Perspective

Challenges and Opportunities in Process Control: Biomedical Processes

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Automatic Control: Past Successes–Future Goals

Control has been an enormously successful discipline affecting essentially every aspect of our lives. Process control, specifically, has had a major impact on process economics by increasing process efficiency, reducing emissions, improving product quality and process safety. For example, as a direct consequence of process automation, from 1980 to 1998, the refining industry in the U.S. was able to reduce the number of operators from 93,000 to 60,000 while increasing production from 5.3 to 6.2 billion barrels.

It is often overlooked that *process control* was leading many of the developments in automatic control. For example, the use of computers in process control that started around 1960 predates the computer use in other control application areas. In the 1970s the process industries pioneered model predictive control (MPC) that takes advantage of the available computer power to determine the control action via optimization executed in real time. Based on thousands of industrial applications, it can be argued that MPC is the most important algorithmic development in control since the introduction of the PID controller. MPC can be found in all modern refineries and chemical companies in the world, it led to numerous startup companies, and its successes were invoked to justify many academic research projects. Only during the last few years MPC has started to make inroads in other application areas like automotive and aeronautics.

Process control is a victim of these successes: it has reached a plateau and a turning point. The research community is nervously looking for the next killer application and the next MPC.

Two considerations should guide this search. First of all, there is little practical interest in new control algorithms that provide moderate performance improvements over existing techniques, because the costs of implementation, training, and maintenance quickly outweigh the benefits. An algorithm has a better chance of adoption, when it addresses a new problem which cannot be addressed at all by the available tools. Second, the potential impact of a new control algorithm is small in application areas that have been investigated by generations of people over decades. Of interest are either new applications where there is no control at present, or applications where the introduction of a new enabling technology has created unprecedented opportunities for control. This “technology” could be new sensors, new actuators, dramatically increased on-line computer power, or simply an improved process understanding.

Interesting and promising developments are starting to take place both in terms of new algorithms and new applications. It is particularly satisfying to see these developments originate with a new generation of process control researchers, who have made it their mission to truly *solve* complex control problems—including the necessary sensors, software, and hardware developments (in pleasant contrast to the “have algorithm–will travel” approach of the past). The efforts in the control of biological systems, of polymers, and of crystallization processes reported at the Conference on Chemical Process Control CPC 6 (Rawlings and Ogunnaike, 2001) are impressive indications of this trend. On the systems theory and algorithm side, Christofides (2001) makes persuasive arguments for nonlinear distributed parameter systems as an important paradigm for a wide range of applications including the control of size distributions, fluid flows, and material microstructure.

Another system class which promises to greatly expand the set of practical problems that can be addressed are hybrid systems, where the term “hybrid” is used to indicate that the systems include both continuous and discrete states. In this framework it is possible, for example, to design not only the classic controller, but also simultaneously the control logic, which often dominates practical control performance. What was left to the trial and error procedures of the experienced engineer in the past can now be done in a systematic automatized fashion greatly reducing the development, implementation, and commissioning effort. The increasing number of sessions devoted to hybrid systems theory and applications at recent meetings (Morari and Bemporad, 2001) attests to the importance of this rapidly growing area.

The newly emerging area of biomedical control meets the criteria discussed above for control engineers to have significant impact. Biomedical engineering is evolving rapidly through new discoveries in biology that provide new actuators and sensors, as well as the improved understanding of the biological functions, which is a prerequisite for feedback controller design. Moreover, there is very little use of automatic control at present. Thanks to their chemical engineering training, process control engineers are positioned singularly well to take advantage of the opportunities in this area. In this article we focus on two problems, blood glucose control via automatic insulin

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delivery and automation of anesthesia. For other examples of automated control in biomedicine, refer to Bequette and Doyle III (2001).

Endogenous vs. Exogenous Feedback Systems

Over the past decades, we have witnessed a significant shift of research effort from the study of endogenous feedback systems (ENFS) to exogenous feedback systems (EXFS). In both domains, control theory plays a major role. The attention towards ENFS arose as early as the first important developments in control theory (Wiener, 1949). The main purpose of ENFS is to maintain homeostasis of several physiological variables: they keep some crucial parameters inside a living organism almost constant in spite of changes in the environment. Examples of ENFS in humans are known by common experience, such as the pupillary light or the muscle stretch reflexes. Unlike ENFS where all the elements of a classical feedback system—sensor, actuator, and control algorithm—lie inside the organism, in the case of EXFS the sensors and the actuators are placed at the boundary between the organism and the external environment. The control algorithm is located outside the organism and must be designed on the basis of the control objectives to be achieved.

