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Engineering Design Methodology for Bio-Mechatronic Products

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Four complex biotechnology products/product systems (a protein purification system, a bioreactor system, a surface plasmon resonance biosensor, and an enzymatic glucose analyzer) are analyzed using conceptual design principles. A design model well-known in mechanical system design, the Hubka−Eder (HE) model, is adapted to biotechnology products that exemplify combined technical systems of mechanical, electronic, and biological components, here referred to as bio-mechatronic systems. The analysis concludes that an extension of the previous HE model with a separate biological systems entity significantly contributes to facilitating the functional and systematic analyses of bio-mechatronic systems.

Introduction

Biotechnical products can be divided into (1) biologics, which comprise those metabolites, biopolymers, and cell structures that are produced through biological processes, and (2) biotechnical machines, which are apparatuses and devices that transform, change, or analyze "biological specimens" for specific purposes, often by using biological systems per se. The first category has been thoroughly treated in bioengineering theory and practice (e.g., Atkinson and Manituna, 1991; Rehm and Reed, 1990−1999), whereas the second has been very scarcely investigated (e.g., Reiss and Woerner, 2002). This article suggests and discusses how general design science theory (Pahl and Beitz, 1996; Roozenburg and Eekels, 1996) can be applied when designing technical systems where biological species or components have key roles in the engineering design solutions. We refer to these systems as *bio-mechatronic systems*, since they are interrelated design achievements between traditional electronic and mechanical sub-systems and biological systems where biological molecules or active microbial or cellular components influence the design solutions in a complex way.

The purpose is to demonstrate that biotechnology and bioengineering design can utilize and benefit from other commonly used design tools. These tools should predominantly be regarded as complementary and supportive, and their use justified by shorter development times and a reduction of the need for prototype testing and verification.

To our knowledge, few attempts have been made so far to elucidate the complexity of design issues in product development in the biotechnology industry, with the exception of more general issues such as research and development networking strategies (e.g., by Azzone and Dalla Pozza, 2003; Stewart-Knox and Mitchell, 2003; Oliver, 2004).

This paper provides an analysis of four characteristic bio-mechatronic products, all of which are based on well-known biotechnology products commonly used in the pharmaceutical, food, and clinical areas: (1) a protein purification system, (2) a bioreactor system, (3) a biosensor instrument, and (4) a blood glucose analyzer. Conceptual design principles (Hubka and Eder, 1988) are applied to these case examples according to an established design methodology for mechanical and electrical products.

Design Theory

The principles of conceptual design have been thoroughly discussed from a wide range of viewpoints in the general design science theory within the mechanical engineering domain. An important part of conceptual design in modern design methodology is the *functional analysis* of the technical system under development. This study therefore investigates how this functional analysis can be performed on biotechnology-related systems and devices that are not pharmaceutical substances, food products, or commodity or fine biochemicals, and where the main functionality is based on using biological components as a part of biotechnical products that also incorporate mechanical and electrical systems. Since such bio-mechatronic products are an even more complex combination of functions then mechanical and electronics products, functional analysis can prove to be a reliable and rational tool in the early conceptual design stages.

The functional analysis approach has become a key means of describing a design concept and has gained wide acceptance due to its broad scope and general applicability to any technical design task (Roozenburg and Eekels, 1996; Pahl and Beitz,-1996). The main objective of a functional analysis is to abstract the designed system's needs from the perspective of *what it must do*, instead of *how this may be done*. It is important to first focus on *what to do* before deciding *how to do it*. Designers often have a tendency to integrate the two.

A variety of approaches to carrying out functional analysis are described in the literature, for example, by Hubka and Eder (1988), Pahl and Beitz (1996), Ullman (2003), and Ulrich and Eppinger (2003). Even if these approaches may seem different, most of the functional analysis originates from the same theory, albeit with certain methodical diversities.

In the present paper, we apply functional analysis according to the *theory of technical systems* established by Hubka and Eder (1988). This theory is one of the most well-founded and makes it possible to generically elucidate the differences between (1) the logical order of the operations (referred to as "transformations") that the system will perform, (2) the kind of sub-

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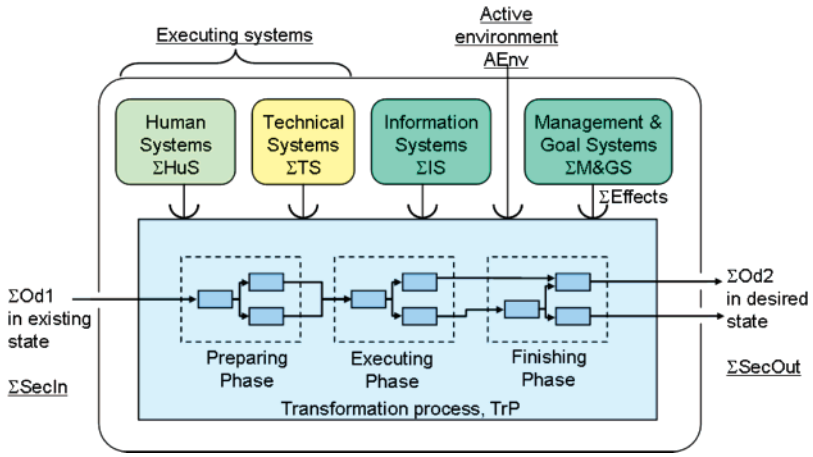

Figure 1. The basic Hubka−Eder model structure, separating the transformation process of the operand phases of preparation, execution, and finishing and relating the transformation process to the executing human and technical systems and other systems that affect the process (adapted from Hubka and Eder, 1996).

system that will carry out these operations, (3) the ways in which these sub-systems will relate to each other, and (4) what each sub-system will do in the different operations (i.e., the functional structure).

In essence, Hubka−Eder theory is based on analyzing the technical system in relation to the *transformation process* (TrP) of operands. The input states of the *operand* (Od1) converted by the TrP are, in its existing state, raw materials and other necessary attributes that the transformation process needs in order to carry out the transformations. The outputs from the TrP are the operand refined to a desired state (Od2) and occasionally some waste products (Figure 1). The operands (ΣOd1) may consist of *energy* (E), *materials* (M), *information* (I), or of special relevance in this work, *biological objects* (B) such as humans, animals, or plants. Energy and materials must be conserved during the process, while information may appear or disappear along the process. Additionally, changes can occur in the state (e.g., sick ⟹ healthy) or the location of the biological objects.

The set model of the main system analyzes how a variety of supplementary systems interact with the transformation process. The supplementary systems are subdivided into *human systems*, ΣHuS (operators); other *technical support systems*, ΣTS; *information systems*, ΣIS; and *management and goal systems*, ΣM&GS. For example, technicians that participate in carrying out the transformation are included in ΣHuS, systems for supply of media such as cooling water or electricity are included in ΣTS, data from instrumental calibrations are included in ΣIS, and the stipulations of a particular calibration routine or a specified purity level of a solution are included in ΣM&GS. In addition, the *active environment*, AEnv, comprises environmental factors that normally cannot be controlled or managed by the transformation process but have a decisive effect on the performance of the transformation process; examples could include the ambient temperature of the manufacturing plant or the occurrence of air-borne contaminants. One of the main purposes of the model is to analyze the effects and consequences of the chosen design in terms of the components that have been identified during the design process. The model gradually becomes more powerful as the sub-transformation processes in the design are analyzed in more detail. Thus, ideally, when the total transformation is broken down into sub-transformation operations, the effects will become more apparent and more tangible to the designer. When the effects of the transformation are identified, the functional structure of each of the interacting supplementary systems may be defined. In order to adapt the modeling to biotechnical products, we focus here on the biological system. In addition, the model is simplified by means of merging ΣIS and ΣM&GS into AEnv. For the same reason, the model in the case studies is kept at a rather superficial level in order to focus on the fundamental ideas and usage of the model.

The Hubka−Eder model is well-known in mechanical design engineering and is supported in that field by numerous application studies and design cases. However, the model has not been used at all for biotechnology applications. To our knowledge, analysis of the design of biotechnical systems has not been described in the scientific literature except for brief mention of its role in a general sense as a source of branch knowledge for technical systems in medicine, pharmaceuticals, and food industries (see, e.g., Hubka and Eder, 1996).

The intention of the present work is to provide additional means for facilitating the conceptual design of new complex biotech products. We believe that it is even more justified to utilize a general theory to support the design of these products, since they have a substantial additional degree of complexity through the inclusion of biological systems, which are hugely complex in themselves.

