal of increasing students' understanding of the three-dimensional structure of molecules, and the way this structure influences

molecular properties. In these studies, MM is part of a larger project, also using physical ball-and-stick models (Dori & Barak, 2001) or 'Case-based computerized laboratories' (Kaberman & Dori, 2009; Dori & Kaberman, 2011). In the MM parts of these projects, students had to draw 2D models on the computer, based on structural formulae. By switching the view setting to 3D, students were able to see the spatial structure from several viewpoints. The students learned to predict macroscopic properties such as a compound's phase at room temperature, based on the models. They also studied macroscopic properties in laboratory experiments. These studies showed an improvement in students' modelling abilities and in their understanding of spatial properties of molecules.

In conclusion, the studies in Israel involved students in the modelling process, using 'case-based' learning. It is not clear if these cases use scientific practice as a context. However, the design described by Gledhill *et al*. (2006) used a clear context and directly involved students in the modelling process, using custom software. While this design is promising, the paper only has a global description of the actual lesson materials, and does not describe how they were used in the classroom. This means we cannot directly adapt parts of the design, and any similar lesson materials have to be designed from the beginning.

University

Barak & Dori (2004) studied using MM in project-based education at the undergraduate university level. In an assignment, students had to model organic molecules 'in daily life'. They defined 'daily life' molecules as substances that are or were used on a daily basis, are found in humans, or are of historical significance. An example is Vitamin A. The purpose of the assignment was to improve students' ability to traverse among different levels of understanding: microscopic (molecular structure), macroscopic ('everyday' properties such as solubility), symbolic (formulae) and process (reactions). The researchers found that their lesson design did improve this ability, as well as the students' ability to view a molecule as a spatial structure.

Coleman names a number of molecules that could be modelled by students to learn about their some of their properties, such as bond lengths, partial atomic charges and aromaticity (Coleman, 2010a; Coleman 2010b). While he has prepared molecular model files, he leaves the lesson design open for a teacher to complete.

Martin (1998) studied the integration of MM education in the Chemistry faculty at the University of North Carolina at Wilmington. The goal was to stimulate students to learn the value and limitations of MM as applicable to various disciplines, such as organic chemistry, biochemistry, medicinal chemistry and physical chemistry. In one of their lesson designs, students use MM to find out for themselves what forces are involved in conformation changes of organic molecules. Students then verify their predictions empirically. The study reports that students gained a better understanding of stereoisomery. In addition, students themselves appreciated the MM education.

Sutch, Romero, Neamati & Haeworth (2012) used pharmaceutical contexts in their MM lesson design. Sutch *et al*. (2012) describe educational materials in which students do a 'case study' on a certain drug. Students use MM to look at the drug's structure and do a 'docking' calculation of the drug to a protein. In this design, students also studied the drug's pharmacological properties, such as the rate of metabolism in the human body.

In conclusion, the design by Barak & Dori (2004) is similar to the pre-academic lesson materials by Kaberman & Dori (2009), as described earlier in this paper. While students become involved in the modelling process, no context is used. Coleman (2010a; 2010b) does not use a scientific practice as a context either. His general lesson ideas could potentially be used to involve students in the MM process, if they are further elaborated. In Martin's (1998) design, students are involved in the MM process. The design reflects scientific practice, as students have to verify their predictions empirically. However, Martin (1998) does not use an existing scientific practice as a context. Coleman and Martin's ideas have potential for involving students in the process, but as they are formulated in a broad manner, they cannot be used as such. In Martin's (1998) study, students are involved in the MM process. The design by Sutch *et al.* (2012) involves students in the MM process and uses a context (drug design). However, promising university designs may be too complicated or extensive to fit into the high school curriculum, and pre-academic students may lack prerequisite knowledge.

Overview

While some of the university level designs (potentially) involve students in MM, there exists no high-quality material suitable for immediate use by teachers in the *pre-academic* level. With the exception of the studies by Gledhill *et al.* (2006) and Sutch *et al.* (2012), no scientific practices were used as contexts. Sutch *et al.* (2012) describe university-level materials that do not fit well in the high school curriculum. In the case of Gledhill *et al.* (2006), no detailed information about the materials in class is available, as the study focused on the implementation of custom modelling software.

Nevertheless, we believe the drug design context used by Gledhill *et al.* (2006) and Sutch *et al.* (2012) could serve as a basis for designing a new curriculum unit, in which students can become involved in the modelling process.

Adapting a scientific practice as a context for a curriculum unit

It has been shown that the teaching of modelling, using recognisable subjects based on scientific practices, fosters students' involvement and motivation (Gilbert, Boulter & Elmer, 2000; Bennett & Holman, 2002; Prins *et al.*, 2009). A promising practice first needs to be adapted into a curriculum unit before it is suitable for teaching. Several design criteria make this design process a non-trivial task. The curriculum unit needs a scientifically sound practice as a context, which should be engaging for students. The unit should have a reasonable difficulty level. Designers need to keep in mind that pre-academic students do not necessarily have an adequate prior knowledge base. MM requires specialist software, and software used in pre-academic teaching should be user friendly for both teachers and students. Of course, student assignments, projects and the curriculum unit as a whole should be feasible in a classroom setting.

A curriculum unit based on a scientific practice should comply with these criteria in sufficient extent. Below each design criterion is elaborated briefly.

A. Scientific soundness & authenticity (according to experts)

In order to adapt the scientific practice into a context for learning, simplifications are probably required (Edelson, 1998). These simplifications have the risk of harming the scientific soundness and authenticity. To ensure that the scientific contents of the lesson design are correct, it should be

validated by experts. The curriculum unit should give students an authentic image of the scientific practice. This criterion is conditional in designing a good curriculum unit.

B. Student engagement

Using a recognisable context fosters students' interest. Students are expected to become active learners by means of such a context. The context should have some relevance to students, and if this relevance is not directly clear, students should be told about it. The curriculum unit and the learning activities can be designed to be motivating as well (Bennett & Holman, 2002; Prins *et al.,* 2009).

C. Student knowledge base

When adopting a scientific practice, we should account for the differences in the knowledge base of students and experts (Prins *et al.*, 2009). Lesson designs should build on students' prior knowledge, skills and attitudes (Duit & Treagust, 1998). This means that any information that may not yet be part of the students' knowledge base should be included in the curriculum unit, if it is required for understanding the scientific practice or scientific content.

D. Software usability (for students)

Software tools are inevitable in MM. It is necessary to find software that does the tasks required by the lesson design. For practical reasons, it should not take a long time for students to get familiar with the program interface. This means it should be user-friendly. Furthermore, as schools have a limited budget, the software tools should be free to use or cheaply available.

E. Feasibility (for students and teachers)

Modelling involves complex thinking and can be difficult for students to be engaged in (Hogan & Thomas, 2001). Considering this, care should be taken to make the curriculum unit feasible for students. While including information that may not yet be part of the students' knowledge base (criterion C) can help students understand, this may not be enough. To make the curriculum unit more feasible for students, the lesson plans should be logical and orderly. The content should be well distributed among the lessons. The difficulty level of assignments and any assessment should be reasonable for the target group, and the design should not have any sudden changes of difficulty.

Another aspect of this criterion is feasibility in a general classroom setting. Chemistry teaching itself is difficult (Gabel, 1998), so we need to ensure that teachers can properly use the curriculum unit in class.

Scope and Research questions

This research is positioned in a current science curriculum innovation in the Netherlands, as initiated by the Dutch Ministry of Education, Culture and Science. The curriculum innovation is aimed at implementing the context-concept approach (Commissie Vernieuwing Scheikunde Havo en Vwo, 2003). The College voor Examens (2010b) states in the new concept syllabus, that at the end of pre-academic education (VWO), "students need to be able to explain the contributions of molecular modelling and data-mining to the development of scientific research, product innovations and new public applications." *

* At time of publication of this paper, the Dutch government has approved the final version of the new syllabus. While the phrasing is somewhat different, students still have to be able to use MM. (Van Bijsterveldt,

The goal of this research project is to sketch a curriculum unit about MM based on the context 'malaria drug design'. In the different curriculum representations (Van den Akker, 1998), the sketch is positioned at the *formal curriculum* stage. The purpose of the curriculum unit (CU) will be to teach MM to students in 11th grade pre-academic chemistry education and to involve them in the modelling process.

The malaria drug design is chosen as context for learning, because this was the most promising context we found in literature. Gledhill *et al*. (2006) specifically named malaria medicines. Malaria is a common disease which is often in the news, and students who travelled to regions where malaria is common may have personal experience with prevention measures. It is a recognisable subject. Furthermore, it is possible for students to do their own modelling within the context, and to focus on multiple modelling aspects, such as protein structure, binding, and the role of modelling within the whole research area of drug design. Gledhill *et al.* (2006) stated that their 'system' was generally well-received by the students.

