A cellular imaging CDIO project for 2nd semester students in engineering biology

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ABSTRACT: The demand for exact engineering within the life sciences is growing and the *Engineering Biology* programme at Linköping University, Linköping, Sweden, prepares students for a career at this interface. *Conceive – Design – Implement – Operate* (CDIO) was recently pioneered in an introductory project course. Groups of six to seven students apply a LIPS scalable project model from traditional engineering educational environments on, for example, a cellular imaging task in a hospital setting, prior to taking courses in cell biology/optics. Besides facilitating the implementation of CDIO in higher courses, students gain early career insight and enhance their communication skills. A *customer* (senior teacher) needs to visualise structures in cells, and the student group is contracted to deliver an applied and optimised *method* to meet specified requirements. The customer reviews deliverables before the *tollgates* and communicates with the student project leader. Other students are responsible for documentation and subsystems. The project is allocated laboratory facilities and hardware, and two fictitious subcontractors supply samples and consumables. Extra teachers perform supervision and methodological consultation. In summary, CDIO is indeed applicable and rewarding in cellular imaging, yet is also challenging.

INTRODUCTION

It has become evident that physics and engineering are increasingly important for the advancement of biology. Linköping University's *Engineering Biology* programme (270 ECTS credits) fosters solid skills in mathematics, physics and engineering, while simultaneously bridging emerging new biology and biomedicine [1]. A pioneer class of 30 students was admitted to the *Engineering Biology* programme in 1994. Since then, the annual admission has increased to 60-90 students. Chemistry and biology correspond to approximately one third of the programme, with the rest devoted to mathematics, engineering and physics. After seven semesters of general courses in chemistry, biology, physics, mathematics and programming (summarised in Table 1), students specialise in one of seven available profile semesters, namely: bioinformatics; biological production; biotechnical physics - materials in medicine; biotechnical physics - microsystems and biosensors; environmental science; microbial biotechnology; biomedical engineering or protein chemistry with protein engineering. The ninth semester is then devoted to the final MSc thesis. The *Engineering Biology* programme attracts approximately similar numbers of female and male students.

ENGINEERING BIOLOGY AND THE CDIO INITIATIVE

The *Conceive – Design – Implement – Operate* (CDIO) Standards are currently mainly implemented in courses and education programmes on traditional engineering topics, eg mechanics, physics and others. With the growing demand of engineering skills within the life sciences, there is an obvious need to find new approaches of teaching at the bio-technological interface. Of course, this introduces several challenges, yet also provides new unique opportunities when implementing the CDIO Standards into the programme curriculum. In light of successful experiences in the Linköping engineering programme in physics and electrical engineering, the board of the *Engineering Biology* programme decided in 2004 to integrate the CDIO Standards into the programme curriculum.

INTRODUCTORY COURSE

Accordingly, a first year introductory 6 ECTS credit course was pioneered in 2005 [2]. The course syllabus is found in ref. [1]. A major aim of the introductory course is to give students an early opportunity to learn how to master the basics of project work, specifically according to a scalable project model (LIPS) created for the educational environment when dealing with an assigned relevant task [3][4]. A direct transfer of certain projects that may perform well in other engineering education programmes will, of course, not always be as rewarding to another group of engineering students. Since engineering biology students will, for instance, study cell biology, imaging and programming in higher classes, a related project was hence designed.

Other objectives of the course are to learn formalised project planning/management, administration/documentation, personal communication and oral/written presentation, and an overall responsible contribution as a member of a team. The 1.5 ECTS credit non-project component of the course consists of lectures regarding the project model, including career example lectures given by alumni students. Other selected topics covered are group dynamics, communication, presentation, as well as linguistic and formal aspects of technical documents. The lectures run in parallel with the engagement in the project work, with critical issues often covered in lectures immediately before they become important in the project work.

Students' early introduction to project work, accompanied with an in-depth insight into the potential future career role of an engineering biologist, will indeed facilitate further adjustments of the programme curriculum in order to meet the requirements of a general integration with the CDIO Standards. This work is of high priority and is in progress at the time of writing.

Table 1: Obligatory and eligible (in italics) courses during the first seven semesters of the *Engineering Biology* 270 ECTS credits programme, as of the 2005-2006 curriculum.

