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# Report and Recommendation of a Workshop on Education and Training for Measurement, Monitoring, Modelling \& Control ( $\mathbf{M}^{\mathbf{3}} \mathbf{C}$ ) in Biochemical Engineering 

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#### Abstract

The following article is the report from a workshop on education and training for measurement, monitoring, modelling and control in biochemical engineering organized by the $\mathrm{M}^{3} \mathrm{C}$ working group of the European Section of Biochemical Engineering Science in the European Federation of Biotechnology. The aim of the workshop was to provide an update on the present status of the subject and to identify critical issues for the furthering of successful education and training according to the needs in industry and in the public sector. The report focus is on the European situation but is also relevant globally. It concludes with recommendations for further work and development.


Keywords: Bioprocesses; Biopharmaceuticals; Quality-by-Design; Process analytical technology; Chemometrics; Measurement; Monitoring; Modelling; Control

Abbreviations: API, active pharmaceutical ingredients; CAE, computer-aided engineering; DoE, design of experiments; E\&T, education and training; $\mathbf{I C H}$, international conference of harmonization; $\mathbf{M}^{\mathbf{3}} \mathbf{C}$, measurement, monitoring, modelling and control; MVDA, multivariate data analysis; PAT, process analytical technology; QbD, quality-by-design;

## 1 Background of the workshop

Measurement, monitoring, modelling and control methodologies $\left(\mathrm{M}^{3} \mathrm{C}\right)$ are critical for many applications of biochemical engineering in industry and medicine.

The relatively recent interest in $\mathrm{M}^{3} \mathrm{C}$ methodology from the regulatory authorities has been clearly stated in U.S Food and Drug Administration (FDA) and (European Medicines Agency (EMEA) guidance and recommendation documents [1] as well as in the quality guidelines from the International Conference on Harmonisation (ICH).

Although these documents are directed towards the pharmaceutical and biopharmaceutical manufacturers, who are expected to adopt them, it is also stated that the academic community has an important role as inventors and as educators.

Thus, the preparedness of the academic education and training (E\&T) systems for realizing $\mathrm{M}^{3} \mathrm{C}$ competences seems a crucial step towards its successful implementation in manufacturing. Obviously, it concerns both basic education at undergraduate and graduate levels but most probably should also include post-university training for those in industry. Overall, both would improve the efficiency of knowledge and competence transfer between academia and industry and probably also stimulate scientific development in $\mathrm{M}^{3} \mathrm{C}$.

With this by way of context an expert panel was formulated focused on mapping how the academic competences in $\mathrm{M}^{3} \mathrm{C}$ education and training are distributed in Europe, how these are made available efficiently and what further specific needs can be identified. This expert report is the output of that panel meeting and provides an overview of the situation and makes recommendations and suggestions for meeting current needs, identifying gaps and mismatches, and strategies for closing these.

## 2. Topics of education and training in $M^{3} C$

Applications of measurement, monitoring, modelling and control in biochemical engineering cover a wide range of diverse techniques and methodologies [2]. Figure 1 shows an overview of $\mathrm{M}^{3} \mathrm{C}$ subjects in relation to their utility in process analytical
technology (PAT). The fact that PAT as well as $\mathrm{M}^{3} \mathrm{C}$ brings a wider interpretation of the analytical science than usual enables the establishment of a much closer relationship between these areas. Although PAT is primarily shaped from a regulatory perspective, it mentions typical $\mathrm{M}^{3} \mathrm{C}$ issues, such as the need for sensitive detection methods, on-line and real-time monitoring, models for prediction and identification, feedback control methods and risk management, as its main tools for achieving quality and efficiency in pharmaceutical processing [1]. Indirectly, this serves as a comprehensive frame work for E\&T since it envisages the direct industrial use of the concepts of PAT and $\mathrm{M}^{3} \mathrm{C}$.
$\mathrm{M}^{3} \mathrm{C}$ in biotechnology however has a significantly wider scope since it also includes bioprocesses other than those specific to biotechnology-related pharmaceuticals. Biomanufacturing of food ingredients, specialty and commodity (bio)-chemicals, bio-energy products, and applications in sewage treatment are all other examples of manufacture resulting in biologics or bioactivity which are obvious objects for $\mathrm{M}^{3} \mathrm{C}$. The principles of PAT and the methodologies of $\mathrm{M}^{3} \mathrm{C}$ hence are applicable to any bioprocess either for quality control or for achieving process economics.