However, their materials cannot be adapted directly to teach about MM within Dutch high school education. The actual materials are not publicly available. Furthermore, Gledhill *et al.* (2006) used a quite complicated set-up using multiple servers. This may not be feasible in a regular high school setting. Sutch *et al.* (2012) also used a drug design context, but as it was designed for university level education, it is probably too difficult for pre-academic education.

The sketch is validated by experts, chemistry teachers and 11th grade students by means of a series of interviews. Each type of respondent is best suited to evaluate to what extent certain design criteria are met. Experts have the expertise to assess the Scientific soundness & authenticity. Students will be asked to reflect on the design criteria Student engagement, Student knowledge base, Software usability, and Feasibility for students. To give the students a better idea of what the sketch would look like in practice, they do a computer assignment before they are interviewed. Teachers focus on Student engagement and Feasibility. The following research questions will be answered consecutively:

1. Does the CU sketch meet the criterion Scientific soundness & authenticity in sufficient extent, according to MM experts?
2. Does the CU sketch meet the criteria Student engagement, Student knowledge base, Software usability, and Feasibility for students in sufficient extent, according to 11th grade pre-academic students?
3. Does the CU sketch meet the criteria Student engagement and in sufficient extent, according to high school chemistry teachers?

Method

Two consecutive research phases were planned. In the first phase, the malaria drug design context was adapted into a sketch of a CU, guided by the five design criteria. In the second phase, students,

M. (2012). Regeling van de Minister van Onderwijs, Cultuur en Wetenschap van 28 april 2012, nr. VO/403948, houdende wijziging van de Regeling examenprogramma's voortgezet onderwijs in verband met het vernieuwen van de examenprogramma's scheikunde havo en vwo. *Staatscourant nr. 11109.*)

teachers, and experts were interviewed about the context and its adaptation, in order to answer the research questions.

Phase 1: Designing the curriculum unit sketch

The purpose of this phase was to design a sketch of a CU that could serve as a framework for a full curriculum unit. The CU sketch should give the respondents in the second phase a good impression of what the CU would look like when taught in class.

The design process

A design approach was used for the sketch of the CU.

Initially, a first version of the sketch was written by the first author based on the Malaria context. For this first version, information on the website used for the project described by Gledhill *et al.* (2006), see E-Malaria Project (2005) was used. This information was combined with additional background information from Wikipedia (keywords: malaria, antimalarial medication, pyrimethamine, DHFR). The first version was evaluated by the second author.

The first version and evaluation were used as a basis for a cycle of improvements and discussion between the two authors. During this process, potential concerns for implementing each of the five criteria Scientific soundness & authenticity, Student engagement, Student knowledge Base, Software usability and Feasibility were identified (Table 1). This cycle of improvements was continued until the authors reached consensus that the criteria were sufficiently met. During the cycle, the authors used several ways of dealing with these concerns:

A. Scientific soundness & authenticity

The authors decided upon using one example of malaria drug design as a basis for the teaching materials and assignments within the CU, namely the drug pyrimethamine, an inhibitor of the malaria DHFR protein. Knowledge about pyrimethamine's operation and binding properties was collected from literature (Rastelli *et al.*, 2000; Yuvaniyama *et al.*, 2003).

B. Student engagement

Student engagement is influenced primarily by two aspects, namely the context and the type of learning activities. We expected that students would be familiar with malaria, or at least heard about is. The design challenge was to implement the malaria context in the CU such that students would become interested and involved in MM. Furthermore, motivating learning activities needed to be designed. For this design criterion, the authors' own teaching experiences were used to decide what makes the CU interesting and motivating to students.

C. Student knowledge base

The Dutch national chemistry syllabus (College voor Examens, 2010a) was used to identify relevant existing knowledge of students within 11^{th} grade pre-university education, concerning MM, computational chemistry, and the drug design context (biochemistry and pharmaceutical chemistry). Background information students were expected to be unfamiliar with was added to the CU sketch. Furthermore, we assumed that the knowledge base also differs between schools and even between individual students. To deal with this design criterion, a vocabulary was added to the CU sketch, and no prior knowledge on computational chemistry or MM was assumed.

Table 1: Concerns for implementing the criteria in the CU, and data sources used to deal with the concerns (phase 1) and to test if they are sufficiently dealt with (phase 2).

Criterion	A. Scientific soundness & authenticity (according to experts)	B. Student engagement	C. Student knowledge base	D. Software usability (for students)	E. Feasibility (for students and teachers)
Concerns	1. Authenticity of the image of the drug design practice. 2. Scientific soundness of the content and data.	1. Student engagement caused by the context. 2. Student engagement caused by learning activities.	1. Connection to prior knowledge and skills.	1. User-friendliness. 2. Financial availability for schools. 3. Contains applications required for CU (molecule editor, 3D-model viewer, docking calculator).	1. Feasibility of learning activities and CU texts. 2. Feasibility of the final assessment. 3. Order and length of the CU.
Data sources	**Phase 1** - Pyrimethamine/ DHFR interaction studies **Phase 2** - Expert interviews	**Phase 2** - Student interviews - Teacher interview	**Phase 1** - National chemistry syllabus **Phase 2** - Student interviews	**Phase 1** - Expert consultation **Phase 2** - Student interviews - Field notes	**Phase 2** - Student interviews - Teacher interview

D. Software usability (for students)

For some of the learning activities, the software at least needed a molecule editor, a 3D-model viewer and a docking calculator. It was difficult to find suitable software, as most software was either too complicated for pre-academic use, did not have all required functions, or was not financially viable. An expert on MM and MM-software was consulted during the design process, and his opinion was used in making a definite choice for the software (Bonvin, A.M.J.J., personal communication, 2012).

E. Feasibility (for students and teachers)

Similar to criterion B, the authors' own teaching experiences were used when considering the feasibility concerns. We considered the fact that MM is an abstract activity, which probably needs to be made comprehensible using step-by-step examples. For this reason, we opted to have a clear sequence within the CU sketch, so that when doing the assignments in order, students are supposed to be able to finish the more complicated assignments near the end of the CU sketch as well. In addition, the learning activities need to be feasible as well. The activities should have a reasonable difficulty level for students. As the activities are dependent on the texts in the CU sketch, the difficulty level of these texts is considered as well. Overall, the difficulty level of the sketch needs to be reasonable. The activities should be feasible for teachers in a classroom setting, too. This criterion is important for both students and teachers.

The final CU sketch

Two versions of the final sketch were made. The 'teacher version' was made for the teacher and expert interviews. A second version with a few changes was made for the student interviews (the 'student version').

The teacher version

The final sketch (see Appendix 1) consisted of five chapters, which each consisted of objectives, example lesson materials, a list of potential learning activities and 'instructional issues' (aspects that need to be resolved when using the sketch to design full teaching materials). The sketch also

contained a list of general learning objectives, an example software tutorial and a vocabulary. Throughout the CU sketch, a variety of possible learning activities are described.

In the first chapter, societal issues concerning malaria are introduced. The second chapter teaches students about the malaria infection, existing medicines and about drug design, and introduces MM. These chapters are intended as an introduction and to interest and motivate students.

For one of the possible learning activities in the second chapter, students listen to a guest speech by an expert on malaria, drug design or MM. We realise that, while such an activity can be greatly motivating, it may be practically unfeasible to organise.

In the third chapter, the main target (DHFR) and drug (pyrimethamine) are introduced and used to treat relevant chemical concepts, such as interactions between the medicine molecule and the target. The students also do a software tutorial, in which they learn to work with the MM software.

The fourth chapter contains the main assignment, in which students do their own modelling project. They model a possibly improved medicine (a pyrimethamine analogue) and run a docking calculation to predict the analogue's interaction strength with the malaria target DHFR.

In chapters 3 and 4, students need to use MM software. In the sketch, the program Arguslab (Thompson, n.d.) was used as for viewing proteins and doing the docking calculations. Using these features was considered straightforward. However, the molecule editor in Arguslab was deemed too complicated. Therefore, PRODRG (Schüttelkopf & Van Aalten, 2004) was chosen for designing pyrimethamine analogues. The online version of PRODRG is freely available, but is only to be used for academic purposes, to a maximum of 5 times per day. Despite this licensing issue, PRODRG was chosen because of its easy to learn interface.