Semester	Course	Credits
1-2	Foundation Course in Mathematics	6
	Linear Algebra	6
	General Chemistry	6
	Organic Chemistry	3
	Biochemistry	6
	Algebra	7
	Introduction to Programming	7.5
	Engineering Project for Engineering Biology	**6**
	Physical Chemistry	7.5
3-4	Calculus, Several Variables	9
	Engineering Mechanics D	4.5
	Electric Circuits	4.5
	Probability and Statistics, First Course	8
	Organic Chemistry	6
	Numerical Methods	7.5
	Biochemistry	7.5
	Physics	6
	Cell Biology	7.5
5-6	*Research at LiTH*	*1.5*
	Molecular Physics	9
	Microbiology and Immunology	9
	Systems Physiology	6
	Molecular Physics	9
	Biological Automatic Control	6
	Databases and Bioinformatics	6
	Analytical Chemistry	6
	Signal and Image Processing	7
	Measurement Technology	5
	Signal and Image Processing	7
	Gene Technology and Molecular Genetics	6
7	*Introduction to Operations Research*	*5*
	Mathematical Models in Biology	*6*
	Complex Analysis	*7.5*
	Biomedical Signal Processing	*6*
	Artificial Intelligence and LISP	*7*
	Programming and Data Structures	*9*
	Object-Oriented Programming	*4.5*
	Computer Networks	*5*
	Industrial Economics, Basic Course	*4.5*
	Environmental Measurement Technology	*5*
	English	*6*
	Intercultural Professional Communication	*6*
	English	*6*
	Communicative French	*6*
	German	*5*
	Image Analysis	*6*
	Cellbiological Methodology	*6*
	Biostatistics	*6*
	Medical Imaging	*7.5*
	Biomechanics	*4.5*
	C++	*7.5*
	Surface and Colloid Chemistry	*4.5*
	Contemporary Sensor Systems	*4.5*
	Bioinformatics-Overview and Practical	*6*
	Applications	*6*
	Industrial Biotechnology	*4.5*
	Leadership	*6*
	Technical Systems and Environment	*4.5*
	Cell Growth and Cell Differentiation	*6*

The main element (4.5 ECTS credits) of the introductory course is devoted to project work. In this article, the authors communicate some recent experiences with a novel project task where groups of six to seven second semester students, with no or very limited previous experience in cell biology or imaging, work as contractors at a pre-clinical department at the Linköping University Hospital. Student groups initially meet a customer who introduces them to some 25 carefully specified technical requirements, and what resources that are available to the group. Students thus enter the present project between

tollgates 1 and 2 in the LIPS project model (see Figure 1) [3][4]. The LIPS model is then applied throughout the project. Students start with a customer-defined task and are given a requirement specification. According to the LIPS model, *how to do it* is initially defined in a crude system drawing. The finished product is then the delivery of a working, tested and applied method that is capable of assaying cellular morphology and sub-cellular localisation of the cytoskeleton in human cells.
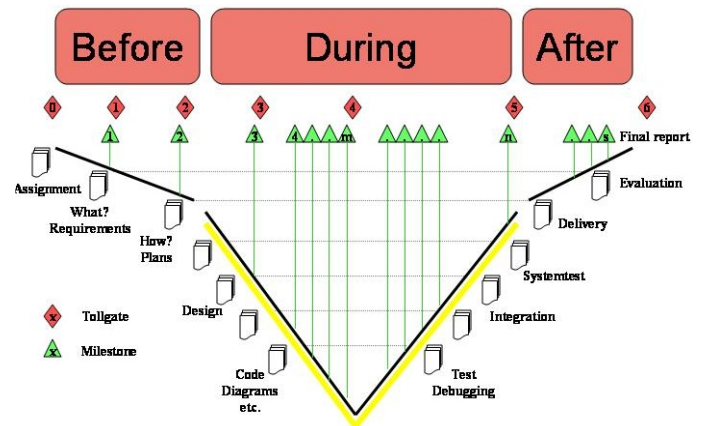

Figure 1: The scalable LIPS project model created by Svensson and Krysander (figure taken from ref. [3]). This includes the three phases of *before*, *during* and *after*. The model also includes templates for all formal documents. The project dealt with in this article starts between tollgates 1 and 2, and ends with tollgate 6. The customer decides on tollgates 2, 3, 4 and 5.

THE PROJECT

In brief, the summarised requirements on the product are that it should achieve the following:

- Allow for the preservation and extended biological evaluation of human cell samples being collected, on request, by the subcontractor, the *Clinic* (fictitious, see Figure 2).
- Include a qualified technical and biological protocol for the analysis of cellular morphology and one vaguely specified part of the cellular skeleton, the *cytoskeleton*.
- Rely on optical methods and cellular imaging; students are given access to a biomedical laboratory and other facilities, and a high quality fluorescence microscope stand at their disposal (upon request).
- Depend on chemicals and related material available by ordering from a second subcontractor, the *Chemicals Company* (fictitious, see Figure 2).
- Acquire images with the given software, yet all subsequent image analysis must be performed by using free, standalone, customisable, scientific imaging software.
- Be applied on *patient* samples from the Clinic. The group is asked to support or reject an assumed preliminary diagnosis and to communicate results to the subcontractor, as well as to the Customer.