Measurement in biochemical engineering $\mathrm{M}^{3} \mathrm{C}$ covers all forms of analytical detection of biochemically relevant analytes - physical, chemical or biological as well as data generated by omics techniques. From the quality viewpoint methodological developments of measurement techniques should focus on increasing sensitivity, accuracy and selectivity. However, such highly sophisticated and powerful measurement techniques only deploy their full potential if their connection to the actual process comprising sampling, sample storage and treatment procedures is of high quality as well. This is particularly important when applying omics techniques for intracellular components [35]. The ultimate goal is to improve the ability to measure reliably critical concentrations of bio-compounds in complex media - in particular in industrial media or environments.

Monitoring commonly refers to the surveillance of states or composition of industrial media and presupposes that the information so-gained shall be useful for certain actions and/or immediate or timely decisions - during manufacture or other industrially relevant processing. Quite often it concerns process control. Monitoring is therefore normally
understood to be carried out on-line, or at least just-in-time, in order to effect a suitable control strategy.

On-line monitoring may also be categorized as being in-situ, in-line or at-line, thereby indicating the character of the sampling technique being applied.

The intention to use on-line monitoring for a control purpose highlights the value of good process models. An accurate mathematical description of the bioprocess where on-line signals can be fed back for control is the goal [6]. Modelling of biological systems opens up for the need for a variety of mathematical methods such as PID controllers, estimators and model-based control algorithms for which theoretical understanding has long been a key subject in several branches of engineering education. The complexity of biological systems makes these methodologies especially demanding and thus requires qualified practitioners and appropriate E\&T for their formation and application in practice [6].

Another well-established application area of on-line monitoring is on-line process estimation. This is, of course, also an integral part of process control. Topics such as software sensor methods, which combine hardware sensors and software-based models, represent challenging opportunities for biological applications where state-of-the-art measurement technology can be upgraded by the use of a deeper model-based understanding. Recent attempts to carry out on-line estimations using basic mechanistic models for describing the biological process systems seem promising.

A third area of application of measurement, monitoring and modelling in biotechnology is prediction based on statistical methods. Chemometrics encompasses a range of powerful methods that can be directly applied to biosystems if data are of sufficient quality. Also when the certainty of the biological process data is low, the statistical treatment has a potential for analyzing the data in a more robust way. Multivariate data analysis (MVDA) - for example using principal components analysis - cluster analysis, as well as different types of artificial neural networks and other similar data-driven modelling methods can be valuable assets for use in biochemical engineering [7].

Clearly, the attention to PAT has in many ways propelled the development of $\mathrm{M}^{3} \mathrm{C}$ significantly [2,6]. The close connection to Quality-by-Design (QbD) principles, for defining design space and control space, and of using design of experiments on the
manufacturing bioprocess data, has further emphasized the usefulness of good $\mathrm{M}^{3} \mathrm{C}$ methodologies [8].

Given the extent and the complexity of the scope of $\mathrm{M}^{3} \mathrm{C}$ methods, a coherent E\&T platform which meets the requirements for the industrial users seems timely and justified.

## 3. The needs in the biotechnology industry for education and training in $\mathbf{M}^{3} \mathbf{C}$ topics

The application of $\mathrm{M}^{3} \mathrm{C}$ tools is widespread in the biotechnology industry, however, the specific needs depend on the industry category, the size of the company, and within each company the type of area, e.g. Production and R\&D.

Pharmaceutical and biopharmaceutical industries are traditionally quite conservative businesses with respect to production technologies due to a high degree of regulation from authorities. Consequently changes to existing facilities and methods have been difficult to implement. Thus, most processes are run at predefined set-points often with little degree of monitoring, control or use of models. With the increased attention to the use of QbD methods in this industry, a mindset change is evolving, and so is the need for education in the methodologies covered by $\mathrm{M}^{3} \mathrm{C}$.

In R\&D, methods for the production of API (active pharmaceutical ingredients) are now developed with intensive application of QbD elements. DoE (Design of experiments) tools [9] and statistical models are all important elements in the development and control of fermentation and cultivation processes, and on-line monitors, i.e. PAT, have always been necessary and used for feedback control of a number of variables like pH , conductivity, $\mathrm{pO}_{2}$ etc. Chemical and enzymatic reactions and synthesis are now characterized by DoE and are the subject of feedforward control by mechanistic rate models e.g. based on fairly simple Arrhenius expressions. Purification covers a number of unit operations, including chromatography, membrane processes, crystallization, precipitation, and centrifugation. Here DoE, mechanistic models and PID control are more widespread tools. For example mechanistic models for chromatography have recently been applied for industrial purposes [10] while PAT tools like pH , conductivity,

UV and even on-line HPLC are used to monitor and control the process. Finally, formulation processes exploit DoE for gaining a better knowledge of the process challenge and robustness and various PAT tools are applied for monitoring/control of mixing, pH etc [11].

