Control in Biological Systems

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Introduction

The field of control and systems has been connected to biological systems and biotechnology for many decades, going back to the work of Norbert Wiener on cybernetics in 1965, the work of Walter Cannon on homeostasis in 1929, and the early work of Claude Bernard on the *milieu interieur* in 1865. Nonetheless, the impact of control and systems on devices and applications in the field of biology has only emerged in recent years.

For this report, we will concentrate on the so-called *red* biotechnology, that is, the medical field of use, as opposed to *blue* biotechnology (aquatic use of biological technology), *green* biotechnology (agriculture and plant use), and *white* biotechnology (industrial applications).[1] For energy and process applications, the reader is referred to other sections of this report.

Hence, the emphasis in this section is on medical applications of control systems technology, which is very different from other areas in this study for multiple reasons:

- It is much less mature.
- It has far wider impact on human life.
- It is much less established.

This report is not meant to be a comprehensive review of all developments in biomedical control systems technology; instead the reader is referred to selected reviews, books, and tutorials on the topic [1]-[5].

Successful Applications of Control: Cardiovascular Systems and Endocrine Systems

As noted above, the field of biomedical control systems is relatively young compared to aerospace, automotive, and the chemical process fields. Nevertheless, some noteworthy recent developments have emerged in two key application areas: cardiovascular systems and endocrinology.

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Cardiac Assist Devices

The area of cardiac assist devices has had a relatively long history of development, although advanced control theory and process modeling have only recently been applied to these devices [6]-[10]. In

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[1] See, for example, the Wikipedia entry for *biotechnology.*

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effect, cardiac assist devices are mechanical pumps that supplement endogenous cardiac output at an appropriate pressure to allow normal circulation through the patient's body. The control challenges include the changing demands for cardiac output as a function of the patient's "state" (for example, level of exercise, emotion, posture). The first such implantable device to receive approval by the FDA (1998) is the Baxter/Novacor left ventricular assist device (LVAD). Clearly, the ideal device would mimic the body's own mechanisms for maintaining cardiac output at target levels; however, the devices currently on the market are rather primitive in terms of automation, requiring the patient to adjust setpoints directly [6]. Recent developments for the pacemaker include real-time analysis and adaptive control [11]. Ventricular assist devices (VADs) are exploring feedback and model-based control to compensate for changes in patient needs (such as exercise) [12].

A more recent development is the use of magnetic levitation in the World Heart Inc. ventricular assist device called Levacor. World Heart recently received an FDA investigational device exemption (IDE) in preparation for clinical trials. The control system is a hybrid passive/active magnetic bearing where the active magnetic bearing employs a single active feedback loop designed by loop shaping. A key component of the technology is the high-reliability electronic design know-how transferred from aircraft control systems to this device.

In the cardiovascular area, another applied technology has been developed by Magnetecs: a magnetically guided catheter system for electrophysiology and other procedures. The control system is a combination of simple feedforward methods involving coordinate changes, feedback, and adaptive synthesis of visual models of the heart.

Blood Pressure Control

The IVAC Titrator was developed to regulate mean arterial pressure in hypertensive intensive care unit (ICU) patients by infusing sodium nitroprusside. The device received FDA approval in 1987 and was marketed for a short time, but was discontinued after a few years. The reasons for its failure in the marketplace include the following: (1) no consistent communication standards existed at the time, so the device had its own blood pressure sensor that was not particularly easy to set up; (2) the computer interface technology was not advanced; (3) the units were overpriced (IVAC chose to recoup R&D costs within a short time period); and (4) although studies showed less variability in blood pressure than with manual control, the effect of the reduced variability on patient outcomes was unclear [13]. Some studies suggested that patients were able to reduce hospital stays by a day. With new communication standards and advances in microprocessor-based pump technology, a closed-loop blood pressure system could probably succeed in the marketplace today.

Anesthesia Delivery

The effect of the intravenous anesthetic propofol is directly related to its concentration in the blood. Target-controlled infusion (TCI) is a model-based open-loop strategy designed to regulate the concentration of a drug in the blood by giving an initial intravenous bolus (shot), followed by time-dependent infusion. A commercial device, the Diprifusor (AstraZeneca Pharmaceuticals), has been available throughout much of the world since 1996 [14], [15], with millions of successful propofol infusions administered [16]. For a variety of reasons, no TCI device has received FDA approval in the United States [17]. Approval may be more likely if the infusion system incorporates a depth of anesthesia monitor, such as the bispectral index (BIS) manufactured by Aspect Medical Systems, to form a fully closed-loop system.