Each student has 120 hours at his/her disposal to devote to the project work and the working time is carefully regulated in the project model. Because of their limited practical laboratory experience, a senior teacher introduces students to the very basic practical concepts of working in a pre-clinical setting at a real research laboratory that specialises in cellular imaging. Obviously, this includes demonstrations on good laboratory practice and serious issues, such as safety concerns. Students are

also told at the very beginning of the project that safety is always the primary concern and they are prohibited to work irregular hours or by themselves. A junior teacher (the Supervisor in Figure 2) supports the group on a regular basis throughout the project work and attends weekly group meetings. The Supervisor is not a part of the formal project group organisation and she/he has no official business with the Customer. Yet for successful performance in the project, it is vital that the Customer and the Supervisor communicate frequently but off the record. Two additional senior teachers are included in the project organisation. These are Experts and they may be consulted for a maximum of four hours by the project group.
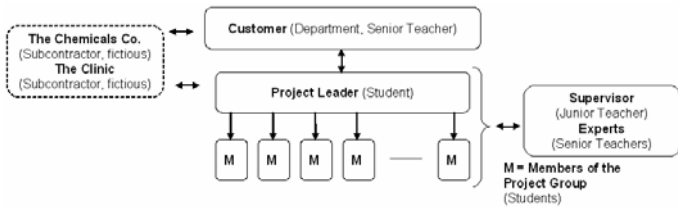

Figure 2: Overview of the project organisation. Project group members (M) all have individual responsibilities. The use of fictitious subcontractors facilitates experimental planning and gives teachers some flexibility, ie to introduce *unexpected* scenarios.

Initially, the student group must assign an individual responsibility to each member of the group. All communication, including negotiations, with the Customer is channelled via the Project Leader. Other obligatory responsibilities include being in charge of project documentation or managing a subsystem. The current project is divided into three subsystems, all interlinked and dynamically dependent on each other, as follows:

1. Preparation of biological samples: This system is both theoretically demanding and hands-on intensive. Commonly raised questions are: *What biological structure is the product supposed to target? Can this be performed with available resources and the current instrumentation? Can we use specific probes? What are the principles for the detection of probes? What are the limitations? What controls are needed? Where and when?*
2. Microscopy, image acquisition, data handling and export: The second subsystem is also a mix of hands-on and theoretical challenges. Apart from the above, it also introduces further details in questions regarding optics, cell biology and software/programming;
3. Technological and biological evaluation and feedback systems: Typical student concerns in the third subsystem are, for example, *What do we see? How do we quantify data? Artefacts? Do we need to adjust the protocols in subsystem 1?* And so on.

A major and extremely important feature of the *before* phase is to identify activities and perform careful planning, including how the resources should be allocated. Before entering the *during* phase, the Customer reviews the detailed plans of the project, summarised in a formal Project Plan (tollgate 2). It is not until the Project Plan is approved that students are allowed to tackle the task with a hands-on approach at the laboratory, ie to enter the *during* phase. In the present project, three additional tollgates have been defined in the *during* phase in the requirement specification, describing what and when the group must deliver (usually a formal meeting with the customer, starting with a presentation followed by a subsequent discussion). The tollgates are as follows:

- Project plan (including time plan), project week 3, tollgate 2;
- Deliverable no. 1: successful pilot test of all individual subsystems (1-3), project week 5, tollgate 3;
- Deliverable no. 2: All subsystems (1-3) must be applicable on biological samples. Approval for application on patient samples, project week 7, tollgate 4;
- Final deliverable: The product must meet all 25 specified requirements (unless negotiations have been performed), project week 10, tollgate 5.

The application of patient samples is thus a full system test. This way of using predefined tollgates has served well in *kick-starting* the project, despite an often encountered state of slight confusion among students in the early project weeks. It also provides a convenient opportunity to interact with the Customer that otherwise would have to rely solely on formal meeting minutes and unofficial contacts with the Supervisor.

An additional teacher (who is not a part of the formal project organisation) specialising in communication provides assistance during the meeting before tollgate 5 to give constructive criticism on presentations and written technical documentation. When tollgate 5 is passed, the group continues to the *after* phase, which includes an important formalised evaluation of the project. The project is then closed (tollgate 6).

EXPERIENCES AND CHALLENGES

The project has received good ratings from students in course evaluations and during informal discussions. Frequent comments have emphasised that the general topics covered, as well as the specific project, are all indeed interesting and relevant to their education and potential career roles. The project is a motivator for further studies on the subject. Many students also tend to appreciate the fact that they work at a real research laboratory (the same equipment is regularly being used by research staff in the department) and teachers may also take advantage of this when emphasising the importance of planning. In addition, not apparent differences in the contributions and reflections made by male and female students have been observed.