Case Studies

A Protein Purification System. The first case study was performed on a technical system based on chromatographic column separation for purifying proteins. Well-known existing commercial products of the system are ÄKTA and FPLC from GE Healthcare (formerly Amersham Pharmacia, Uppsala, Sweden) and similar products from BioRad Laboratories (Hercules, CA). Chromatographic column separation of proteins is regularly used in academic and industrial research for biomedical, molecular, and biochemical studies, as well as in industrial manufacturing for purification of pharmaceuticals, food substances, and fine and commodity biologics. The separation media used in the chromatographic columns have the capacity to retard biological compounds passing along the column in a selective way, so that the effluent from the column is in a purer or more concentrated state. The combination of appropriate methods and properties of flow transportation, flow distribution, materials, and detection has allowed the creation of efficient technical systems based on a variety of principles and designs.

When following the Hubka−Eder modeling approach based on operands, transformations, and interactive supportive systems, including the biological system, a generic and comprehensive

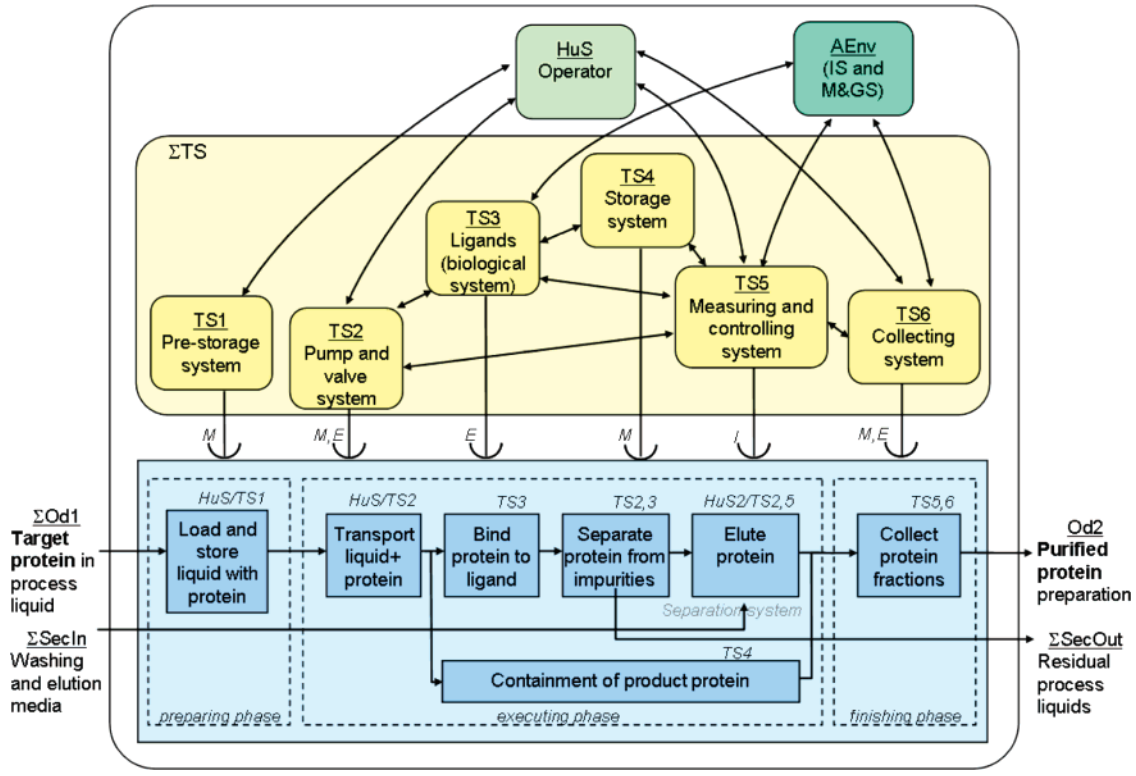

Figure 2. Protein purification system based on preparative chromatography according to the Hubka−Eder model. The transformation of the operands, consisting of the impure protein to prepared and chromatographic elution and washing media, is carried out in three phases. The first is the pre-preparation phase, with loading of process liquid. The second phase is the executing phase, in which process liquid is transported to the chromatography separation medium/gel in the column, the protein binds to the ligands of the gel, impurities are removed, and the product protein is eluted. The final phase is the finishing phase, where the protein is separately collected. The dark-gray area denotes those parts of the instrumentation that are separate devices. The supportive technical systems, ΣTS (light gray), include the storage of process liquid; the pumps and valves involved in the transformation process; the supply or procurement procedures for the ligands/gels; the measurement and control systems with detectors for UV, conductivity, temperature, and so on; and the devices for collecting the prepared protein. The effects executed by these are mediated through materials (M), energy (E), or information (I). Interactions with the human operators, HuS, as well as the active environment, are indicated.

model may be defined that merges special and constrained methods and procedures from different knowledge and competence backgrounds, such as electrical circuit diagrams, mechanical CAD drawings, or bioprocess flowsheeting (Sofer and Nyström, 1989; Petrides and Shabram, 2004). This then makes it easy to obtain an overview of the interactions between the biological and technical functions, which in turn provides a basis for design and evaluation.

Figure 2 depicts a typical Hubka−Eder representation of a protein purification system (in this figure, based on adsorption or affinity ligand chromatography techniques) where the above-mentioned operations are contained within the transformation process boundary onto which the technical (ΣTS), information (ΣIS), human (ΣHuS), and management (ΣM&GS) systems, as well as the active environment (AEnv), interact. Here, the technical systems include all units such as pumps, valves, sensors, and control systems that will be contained in the designed product, as well as the biological systems with chromatographic gels and ligand biomolecules or organic molecules for these gels used for affinity and hydrophobic interaction with the target molecules to be separated. The human system (∑HuS) includes, for example, the technician that operates the system; the information system (ΣIS) includes the methods and protocols being set up (both today replaceable by computer expert software programs); and the active environment (AEnv) includes the effects on the product (i.e., the transformation system) in terms of temperature, pH, pressure, and so on.

The most relevant transformation properties appear at the next level of detail, where the favorable values of the ligand-ligate affinity rates are attained, and where high separation factors and efficient plate number of columns are reached. What is of utmost interest at this level of detail is how the properties and transformation process by the biological system, as defined here, interact with the other sub-systems of the technical system; that is, the active environment, the information systems, and other technical sub-systems such as pumps, valves, and detectors. This is seldom done in a straightforward way and is often overlooked.

The depiction in Figure 2 is the result of a detailed analysis of the function and operational procedure of the protein purification system. Although seeming obvious at first, it reveals the functions and consecutive operations of the technical system in a different and clearer way than would be possible with a conventional design drawing, thereby illustrating the Hubka−Eder reasoning.

A Bioreactor System. The second case study exemplifies another apparatus that is common in the biotechnology industry as well as in biotechnology research and development: a bioreactor system. The basic function of a bioreactor is to cultivate microbes and cells, either for the purpose of producing cell mass, as in baker's yeast manufacturing, or to produce proteins or biochemicals via the conversions taking place in the cells. In all bioreactor applications, a primary function of the technical systems is to achieve an environment around and conditions inside the cells that are optimal, or at least favorable, for the microbial or cell culture; that is, an environment that supplies nutrients and gases in an efficient way and protects the cell culture from any potential harmful effects of an active surrounding environment, such as contaminants or toxic substances. Since bacterial cultures may have detrimental effects