In the final chapter, it was planned that students discussed their results and talked about how MM could be used in scientific practice. This way, students' work would be once again linked to the larger drug design context. This chapter finishes with a written assessment, which is a report of the student's activities in chapter 4, possibly combined with a 'research proposal' of the next steps within the scientific practice of drug design. This entire CU sketch takes an estimated 8-10 hours of class time.

The student version

The student version was in two ways different from the teacher version. First, the 'instructional issues' were removed, because these were potential problems that need to be resolved by teachers or curriculum designers, and are irrelevant to student respondents. Second, the software tutorial was expanded to an independent computer assignment. In this computer assignment, students use PRODRG and Arguslab to dock pyrimethamine to DHFR. Additionally, the computer assignment contains a small number of contextual questions based on the first two chapters of the CU sketch. These can be answered by using two websites (E-Malaria Project, 2005; Kennislink, 2012). The authors considered it unlikely that students are familiar with computational MM tools. The aim of the computer assignment is to prepare student respondents (in Phase 2) for the interview by showing them what an implementation of the CU sketch would look like.

Phase 2: Interviewing experts, students and teachers

The purpose of this phase was to map the valuations and perceptions of experts, students and teachers, related to the sketch of the CU. The aim was to evaluate to what extent the criteria are met, in order to decide whether it is worthwhile to extent the sketch into a full CU.

In this phase, four interviews were held: two interviews with experts, a group interview with two 11th grade pre-university students, and an interview with a teacher. In each interview, a selection of the criteria was tested, such that the combined results cover all criteria.

Interviews with experts

Two experts on MM were interviewed individually. Expert A is a professor of Computational Structural Biology. He is involved in the development of MM software that is used in research to calculate intermolecular interactions. Expert B is a researcher in Computer-aided Drug Discovery and is involved in both university and high school educational design.

In these interviews, the conditional criterion *Scientific soundness & authenticity* was tested.

The experts received a copy of the teacher version of the sketch a week in advance, together with a few general preparatory questions based on the design criteria. They were asked to read the outline while keeping the preparatory questions in mind. These interviews (Table 2) took about 30 minutes each.

Table 2: Expert interview protocol

Criterion	Questions
Scientific soundness & authenticity	1. Do you think this outline gives students an authentic image of the methodology used in this scientific practice? 2. For each chapter: To what extent are the information and activities in each chapter scientifically sound?
Other	3. Do you have further comments about the lesson outline?

Small group interview with students

Two 11th grade pre-academic students were interviewed. The purpose of this interview was to find the students' views on the criteria *Student engagement, Student knowledge base, Software usability,* and *Feasibility.* Both students were enrolled in the Dutch 'Nature and Health' track in which chemistry is compulsory, while one student also took physics.

The students received a copy of the student version CU sketch (without the computer assignment) a week in advance, together with a few general preparatory questions based on the design criteria. They were asked to read the sketch while keeping the preparatory questions in mind.

Preceding the interview, the students conducted the computer assignment. The assignment started with the contextual questions, followed by the software practical. During the assignment, the two students worked together, while the interviewer observed their work and made field notes. He interfered a few times by giving additional instructions related to working with Arguslab. The assignment took about 45 minutes in total and was meant to properly involve the students and give them an idea of what MM comprises.

Next, the semi-structured interview took place (see Table 3). In this 40-minute interview, the assignments and the sketch were discussed. By asking questions about each part of the outline, the interviewer urged the students to elaborate on their views.

Interview with a teacher

An experienced chemistry teacher was interviewed. The purpose was to map the teacher's thoughts on the criteria *Student engagement* and *Feasibility*. Similar to the other interviews, the teacher received a copy of the teacher version a week in advance, together with a few general preparatory questions based on the design criteria. He was asked to read the sketch while keeping the preparatory questions in mind.

This semi-structured interview (Table 4) took about 40 minutes.

Coding and analysis

An audio recording of all interviews was made and transcribed verbatim. As a respondent validation step, the interviewees were requested to give feedback on the transcript of their interview.

The first author made a coding scheme with each code based on one of the concerns for the 5 criteria, as given in Table 1. The first author discussed the coding scheme with the second author.

The expert interviews were coded and analysed by the first author. A thick description of the analysis results was made. The results were discussed with the second author, and it was decided that continuing with the teacher and student interviews was viable.

Table 3: Students interview protocol

Criterion	Questions
Student engagement	1. How did you like doing the assignments? 2. Would you like to get this lesson outline taught in class? What parts did you (not) like? 3. What do you think of the possible learning activities? Which one would you choose for each chapter? 4. Do you think it's useful to learn about malaria at the same time you learn chemistry? a. Do you think malaria is an interesting subject? b. Would a subject such as malaria motivate you to work harder for chemistry class?
Knowledge base	5. Was the material in each chapter clear or were there things you did not understand?
Software usability	6. Could you complete the software assignment? 7. Do you think this computer program could be used in class?
Feasibility	8. Were you able to complete the website assignment? 9. What is your opinion on the difficulty of each chapter and of the learning activities? 10. Do you feel that after reading the outline and doing the assignments, you have enough knowledge to design a new medicine and test it on the pc?
Other	11. Do you have further comments about the lesson outline?

Table 4: Teacher interview protocol

Criterion	Questions
Student engagement	1. Do you think that a module in which students design and test new molecules with MM, with a context as a basis, is a good way to teach this subject? 2. Do you feel malaria drug design is a good context for MM education?
Feasibility	3. Do you think the lesson outline in general is feasible for use in a class? 4. What do you think of the outline's structure and the distribution of the material among the chapters? What do you think of the length of the entire outline?
	5. What is your general opinion on each chapter? 6. What do you think of the possible learning activities? Which one would you choose for each chapter? 7. Which assessment possibility would you prefer to use, the report in chapter 4 or the research proposal in chapter 5?
Other	8. Do you have further comments about the lesson outline?

The teacher interview was coded by both authors. For the teacher interview, the inter-rater agreement was 63%. Each author analysed the interview independently and made a thick description. There was a high level of agreement between these descriptions.

While the agreement of the thick descriptions shows that the interview analysis itself was reliable, the relatively low inter-rater agreement on the coding suggested that some codes could be interpreted in a broad way. For the analysis of the student interview, the first author made the description of the codes more clear. He gave the improved coding scheme to the second author and to an independent researcher. He discussed the coding scheme with the independent researcher, in order to ensure that the meaning of the codes was clear to her.

The second author and the independent researcher coded the student interview separately, resulting in an inter-rater agreement of 78%. The coded interviews were merged and both authors made a thick description of the student interview results and analysed the results. Relevant field observations made during the assignment were added. Again, there was a high level of agreement for the descriptions.

Results

This section describes the results of each interview (2 expert interviews, an interview with 2 students, and a teacher interview). For each interview, the respondents' opinions will be described per criterion.

Experts

The experts were interviewed about the criterion Scientific soundness & authenticity only.

A. Scientific soundness & authenticity

According to expert A, the full practice of drug design takes 12 years on average. First, MM is employed on a library of about 1 000 000 potential drugs. 1 000 to 10 000 potential lead compounds ('leading' compound) are selected and tested in a laboratory environment. The small number of lead compounds found this way will be analysed more thoroughly, and a cycle of MM and laboratory research is done to find the best drug. After that, years are spent for physiologic tests with animal and human subjects.

Both experts noted that the description of MM given in the CU sketch only shows a single step in the cycle. Expert A stated that the large scale use of MM on the library can probably not be used in a meaningful way in class. However, describing that MM is always used in combination with lab tests is important. Using the introduction to state that MM is not only used for drug design but also in other fields of chemistry (e.g. inorganic chemistry) may also be a good idea.

Resistance of pathogens against drugs is a recurring issue in drug design and health care. Both experts considered focusing more on this issue to be a good idea. Expert A suggested to include the details of resistance in the CU sketch. It would be necessary to explain what causes resistance in the malaria parasite. A known resistant mutation of the target protein DHFR could be used to show that the drug binds to the original protein but not to the mutated version. This gives students a new goal: to change the drug in such a way that it starts binding with the mutated target. If there is a working medicine for the pathogen, there is no reason to design a new one, so this new goal is more relevant.

The small differences between the original and mutated protein and its interaction properties could help increase student understanding of the importance of molecular structure for drug interaction.