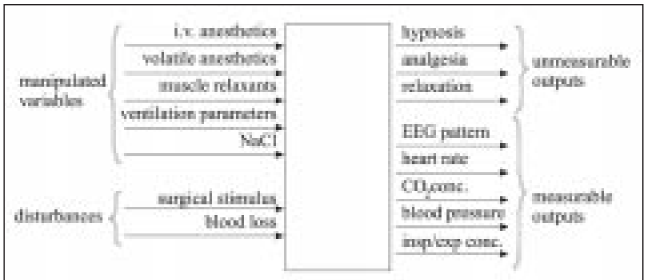

Figure 1. Input/Output (I/O) representation of the anesthesia control problem.

EXFS have been designed to serve different needs and quite interestingly, these can be classified in terms of their interactions with ENFS. The interactions between EXFS and ENFS are of two types. In some cases EXFS suppress existing ENFS. In anesthesia, for example, analgesic drugs and muscle relaxants can be delivered automatically to suppress the patient's autonomic reactions and the movement responses to surgical stimuli. In other instances, EXFS are designed to replace an ENFS which is not working properly, either because its action is suppressed by the pharmacological activity of a drug, or because it is permanently damaged as a consequence of a disease or injury. Artificial ventilation, for example, is used during general anesthesia in substitution of the respiratory reflexes, which are suppressed by most anesthetic drugs. EXFS in insulin therapy compensate for the missing insulin producing β-cells in the pancreas of type I diabetes patients. From the preceding discussion, it is clear that ENFS must be understood thoroughly before designing EXFS.

Control of Insulin Delivery

Type I diabetes is characterized by the absence of the insulin-producing β cells in the pancreas. In this situation, exogenous injections of insulin are necessary to regulate blood glucose levels. Maintaining blood glucose levels within tight physiological ranges can drastically reduce the occurrence of long-term complications such as nephropathy and retinopathy, which result from sustained hyperglycemia. Further, it minimizes the short-term hypoglycemic risk of insulin shock and death. The current therapy for insulin-dependent patients consists of a partially closed-loop strategy which combines a feedforward and a feedback action. The feedforward policy consists of three to four subcutaneous insulin injections per day whose doses and intervals between doses are imposed by the physician on the basis of the life-style of the patient. The prescribed policy is then adjusted by the patient on the basis of three to eight capillary blood glucose concentration measurements, which represents the feedback correction.

It is not hard to imagine—at the current point of the discussion—that a closed-loop system for insulin delivery to insulin-dependent diabetes patients can have a tremendous impact on health care. Such systems are often referred to as artificial pancreas. Two insulin administration pathways are under consideration in this respect: the subcutaneous (SC) and the intravenous (IV) route. Both exhibit advantages and drawbacks when evaluated across the major issues for continuous delivery: long-term reliability and short-term action. Specifically, the SC route provides the safest and easiest administration, though it is penalized by long delays in absorption. The introduction of Lispro insulin, a monomeric analog of the regular insulin which is absorbed two or three times faster than regular insulin through the SC route, has partially compensated for this deficiency. The IV route provides rapid delivery, faster responses to overdosing and a higher percentage of insulin reaching the blood stream. However, similar to other catheter systems, undesirable events such as occlusion of the catheter or irritation of the vessel may occur. Despite these differences, both administration pathways drastically reduce the injection pain.

The major obstacle to be overcome before an artificial pancreas becomes a reality is the development of a reliable glucose sensor. The approaches which have been proposed in this respect can be classified into minimally-invasive and noninvasive methods. Low precision is the major issue of noninvasive methods which detect the absorption or scattering of a light beam sent across the skin. On the other hand, long-term reliability and measurement delays are the current bottlenecks of minimally-invasive techniques, which measure blood glucose concentrations in the interstitial fluid.

The technical shortcomings of sensors and actuators located outside the blood pool may be avoided by transforming the glucose-insulin regulation problem from an EXFS into an ENFS. This would be made possible by controlled drug delivery technology, where the sensor and the actuator of the feedback system are both located inside the blood pool. In this approach, insulin circulates in the blood stream coated by a synthetic polymer, which swells or degrades in acidic environments.