Robotic technologies now play an increasingly central role in the implementation of QbD for the generation of parameters for mechanistic models [12] as well as in experimental DoE set-ups. These QbD methodologies are typically developed in small or lab scale environments and then transferred and implemented in pilot plants, and later in production. Transfer procedures are highly dependent on the extent of process knowledge that exists. The mathematical models of some unit operations are easily scalable, like chromatographic steps, while others are not, such as fermentation and mixing processes. Mathematical models are crucial to ensuring that any process developed at small scale translates effectively to that used at large scale, as any changes and deviations may have a significant impact on both the yield and quality of the product. In biopharmaceutical production LEAN/Six Sigma tools are increasingly implemented and mathematical models and PAT tools are perfect elements for production planning/optimization and reduction of off-line measurement and control, respectively. Finally, robust mathematical models are extremely useful for trouble-shooting in pilot plants and production environments.

The ability to evaluate QbD methodologies is also an important need, e.g. uncertainty analysis by Monte Carlo simulation of mathematical models [13] and MSA (measurement system analysis) of PAT tools, and an increased demand for personnel capable of mastering mechanistic modelling and chemometrics is foreseen as an industrial pre-requisite.
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## 4. Educational organizations with capacities for $M^{3} C$ education and training

Organizations providing E\&T in $\mathrm{M}^{3} \mathrm{C}$ include universities, companies offering E\&T services and company's in-house training. Thus, a complex flow of trained people between different types of training facilities are involved (Figure 2).

### 4.1 Universities

There exists today a variety of university departments and centres which have developed in response to the advances in the life sciences. Their areas of focus are correspondingly diverse; from bio-refining, bioremediation and food to biopharmaceuticals and regenerative medicine. Even the largest only cover subsets of the above in any depth. These educational centres provide a range of undergraduate and postgraduate programmes addressing the challenges posed by relevant industries. The postgraduate programmes usually align with the providers' areas of expertise, whilst the undergraduate courses tend to reflect the origins of department be that either life science or engineering. This strongly affects how $\mathrm{M}^{3} \mathrm{C}$ skills are delivered. Where an engineering background prevails more emphasis tends to be placed on processing and system analysis, modelling and control, often using engineering nomenclature not naturally applied in the life sciences. Equally a life sciences background will usually result in superior consideration of measurement principles for biologics and some practical exposure to these but coverage of monitoring and control will generally be less established. On the one hand it is easy to point out such a weakness though on the other hand it is a real challenge to find suitably trained teaching staff and the quality teaching materials expected by students in a global education marketplace. This gap has not gone unnoticed; US academics have created a Bioengineering Educational Materials Bank (BioEMB) [www.engr.sjsu.edu/~bioemb] as a step towards meeting this need. In order for the European Universities to create a balanced, well supported $\mathrm{M}^{3} \mathrm{C}$ skills provision it is perhaps necessary to develop a similar collection of teaching materials and also to provide a forum for educators to develop further their own skills in complementary areas. As the manufacture of biologics becomes global certain regions have sought to attract facilities, investment in manufacturing capacity. So for example, Ireland in Europe,

Singapore in Asia and Puerto Rico in the Americas have each demonstrated a succession of high-profile biotech industry investments over the past decade. Local universities have developed courses to support the mover. However the multinational companies involved will draw key staff from further afield as required to get the best. Consequently the market for students from leading universities is also increasingly global and as a result many students often wish to use the opportunity of studying in another country as one during which to broaden their experience.

### 4.2 Education by companies

In parallel with the university E\&T approaches different types of teaching and educational services related to $\mathrm{M}^{3} \mathrm{C}$ subjects are offered by private companies. For example, some companies offer courses on different topics within their own training centres or in collaboration with universities. Such courses are sometimes also offered by non-profit organizations at moderate fee levels. In addition to this, most biotech companies offer opportunities for their own staff through internal in-house training programmes, workshops and symposia on particular monitoring, measurement, modelling and control topics (see also below) (see Table 1).