Other Applications

Beyond those highlighted here, a number of biomedical devices that have been successfully translated into commercial products using closed-loop technology include the implantable cardioverter defibrillator (ICD), the intracardiac electrogram (IEGM), and the oxygen saturation monitor. In other biomedical device areas, sensors are used to provide feedback to control and deliver electric signals that stimulate the brain to ease the tremors of Parkinson's disease and epilepsy by determining the extent and timing of stimulation. Additionally, closed-loop biomedical devices are used to treat peripheral vascular disease by using sensors to measure blood flow in a patient's limbs and determine the level of spinal cord or peripheral nerve stimulation required to improve blood flow, thereby reducing ischemic pain in the limbs. Closed-loop temperature control has been employed in ablation systems (such as the Atakr from Medtronic) with thermocouple feedback for safety.

Market Sizes and Investment

The potential market for the ventricular assist device is roughly 35,000 end-stage heart disease patients per year in the U.S. alone. The market capitalization of VAD companies exceeds $1B in the U.S. The pacemaker, with 250,000 implanted per year worldwide [11], is a ubiquitous biomedical device reliant on control algorithms to continue functioning. Catheter system companies have a collective market capitalization on the order of $0.5B.

Approximately 17 million individuals in the U.S. are diagnosed diabetics, 5-10% of whom have type 1 and require insulin therapy. Similar incidence rates apply to other regions of the world. A 2005 estimate put the number of insulin pump users worldwide at 400,000 and growing by 10-12% per annum [18].

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It is worth noting that regulatory factors and the cost of clinical trials often mean that market interest is less than patient demand. Regardless of the regulatory issues, however, the medical interest in developing tools that assist patients remains high because of the potential for impact at the patient level if a treatment intervention or device is successful.

Several government agencies are investing in research technology (including control systems) for the artificial pancreas (see below). The U.S. National Institutes of Health (NIH) recently announced a competition for the artificial pancreas ("Closed Loop Technologies: Clinical and Behavioral Approaches to Improve Type 1 Diabetes Outcomes," total of $5.5M funding). The EU sponsors multiple initiatives on the topic of the artificial pancreas, including "Development of a bio-artificial pancreas for type 1 diabetes therapy" and "AP@home." The NIH National Institute for Biomedical Imaging and Bioengineering (NIBIB) is a key player in research investment for biomedical devices. Several private foundations fund research in this area as well, including the Hillblom Foundation (endocrine and neurodegenerative disorders) and the Juvenile Diabetes Research Foundation (JDRF). The JDRF funds the Artificial Pancreas Consortium at a level of over $5.5M per year. A related topic is closed-loop control of blood glucose in the intensive care unit; several companies (such as Luminous Medical) are funding the development of sensors and closed-loop control algorithms for this application. Medical technology companies are hiring in this field, including Johnson & Johnson, Roche, Medtronic, and others. Small start-ups in this field have attracted venture capital (VC) funding at significant levels: World Heart received $30M in VC support in 2009, and Magnetecs has also attracted VC support.

Opportunities for New Applications and Research

“Red” biotechnology is an emerging and vibrant area for research in control systems. Below we discuss two topics of particular interest and then offer some general remarks on new research and development opportunities.

The Artificial Pancreas

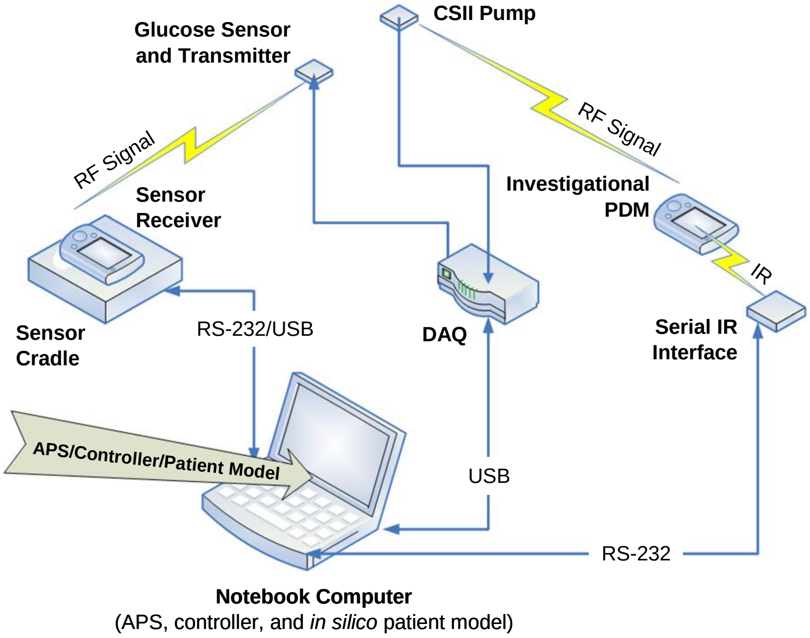


Figure 1. Components and communication protocols for the artificial pancreas [32].