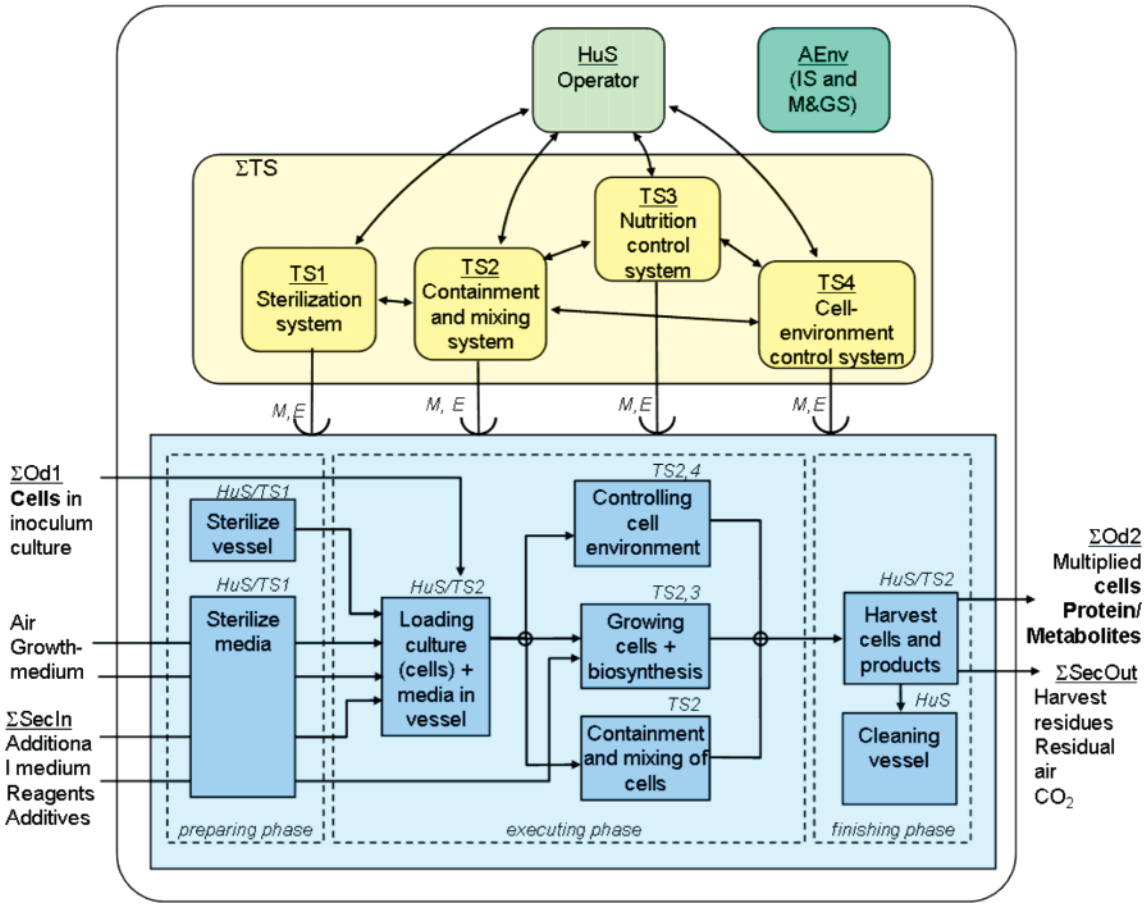

Figure 3. Bioreactor cultivation system according to the Hubka−Eder model. The transformation process of the operands, consisting of the inoculum culture, the growth medium, and other nutrients and additives, is divided into three phases. The first is a preparatory phase, where the bioreactor vessel is sterilized along with the growth medium and sensors. The next phase is the execution phase, where the cells grow under controlled conditions with further additions of nutrients, reagents, and oxygen. Finally, in the finishing phase, the cells are transferred from the reactor vessel (harvesting). The supportive technical systems, ΣTS (light gray), include the supply of steam and sterilization procedures, the device for mixing, and the systems for controlled additions and for controlling temperature and pressure. The interactive role of the operators and planners of the cultivation and the effects of the active environment are also included.

on humans, the bioreactor can also serve to protect the environment in which it is operated.

A bioreactor in operation is a pertinent example of a biomechatronic system where the function of the biological system is clearly separated from the mechatronic objects and functions. This separation facilitates the conceptual design work.

In the Hubka−Eder model for this case, the input state of the operand is the inoculum culture, and the output state is the multiplied number of cells due to growth of the culture and the biologics produced by the culture (Figure 3). Thus, the transformation process covers (1) the preparation of the system, (2) the conversion carried out by the cells based on their cellular transportation and intracellular metabolic activity, and (3) the final recovery of the products produced in the bioreactor. Furthermore, the transformation process also includes the mechanical parts that are responsible for transport and mixing of cells and growth media, sterilization and heating of the reactor vessel, and the electronic parts that are responsible for signal transduction to and from valves, pumps, heaters, and sensors and controllers. ∑HuS again represents the individuals that make decisions about operations, and ΣTS represents external supply systems for air, water, vapor, electricity, reference analyzers for cell mass, incubators, shake tables, and so on. ΣIS comprises information from the external analyzers, and ΣM&GS includes the PC program that provides algorithms for monitoring and control and the protocols and procedures worked out by the process engineers for the particular bioprocess to be run. AEnv includes the effects of the varying climate conditions in the lab and the contamination risks from the ambient environment and also the inherent biological variability of the cells due to unknown environmental variations. From the list of possibilities, which in reality is significantly longer than mentioned here, the Hubka−Eder model highlights many of the most important design issues for bioreactor systems.

The typical functions of the different supplementary technical systems are objects for mixing of air, nutrients, heat supply, pH control, containment, cleaning and sterilization, and devices for inoculation and medium addition (Figure 3). These functional objects are clearly interrelated with input and output materials, energy, and signals. An important requirement in large-scale industrial processes is to minimize consumption of materials and energy through control signals. In this respect, too, the Hubka−Eder model may be an appropriate analytical tool.

A Biosensor System. The next case is a biosensor based on the optical phenomenon of surface plasmon resonance (SPR). The most well-known commercial product is Biacore from Biacore AB, Uppsala, Sweden. Other commercial SPR products are the Fison, AMI, and SPREETA (Texas Instruments Inc.) instruments. Biosensor devices exploit the capacity of a biological molecule to selectively capture or convert the sample (the analyte) to be analyzed. The capturing or conversion event is transduced to a detector or sensor that is able to record the extent of the capture or conversion. The Biacore device makes use of antibodies or other recognition molecules (ligands) bound to a

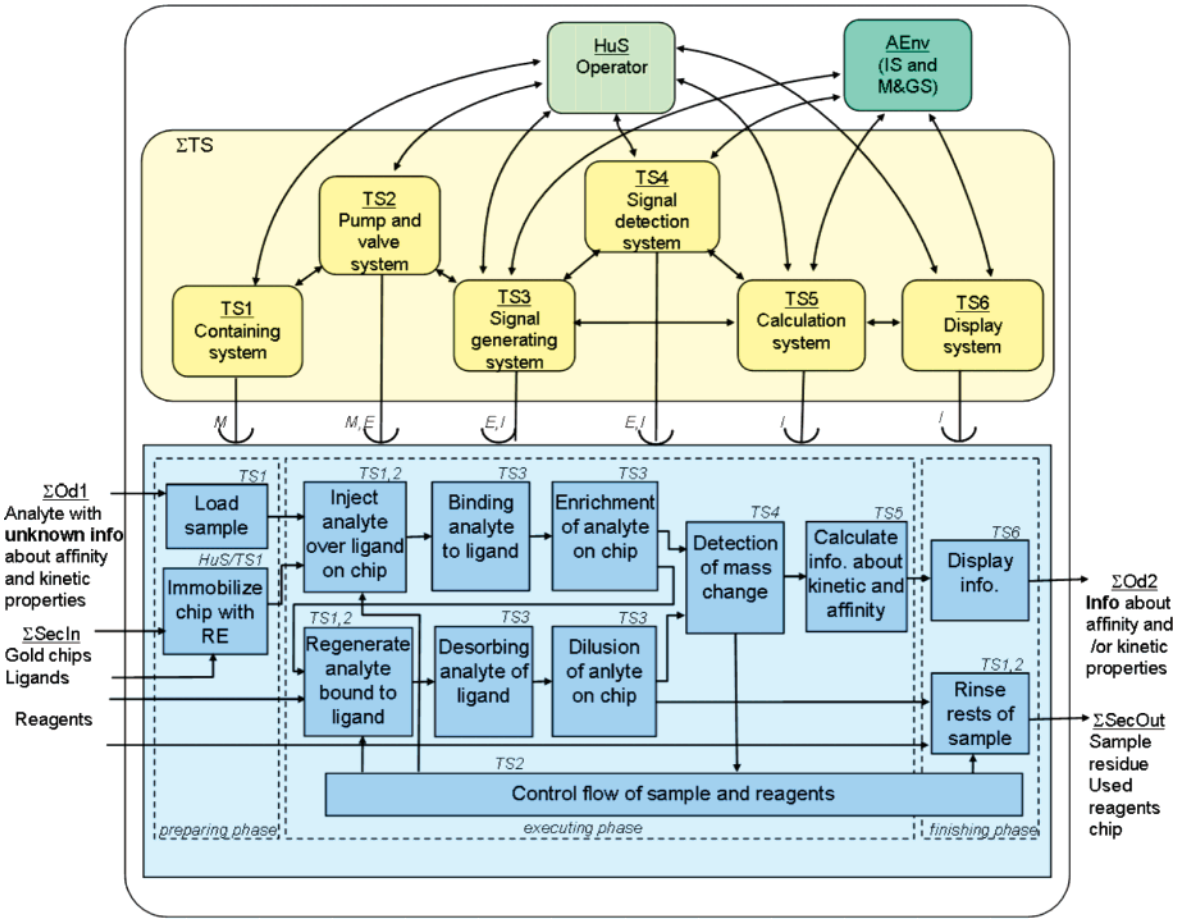

Figure 4. Biosensor system for biomolecular analysis based on surface plasmon resonance according to the Hubka−Eder model. The transformation process of the operands, consisting of the biomolecular analyte sample with as-yet-unknown kinetic properties, a sensor chip, a ligand able to capture the analyte, and other buffers/reagents used, is divided into three phases. The first is a preparation phase for analyte sample loading and for immobilizing the ligand on the chip; the second is an execution phase for sample injection, analysis of the binding event through the SPR effect, measurement of the signal shift, calculation of kinetic data from the signal, and restoration of the chip ligand surface by regeneration; and the third is a finishing phase for displaying the results and rinsing the system to be ready for the next sample. The area in dark gray denotes procedures housed in the SPR instrument. The supportive technical systems, ΣTS (light gray), include the containment system, the pumps and valves of the instrument, the optical system for generating the SPR signal, the detector system, the calculation software, and the system for the presentation of the results. A separate TS is denoted for the selection and preparation of the ligands to be immobilized on the chip. Some of these sub-systems provide materials, others energy, and others information. The interaction of operator personnel and scientists are included in both HuS and AEnv.

thin gold film in a polymer layer. The film is attached to an optical prism in such a way that light can be multiply reflected between the ligand and film, resulting in the SPR effect. This effect is mass-sensitive via the refractive index change, and so the extent of any interaction between the ligand and the analyte can be detected very sensitively.