However, many of these training services are closely related to commercial soft- or hardware products rather than focusing on the special needs for a comprehensive $\mathrm{M}^{3} \mathrm{C}$ education specific to biochemical engineering. Additionally, supportive products for education and training such as software, hardware or educational plants are available, sometimes equipped with special elements covering $\mathrm{M}^{3} \mathrm{C}$-topics. Most companies offering products in the field of measurement, monitoring, modelling and control also offer training versions of their products. However, although the products are frequently used in biotechnological production very often tutorials or teaching aids with a particular emphasis on biochemical engineering are missing.

More introductory and general education is provided by dedicated textbooks covering many aspects from material and energy balancing to on-line measurement and control as well as bioprocess technology that are also used in dedicated post-university training courses [14, 15].

Of particular interest for $\mathrm{M}^{3} \mathrm{C}$ is post-graduate $\mathrm{E} \& \mathrm{~T}$ in chemometrics. Post-university education in chemometrics $[16,17]$ for those already working in industry or for PhD students is today available from a number of companies. Of necessity these courses are limited in time, typically 2-3 days, and provide a basic, general view of the topic and are designed to provide the skills to use the techniques confidently. For this type of training access to software is vital and explains why software providers in general offer such training. Courses are also offered by specialized training companies who have agreements with a software provider. As a result the participants of these courses learn both the necessary theoretical basics and also how to use the techniques encoded within the specific software tool used in their company. There is also an increasing trend for targeted courses which provide the participants with the knowledge they need for applying chemometric tools in their specific application.

### 4.3 In-house education at biotech companies

Small and medium size biotech companies may have difficulties, both financially and due to lack of in-house competences, in establishing their own educational platform, and hence creating a pool of in-house trained personnel. As such far greater reliance has to be placed on recruiting personnel already strained within companies or from universities providing education or self-studies. For larger companies these approaches may also apply, but typically larger companies have established their own internal education departments and/or organizations.

Education in $\mathrm{M}^{3} \mathrm{C}$ areas as well as other scientific and engineering fields is usually handled in one or several ways depending on the level needed. As an example, applied industrial levels of mathematical modelling education may be (1) technician/operator level, e.g. use models to run processes through simple user interfaces; (2) scientist/engineer level, e.g. apply models to develop, optimize or trouble-shoot unit operations; and (3) expert level, e.g. change and optimise model computer codes etc. Several education approaches are applied, but high level plans are mostly used for those typically in production areas optionally involving education departments, while more specific approaches are taken for higher level education, e.g. custom-designed courses,
invited experts, and use of consultants. Special sessions and mini-courses/seminars by internal experts for knowledge-sharing and transfer are also widely used, as is secondment of key personnel.

## 5 Educational tools for training in $M^{3} C$

Efficient training requires good teaching tools. This includes access to laboratory bioreactors and downstream operations, sensors and control equipment and analytical instrumentation. Some of these may be computerized and/or based on user-interfaces linked to mathematical models. The theory and handling of the equipment, based on these models and the operation of the processes taking place in them is the object for the E\&T at universities and companies. Tools, either hardware or software-based simulators where the theory can be represented and the time course and 3D environment visualized in training sessions are useful. The further development of such tools seems to be at the core of the $\mathrm{E} \& \mathrm{~T}$ of most $\mathrm{M}^{3} \mathrm{C}$ methodologies.

### 5.1 Software programs for modelling

Access to appropriate software programs is an essential prerequisite for successful E\&T on modelling and simulation (Table 2). A broad range of programs is available and can be subdivided into (1) software for general process applications and (2) simulator packages which are dedicated to specific bioprocesses. For the first group modelling and simulation are typically offered for one type of functionality, while the user usually has to implement the models based on available process examples. The latter has the advantage of offering great flexibility, but requires skilled users. Moreover, error-free model implementation is a crucial issue - normally this requires multi-site testing by different users who implement the same model independently.

Examples of commercial softwares for general applications currently used in academia are MapleSim ${ }^{\text {TM }}$, Matlab ${ }^{\mathrm{TM}}$-Simulink $^{\mathrm{TM}}$ and Mathematica ${ }^{\mathrm{TM}}$. In addition to that, a number of free multi-purpose software products can be downloaded, for example SciLab ${ }^{\text {TM }}$ and Octave ${ }^{\mathrm{TM}}$. Examples of commercial simulator packages are Aspen Plus ${ }^{\mathrm{TM}}, \mathrm{COMSOL}^{\mathrm{TM}}$,

Dymola ${ }^{\text {TM }}$, gPROMS ${ }^{\text {TM }}$, BioSolv ${ }^{\text {TM }}$ and SuperPro Designer ${ }^{\text {TM }}$ [18]. Commercial software is frequently used in industry, and comes with the advantage that the code is validated, i.e. should contain a minimum of coding errors. An example of free simulator packages is OpenModelica ${ }^{\mathrm{TM}}$ (see also Table 2).