Expert B suggested adding selectivity. In an authentic practice, two assays are done: one to test interaction with the pathogen enzyme and one for its human analogue. The results are compared. In this case, a comparison of human DHFR with malaria DHFR should be included in the CU. According to expert B, the medicine should target only malaria DHFR, not the human analogue. This is denoted as selective toxicity. Interestingly, according to the website used in the materials of Gledhill *et al.* (2006) making the drug selective is not necessary in the case of DHFR (E-Malaria Project, 2005). The website states that the human DHFR protein is quickly replaced when all current enzymes active sites are filled, whereas malaria DHFR is not. Basically, the website says that a DHFR inhibitor cannot kill human cells. Expert B also noted that in drug design, it is important that the target is essential for the pathogen, the target should be reachable by the drug, it should be expressed at that time, and for MM, its structure needs to be known. These factors could be added to the CU sketch.

Both experts noted a number of issues concerning the scientific soundness of the CU sketch. The first of these was the use of 'interaction strength'. Interaction strength, especially when calculated by software, is a relative value that is hard to compare with any other calculations.

Expert A: 'Strength' […] is one of the hardest quantities to predict. I think it would be more important to say something about 'understanding the molecular chemical principle of the interaction'.

It is important to ensure that interaction strength is not used as an absolute value in MM education.

For chapter 1, according to expert A, the disappearance of the malaria mosquito as named in that chapter is, most likely, not only caused by pest control, but also by a decrease in average temperature. Expert B disagreed with the statement that there are 'many medicines'. He stated there are never enough of them. He also said that resistance does not always happen quickly; for instance, quinine worked well as a malaria medicine for 300 years.

In chapter 2, it should be explained to students that MM can only be used if there is already information about the target's structure available (Expert A). Expert B said that the definition of 'lead' should be 'a substance of which we know it has an effect on the life cycle', instead of 'a substance which is known to have an interaction with the target'. Most substances will have some interaction with a target molecule. Additionally, often the actual target molecule is unclear.

While discussing chapter 3, Expert A commented on the disulphide bonds in the list of possible protein-drug interactions. A disulphide bond is a covalent bond, which is significantly different from the others and does not belong in the list. Expert B said that these bonds do sometimes occur in drug-target interactions, but are rare.

Both experts stated that salt bridges/electrostatic interactions, which are important in protein-drug interactions, are missing from the list. Expert B believes the N1-nitrogen in pyrimethamine probably has an H^+ attached, which makes this interaction important for the example used in the CU sketch. This information makes the software assignment more complicated, as it should be decided in advance if the H^+ should be used in the docking calculation.

Another issue in this chapter noted by Expert A is the comparison of an interaction strength as calculated by Arguslab with the value of the Cl_2 bond strength from literature. These are not calculated using the same mathematical model, which makes the comparison faulty.

Expert A considered that students should not define the binding site themselves, because it would be confusing to them, and for computing purposes it is commonly defined by choosing a 'box' that is certainly big enough, e.g. by including all amino acids that are involved in any active site interaction recorded in literature or by putting the edges of the box at least 8 Å away from any atom in the lead binding site. The software will have no trouble with a binding site that is larger than necessary, and both experts suggested to set up this binding site in advance, so students do not have to deal with it. Furthermore, according to expert B, many programs do not require the user to define a binding site at all.

Other

Expert B named materials that according to him are useful as background information for the CU or are in another way related to the CU sketch, such as the book 'Het geneesmiddel' by W. van den Broeck, and some NLT-modules (NLT is an optional course in Dutch high schools). He also named possibly relevant software, such as YASARA, which has some similarities to Arguslab. A full list of the materials named by all respondents can be found in Appendix 2.

Overall

Considering the drug design context, both experts agreed that only a small part of the full process was treated. While it is practically impossible to teach about the full drug design process, they considered it important to at least mention the other parts of the process. Another important aspect is that medicines are not designed without a reason. Resistance is a good reason for designing new drugs, and can be easily implemented in the CU sketch. Both experts named several issues concerning the scientific accuracy of texts about the drug design context and the subject of malaria.

The experts made a few comments about the implementation of MM within the sketch. For the instructional issue of defining a binding site, they gave the advice to set this up beforehand. The experts noted that the interpretation of the resulting value of the MM calculation should be clarified to students. While the experts suggested improvements for these details, they considered the *general* depiction of MM within the sketch sufficiently accurate.

Students

The two students were interviewed about the criteria Student engagement, Student knowledge base, Software usability and Feasibility (for students).

B. Student engagement

Both students considered malaria to be a motivating subject. They felt 'real life applications' such as malaria medication would make chemistry lessons in general more interesting.

Student B: "I would enjoy learning it [MM] in this way."
Student A: "Yes, because you have an application."

The students felt engaged because of the malaria subject, even though they were less interested in the MM content. Student A mentioned that the final chapter increases the feeling that they did

something useful in class, because in that chapter they see a broader picture of drug design (beyond MM).

Considering the learning activities, the students tended to speak in terms of 'effort' and 'amount of work'. They did not mind using a web source to answer direct questions, but they were afraid that actually searching for and collecting information from different resources might be too much work. There were several learning activities they found particularly motivating, such as inviting an expert guest speaker or watching a video about the subject (chapter 2), and the drug design assignment in chapter 4, which, according to student A, makes students feel they really achieved something.

C. Student knowledge base

Because the students had only read most of the sketch (instead of doing it in class), it was difficult for them to tell if they understood the chapters well. Both students said they had no prior knowledge of chemistry software or MM, confirming our assumption in the design phase. They had no problems understanding the first chapter, as it does not have much chemistry content.

Student A mentioned that she needed the vocabulary appendix to understand the text, especially in chapter 2. The students expected to have trouble with chapter 4, because they do not know the properties of functional groups well:

Interviewer: Would you think, after doing [the assignment], […] that you can attach something like a NH_2 group and test it with the program?
Student A: Yes… but I wouldn't know what to attach, because you just don't know what those things do. If they say, attach a new NH_2, I think I could, but…
Student B: But its function, I don't know…

Apparently, the properties of functional groups are not part of their prior knowledge.

When Student A saw a discussion question in the final chapter about other issues that might be important in drug design, she immediately said 'side-effects'. This shows she has at least some prior knowledge for the chapter's discussion.

D. Software usability (for students)

While the students had not used chemistry software before, they were able to complete the software assignment together. Following the steps in the assignment was not very difficult. However, completing the assignment still took them some effort. A cause for this difficulty may have been their unfamiliarity with the software. They were sometimes uncertain what they were telling the software to do.

During the interview, the students stated that it was not entirely clear what Arguslab did. For instance, student B did not understand the 'interaction strength' result. According to her, the tutorial should explain what the software does with the 'molecule' after each step.

Student B: Explain what you are doing.
Student A: Yes, explain it in advance, when you're doing it.
Student B: […] For instance, when you put those two together and they react, what you said, what those molecules are, you should put that in the text. Otherwise it's just a magic trick.

Student A stated that drawing a molecule within the molecule editor (PRODRG) gave her a better overall understanding of its molecular structure, which indicates that having students do their own MM may increase understanding.

E. Feasibility

Both students appreciated the 'slow' introduction in the first two chapters of the CU sketch, as it gives them a good view of the context and topic of the CU. For the learning activities in these chapters, they preferred a lecture combined with reading a prepared text individually. The questions should slowly increase in difficulty. They disliked the expert method because they felt they learn better individually:

Student A: I think, in groups… if you work individually, you are forced to look at the content; but if your partner already understands it, he will just present the results.
Student B: Students don't like presentations anyway, and I never found them useful, just because… nobody listens, either.

About chapter 3, Student A commented that it is important to clearly explain the chemistry content. She felt it was unnecessary to use a physical molecule building set in addition to the molecule editing software.

For chapter 4, both respondents considered it difficult to know 'where to start' when designing a new drug molecule. The interviewer told them about changing an existing medicine specifically to block a mutated protein (an idea proposed by one of the interviewed experts). This content related motivation appealed to both students. They said that they would know better what is expected of them. They considered working in small groups (2 students) best for these assignments. In their experience, two students are able to work together to find solutions to problems, while larger groups have worse group dynamics, and the information gets spread thinly.

Student B was of opinion that chapter 5 is important, because the content is viewed from a different angle. Student A felt that the discussion in this chapter only works if every student in class takes part. The designed drugs that are discussed should be chosen beforehand, as it takes probably too long to discuss every group's design. Both respondents liked discussion based on questions prepared beforehand, because they allow for a deeper discussion than just asking "are there any questions?"

Finally, considering the assessment, the students were not in favour of writing a new research proposal, unless extra time is available. They thought writing a report on the 'research' the students do within the outline fits better. Student B also considered a written test, but decided it would be difficult to have good exam questions for the subject of this CU.