The Hubka−Eder model provides, as above, an important focus on the disturbances caused by the environment (AEnv), on the calculation work necessary to manage the interpretation of the kinetic results and the planning of the experiment (∑HuS), on the requirements of the lab supply systems and the support from the vendor for instrument operation and chip fabrication and consumables (ΣTS), and on the biotechnical system, including the availability and development of suitable biological ligands and the preparation of the sample to be analyzed (Figure 4). The Hubka−Eder representation addresses, at an early stage, how many of the functionalities are placed outside the product (the Biacore device) and how demanding the product is, both of the user, who must provide these competences, and of the selling company, which must be prepared to provide support and consumables.

If each of the systems in the ΣTS domain (Figure 4) is decomposed further (cf. Figure 6), the technical operation of the biosensor instrument through the functions and sub-functions of binding of ligands to the gold chip, sample distribution, irradiation and detection by emitter and diode array multiplier, and analysis of signals comes out clearly. The relationships to materials (sample, ligands, and chips), energy (to pumps and valves), and signals (from the detector and for operating valves and pumps) can be understood similarly to a flow scheme.

A Blood Glucose Analyzer System. The final case study is another biosensor application, a blood glucose analyzer. Blood glucose concentration is determined by a colorimetric monitoring device in which a blood sample is transferred by capillary force into a plastic cuvette that contains lyophilized enzymes and reagents that disrupt the blood cells and convert its glucose content to a colored complex via an enzymatic reaction. The cuvette is subsequently inserted into a desktop or handheld colorimetric monitor that measures the absorbance at 600 nm. The device is designed and manufactured by Hemocue AB, Sweden, under the brand name HemoCue.

When modeling the system with the Hubka−Eder approach (cf. Figure 5), the operand is defined as the information about the glucose level in the blood, with the input state *unknown level* and the output state *known level*. The transformation process describes how non-colored glucose molecules in the blood sample are transferred to a space inside the cuvette where blood cells are disrupted and their glucose released and

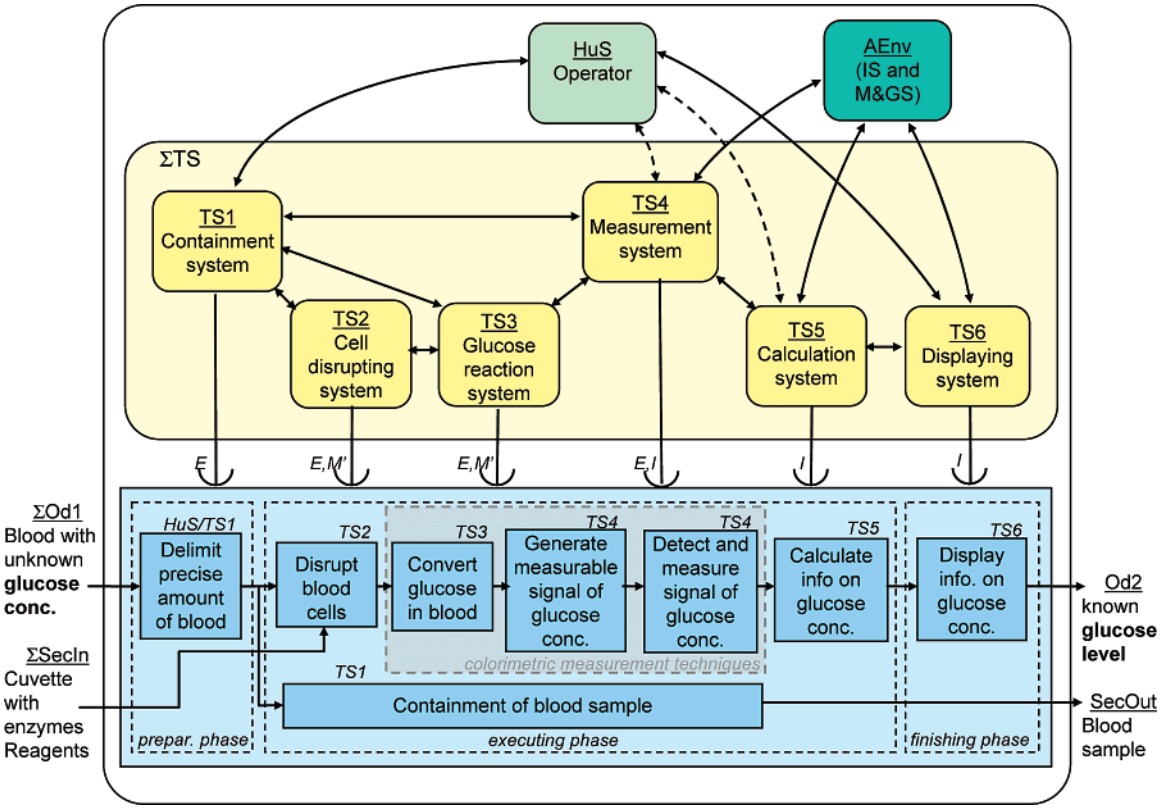

Figure 5. Blood glucose analyzer based on enzymatic colorimetry according to the Hubka−Eder model. The transformation process of the operands, consisting of the glucose-containing blood sample and the capillary cuvette with analytical enzymes, is divided into three phases: a preparation phase for blood analyte sampling by the capillary cuvette; an execution phases in which the sampled blood cells are disrupted, glucose is converted to a colored molecule, the absorption is measured, and the glucose concentration calculated from calibration; and a finishing phase where the result is presented to the user. The supportive technical systems, ΣTS, include the systems for containment, disrupting, converting, measurement, calculation, and display of results.

converted by dissolved and activated hydrolytic enzymes, and where a color reagent, also dissolved, changes to a detectable color when the glucose in the sample is enzymatically converted. The subsequent transformation process extracts this information by a colorimetric reading carried out by a photosensitive device that delivers electronic signals that are then converted to information interpretable by the user.

The analysis is carried out with little input from the operator (HuS), whose main task is to supply the instrument with the sample and to supervise the process; thus, the knowledge required by the operator is rather limited, contrary to the previous cases. The essential parts of the technical system (ΣTS) include the necessary preparation of the cells to generate a signal, the measurement of the signal, and calculation of the glucose level. The biological transformations are the enzyme processes that disrupt cells and convert the glucose in the blood to a measurable entity. The active environment (AEnv) may affect the measurement process by cross-interference related to the blood sampling procedure for the patient or climate effects when sampling on the device that are not compensated for by the calibration; the TS should be further designed to do this.

Extended Model

In the modeling above, the biological system is treated as one of the technical systems. However, since the biological components are different in properties, characters, and requirements and interact in unique ways with the other participating sub-systems, we have found that when modeling a biomechatronical system it is beneficial to extend the model with a separate biological systems entity. In order to enhance the rendering of the biological components, we suggest that the executing system entities (i.e., ΣHuS and ΣTS) are complemented by a separate biological system entity (ΣBS), which may model the significant biological contribution of the transformation process. In this way, the functions of the biological system are explicitly described, which will facilitate both the analysis and interpretation of its effects on the transformation process and the analysis of its interactions with supplementary systems. Figures 6 and 7 provide exemplifications of the proposed extended model. Besides showing the extended biological system entity, the figure also depicts the beginning of the next step in the modeling process, which is to define the functional structure of the different technical and biological systems. In the bioreactor case, as shown in Figure 6, it is not feasible to model the functions that the biological system performs with traditional models without the extended ΣBS entity. In that case, the functions of the biological system (i.e., the cell) could be subdivided into (1) its capacity to grow, thus forming new cells (output operand); (2) its capacity to transform the nutrients (input operands) into new metabolites, partly as building blocks for growth, partly as new products (output operands); (3) its capacity to form macromolecular products (output operands) from the metabolites and based on DNA/RNA translation; and (4) its capacity to direct the cellular transformations from genetic or other cell signaling systems.