However, this system has never been used in humans with safety the major issue to be addressed. As a matter of fact, the rate of insulin release from the polymeric reservoir cannot be predicted with sufficient accuracy. From this perspective, externally located actuators guarantee higher safety and the control literature has mostly focused on these types of systems.

Control Strategies in Anesthesia

Clinical anesthesia can be seen as a feedback control system where the anesthesiologists represent the control algorithm. From an input/output point of view the anesthesiologist faces the control problem shown in Figure 1.

During surgery, anesthesiologists induce a reversible pharmacological state were the patient's *muscle relaxation, analgesia* and *hypnosis*—the outputs of the system—are guaranteed. They administer drugs and adjust several medical devices—the inputs of the system—

to control these outputs and to compensate for the effect of surgical manipulation and blood losses, which are the disturbances entering the system. At the same time, the patient's vital functions must be maintained, which are the constraints of the system. Given that premise, it is natural to ask whether automatic controllers can play a role in anesthesia. The potential benefits of their use reside in two factors. First, they can relieve the anesthesiologist in part of her/his decision process. Second, they can improve the quality of anesthesia by providing drug administration policies which pursue multiple control objectives such as tracking of reference signals, disturbance compensation, handling of input and output constraints and drug minimization. The consequences would be improved patient care and reduced health care costs.

The outputs to be regulated during general anesthesia are qualitative by nature and consequently must be assessed by correlating them with available physiological measures. Even though several sensors are available in the clinical practice, the correlation still remains a subject of vivid debates.

Muscle relaxation is induced to facilitate the access to internal organs and to depress movement responses to surgical stimulations. Among the three components of anesthesia, *muscle relaxation* appears as the most straightforward to quantify and consequently to control. However, since overdosing of muscle relaxants neither represents a risk for the patient nor delays the time to awakening, feedback controllers are rarely used in clinical practice.

Analgesia is pain relief and at present there are no specific measures to quantify it intraoperatively. An apparent reason for this is that there is no pain perception when the subject is unconscious. Consequently, the state of art for intraoperative analgesic administration are open-loop infusion policies which target predicted drug concentration in the plasma or at the site of effect.

We designed an explicit model predictive controller (MPC) whose primary objective is to blunt MAP reactions to surgical stimulation with the analgesic alfentanil. The MAP is determined from blood pressure measurements taken at 128 Hz via a catheter (Figure 2). The secondary objective of the controller is to maintain predicted analgesic concentration in the plasma around a reference value specified by the anesthesiologist. As such, the controller realizes a trade-off—optimal in the sense of the MPC algorithm—between open- and closed-loop infusion policies (Gentilini, 2001).

MPC control design offered three significant advantages beyond the unique capability of handling both input and output constraints in a systematic way. First, the control performance can be adjusted to the particular subject's characteristics automatically by modifying the internal model of the control system and leaving the control parameters unperturbed. Second, the observer embedded in the control algorithm allowed us to implement an efficient algorithm to reject measurement artifacts, which may lead to harmful control behavior if not detected appropriately. Blood pressure artifacts occur routinely during surgery when catheter systems are used like in our case (Frei 2000). Third, the explicit formulation of MPC as a piecewise affine control law allowed us to represent graphically the relationship between the MPC design parameters and the actual control reaction to disturbances and set-point tracking. This facilitated greatly the acceptance of the controller in the operating room.

Hypnosis indicates unconsciousness and the absence of post-operative recall of events occurred during surgery. Despite the fact that the mechanisms of drug induced unconsciousness are still unknown, the electroencephalogram (EEG) is considered as the major source of information to assess hypnosis. The Bispectral Index (BIS, Aspect Medical Systems, Newton, MA) is a commercial monitor which extracts a measure of the depth of hypnosis from the EEG and has gained wide acceptance as a target to adjust the administration of hypnotic drugs. Our group developed and tested an automatic controller for BIS with isoflurane (Gentilini et al., 2001). Also, it guarantees safe operation in the case of BIS sensor failure.

Figure 2. Blood pressure measurement during anesthesia experiment via catheter.

Research Challenges Related to Anesthesia Control

In this section we will mention some specific research themes encountered in anesthesia control and also comment on the general prerequisites for a research program in this area.