Overall

Overall, the students were positive about the CU sketch, especially the implementation of the context. Their recommendations were focussed on clearly explaining the chemistry content and elaborating what really happens in the modelling software. This focus seemed to be partially caused by the fact that they considered (some) explanations in their regular chemistry lesson unclear.

The difficulty level at the start of the CU sketch, and the difficulty increase along the chapters, seems reasonable, except for the chapter 4 assignment. The students considered it difficult to know where to start, and they did not know the properties of functional groups well.

The students seemed to dislike most kinds of group work and preferred 'classic' teaching using lectures and assignments consisting of reading a text and answering questions, especially for the first part of the CU sketch.

Teacher

The teacher was interviewed about the criteria Student engagement and Feasibility.

B. Student engagement

The teacher stated that malaria is an interesting subject for students, and that diseases in general are appealing as 'teaching contexts'. He favoured the use of such teaching contexts, in general, but stressed that sometimes it is needed to teach the 'basics' without any context.

He felt the text, on average, is boring for students, e.g., chapter 1. He suggested using e-class learning activities. Additionally, students should be allowed to (partially) decide for themselves what they want to learn about malaria:

Teacher: I wouldn't, like 'students read the material on their own'; give them six pages of text and make them read it. I would add students' own wishes, 'What would I like to learn about malaria?'

The expert guest speaker in chapter 2 is a motivating learning activity, while using a video clip is a good alternative if inviting an expert is not feasible. He also considered 'research' activities in general fun, so he liked the chapter 4 activity.

The respondent noted that students may wonder *why* MM is used in drug design. Explaining this may be motivating to them. He also considered the topic of resistance, which gives the research activities a clearer purpose, to be a motivating addition to the CU.

E. Feasibility

According to the teacher, the estimate of 8-10 lessons for the entire outline is correct. The teacher felt that the general sequence of activities is logical, and that he could use this arrangement of chapters well in teaching.

He considered it good to start the CU with naming the problem of resistance and the need to make new medicines. For the first chapter, he regarded that two learning activities are feasible. One of these was the expert method activity.

Teacher: I think, at this first chapter about malaria, I would have students search for information on their own. Maybe some directed questions, or making some questions with the class in advance, then putting [students] into groups and saying every group has to find information about one question, and then having them give feedback by having each group tell about their findings.

The other was an e-class, which uses an electronic document that links to source materials. He stated that having students fill in the vocabulary themselves could be done only if enough time is available.

As stated in the Student engagement section, inviting an expert guest speaker for chapter 2 is a good idea. However, in that case students need to receive a summary of the important points, preferably with some questions, because it is important that students can reproduce these points.

The switch to 'real chemistry' in chapters 3 and 4 was appreciated by the teacher. In chapter 3, students should be taught about the importance of amino acid side chains and the effect a substitution could have on an interaction. Steric hindrance is also an important concept. He was in favour of using a physical molecule building set simultaneously with the molecule editing software.

The respondent considered that resistance is an important issue, and said that having students design a medicine for a resistant mutation of the malaria protein may be a good idea. He felt that showing that protein variants could have slightly different binding sites is not feasible, as it is too complicated for students. He added that such an activity should be tested in class. He also noted that chapter 4 becomes more feasible if the software introduction in chapter 3 is well-designed.

Considering chapter 5, the respondent said the first two questions are not fit for a discussion, as they are more like tests of understanding. He thought question 3 is a good basis for discussion. He also mentioned that it could be difficult for students to think of physiologic reasons for medicine effectivity by themselves. This could be resolved by treating this subject in an earlier chapter. Furthermore, information on how medicines 'find' the right place in the body (pharmacokinetics) and why the medicine does not target human proteins could be added.

The teacher suggested to combine the report of chapter 4 and the discussion of chapter 5 into a single assessment report, and to not use a theory examination.

Other

The respondent named some materials that according to him are somewhat related to my design, such as the NLT-module 'Eiwitkristallografie'. A list of the materials named by all respondents can be found in Appendix 2.

Overall

The teacher was positive about the general CU sketch and the context. He felt the CU sketch could be engaging to students, but some of the learning activities could still use improvements. He also considered the sketch to be feasible to teach, but he said that it should treat some subjects, such as functional group substitution and the meaning of resistance in more detail.

Conclusion and discussion

In this study, we designed a sketch of a CU with the purpose of teaching MM to 11th grade students and involving them in the MM process. The CU sketch was validated by experts, a teacher and students on five criteria. This section will start with an overview of the quality of the CU sketch according to all respondents. Next, the limitations of this study will be discussed. Finally, the results of this study will be considered within a broader perspective of pre-academic MM education.

The quality of the CU sketch

This section will describe the quality of the sketch concerning each criterion. See Table 5 for an overview of the criteria, their concerns, and to what extent the concerns were dealt with and the criteria were reached.

Table 5: The extent to which the criteria concerns were dealt with in the final CU sketch. + Sufficient; +/– Partial; – Insufficient.

Criterion	A. Scientific soundness & authenticity (according to experts)	B. Student engagement	C. Student knowledge base	D. Software usability (for students)	E. Feasibility (for students and teachers)
Concerns	1. Authenticity of the image of the drug design practice. **+/–** 2. Scientific soundness of the content and data. **–**	1. Student engagement caused by the context. **+** 2. Student engagement caused by learning activities. **+**	1. Connection to prior knowledge and skills. **+/–**	1. User-friendliness. **+** 2. Financial availability for schools. **+/–** 3. Contains applications required for CU (molecule editor, 3D-model viewer, docking calculator). **+**	1. Feasibility of learning activities and CU texts. **+** 2. Feasibility of the final assessment. **+** 3. Order and length of the CU. **+**
Overall	**–**	**+**	**+/–**	**+**	**+**

All five respondents considered the CU sketch at least a good idea, and would like to see something like it taught in class. For criterion A, while the experts felt that the general depiction of MM is accurate, they felt that improvements were necessary for the authenticity of the context and the soundness of the chemistry content.

Criteria B, D and E were met to sufficient extent according to the respondents, but there is still room for improvement for each of these criteria. While the sketch goes a long way towards meeting criterion C, the students did not seem to have all the prior knowledge required by the CU sketch. As this makes some parts too difficult for them, changes to the sketch may be necessary.

Below, the extent to which each criterion is reached is described in more detail. For each criterion, implications for a redesign are given. These are possible improvements that could be implemented and tested in subsequent research.

A. Scientific soundness & authenticity

It was made clear that the drug design process is much longer than depicted within the CU sketch. The full process takes about 12 years. The CU sketch only treats a small part of this process. The experts considered it important that students understand that the entire process is much larger. While a part of chapter 5 of the sketch is designed to make students realize this, the experts felt this was not clear enough.

Furthermore, while the basic drug design context of the CU sketch is authentic, there is no reason to change a working drug. Pathogen resistance to the drug is a good reason to improve a drug, and gives a much clearer goal. The experts agreed that resistance is necessary for making the CU sketch reflect authentic practice. One of the experts considered selectivity to be another important topic.

Both experts also noted a number of issues concerning the scientific soundness, which were mostly about the nature of the chemical interactions (bond types) between drug and target. They solved the issue of defining the binding site by stating that it should be no problem for Arguslab to use a binding site that is too large.

The experts thought the CU sketch in general was an interesting idea. According to them this criterion has been met in sufficient extent considering the general implementation of MM, but it has not been met considering the depiction of the context (the full process, and the importance of resistance and selectivity) and the chemistry content (nature of chemical interactions).

Implications for a redesign

In summary, the experts' consultations resulted in the following implications for redesign:

- Have students design a drug for a resistant variant of DHFR.
- Treat the selectivity of a drug, for instance by asking students to calculate the interaction strength of the drug with human DHFR and comparing this to the interaction strength with the malaria protein.
- Show that the student project is only a small step in the professional drug design process. Possibly, learning activities about earlier stages in this process or about the laboratory research that goes hand in hand with MM could be added.
- Use a scientifically sound and consistent way to teach about the chemical interactions that matter in the pyrimethamine-DHFR interaction.
- When defining the binding site in the software, choose a 'box' that is certainly large enough.

B. Student engagement

In the interviews, both the students and the teacher agreed that malaria is an interesting subject in its own right. The teacher stated that diseases in general make interesting contexts for teaching. Malaria drug design and drug design in general are 'present-day topics', as malaria still causes many deaths in several parts of the world, and new medicines are necessary to overcome drug resistance.

Some of the learning activities were considered motivating by the students: a lecture by an expert guest speaker and the drug design assignment. The teacher was in favour of using these activities, as well.