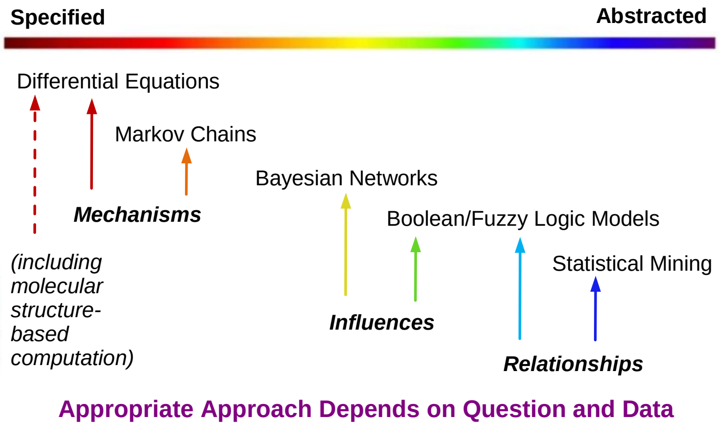
In the area of endocrine systems, the most active area for control systems development has been the artificial pancreas for type 1 diabetes (Fig. 1). Such a device would be composed of a continuous glucose sensor, an insulin infusion pump, and an algorithm to regulate the insulin dosing in accordance with the measured glucose levels. Following is a brief summary of some of the key contributions, consisting primarily of the application of linear and nonlinear proportional-derivative (PD) algorithms to emulate the naturalistic biphasic insulin secretion profile. Some of the earliest work includes the glucose-controlled insulin infusion system (GCIIS) [19], which used some patient data (10-sec glucose sampling with a 4- to 5-min delay). The Biostator [20] also features a nonlinear PD algorithm, with the added nuance of a five-measurement window for filtering glucose measurements. It was implemented bedside and required specific patient customization. A nice review of the early algorithms is provided by Albisser [21], along with some patient data. Another detailed review is given by Broekhuyse et al. [22]. These reviews concluded that no controller was uniformly superior and that much more development was needed.

More recently, advanced control technologies have been developed for the artificial pancreas, including variations on PID control [23], run-to-run control [24], and model predictive control [25]. In the last several years, clinical studies of advanced control methods have shown promise for future device developments [26]-[31]. Most of these trials use some degree of human intervention, for example, to input the size of a meal in advance of eating the meal.

To date, however, the state of the art in feedback control technology for insulin pumps and glucose sensors is limited mainly to bolus “wizards” and hypoglycemic alarming. The bolus wizards are effectively feedforward manual control algorithms that allow a patient to calculate an appropriate bolus of insulin to “cancel” the expected glucose rise from an anticipated meal or to recover from an elevated hyperglycemic state [33]. Hypoglycemic alarming refers to the prediction of low blood sugar in advance (say 30 minutes or more), generating an audible warning alarm so that the patient can take corrective action or, with newer products, shut off the insulin pump. The hypoglycemic alarming technology is appearing in European markets and is expected to appear in the U.S. soon.

Opportunities in the Field of Systems Biology

Here we briefly summarize some of the key technical issues in the area of systems biology. A broad spectrum of mathematical and analytical methods can be applied in the development of models for biomolecular regulatory networks and their subsequent analysis, with the twin goals of predicting their dynamics and generating conceptual insights about their operation. These methods range from highly abstracted (such as partial least-squares regression) to highly specified (for example, mass action kinetic differential equations, discrete stochastic and multiscale models). Fig. 2 illustrates only part of the range of computational mining and models.



Source: D. Lauffenburger, MIT

Figure 2. Spectrum of computational mining/modeling methods.

The highly abstracted methods are most powerful when little prior knowledge exists concerning the key network components, and the most highly specified methods are most powerful when a deep and comprehensive amount of knowledge is available concerning not only the components, but also their connectivity and the mechanisms of their associated interactions. Intermediate to these two extremes are methods that enable determination of logical influences characterizing network component interactions—going a vital step beyond mere connectivity but not mandating intense knowledge of kinetic mechanisms. These methods include Bayesian network, Markov chain, decision tree, Boolean logic, and fuzzy logic models. At the more detailed end of the modeling spectrum is the development of numerical methods and software for ordinary differential equation (ODE) solution, differential-algebraic equation (DAE) solution, and sensitivity analysis of these types of systems. Discrete stochastic simulation—and hence multiscale simulation, since discrete stochastic simulation by itself often involves so much computational complexity that both algorithmic (multiscale algorithms) and high-performance computing must be brought to bear to speed up the simulation—is a necessary part of the computational arsenal for biochemical simulation.

Early advances in the field of modeling and analysis for systems biology have guided therapeutic interventions. Specific drug/disease combinations include heparin/anticoagulation (optimal control) and HAART/HIV (plasma PK targets) [34]. Targeting measurable quantities in a patient-tailored way (patient-specific medicine) is becoming more common as models and measurements coincide in diseases such as HIV [34] and diabetes [35].