The project is important since it facilitates a growing understanding of that the business is not straightforward. Even though the analytical method may be precise, this does not always mean that the biological relevance of the finding is obvious. The task that students are supposed to solve is complex, as is biology itself, and interdisciplinary in nature. It is thus necessary to introduce a creative but critical thinking among the emerging generation of bioengineers; this project is a good starter in this regard.

It is only natural that most students feel a varying sense of confusion at some stage during the project, most commonly experienced in the early project weeks. This is perhaps best illustrated by the only question being raised to the Customer on one particular project start-up meeting, immediately after facing the 25 requirements on the product: *Are we going to do this* for real*?* The sense of initial *despair* is not necessarily restricted to the scientific task. A logical question for each individual is, of course: *What, specifically, am I supposed to do within this project?* A detailed project planning is, of course, the only way to overcome such concerns. In concert, students often state that they have learnt at least some important lessons regarding planning, collaboration, communication and group dynamics.

One view is that the project is *tough at some stages, but rewarding*. A teaching strategy has been maintained where the Customer has set an initial high standard when reviewing the draft of the Project Plan by giving plenty of feedback and raising concerns regarding details. Also, when the Project Plan is accepted on the first submission, a list of remainders is always appended by the Customer. Negotiations are also continuously declined during the early project weeks. As the project progresses, the Customer becomes more reasonable once students have put some real effort into the project.

To date, all projects have delivered good products on schedule and well within the allocated resources (see Figure 3).
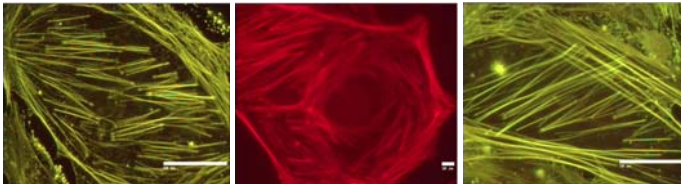
Figure 3: Successful image acquisitions performed by one student group during a recent project. Each image is a visualisation of the microfilaments in human cartilage cells, obtained using three different specific fluorescent probes. After acquisition, several operations remain, including quantifications.

It has become evident that the Supervisor is of critical importance for a successful outcome of the project. Obvious tasks, such as attending official group meetings and performing an active support of the Project Leader, have its fair share of delicate issues. The aim is to support without giving away too much information to students. Good improvisational skills are indeed a precious asset in this regard! An equally important role for the Supervisor is to act as the *sensor* in the group.

The Customer must also be regularly briefed about the unofficial status of the project and the contributions and efforts made by individuals. Furthermore, the Experts fill important functions. Students have someone to ask the really tricky questions and these contacts are somewhat less formal. An additional bonus when fighting to meet the approaching deadlines is when students realise that not even an expert can answer all questions that are being raised in the life sciences.

But what happens if one or several project group member(s) know too much about the project and how one should solve all the various problems from the start? This may be the result of attendance in a similar university education, or if the project group has communicated extensively with students in higher courses. One potential solution to this would be a creative use of the fictitious subcontractors so as to introduce the unexpected! For whatever the reason, a certain chemical may become permanently unavailable from the Chemicals Co., or the Clinic may encounter an unfortunate rare sampling error. One could also introduce challenging artefacts when appropriate.

This project also provides several opportunities to touch upon ethical concerns. These may range from being critical of literature and software sources, to the ethics involved when communicating results that are not properly secured in relevant controls, inappropriate image manipulations and the handling of patient data.

All teachers involved in the project must understand and apply the LIPS model. It is also essential that faculty asks questions rather than giving direct answers.

Other challenges with this specific project are that it is time-consuming for the involved teachers, and one can never leave students alone at a biomedical laboratory because of safety issues. It is a delicate balance to perform a risk assessment with students without actually giving away the *how-to-do-it* aspect.

Obviously, one also needs access to suitable cellular imaging equipment, ie at least one good fluorescence microscope with a digital camera. Furthermore, most chemicals and consumables are relatively expensive, fluorescent probes and cell-culture perhaps in particular. The good news is that there are several useable open source code imaging software available, of which some are being supported by the US National Institute of Health (NIH) [5]. Apart from traditional literature sources, eg textbooks and databases, some companies also gladly provide students with handbooks on the use of chemicals and probes.

CONCLUSIONS

The CDIO Initiative and the LIPS project model are indeed also applicable for teaching within the traditional engineering settings, as evidenced with a pioneer project in cellular imaging. The transfer to the bio-technological interface presents tedious challenges, but it is rewarding for both students and teachers in that it promotes solid engineering frameworks, as well as creative and critical thinking.

ACKNOWLEDGEMENT

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