There are possible improvements concerning this criterion. According to the teacher, reshaping the first chapter into an e-class and giving students a choice in what they want to learn about malaria improves their motivation and interest. Additionally, adding an explanation of why MM is useful in drug design could help.

The students judged the CU sketch sufficiently in line with this criterion and its concerns (Table 5). While the teacher saw some ways to make the CU sketch more motivating, in general he was also positive about the student engagement criterion.

Implications for a redesign

In summary, in order to improve the CU sketch for this criterion, the following options for redesign can be considered.

- Implement the e-class activity and/or a partial choice for students in what they want to learn in the first two chapters.
- Explain why MM is useful in drug design. This can be done by expanding discussion question 4 in chapter 5 of the sketch, or by treating this earlier in the CU. In that case the discussion question forms a reflection.

C. Student knowledge base

The CU sketch was designed while keeping the Dutch national chemistry syllabus (College voor Examens, 2010a) in mind. We assumed that 11th grade students do not have prior knowledge on MM. This assumption was confirmed by the student interviews. It was found that the vocabulary was required, as the students were not familiar with some of the terms used in the CU sketch.

The students expected trouble with the drug design assignment, as they do not know the properties of functional groups well. The teacher expressed a similar concern, stating that in chapter 3, the importance of amino acid side chains and the effect of an amino acid substitution on an interaction should be explained. Furthermore, while the students could follow the instructions in the software assignment, they did not really understand well what they were doing. This was possibly caused by the fact that the students were not familiar with chemistry software. This finding suggests that the software tutorial should be clearer about the functions of the software.

While the teacher suggested to prepare the students for the final chapter discussion by naming other aspects of drug design in more detail, one of the students named one of these aspects (the possibility of side effects) herself. This may mean that the teacher's suggestion is not necessary. Classroom testing may be necessary to find out if this is the case.

To summarise, according to the students, the CU sketch goes a long way towards meeting this criterion, but improvements, such as adding an explanation of amino acid side chain effects, may be necessary.

Implications for a redesign

In summary, the following changes could improve the quality of the CU sketch.

- Either explain the properties of functional groups during this CU or make sure this topic is treated earlier in the chemistry curriculum. In any case, it may be good to recapitulate this subject during this CU, and then show how this information is related to the DHFR-pyrimethamine interaction.
- Add an explanation of or visualize what students are doing to the molecules during the software assignments.

D. Software usability (for students)

The software used in the CU sketch was Arguslab and PRODRG. During the design process an expert was consulted, and his opinion was considered when choosing the software. Concern 3 (Table 5) was already dealt with in this software choice, while 2 was partially dealt with, as Arguslab is free, but PRODRG can only be freely used for small-scale academic purposes. The students gave their opinion on concern 1 (software user-friendliness).

The students were able to complete the software assignment. However, it was not entirely clear to them what the software did and what the output meant. One of them mentioned that using the molecule editor did increase her understanding of the molecular structure.

The teacher and one of the experts named some potentially useful software we did not find during the design process. If the CU sketch is further elaborated, it may be valuable to find if using those programs, such as Deepview or YASARA could improve Software usability. See Appendix 2 for a full list of the software.

The students were positive about PRODRG. As concern 2 was not fully dealt with for PRODRG, it may still be necessary to find alternative software, such as ISISdraw (Appendix 2). Except for concern 2, PRODRG meets the criterion. While the students had some more trouble with Arguslab, this was not caused by a lack of user-friendliness but by the fact that they did not understand well what they were doing. This problem could be solved by explaining the software steps in more detail within the

CU sketch. Alternatively, if it is found that students find a program like YASARA (Appendix 2) easier to work with, that program could be used instead of Arguslab.

The criterion has been met to sufficient extent. However, a better implementation of the software within the CU sketch may improve student understanding.

Implications for a redesign
In summary, the students' computer assignment and interview led to the following possible improvements.

- Explain more clearly how the software works and what it does.
- Test Arguslab in more detail. Arguslab contains a molecule editor and other features that were not used in the CU sketch. The molecule editor was not used because the researchers considered it to be too complicated for classroom use. It is possible that these features would become easier to use if a more detailed manual or tutorial on Arguslab is written.
- Use other software that is better suited for this CU. This means other available software first needs to be tested in more detail. Possibly, the software suggestions in the interviews (Appendix 2) can be used for this.

E. Feasibility (for students and teachers)

There were large differences between the students and the teacher concerning their opinions on the feasibility for students. Because of prior experiences, the students mostly preferred individual learning activities, while the teacher thought that an activity such as the expert method could work well. The students also worried about the time involved regarding the entire CU or certain learning activities, as they feel that within their current chemistry curriculum there is not enough time to treat subjects in enough detail. The teacher thought that 8-10 lessons is a good estimated length for the CU.

The teacher considered the general sequence of activities logical, and both students and teachers judged the general difficulty level reasonable. However, they all were of opinion that a more elaborate/clearer explanation of the chemistry concepts involved is needed.

Considering the learning activities, most were considered feasible, but for some activities improvements were suggested. The respondents said that it may be unfeasible to invite an expert guest speaker to the school, but they considered watching a video clip to be a good alternative. The teacher thought that the use of a physical molecule building set helped the students to understand steric hindrance, while students felt this step was unnecessary. In chapter 4, the respondents preferred adapting a drug for a resistant DHFR-mutant. The teacher felt resistance is an important issue that should be taught anyway. The students thought that this gave the drug design assignment a clearer goal than 'improve the medicine as best as you can'. The teacher considered that showing different binding site definitions to students is not feasible. Of course, a binding site comparison will be more important when students are working with resistant mutants. The teacher did say that such a learning activity should be tested in class. In chapter 5, the teacher felt the first two discussion questions cannot be used for a meaningful discussion.

Both the students and teacher thought that writing a report is a good assessment method for this CU. Their opinion on what to include in the report slightly differed. The teacher suggested a report

on the chapter 4 activities and the chapter 5 discussion, whereas the students preferred a report on the chapter 4 activities only.

In short, according to the students and the teacher, the first concern (Table 5) was sufficiently dealt with for most of the CU sketch. The general design of the activities was considered feasible. The students and teacher considered the assessment to be at a reasonable level (concern 2), but had a different opinion on what it should contain. The teacher thought the CU sketch has an adequate length and a logical order, so according to him concern 3 has been dealt with as well. According to both students and teachers, the Feasibility criterion has been met sufficiently. A number of details could be changed to further improve this criterion's quality.

Implications for a redesign

In summary, the following options for redesign can be considered in order to improve the Feasibility criterion.

- Elaborate the explanations of the chemistry concepts.
- Test if (controversial) learning activities, such as building the drug with a physical building set, or comparing the binding sites, are feasible and increase student understanding.
- Test the quality of the chapter 5 discussion questions and change them if necessary.
- Have students design a drug for a resistant variant of DHFR.
- Implement a good assessment method. It should be tested which parts of the CU are best suited for assessment.

Limitations

The methodology used in the first phase of this study is common in educational design research. An iterative approach was used in which each version of the CU sketch was discussed with the second author and further improved based on that discussion.

During the design process, mostly for the 'Student's knowledge base' criterion, the Dutch 'VWO' curriculum was kept in mind, because of the intention to test this CU within Dutch educational system. This may limit direct translation to school practices in other countries. However, we expect that the general outline of our CU sketch can easily be adapted to different educational practices.

Furthermore, during the design phase an expert was consulted concerning the Software usability only. In the interviews, we found that using the experts' comments could strongly increase the Scientific soundness & authenticity of the CU sketch context and chemistry content. Another design cycle after consulting experts on Scientific soundness & authenticity should be considered to increase the CU quality.

For the second phase of the study, important aspects concerning validity and reliability are the research population and the interview coding. We interviewed 2 experts, 1 teacher and 2 students. This is a small population, and the students and teacher were from a single school. In other words, both students and the teacher were used to the single educational philosophy used by their high school. Additionally, all respondents volunteered to be interviewed after reading a general description of the purposes of this study. This may mean that they are naturally inclined in favour of new lesson material about a practice such as MM. The small population did, however, give us the time to collect and analyse detailed information from each respondent.

The inter-rater agreement of 63% on the teacher interview coding suggests that there is much room for interpretation to which concern respondent statements belong. The overlap of the criteria was also found in the student interview analysis. Of course, the respondents can easily combine concerns, e.g. by saying that a gap in the knowledge base (C) can make a learning activity less feasible (E). Though the concerns and therefor the codes show overlap, the respondents' opinions could be clearly analysed. The authors had a high level of agreement on the final analysis of each interview. While the categorization chosen for this research might be somewhat less reliable in the interview coding, the analysis of opinions on the CU sketch still is.

