Biomechatronic Design for Sensors:
Biomechatronic Methodology

Biomechatronic design combines mechanical and electric product design principles with biotechnology [1]. Systematic conceptual design, used for decades in product development for mechanical products is here adapted to cope with the complexity of biological systems and processes. Typical examples are bioreactors and biosensors. The biomechatronic design facilitates and coordinates the product development work by using a few simple procedures, tools and models. In this report these tools and models are applied on the design of sensor systems used for monitoring and controlling biotechnology production processes.

Introduction
Good design of reliable monitoring systems for biotechnological manufacturing is essential for securing high product quality and economical processing.

The principles expressed in the regulatory authorities guidelines, such as FDA Process Analytical Technology guidance for industry and ICH Quality guidelines, are based on the access or development of analytical systems that can accomplish efficiency and high reliability under long-term operation.

The purposes are several: allowing early or immediate release of batches, reducing the number of discarded batches, reducing consumption of materials and energy, and allowing continuous and down-sized process equipment. As essential means are considered use of on-line monitoring and control methods, early identification of quality attributes, and statistical data evaluation.

Systematic conceptual design methodologies provide additional tools that can contribute to a more efficient path for reaching many of these objectives [1]. The systematic conceptual design has its roots in mechanical engineering and production and had originally the purpose to rationalize design and development of new mechanical products. In the biomechatronic design methodology these systematic approach is further developed for products where also biological systems and their functions are an integral part of the designed product [1, 2].
Methodology
The methodology is based on a consecutive and iterative procedure where graphical and tabular tools are used (fig. 1). The work flow in the figure outlines the recommended steps in a sequential order of steps. In the first step, the design mission is concisely stated. This is followed by identifying the needs of the users of the intended product or production process. These needs are further specified with target values. With the help of these specifications an overview flow chart (a Hubka Eder map) that shows the functions required for accomplishing the specification is drawn. The functions in this chart are represented in abstract functional components that are combined in as many alternatives (permutations) as imaginable. This is the key step in the design and is referred to as concept generation. The concept alternatives are screened and scored towards the specification target values. This results in a ranking from which just a few design alternatives are selected. First at this stage, actual physical objects, chemical or cells, are brought into the design work. These objects, so called anatomical components, are identified as existing technical devices, instruments or other technical gears, usually commercially available, or feasible to construct or prototype. The assessment of these anatomical structures is forming the final design solution of the product.

A Monitoring and Sensor System for Bioprocesses
The methodology can be applied to any biomechatronic product or system. Monitoring and sensor systems for bioprocesses are examples of system products that could benefit from the methodology. By systematical investigating the needs of the bioprocess engineers and their expectations on the monitoring system, a list of needs and target specifications is established (see fig. 1, top). These needs are critical for creating the Hubka Eder map and for highlighting the functions required for meeting the needs.
From these functions, the basic design components are identified (fig. 2). This can typically be a sampling function component, a detection function component, a conditioning component, and an interpretation component. The Hubka Eder map has indicated that these functions are necessary for the transformation process of the bioprocess to take place.

Then, the basic components are used to generate several new design concepts (fig. 2).

Figure 3 shows an example where this is applied to a biopharmaceutical bioprocess for production of recombinant human insulin. The bioprocess shown in the figure is here significantly simplified for highlighting the design methodology. Thus, only five upstream and downstream stages are included: the bioreactor for cultivation the host organism and expression the insulin product, a homogenizer for disrupting the cells in order to release the intracellular protein, a microfilter for removing cell debris, a chromatographic step for capturing the insulin, and an ultrafilter for concentrating the protein. The monitoring needs listed by the users, i.e. the bioprocess engineers developing the insulin bioprocess, are mainly related to monitor the authentic pancreatic form of the insulin product, the modified insulin molecules formed a result of the expression system as well as other impurities that are unacceptable in the final product formulation. The range of measurements and desired response times are included in the target specifications. Also economical parameters and restrictions are included in the targets, such as operational and maintenance costs for the monitoring procedures, and capital costs for sensor equipment.

The six generated concept alternatives in figure 2 are screened and scored versus the targets specification metrics. This results in a ranking of the alternatives. The two highest ranked alternatives (see fig. 3) are selected for further testing and evaluation with various anatomical objects. These objects are existing commercial sensor devices or analytical instruments such as on-line HPLC, biosensors and bioreactor in situ probes. Also the anatomical objects are compared and ranked using screening and scoring versus the target metrics. It results finally in a design solution of the monitoring system that is applied on the full scale bioprocess and is validated according to recommendations in official regulatory guidelines.

**Conclusion**

The biomechatronics methodology provides several technological gains: it adapts academic research to the actual industrial needs more precisely, it speeds up the design work process and it stops or identifies adverse design solutions earlier. Also, the biomechatronics methodology provides several management gains: The
work of the design team is simplified, especially in cross-disciplinary projects. The communication and decision-making with participants in a company can more easily be integrated early in the design work (e.g. marketing people, manufacturing people, regulatory people and management). Finally, the biomechatronics methodology also provides tools to trigger and identify new potential developments that may stimulate new products or research projects.

References

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