### 5.2 Tools for chemometrics

Depending on the required level of training to be achieved different tools for chemometrics education are necessary. DoE and MVDA [18] can only to a limited extent be taught by practice without losing deeper theoretical understanding. Therefore a better approach is to conduct the basic theoretical training by hand, or in tools such as Excel ${ }^{\mathrm{TM}}$, and move over to specialized software packages when the applications become more complex.

DoE is a fairly specific and well developed topic where there exist many commercially available software packages which, when it comes to basic DoE theory, are similar. The differences in these software packages are in terms of the ease of use, visualization of results, data analytical tools and diagnostics which differ depending on target group. Examples of software are MODDE ${ }^{\mathrm{TM}}$ (MKS Umetrics AB), Design-expert ${ }^{\mathrm{TM}}$ (Stat-Ease Inc), Jmp ${ }^{\text {TM }}$ (SAS Inc.), Statistica ${ }^{\text {TM }}$ (StatSoft Inc.) and Minitab ${ }^{\text {TM }}$ (Table 2).

MVDA is a broader topic where different software packages are specialized for different types of multivariate modelling. For instance, the multivariate projection techniques principal component analysis (PCA), partial least square (PLS) and extensions of these are available in specialized softwares. These techniques are especially suitable for advanced process modelling and monitoring of both continuous and batch processes and there is a high demand for people with skills in this area. There are other multivariate techniques such as artificial neural networks and which technique to teach depends on the expected challenges for the students in their future. For statistical experts there is the group of major statistical software packages Statistica ${ }^{\text {TM }}$, SPSS $^{\text {TM }}$, Minitab ${ }^{\text {TM }}$ and for researchers Matlab ${ }^{\mathrm{TM}}$ and $\mathrm{R}^{\mathrm{TM}}$ based toolboxes. Matlab ${ }^{\mathrm{TM}}$ and $\mathrm{R}^{\mathrm{TM}}$ are vital tools in the
search for new algorithms but for the basic user and during training they can be overwhelming.

### 5.3 Simulator tools for automatic control

Different groups of automatic control simulators and software tools assisting the development of automation strategies and controllers are available.

An important group of simulators has its origin in the automation and control industry. The simulators may be used in order to simplify and assist the development and to test complex automation strategies. These tools are also useful for the development of specific operator training systems for the education and training of engineers and plant personnel in the field of plant operation (Table 2). Educational versions are often derived from this type of simulator and these are particularly suitable for higher education.

A second group of simulators has their origin in universities and the scientific community. Tools like the Matlab ${ }^{\mathrm{TM}}$ control tool box or the software WinErs ${ }^{\mathrm{TM}}$ [20] are also useful to develop highly sophisticated controllers and control strategies. In addition, they offer a great variety of mathematical functions, such as solvers for systems of differential equations. Thus, they may be used as modelling software as well (see above).

Recent developments close the gap between automatic control systems, simulators and modelling software. A new interface between LabVIEW ${ }^{\text {TM }}$ and Matlab ${ }^{\text {TM }}-$ Simulink $^{\text {TM }}$ [21] enables the development of operator training systems or automatic control test systems with a broad variety of functions. With the software WinErs ${ }^{\text {TM }}$ numerous interfaces and drivers are offered, which also allow the inclusion of modelling software, or even dynamic link libraries (DLL), compiled from "C" or "FORTRAN" source codes [20].

With respect to biochemical engineering education the software packages may be used for the development of branch-specific training and education simulators. Examples for such simulators, specifically designed for the training and education in biochemical engineering, have been published [22-24]. However, further development of these simulators in combination with didactic concepts on different levels would be of great value.

### 5.4 Databases as a training resource

E\&T would certainly benefit from publicly available databases or datasets that could be consulted and used as a teaching resource. One type of such a database would be repositories of implemented and validated models. In particular, this could be useful for teaching process modelling and simulation techniques, or used as process models in the teaching of process control. The fact that many published models are only partly documented, or even contain model errors, makes it difficult to interpret data correctly when developing the model code [24]. Access to validated datasets in a repository would strengthen the quality of training models considerably and could, for example, be created as the result of academic collaborations or network actions.