As the interviewed teacher noted, the best way to confirm the quality of a lesson plan is by trying it out in class. This would be a good approach for a follow-up research study.

Pre-academic molecular modelling

The CU sketch was created as a first step for the design of a potential curriculum unit that would give students a broader and more complete understanding of MM. The general design of the sketch was received well by the interview respondents. The CU sketch certainly has the potential to be further elaborated into a complete CU. However, the respondents also noted that the sketch has much room for improvement. Designing learning materials about MM is not a trivial task.

Even though MM is a complicated and broad topic, we have shown that it is possible to design materials which are generally feasible for pre-academic students. Using a context and well-designed learning activities, these lesson materials also can be engaging to students.

As it is advisory to use multiple contexts, it may be necessary to design pre-academic MM learning materials using other contexts. These can be similar biochemical contexts, or completely different ones, such as modelling of inorganic compounds or crystal structures. As the scientific practices employed in such a different context are largely different compared to drug design practice, use of such a context could lead students to see MM in a different light. In any case, designers need to take care that the context is (in some way) relevant or recognisable to students and it is based on an authentic scientific practice. Collaboration with experts on the scientific practice during the design process is helpful in depicting the context and the use of MM within the context in an authentic way.

We have shown how a pre-academic curriculum unit sketch can be designed, including some of the details and criteria that need to be considered. In a following research step, the implications for a redesign we have collected would need to be implemented and tested. It is advisable to collaborate with experts and possibly teachers during the further design process. The improved CU sketch could then be expanded into a full set of lesson materials, which could be used for a large scale classroom test.

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Appendix 1 – Summary of the curriculum unit sketch

This appendix contains an English summary of the (Dutch) CU sketch, which takes an estimated 8 – 10 hours of class time. See Table A1 for an overview of the CU sketch contents.

Table A1: Overview of the contents of the CU sketch

Chapter	Contents
1 – Malaria, a grave disease	- Malaria (societal level). - Consequences of malaria. - Prevention of malaria.
2 – The malaria parasite and medicines	- Malaria infection. - (Malaria) medicines and the way they work (cellular level). - Drug development.
3 – Interactions in malaria proteins	- Interactions between active substance and target (molecular level). - The active substance pyrimethamine and the target protein DHFR. - Software tutorial.
4 – A new drug	- MM assignment. - Students attempt to improve the active substance so that it interacts more strongly with the target. - They describe their work and explain their results in a report.
5 – Reflection and assessment	- Students discuss their results so far - They discuss the usefulness and the place of MM within the drug design process.

General learning objectives

- Students can explain why it is important to *keep* designing new drugs, using malaria as an example.
- Students can name the molecular interactions and their main properties, which play a role in the operation of medicines within a cell.
- Students can explain what role MM has within the drug design practice.
- Students can show how MM is used to test interaction strength, using the DHFR target and the pyrimethamine lead as an example.

Chapter 1 – Malaria, a grave disease

Objectives

- Students learn why malaria is a relevant and important subject.
- Students see that drug design (at least for malaria drugs) is a current issue and will probably stay that way.
- Students learn that designing malaria drugs is the subject of these lessons.

Example materials

This section starts with some general facts and figures about the disease (societal level). It explains that malaria is spread by mosquitoes, and explains that infections can be prevented by preventing the mosquitoes from reaching humans.

This chapter's materials end with an introduction on malaria drugs and the problem of resistance.

Potential learning activities

The first chapter has four potential learning activities. They can be used individually or be combined.

- Students read the prepared text individually.

- Students read a variety of sources (websites, newspaper articles, etc.), which they either have to find by themselves or are available as part of the CU.
- Students receive the vocabulary (a separate part of the CU sketch) to help them understand the sources.
- Students make their own vocabulary, for instance by having to find a definition of every bold word in the text.

Instructional issues

- The learning activities require source materials. A potential problem with prepared materials is that they quickly age. Would it be better if the CU simply points at potential resources instead of using prepared materials or not?
- Could it be a good idea to spend more time on the societal concerns of malaria, and if so, how would this be implemented?

Chapter 2 – The malaria parasite and medicines

Objectives

- The molecular mechanism used by drugs within a cell is introduced to students.
- Students learn how medicines are designed and what role MM has in this process.

Example materials

It is explained that malaria is caused by a single-celled parasite which infects red blood cells, and that dying red blood cells and the toxins released cause the symptoms.

Next, this section explains that medicines contain an active substance which interacts with a target, which is a molecule that is necessary for the pathogen to survive. However, malaria can get resistant, and if even one parasite gets resistant, it will be able to spread itself. That is the reason why drug design will stay important. Medicines are developed by starting from a 'lead', which needs to be changed, so it blocks the target.

The chapter ends with introducing MM: It takes much time to test every possible new medicine, so molecular modelling is used to predict how well a possible drug binds with the target protein.

Potential learning activities

The second chapter has four potential learning activities. These can be used individually, but they can also be combined, or combined with activities from chapter 1.

- Expert method: Groups of students each examine a part of the material, and then each group presents their results verbally.
- Students receive the full text and questions. They answer the questions while reading the text.
- Students do a small literature study about the subject.
- An expert explains the subject. The expert can be invited at to talk at the school. Alternatively, a video clip of an expert explanation could be used.

Instructional issues

- It may be hard to divide the content into equal parts for the expert method activity, as it is designed to 'zoom in' on the subject. For the other activities, more design work is needed as

well. For the literature study, of course literature that can be used by the students is needed, while the last activity requires the help of an expert.
- Confusion may arise about the difference in meaning between the macroscopic concept of 'medicine' and the microscopic concept 'active substance'. This needs to be resolved by using definitions that are clear to students.

Chapter 3 – Interactions in malaria proteins

Objectives

- Students learn about the various intermolecular forces and their main properties.
- Students learn that the combination of all these forces causes the interaction between target and the active substance of the medicine.
- Students learn about the target protein DHFR and the active substance pyrimethamine.
- Students see how functional groups can have an effect on interaction strengths.
- Students learn how to use the software.
- Students learn how to interpret software results.

Example materials

The materials of chapter 3 start with a section on molecular interactions. These are not the same as chemical reactions, as usually no covalent bonds are changed. The following forces are listed: disulphide bonds, hydrogen bonds, dipole-dipole bonds and Van der Waals forces. Most interactions use a combination of these forces. Another important issue is that of steric hindrance.

Next, antifolates are introduced. Antifolates are active substances that block the function of the essential DHFR-protein. Pyrimethamine is an antifolate, but many malaria parasites are resistant to this drug. Another antifolate is proguanil, which has problematic side effects. Some pictures of the pyrimethamine-DHFR interaction are given. At this point, there is room to add an explanation about the active site/binding site of the protein.

The calculated interaction energy of pyrimethamine-DHFR is compared with the binding energy of the 2 chlorine atoms in Cl_2 according to literature, to show that drug-target interactions are weaker than covalent bonds.

The final section of the materials in chapter 3 is about the use of the software (Arguslab and PRODRG). This section refers to the Software Tutorial, and should be further completed with a number of specific assignments and explanations. This list could possibly be used:

- Building pyrimethamine with a physical molecule building set
- Building pyrimethamine with molecule editing software.
- Explaining how the software treats binding sites.
- Calculating the interaction energy of pyrimethamine-DHFR.
- Calculating the interaction energy for other molecules.
- Explanation/assignment about analysing the software results.

Potential learning activities

The list of learning activities in this chapter differs from those in chapter 1 and 2, as it is a suggestion for a sequence of activities that could be done one after the other.

1. Students receive a full text based on the example materials and questions. They answer the questions while reading the text, individually or in groups. In this step they learn about chemical concepts: intermolecular forces, their properties and interaction strength.
2. Antifolates, DHFR and pyrimethamine are introduced. This can be done similarly to activity 1, or in combination with steps 3 and 4.
3. Students look at DHFR's binding site in more detail. They also learn that defining the binding site can be a difficult process.
4. Students follow a software tutorial to learn how to use the software, how to draw molecules, and how to start a docking calculation. They will focus on hydrogen bonds and steric hindrance, because Arguslab cannot visualise other intermolecular forces.
   In this step, there are multiple ways to deal with defining the binding site within Arguslab: a binding site which is valid for the lead according to the literature is used for all molecules based on that lead (a); a number of potential binding sites are prepared and students try all of them (b); or students define binding sites themselves in some way (c).
   In this step, students can also use a physical molecular building set to practice. There is also a possibility to dock 2 different molecules to DHFR during the tutorial and compare the results, so students are better prepared for chapter 4.