Modeling and Identification. Linear models are generally inadequate for control. While the classic compartmental modeling approach provides important structural information, the specifics and the parameters of the model need to be determined from experiments. Appropriate nonlinear identification schemes taylored to these systems have to be developed and tested. Volterra models are not suitable; piecewise linear models have been shown to be successful for some applications (Ferrari-Trecate et al., 2001). They have the advantage that the new controller synthesis methods for hybrid systems (Morari and Bemporad, 2001) can be directly applied to such models.

Learning Systems. Whichever model is adopted, the variability is higher than typical in process control. The same patient will not react in the same manner at different times and under different conditions. For different patients we have attempted to normalize the models by accounting for factors like body weight and height. The variability is reduced, but still large.

We have dealt with this problem by robust controller design. The theory in this area has proven to have great educational value, but the actual controller parameters were arrived at after extensive simulation studies together with the responsible anesthesiologist who needed to be convinced that the controller behaved correctly in different scenarios. Using one set of controller parameters (possibly adjusted for body weight and surface area) for all patients of widely different age, body condition and medical history will hopefully result in a robust, but necessarily also a sluggish, controller. While adaptive control in the classic theoretical sense is unlikely to find use for the control of anesthesia, a more limited form of "learning controller" which uses patient and situation specific data determined in the initial phases of the operation should be developed and tested.

Signal Processing and Estimation. We mentioned BIS as a possible indicator of hypnosis. Other approaches may be considered, each one having its supporters, but the general problem of determining the depth of anesthesia is certainly not solved. Alternate processing of the EEG needs to be investigated, as well as a combined use of the many available types of measurements (*sensor fusion*) to arrive at a more reliable indicator for the depth of anesthesia. To find such a combination, we can exploit the tools for *Data Mining*. As an example, we have acquired data from 20 volunteers who were put under anesthesia for about six hours each. Special techniques are needed to extract information out of these 1.2 GByte of data.

Multiobjective Constrained Control. Contrary to many process control problems and most problems studied in the theoretical literature, anesthesia is not a simple trajectory tracking or disturbance rejection problem. There are no set points, but the physiological state of the patient has to be kept in a certain range defined by about a dozen constraints of different priorities. Available for this complex task are only a couple of manipulated variables related to drug dosing and ventilation. Controller design approaches in the spirit of model predictive control (MPC) appear to be the only alternative at present, but the robustness of these controllers and their ability to obey constraints in the presence of model uncertainty is barely understood (Bemporad et al., 2001).

Safety-Critical Real Time System. The computer systems provided at present by the major anesthesia equipment manufacturers, for example, our industrial partner Dräger, are not designed for researchers to simply plug in their favorite controllers, as this is the case with the modern control equipment in the process industries. Thus significant computer engineering effort was necessary before any controller use in the operating room could even be considered. It is to be expected that these obstacles will decrease as new generations of computer integrated anesthesia systems become available. The on-line use of nonlinear programs as needed for classical MPC is unlikely, however, because the correct functioning of such complex algorithms is impossible to verify. "Explicit MPC" (better called "Constrained Linear Quadratic Regulator") (Bemporad et al., 2000), where the MPC law is presented explicitly in a piecewise linear form, is a preferred alternative, but specific aspects of safety have not been studied to date.

Conclusions

We find our work in the area of anesthesia control rewarding and intellectually stimulating because of its interdisciplinary nature and the variety of challenges. The results are met with interest by the anesthesiology community, as well as the companies developing and manufacturing anesthesia equipment. Together with us, Dräger decided to file a patent application for the BIS controller. Over the last eight years, more than 160 operations were done at the Inselspital Bern where automatic control systems from our institute were employed. In the recent past many of these operations were carried out without any control engineer present.

The success has not come easy, however. It has taken years to build up the required infrastructure in terms of computer hardware and software, and to form the necessary relationships with the partners at the hospital and the companies, foremost Dräger, but also with Aspect Medical Systems, Organon/Akzo Nobel, and Pharsight Corp. While this base allows us to generate interesting research results relatively easily now, the first few years passed with little measurable output. It is not clear if the U.S. research funding environment would have allowed such research to prosper. Extensive literature on many issues discussed in this article is available on our Web site www.control.ethz.ch.

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