A second type of database which is currently lacking is a repository of validated, or at least documented, bioprocess data. This could be used for the purposes of E\&T of process monitoring applications and model parameter estimation. Establishment of this type of repository would require substantial industrial support. However, if companies could make such data sets available, the impact of $E \& T$ quality would benefit greatly.

As noted earlier important simulators for plant design are CAE tools such as Aspen ${ }^{\mathrm{TM}}$, ChemCad ${ }^{\mathrm{TM}}$ and SuperPro Designer ${ }^{\mathrm{TM}}$. In recent developments, these simulators allow the use of customer developed models as well as dynamic models. However, some further development of these simulators is necessary, in order to be able to use them as tools for the development of plant operation and control strategies and thus for the education in this field.

## Conclusions and Recommendations

1. This report attempts to crystallize the current definitions of the $\mathrm{M}^{3} \mathrm{C}$ core competences. This is however a much more extensive task than a short report allows. Additional general workshops in which fundamental issues and definitions are discussed and developed will be needed in order to progress this key aspect to words in biochemical engineering practice.
2. Input from different stakeholder groups into such discussions is of vital importance for (1) academic E\&T provision that meets industrial requirements and the perceived real needs of training, (2) better definition as to the expectations of academic, postuniversity and industrial in-house training, and (3) to adapt pre-university training and undergraduate teaching to prepare students for $\mathrm{M}^{3} \mathrm{C}$ courses/programmes in terms of fundamentals of mathematics, basic chemistry, physics and biology.
3. Establishment of $\mathrm{M}^{3} \mathrm{C}$ networks where both academia and industry take part would strengthen the advancement of $\mathrm{M}^{3} \mathrm{C}$. From a funding perspective $\mathrm{M}^{3} \mathrm{C}$ seems as an excellent example of an area where academia/supply, firms/large-scale and industry/regulators can mutually benefit and encourage private as well as public interest, providing new job opportunities and strengthening the quality of life. It should be of particular interest for international grant programmes such as EU Framework, National Science Foundation, NATO supported research as well as for national research and technology development programmes to stimulate the industry in this field.
4. Academia and other E\&T suppliers would benefit from the creation of new educational tools. This includes better software programs, access to databases with industrial data, visualization of processes, videos, materials and modern text books of a good standard and at an affordable price. Other areas in life science have been significantly more successful with this. There is a potential in industry to provide non-confidential data and collections of case studies for stimulating teaching and to bring a higher degree of realism into the basic studies.
5. Dedicated workshops to develop the constituent subtopics of $\mathrm{M}^{3} \mathrm{C}$ on a number of areas: such as competences of students and young professionals, and E\&T didactics are needed.
6. Establishment of a short international $\mathrm{M}^{3} \mathrm{C}$ master course (with a modular version for realization at training sites or embedded into current university led programmes) would raise awareness and the general level of competences in the $\mathrm{M}^{3} \mathrm{C}$ field
7. A set of tailor-made post-university E\&T modules for technicians, management, nonengineers, at $\mathrm{B} / \mathrm{M}$ level, PhD levels would provide a vital resource for this field and an up skilling of staff across the EU. The result would be a gain in industrial competitiveness.