Instructional issues

- Is it useful to use a physical molecule building set during the tutorial?
- Even though Arguslab and PRODRG were the most useful programs we found, they have some problems which students could run into. Should a more comprehensive software guide be written for teachers?
- As stated in the 4th learning activity, defining the binding site is difficult, because it is difficult to know in advance what amino acids play a role in binding a new drug. Which of the three options a, b, or c named in that activity's description is best?

Chapter 4 – A new drug

Objectives

- Students learn how they can design new active substances, starting from a lead.
- Students can argue why they believe their active substance works well.
- Students can use the software to calculate the interaction strength of their active substance with DHFR.
- Students can compare their results with those from pyrimethamine and conclude if their new active substance has a stronger interaction with DHFR or not.
- Students can explain the cause of the change in interaction (e.g. an extra hydrogen bond can be formed).

Example materials

This chapter contains the main modelling assignment. The example materials consist of an explanation of the assignment. The students' goal is to design a 'drug' (active substance) which has a significantly stronger interaction to DHFR than pyrimethamine does. The assignment is as follows.

1. Use what you have learned so far to improve pyrimethamine. For example, you can try to increase the strength of a bond or to make an additional bond. Do not try to change too

many things at once, because your new drug still has to fit in the active site. Draw the structure formulas of your ideas on paper.
2. Decide which of your designs is probably best. Write down why you think this is the best improvement of pyrimethamine. What did you change in the structure and why?
3. Use PRODRG to draw the new molecule, and Arguslab to calculate the interaction strength.
4. Compare this interaction strength with the value you calculated for pyrimethamine-DHFR. Did the interaction improve or not? Try to explain this result.

Potential learning activities

In this case, the learning activities mostly follow from the assignment. Some notes:

- This assignment is a kind of semi-structured research study.
- The assignment is done in groups of 2 or 3 students.
- The students write down their actions, choices and findings in a report (which can become part of the final assessment).
- It is possible to focus more on steric hindrance, by expanding step 1 so students also make a drug that is too big for the active site.

Instructional issues

- It is important to keep the learning process structured during this chapter. The teacher can have a large role here. For instance, he can check on students' progress and help them along if they get stuck or make mistakes.
- If the report is used as an assessment, this will give students an extra reason to take this assignment seriously.
- If the physical molecule building set is used in chapter 3, it can be used in this chapter as well.
- Of course, any choices made in chapter 3 on what students should learn about the software are important for this chapter as well. This is also the case for the binding site definition issue.

Chapter 5 – Reflection and assessment

Objectives

- Student groups can compare their chapter 4 results and reflect on the CU so far.
- Students see how MM fits within the entire process of drug design research.
- Students practice writing a research proposal.

Example materials

The example materials of this chapter consist of 4 discussion questions.

1. What new active substances did the students make in chapter 4, and how well do these interact with the DHFR target? The designs are compared with each other and the pyrimethamine (lead). Is any student design better than the lead? What could be the cause of the differences in interaction strength?
2. All results have been compared. Are there clear possibilities to improve the active substance further?

3. We saw that MM is used to calculate interactions between an active substance and the target. Is it certain that a substance with a strong interaction makes a good medicine, or are there other issues involved as well?
4. Do you feel that MM is really useful in drug design, or would you prefer to only use laboratory work?

Potential learning activities

Each discussion question is meant as a basis for a whole-class discussion.

- At the first question, students reflect on the importance of functional groups.
- At the second question, students can for instance discuss if they found a functional group which is very important for the interaction. In that case, the interaction can be improved by optimising that functional group.
- For question 3, it is possible that students find molecular issues. For instance, the active substance should not only bind strongly to the target, it should also block its functionality. However, the true purpose of this question is to broaden the discussion to the macroscopic level. The drug should be able to reach the pathogen, it should have as little side effects as possible, and it should of course be actually possible to synthesise the molecule. This way, the students can reach the conclusion that laboratory experiments are still necessary after MM.
- For the final question, students think about the usefulness of MM. A conclusion they could reach is that MM is useful to test many medicines in a short amount of time, but it cannot be used by itself to create drugs. A combination of MM, laboratory experiments and physiological research is required for the best results.

Of course, the teacher can lead the discussions into the right direction if necessary. A final and optional learning activity is the following:

- Students write a research proposal based on chapter 4 results and this chapter's discussions. They describe how one of the molecules designed in the class could be tested for use as a real medicine. In the proposal, three questions need to be answered: Why do you think the molecule you chose can potentially be used as a medicine? What needs to happen before this molecule can be produced as a medicine? In what way could those steps be accomplished?
  The steps they would have to describe include laboratory synthesis of the molecule; testing the molecule on malaria cells; testing the molecule on side effects in humans; and possibly starting up industrial production of the drug.

Instructional issues

- It may in some cases be difficult for the teacher to lead the discussions. Depending on the chapter 4 results, it may be impossible or too difficult to answer the second question at all.
- There are 2 potential assessment methods: the report of chapter 4 and the research proposal in this chapter.
- For the research proposal activity, general research and writing skills are required. These will differ for each class. Discussion questions 3 and 4 are required for this activity, but it is best to leave the details for this activity for the teacher to fill in.

Software tutorial and vocabulary

The software tutorial consists of a step-by-step tutorial with the following subchapters:

1. Modelling pyrimethamine
    - Preparing PRODRG*
    - Drawing pyrimethamine
2. Visualising DHFR
    - Installing Arguslab*
    - Looking at DHFR
3. Docking pyrimethamine in DHFR
    - Selecting the binding site of DHFR*
    - Preparing pyrimethamine *(so the software recognises it as a ligand)*
    - Executing the docking calculation and viewing results

* These sections have been removed for the student version.

The vocabulary is a list with explanations of 14 terms which are used in the chapters. When vocabulary terms are used in the example materials, they are printed in a bold font.

Appendix 2 – Additional materials

The following materials were named by respondents of the interviews. They have only been very briefly analysed during this project.

Software

- **Deepview.** This molecule viewer is used in the *Eiwitkristallografie* NLT-module (see below). Deepview, also known as Swiss-PdbViewer is a program designed to view proteins and their properties. Its capabilities seem quite extensive, and guides and tutorials are available. It is possible to change proteins and to calculate a number of properties with this program. However, the program cannot work with non-protein molecules such as pyrimethamine.
- **YASARA.** A versatile piece of software with some similarities to Arguslab. Molecules other than proteins and DNA can be used for modelling calculations. According to expert B, it has already been used in Dutch high school education. Free and paid versions are available.
- **Chemdraw, ISISdraw, etc.** Free and commercially available digital molecule building tools. These are possibly more user-friendly than PRODRG, and probably do not have PRODRG's licensing problems. A disadvantage is that they output 2D models, instead of PRODRG's 3D models. According to expert B, most MM software can easily turn 2D models into 3D ones.
- **LIGPLOT** and **PoseView** are programs that can be used to make a schematic, flat view of a protein-ligand interaction. According to expert B, this could be considered an extra step between a 2D and a 3D model, and could increase student understanding.
- **Sleutel-slot.nl**, supposed to be an interactive animation in which the user can create a drug for a certain active site, step by step. It also shows additional requirements such as solubility. However, the website appears to be partially broken.
- **TDRtargets.org** can be used to find the best targets for a certain pathogen. While this website is meant for researchers, expert B believes it may have use in class as well.

Books and lesson materials

- **NLT-modules** that are in some way related to our lesson plan design, according to the experts or teacher: (NLT is 'Nature, Life and Technology', an optional course in Dutch high schools)
    - **'Medicijnen: van molecuul tot mens**' – This module treats many aspects of drug design, both on the macroscopic and microscopic scales. It includes a number of laboratory experiments. However, it does not treat MM. Information from this module could possibly be used to expand the chemical content of the CU sketch.
    - **'Eiwitkristallografie'** – This module is about protein X-ray diffraction. It treats properties of crystals, properties of X-rays, and properties of proteins. It does not seem directly relevant to the molecular modelling CU, but the chapter about proteins could be used before the CU in order to improve students' knowledge base.
    - **'Moleculen in leven'** – Cystic fibrosis is used as a context to explain how proteins are formed in human cells and how proteins operate. This module could again be used to improve students' knowledge base. Possibly, the proteins relevant for cystic fibrosis could also be used in a MM CU, as an alternative context.
- **'Het geneesmiddel'**, a book by W. van den Broeck. According to expert B, this book is generally available in Dutch school libraries, and can be used as a source of information by

students. For instance, it explains all the ‘barriers’ a medicine has to cross in the human body before it can reach its target.