The example in Figure 7 is based on the case of the blood glucose analyzer system. For the ΣBS entity, two biological systems have been identified: (1) the cell disruption system and (2) the glucose reaction system. The second biological system has been subdivided into two functions: *mixing the blood with disrupting reagents* and *enzymatically reacting with the glucose in the blood*. The enhanced decomposition facilitates

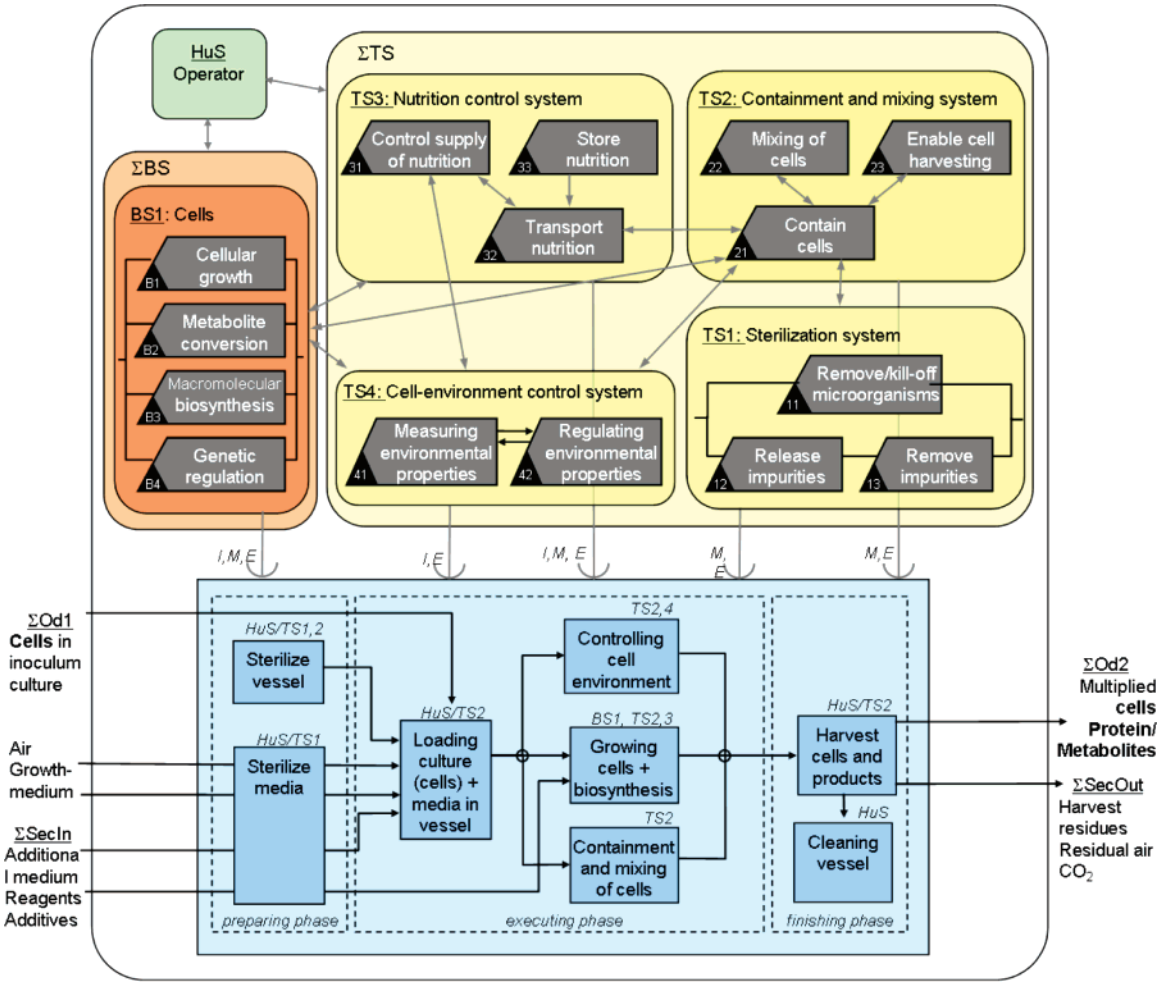

Figure 6. The bioreactor according to an extended Hubka−Eder model where the biological/biotechnical systems, ΣBS, are analyzed separately from ΣTS. In this case, the functions of the biological system (i.e., the cell) could be subdivided into (1) its capacity to grow, (2) its capacity to transform the nutrients, (3) its capacity to form macromolecular products, and (4) its capacity to direct the cellular transformations from genetic or other cell signaling systems.

an understanding of how the biological system(s) interact in the total technical system. The sub-functionality could be further described based on general cell biology knowledge. However, the level of detail should not exceed what is needed for the purpose of the model.

An even more detailed description of the biological subsystems can easily be envisaged where, for example, additional functions of the biological cellular systems are included, such as genetic information transfer in the cell, the regulation of the protein expression system, the function of genetic engineering vehicles, and so on. The purpose should then be limited, in order to disentangle the complexity of interactions between the subfunctions of the biological system as well as between the subfunctions of the technical system.

Similarly, the two other systems in Figures 4 and 5 can be subdivided into biological systems and other technical systems.

User Experiences of the Methodology

The above case models have been constructed by retrospectively interviewing product developers involved in the development and design of the commercial products and by systematic and detailed study of the design results, i.e., the final products. The product development has in each case spanned over 5−10 year periods or more. From the interviews the applied design methodology, procedures, and reasoning have been unravelled and compared in relation to the HE methodology.

These studies showed that the design and development work of the *biosensor system* product, Biacore 1000 (Biacore AB, Sweden), was carried out much according to the HE methodology even though formal HE models were not established and documented as such. (The model structure depiction and the evaluation and morphological matrices shown here are a retrospective description according to the HE methodology based on analysis of the construction methodology applied during the biosensor development work.)

Multidisciplinary development teams systematically considered and investigated alternative technical principles from defined user purposes and needs in order to identify and develop an optimal biosensor-based product.

Functional analysis of the technical and biological subsystems (ΣTS_i and ΣBS_i) considered and their interdependence was done in parallel or iteratively but also to a large extent sequentially.

The structure depicted in Figure 4 was stepwise generated in this work where the effects of various combinations of subsystems of the transformation process to take place in the biosensor were investigated.

Fundamental for the design work was to clearly define the main technical principle to be exploited and how the design space was utilized in relation to that principle. Abstractly, the goal was defined as: *Exploiting the capacity of a biological*