## References

[1] United States' Food and Drug Administration (FDA), Guidance for industry: PAT a framework for innovative pharmaceutical manufacturing and quality assurance, http://www.fda.gov/cvm/guidance/ published.html. 2004
[2] Mandenius C.F., Recent developments in the monitoring, modeling and control of biological production systems. Bioproc. Biosyst. Eng. 2004, 26, 347-351
[3] Bolten C.J., Kiefer P, Letisse F., Portais J.C., Wittmann C., Sampling for metabolome analysis of microorganisms. Anal. Chem. 2007, 79, 3843-3849.
[4] Wittmann C, Kromer JO, Kiefer P, Binz T, Heinzle E. 2004. Impact of the cold shock phenomenon on quantification of intracellular metabolites in bacteria. Anal Biochem 327(1):135-9.
[5] Taymaz-Nikerel H., de Mey M., Ras C., ten Pierick A., Seifar R.M., van Dam J.C., Heijnen J.J., van Gulik W.M., Development and application of a differential method for reliable metabolome analysis in Escherichia coli. Anal. Biochem. 2009, 386, 9-19.
[6] Gernaey K.V., Woodley J.M., Sin G., Introducing mechanistic models in process analytical technology education. Biotechnol. J. 2009, 4, 593-599.
[7] Eriksson L., Johansson E., Kettaneh-Wold N., and S. Wold S., Multi- and Megavariate Data Analysis. Umetrics AB, Sweden, 2001.
[8] Mandenius C.-F., Graumann K., Schultz T.W., Premsteller A., Olsson I.-M., Periot E., Clemens C., Welin M., Quality-by-Design (QbD) for biotechnologyrelated phamaceuticals. Biotechnol. J. 2009, 4, 600-609.
[9] Box G.E.P., Hunter W.G., Hunter J.S., Statistics for Experimenters: An Introduction to Design, Data Analysis, and Model Building. John Wiley \& Sons, New York, 1978.
[10] Mollerup J., Hansen T.B., Kidal S., Staby A., Quality by design: Thermodynamic modelling of chromatographic separation of proteins. J. Chromatogr. A, 2008, 1177, 200-x.
[11] Mandenius C.F., Brundin A., Bioprocess optimization using design-ofexperiments methodology. Biotechnol. Prog. 2008, 24, 1191-1203.
[12] Wiendahl M., Wierling P.S., Nielsen J., Christensen D.F., Krarup J., Staby A., Hubbuch J., High-throughput screening for the design and optimization of chromatographic processes - miniaturization, automation and parallelization of breakthrough and elution experiments in flow-through mode. Chem. Eng. Technol. 2008, 31, 893-x.
[13] Sin G., Gernaey K.V., Eliasson Lantz A., Good modelling practice (GMoP) for PAT applications: Propagation of input uncertainty and sensitivity analysis. Biotechnol. Prog. 2009, 25, 1043-1053.
[14] Dunn I.J., Heinzle E., Ingham J., Prenosil J.E., Biological Reaction Engineering: Dynamic Modelling Fundamentals with Simulation Examples. Weinheim: WileyVCH, Weinheim. 508 p. 2003
[15] Hass V.C., Pörtner R., Praxis der Bioprozesstechnik. Spektrum-Akademischer Verlag, Heidelberg, 2009
[16] Geladi P., Esbensen K., The start and early history of chemometrics: Selected interviews. Part 1. J. Chemometrics 2005, 4, 337-354
[17] Esbensen K., Geladi P., The start and early history of chemometrics: Selected interviews. Part 2. J. Chemometrics 2005, 4, 389-412
[18] Heinzle E., Biwer A., Cooney C.L., Development of sustainable bioprocesses modeling and assessment. Chichester: John Wiley \& Sons, Chichester, 2007.
[19] Fisher R.A., The Design of Experiments. 9th Edition, Macmillan 1971
[20] Schoop K.M., (2008): Technical description of the process control system WinErs. www.schoop.de (Access: 02.12.2008)

Outline Report / Manuscript for Biotechnology Journal (Wiley)
[21] National Instruments: NI LabVIEW Math Interface Toolkit: //sine.ni.com/nips/cds/view/p/lang/en/nid/12922
[22] Hass V., Verbesserung der bioverfahrenstechnischen Ausbildung durch einen "Virtuellen Bioreaktor". Chemie Ing. Technik 2005, 77, 161-167.
[23] Blesgen, A. et al. (2006): Towards a "Virtual (bio-) chemical engineering laboratory. In: Proceedings of the $17^{\text {th }}$ International Congress on Chenical and Process Engineering, I1.05. Process Engineering Publisher, Prague, Czech Republic.
[24] Gernaey K.V., Rosen C., Batstone D.J., Alex J., Efficient modelling necessitates standards for model documentation and exchange. Water Sci. Technol. 2006, 53, 277-285.

## Tables

Table 1. Examples of commercial providers of $E \& T$ in $M^{3} C$ subjects

| Type of provides | E\&T Product | Provider |
| :---: | :---: | :---: |
| Commercial provider | Training product software | Sartorius Stedim Biotech S.A |
| Commercial provider | Cell culture analysis, biostatistics | PromoCell Academy |
| Non-profit provider |  | Haus der Technik |
| Non-profit provider |  | DECHEMA |
| Non-profit provider |  | Europäisches Bildungswerk für Beruf und Gesellschaft |
| In-house training | Training product software | COMSOL AB |
| In-house training | Training product software | Endress+Hauser |
| In-house training | Training product software | Pepperl+Fuchs |
| In-house training | Training product software | Hach-Lange |
| In-house training | Training product software | Siemens |
| In-house training | Training product software | ABB |
| In-house training | Training product software | Rockwell Automation |
| Supportive products for E\&T | Tutorial software | Armfield |
| Supportive products for E\&T | Tutorial software | LD Didatic |
| Supportive products for E\&T | Tutorial software | Landgraf Laborsysteme GmbH |
| Supportive products for E\&T | Tutorial software | s\&h Ingenieurgesellschaft mbH |
| Supportive products for E\&T | Tutorial software | Ingenieurbüro Dr.-Ing. Schoop GmbH |
| Training simulators | Plant operation training | Siemens: SIMIT SCE |
| Training simulators | Plant operation training | Siemens: SIMIT OTS |