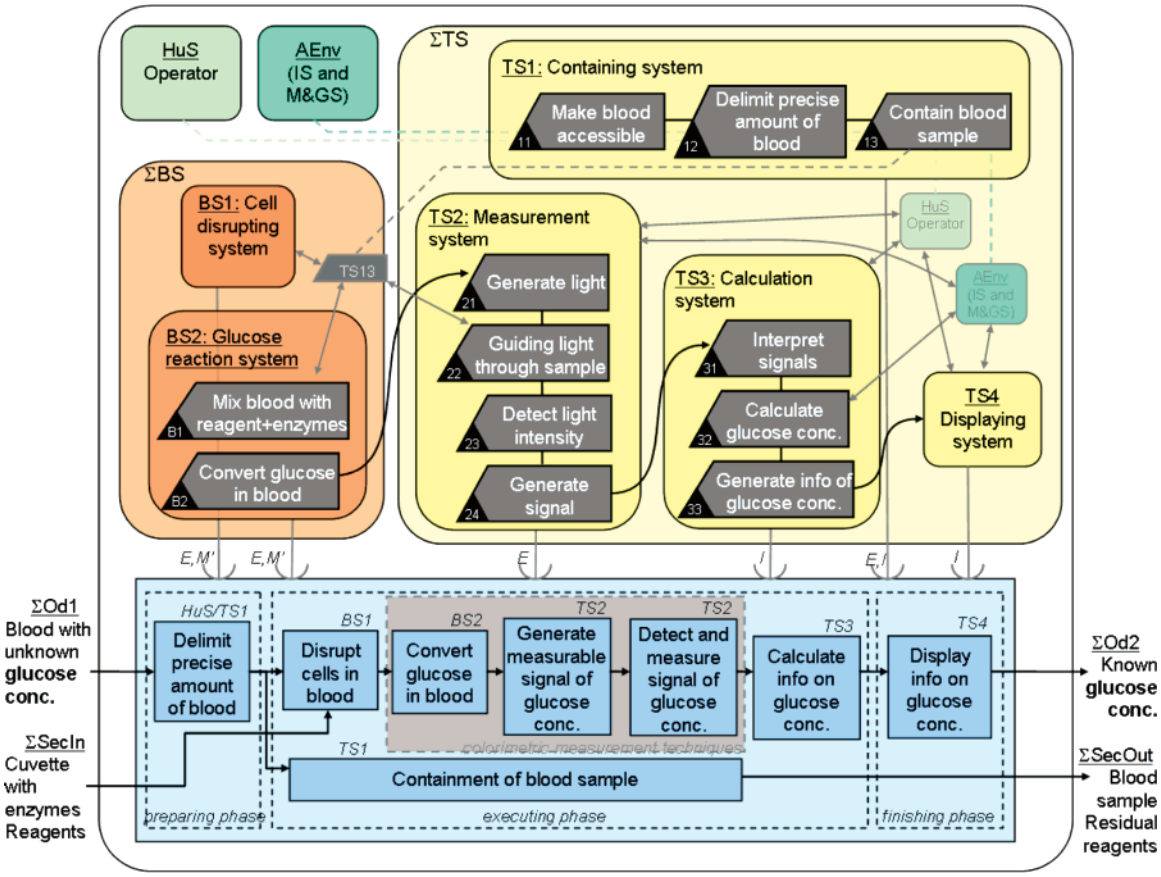

Figure 7. The blood glucose analyzer according to an extended Hubka−Eder model where the biological/biotechnical systems, ΣBS, are analyzed separately from ΣTS. The enzymatic reactions for blood cell disruption (BS1) and for conversion of the released glucose (BS2) are depicted. New interactive connections are identified between ΣTS and ΣBS as shown by the gray lines. Similarly, the HuS and AEnv are analyzed toward the ΣTS.

molecule (i.e., the ligand) to selectively capture or convert the analyte in proximity to a sufficiently sensitive detector.

By further decomposing the HE model in Figure 4, additional key functions for each technical or biological system essential for the performance and the design become possible to be identified. In this example the decomposition has been focused on four different sub-systems, each providing critical functions (cf. Figure 8):

(1) $F_{capture}$: capturing the target analyte in a complex matrix of the analyzed sample.

(2) $F_{mass\ change}$: generating a detectable physio(bio)chemical change from the captured analyte.

(3) $F_{mass\ detection}$: detecting the physiochemical change with a signal-generating device.

(4) $F_{analyte\ transport}$: transporting the analyte sample in a time-efficient way in order to carry out the abovementioned functions.

In order to emphasize the particular properties of the biological system, it has been separated from the technical system (TS3), as proposed in the extended model above.

Thereafter, the design challenges were to identify separate efficient *means* to accomplish these functions. Moreover, these means had to be congruent and able to co-utilize their functions in an integrated design solution.

Early in the design work, the key functions for the creation of a unique new product were considered to be $F_{analyte\ transport}$, $F_{mass\ change}$, and $F_{mass\ detection}$.

First, the alternatives for accomplishing the mass detection function were considered and investigated. Several means for this functionality were carefully evaluated and compared on the basis of the collection of literature data and information and, subsequently, on in-house experimental studies. Special attention was devoted to the methods of surface plasmon spectroscopy (Liedberg et al., 1983), ellipsometry (Jin et al., 1995), field effect transistors (Bergveld, 1986), bulk (Guilbault, 1989; Brederlow et al., 2003) and surface acoustic wave sensing (Welsh et al., 1996), photoacoustic spectroscopy (Helander, 1982), and Brewster-angle reflectometry (Arwin and Lundström, 1985). In the evaluation, critical performance criteria and other properties were compared. These included typical analytical parameters such as analyte sensitivity, reproducibility, response time, and background effects but also more general criteria related to the design such as robustness, manufacturability, software processing of signals for further exploitation of the data, prospects for multisensing and miniaturization, and other integration aspects such as interfacing sample with chips and optical signals. The importance of the design criteria for the detection means was qualitatively weighed and later more thoroughly compared and ranked (Table 1). With the criteria listed in Table 1, the SPR came out as a superior method followed next by ellipsometry.

The next key function contributing to a unique product concept, $F_{mass\ change}$, was analyzed in a similar way. In order to achieve a mass change, the capturing of the target analyte must take place on a surface whose chemical structure permitted the capture to result in a mass change that was reflecting both the biological specificity and molecular mass for the target analyte. From this means the $F_{mass\ change}$ could be further decomposed into sub-functions, such as *immobilize ligands*, $F_{immobilize}$, and *accumulate mass* of the analyte, $F_{accumulate}$ (cf. Figure 8). The identified means for these sub-functions were mainly different

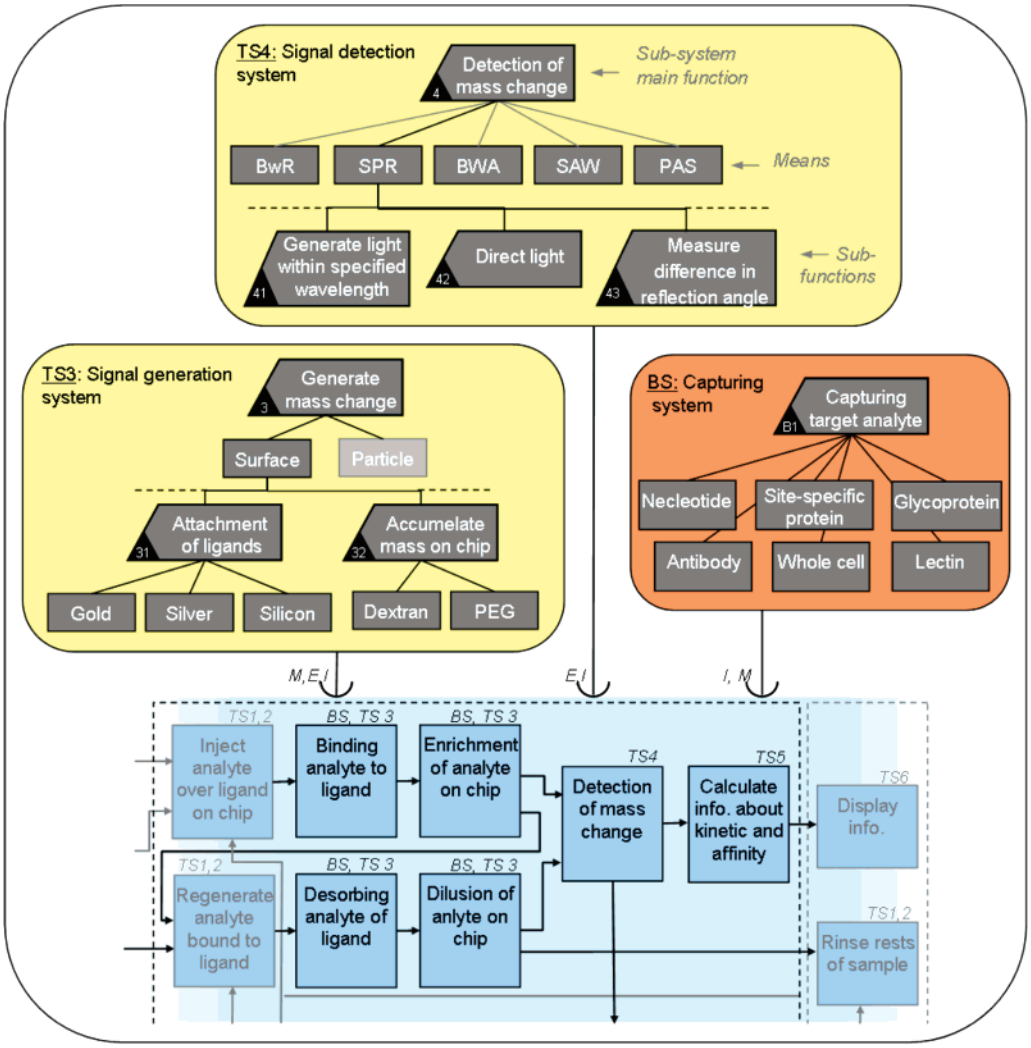

Figure 8. Hubka−Eder representation of the analysis leading to the SPR biosensor product design. Each TS and BS square depicts the alternatives of means considered in the design process.

Table 1. Evaluation Matrix for the Function $F_{detection}$

means	criteria[a]						sum	rank
	analyte sensitivity	manufactu ability	response time	referencing options	miniaturization ability	integration with optic systems		
surface plasmon resonance	+++	+++	+++	+++	+++	+++	18	1
ellipsometry	++	+	+++	+++	++	++	13	2
field effect transistor	+	++	+++	+++	++	+	12	3
Brewster-angle reflectometry	++	+	+++	+++	++	++	12	3
surface acoustic wave	++	++	+++	+++	+	+	11	4
bulk acoustic wave	+	++	+++	++	+	+	10	5
photo acoustic spectroscopy	+	+	++	+	+	+	7	6

[a] Criteria considered highly (+++), medium (++), or less favorable (+).

metal surfaces to support the attachment of ligands, e.g., gold, silver, copper or silicon materials that could mediate the detector signal(s) and serve as a first matrix for grafting the capturing structure, various reaction chemistries for immoblizing accumulating films including thiol and silane coupling, various organic hydrogel films, such as dextran, agarose or poly(ethylene glycol) (PEG) in which analyte could accumulate and to which ligands could be immobilized in high yield.

These means' relations to critical performance criteria such as ability for film formation, capacity of ligand derivatization, accumulation capacity, long-term stability, sensitivity to contamination, side reactions, corrosion, and durability to reagents and sample solutions were analyzed. Table 2 compares these criteria, although, as is easily realized, the selection matrix was in reality much more complex. Table 2 focuses on those methods that are applicable to SPR in particular.

For the biological systems (ΣBS) function $F_{capture}$, i.e., *capacity of capturing target analyte*, different means were analyzed as well. The function can be attained by introducing biological ligand molecules at or very close to the place, or system, where the mass change takes place ($F_{mass\ change}$), and subsequently, can be detected ($F_{mass\ detection}$). Thus, these biological ligands became the main biological component of the biological system ΣBS, for which the functional interconnections between the detection method, the surface chemistry and biological capture methods, became visible. Table 3 shows the evaluation of various ligand means versus some of the most critical properties.

Table 2. Evaluation Matrix for Function F_{mass} Change

means	criteria[a] surface stability	reagent stability	corrosion	accumulation ability	film formation	ligand density	sum	rank
dextran/thiol gold chip	+++	+++	+++	+++	+++	+++	18	1
agarose/thiol gold chip	+++	+++	+++	++	+++	++	16	2
PEG/thiol gold chip	+++	+++	+++	+	+	+	12	3
dextran/silver chip	+	++	+	+++	++	+++	12	3
dextran/silane silicon chip	+	+	+++	++	++	++	11	4

[a] Criteria considered highly (+++), medium (++), or less favorable (+).

Table 3. Evaluation Matrix for the Ligand Capturing Function ($F_{capture}$)

means	critical properties of the means[a] thermostability	site-specificity	pH-dependence	variability	access	sum	rank
antibody (Ab)	++	+++	+++	+++	+++	14	1
nucleotide (Nt)	+++	+++	+	+++	+++	13	2
site-specific protein	++	+++	+++	++	++	12	3
glycoprotein	++	++	+++	++	+	10	4
lectin	++	++	+++	++	+	10	4
whole cell	+	+	+	++	+	6	5

[a] Criteria considered highly (+++), medium (++), or less favorable (+).

Table 4. Morphological Matrix

Function	Means					
Detection of mass change	SPR	Bulk acoustic wave	Surface acoustic. wave	Photo-acoustic Spectrom	Brewster Reflectom	Ellipso-metry
Sensor surface accumulation and ligand binding	Dextran/ Thiol gold chip	Agarose/ Thiol gold chip	PEG/Thiol gold chip	Dextran/ Silver chip	Dextran/ Silane Silicone	
Capturing analytes by surface ligand	Antibody	Nucleotide	Site-specific protein	Glyco-protein	Lectin	Whole cell

In addition to that, the evaluation in Table 3 is close to the user's analytical purpose, to analyze a particular sample. The sample must also withstand the analyzer conditions according to the critical properties.

The fourth functional requirement, to transport the target analyte in the sample, depended on different flow conduit systems. Existing well-known means, such as peristaltic pumps, rotary valves. and silicone tubing systems were redesigned and compared in microsystem formats using various polymeric materials (e.g., silicone-based polymers, polycarbonate), hydraulic microvalves as well as devices made in silicon circuits with lithographic methods.

Although already listed and preliminarily ranked in the initial specification, potential analytical applications were recurrently reconsidered on the basis of opportunities created in the functional analysis. These applications included antigen concentration determination, epitope mapping of antibodies, and kinetic evaluation of affinity interactions.

The three tables evaluate the means for each function separately and take no or little consideration of how well they fit together with each other or with other means of the final technical system. However, in order to design an "optimal solution", not only the most potential means had to be identified and evaluated but also the effect of the integration of the different means. To do so, several design solutions were conceptually synthesized. In design science, this synthesis is commonly systemized by a morphological matrix (Pahl and Beitz, 1996). In the matrix in Table 4, the functions are listed vertically and the different possible solutions horizontally. The concepts are synthesized by selection of different sets of means in the matrix. Already with this rather small morphological matrix the designers had, at least theoretically, 180 different concepts or solutions. For obvious reasons, all combinations possible from Table 1−3 should not be further analyzed.

The most interesting abovementioned alternative morphologies were compared versus general overall criteria. These included total quality of the biosensor, the time required for the development work, time-to-market, evaluation of various cost aspects (including, e.g., R&D costs, manufacturing costs, sale and support costs), an evaluation of the market possibility/opportunities for the biosensor, and requirement of support systems of consumables (i.e., biochips, reagents, ligands). Here, the SPR system with the stable dextran and thiol-coupled gold chips for antibody-based applications was ranked as the most favorable product design alternative, while other morphologies were considered less favorable or even unrealistic. On this basis the development of the SPR biosensor was accomplished.

The cases of the bioreactor, protein purification, and blood glucose analyzer systems may be described by similar structures of HE-based functional analysis. Key functions and means of particular interest are the development of alternative technical systems for heat coils, impeller turbine and sensor electrodes ($\Sigma TS_{bioreactor}$), biological systems of gel materials and for immobilization of gel ligands ($\Sigma BS_{bioseparation}$), and technical system for enzyme detection and color reagents ($\Sigma BS_{blood\ analyzer}$).

Discussion and Conclusion

The design modeling approach for bio-mechatronic systems presented above can be used in several ways during product development. It is probably most useful in the conceptual design stage, when functionality and identification of major sub-systems and their relationships are typical and important activities. The overall goal of the modeling is naturally in the end to realize the best functionality and performance for the customers and

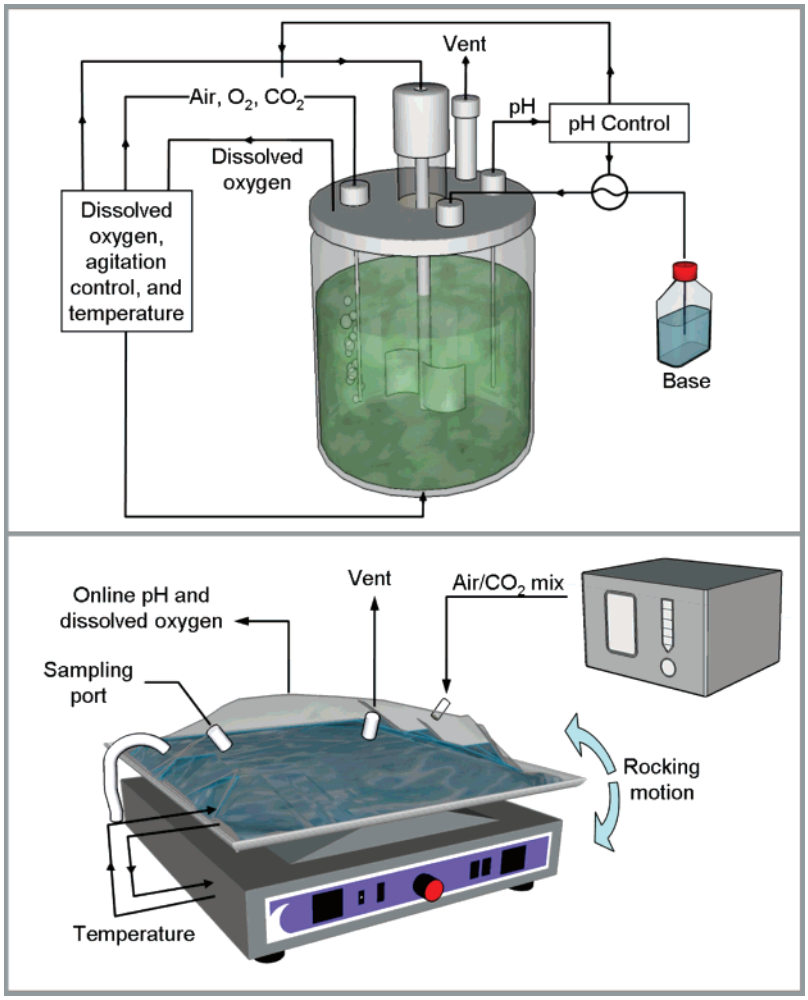

Figure 9. A traditional stirred tank steel/glass bioreactor with sensors and control equipment (upper figure) compared with a single-use wave bioreactor system (lower figure). The traditional bioreactor is sterilized in place or in an autoclave; the wave bioreactor uses a presterilized plastic bag. The wave reactor has sensors and media supply connections and ports and is placed on a rate-controlled rocking table. The plastic bag is inoculated with the cell culture and perfused with medium and nutrients using auxiliary pumps. When the cultivation is finished and the cells are harvested, the reactor is discarded.

to improve the development process. However, there are some applications where it is obvious that this modeling technique can bring some significant and specific advantages to the design work. In the following, three such development situations will be discussed briefly.