Table 2. Examples of software tools useful for $\mathrm{M}^{3} \mathrm{C}$ training

| Main use | Tool /Product name | Functionality | Refs/Website |
| :---: | :---: | :---: | :---: |
| Modelling | MapleSim ${ }^{\text {TM }}$ | Wide applications | www.maplesoft.com |
|  | Matlab Simulink ${ }^{\text {TM }}$ | Wide applications | www.mathworks.com |
|  | Mathematica ${ }^{\text {TM }}$ | Wide applications | www.wolfram.com |
|  | $\mathrm{SciLab}^{\mathrm{TM}}$ | Wide applications | www.scilab.org |
|  | Octave ${ }^{\text {TM }}$ | Wide applications | www.gnu.org/software/octave |
|  | AspenPlus ${ }^{\text {TM }}$ | Simulation package | www.aspentech.com |
|  | Comsol ${ }^{\text {TM }}$ | Simulation package | www.comsol.com |
|  | Dymola ${ }^{\text {TM }}$ | Simulation package | www.3ds.com/products/catia/portfolio/dymola |
|  | $\text { gPROMs }^{\mathrm{TM}}$ | Simulation package | www.psenterprise.com |
|  | SuperPro Designer ${ }^{\text {TM }}$ | Simulation package | www.intelligen.com |
|  | Open Modelica ${ }^{\text {TM }}$ | Simulation package | www.ida.liu.se/labs/pelab/modelica/OpenModelica.hTMl |
|  | BioSolv | Simulation package | www.biopharmservices.com |
|  | WinErs ${ }^{\text {TM }}$ | Simulation package | [19], www.schoop.de |
| Chemometrics | $\begin{aligned} & \mathrm{MODDE} \\ & \mathrm{P}+ \end{aligned}, \quad \mathrm{SIMCA}^{\mathrm{TM}}$ | DoE and MVDA packages | www.umetrics.com |
|  | Design-Expert ${ }^{\text {TM }}$ | DoE package | www.statease.com |
|  | Jmp ${ }^{\text {TM }}$ | DoE package | www.jmp.com |
|  | Statistica ${ }^{\text {TM }}$ | DoE and MVDA package | www.statsoft.com |
|  | $\operatorname{MiniTab}^{\mathrm{TM}}$ | DoE and MVDA package | www.minitab.com |
|  | $\mathrm{R}^{\text {TM }}$ | DoE and MVDA package | www.r-project.org |
|  | Matlab ${ }^{\text {TM }}$ | MVDA package | www.mathworks.com |
|  | SPSS ${ }^{\text {TM }}$ | MVDA package | www.brothersoft.com |
| Control | Matlab ${ }^{\text {TM }}$ | Control toolbox | www.mathworks.com/control-systems |

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| WinErs ${ }^{\text {TM }}$ | Linking software | [19], www.schoop.de |
| :--- | :--- | :--- |
| LabView ${ }^{\text {TM }}$ | Linking software | [20], sine.ni.com/nips/cds/view/p/lang/en/nid/12922 |
| SimApp | Control simulation | www.simapp.com |

## Figures

## Figure 1

$\mathrm{M}^{3} \mathrm{C}$ competence areas

## Figure 2

Diagram showing the flows of competence and human resources in E\&T. The diagram illustrates the generation and flow of competences in $\mathrm{M}^{3} \mathrm{C}$ from different educational organisations to industry and public sector. Blue arrows represent knowledge and competence transfer. Yellow arrows represent human resources.

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## $M^{3} \mathrm{C}$ competence areas

## Measurement

- Quality analysis
- Advanced instrumentation
- Omics methods

Monitoring

- Process Sensors
- On-line sensors
- Biosensor


## Modelling

- Chemometrics
- Mechanistic modelling

- Modelling for data analysis
- Modelling for control


## Control

- Basic control methods
- Automation
- Advanced control methods

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Figure 2


## $M^{3} \mathrm{C}$ competence areas

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