Market Pull Projects. Sometimes, the development work is focused on a specific and well-known market need. This modeling approach is probably best used to identify the needed functionality in order to determine a clear picture of what the product should do before going into the technical solutions. The functional decomposition can also act as a means to systematically generate many different concepts and to evaluate them against each other, thus decreasing the risk of focusing prematurely on a certain concept.

Technology Push Projects. This is a very common type of project in many new biotechnical venture companies. A certain discovery in the lab leads to a search for applications/markets. When a market is found, venture capital enables the development of the first product. In this case, the modeling approach may play several roles. First, it facilitates the communication between different competences early in the process by providing a complete picture of what the product should do. Second, it will help in the identification of what is needed beyond the functionality that is provided by the biochemical innovation. For instance, the early identification of adjacent technical systems will point out the need for other competences and what they must develop. A third role is identification and clarification of the actual interfaces between different sub-systems and especially between the biotechnical system and other systems. This will facilitate division of the product into separate subtasks. Later, if and when other applications based on the same innovation are developed, the model may serve as a suitable starting point for modifications leading to new products.

Reengineering. In all cases where an existing product is the starting point for new product development, the modeling approach can enable creative thinking by separating technical solutions from functionality. Functional decomposition and abstract thinking can help to find entirely new solutions for the sub-functions as well as for the main function of the product.

The proposed modeling techniques not only provide an enhanced understanding during the development phase but may also serve as basic material for analyses of such things as system safety, reliability, and quality, which are essential in order to conduct safety assessments, reliability predictions, CE marketing, service and maintenance plans, and so on. These kinds of synergy effects are further motivation for adopting a generic and abstract modeling approach.

For the protein purification and bioreactor system cases, these aims are well-known and have long been recurrently challenged by bioprocess engineers. Much of the focus has been on

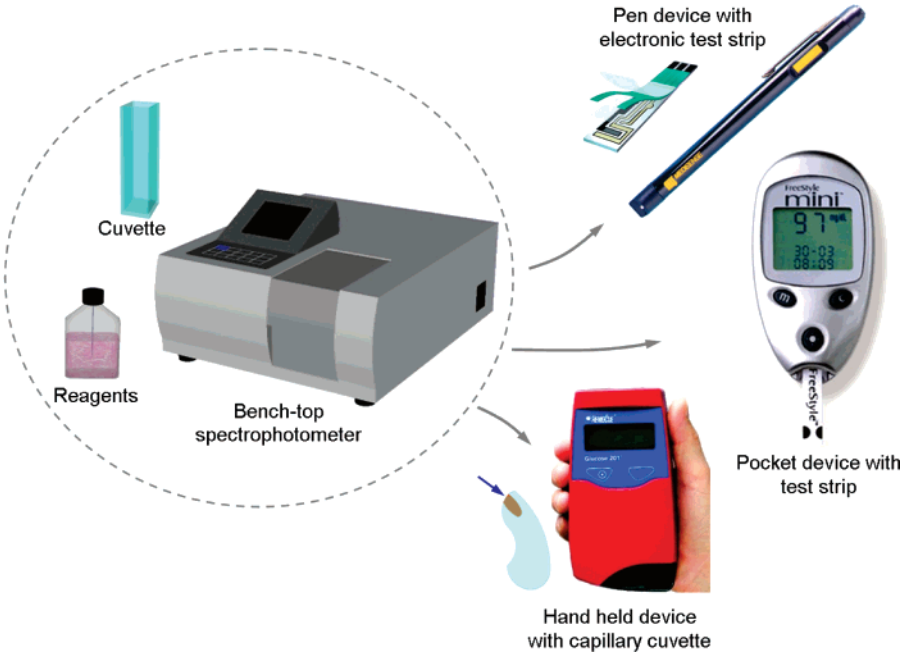

Figure 10. Compact blood glucose sensors developed from the traditional blood glucose assay method with a benchtop spectrophotometer (A). New design solutions based on electronic transduction from single-use enzyme/redox substance strips (B), compact single-use plastic cuvettes for handheld monitor device (C), and a single-use reflectance filter with enzymes and co-enzymes for colorimetric reflectance reading in a pocket-detection unit (D).

technical issues such as the interplay between rheological properties of the fluids and the mechanical and geometrical design of adapters, columns, impellers and baffles, and other agitation devices of the bioreactors.

For example, protein purification columns have previously been constructed in glassware cylinders that were intended for long-term use but complicated sanitation and replacement and packing of separation materials; today, plastic presterilized and prepacked columns dominate the market with retained separation functionality. Supportive technical systems are still extensive, spacious, and costly. Design improvements seem to be a potential for product development.

Interestingly, it was not until a few years ago that bioreactor systems took a design leap in the form of the so-called single-use wave bioreactors, which systematically address the above-mentioned objectives of reduced weight, space, cost, and delivery time (Freis et al., 2005) (Figure 9). This reactor design replaces the traditional needs of steel construction materials with plastic materials, in a single-use design with compact mixing, pumping, and control facilities and with retained performance characteristics (Singh, 1999; Pierce and Shabram, 2004). If still not a commercial success, it illustrates how a fundamental and systematic design engineering approach, where functions and transformation tasks rather than design of parts are placed in focus, could significantly impact on the final design in a very decisive way and where price, space, weight, and production costs were radically optimized.

Clinical blood glucose analyses have traditionally been carried out manually at a routine laboratory. The functions of the acting biological, technical, and probably also management and goal systems have been the same as shown in the Hubka−Eder diagram, with reacting enzymes and reagents, photometric measurements, calibrations and calculations of results and data treatment. The tools have been bottles of biochemicals, quartz glass cuvettes, and benchtop spectrophotometers, handled by skillful technicians. The technology development of biosensors initiated the design of new blood glucose sensors with the same functionalities. Enzymes and reagents could be immobilized onto single-use supports such as plastic on filter-based strips (glucose dehydrogenase, Boehringer) or small containers (plastic cuvettes with glucose dehydrogenase, mutarotase, diaphorase; Hemocue). Measurement of the blood glucose-enzyme reactions with glucose oxidase could be transduced either optically in compact miniaturized photometers or electronically to redox active compounds, such as ferrocene, conducting electrons through leads in the single-use strip to a pen or card reader containing an integrated circuit (Abbott). Figure 10 provides an overview of different development routes. The performance of the attained sensor designs has been thoroughly scrutinized and validated by clinical evaluators and displayed acceptable precision, accuracy, and stability (Solnica et al., 2003; Solnica and Naskalski, 2005). Obviously, new design solutions are generated based on the functionality of the original design concept, but with a variety of integrated biological, optical, and electronic technologies (Figure 10).

The biological system described in the bioreactor and glucose sensor cases above shows how a more detailed analysis of the sub-structure of the cellular system yields a better functional understanding of the cell's transformation capacity. A more shallow description of the biological system would still have permitted an analysis of its interaction with the remaining functions of the technical systems and could have paved the way for a different design solution such as the single-unit bioreactor. However, a more detailed sub-function description of the biological system certainly increases the understanding and reliability of the new design solution. It can most likely also accelerate the generation of alternative solutions.

The results of the analysis of system cases are represented here in typical Hubka−Eder depiction, a formalism previously applied to various mechanical systems. The Hubka−Eder modeling approach helps conceptual designers to identify the roles and functions of the biological components in a more multidimensional way than most of the common design methods. One of the most pertinent characteristics of biological systems is their sensitivity toward the active environment. Successful design must, at an early stage, take adequate

measures in designing the other systems necessary for the transformation process in order to secure the consistency and quality of the output state of the operands. This cannot be accomplished with traditional bioengineering tools.

Furthermore, the extended Hubka−Eder model suggested above is supported by results from an interview study with small- and medium-sized biotechnological enterprises (SME). One conclusion of that study is that there is a pronounced need for better understanding of the interactions between different scientific disciplines and technology areas when designing biomechatronic products; this is an issue that may be successfully addressed by the functional modeling tool proposed in the present paper (Derelöv et al., 2007).

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