General Comments

- The most promising opportunities are those problems that formulate in a manner most closely associated with “traditional” systems engineering problems: medical problems subject to high economic burden and having a suitable number of “easily accessible” measurements that characterize effect or from which treatment effect can be estimated.

- The maximum potential for (economic) impact of control in medicine and medical devices is probably in the area of poorly understood diseases having complex dynamic responses and sparse (in time or state dimension) measurements. Examples of this class include inflammation and highly prevalent cancers. Low customer expectations further motivate these applications for control-theoretic approaches.

- Measuring impact on a social scale provides a different perspective. Here impact can be made in those disease populations that are too small (for example, those with low-prevalence cancers) to economically justify involvement by a major drug company. Another socially motivated potential impact is the development and deployment of biomedical devices and medical treatments to the geographically or economically disadvantaged (for example, those living far from a major medical center in developed countries or patients in Africa). Again, low customer expectations further motivate these applications for control-theoretic approaches.

- The VAD application could employ extremal seeking methods in a periodic system. Adaptive imaging based on catheter tip position data combined with imaging technology is an opportunity. Another imaging challenge, this time in cancer, is automated image identification for cancer volume assessment.

- Model structure analysis and structure selection tools, used to quickly evaluate when the available measurements are adequately captured by the model structure chosen, are important to medical decision making. Prediction quality may depend on model accuracy and the ability to quickly identify a model that is lacking—and to simultaneously highlight the portions of the model in need of refinement—could provide both better healthcare decisions and rapid model improvement. As alluded to above, the continued development of parameter identification tools for data-sparse systems, as well as nonlinear identifiability tools to establish which model structures can be supported from a given data set, would assist in diseases where insufficient state or measurement information (either spatially or temporally) is a concern.

- Another need is for improved (white box) tools for modeling data from populations of individuals and individuals of a given population, and for making sure the population and individual models are consistent. With the levels of uncertainty involved and the nonlinear dynamics of populations, multiple statistical and parameter-estimation tools will need to be used in combination.

Challenges and Barriers to Translation

As noted in the introduction, the field of biological systems is relatively young in terms of practical applications (market products), and several challenges must be overcome in translating closed-loop technologies to practice. The sheer complexity of (non-engineered) biological (networked) systems is the overarching daunting challenge. More specific obstacles include:

- The translation of relevant clinical outcomes for patient health into corresponding metrics on the measured variables in the body remains a challenge for sensors and control design.

- In the case of ventricular assist devices, high-level physiologic control is a promising technology. How does one control the speed of the pump and in response to what sensors?

- Notably, the objective in many medically oriented problems is patient quality of life, a “soft” objective. Changing to quality-adjusted life years (QALYs) can provide a numeric metric, but this is only in the aggregate; it is also controversial because it may lead to some patients not being treated due to the insensitivity of their QALY score to a particular intervention or treatment.

- A critical theoretical challenge for controlled drug delivery is the handling of both intrapatient and interpatient variability. This problem is quite different from engineering systems where uncertainty may be present, but it is typically of fixed (for example, stationary) structure. In biology, the variability is profound, and the same subject can differ significantly from one day to the next, depending on such factors as stress and environment. In some specific situations, such as diabetes, the intrasubject variation in critical subject parameters (such as insulin sensitivity) far exceeds the interpatient variability.

- The advances made in biomedical devices with closed-loop control capabilities have been enabled by developments in sensing and actuation. Conversely, the lack of appropriate and safe measurement and actuation devices precludes many applications.

Barriers that have delayed the marketing of some control-enabled devices include:

- Regulatory approval (by the FDA in the U.S.) for the artificial pancreas (see below). These agencies have not handled feedback algorithms in the past, so they are adapting to specify requirements for regulatory approval. The control community could play a role here in designing protocols for “stress testing,” in other words, suitable disturbance scenarios to challenge the closed-loop designs.

- The barriers for cardiovascular devices are comparable to other aspects of FDA approval.

- The need for appropriate models and especially modeling paradigms for model-based control systems raises questions that do not have easy answers. How does one develop a reliable model for patients with widely varying physiological characteristics; how does one maintain such models; what model paradigm will facilitate model development for biomedical applications?

- Communication between systems engineers and clinicians is also a barrier. Each group speaks its own language, with associated jargon. Until representatives of the two groups develop a common language, often as a natural outcome of a close collaboration, engineering solutions may not be solving clinical problems in an optimal way (if at all).

From a regulatory standpoint, the focus should be on device (rather than drug) development, as the pathway to acceptance is generally faster. A further concern in control algorithm development is the burden of proof required for algorithm-based device approval (superiority vs. non-inferiority trials); the technical complexity in the algorithm (for example, closed loop, model-based, predictive, adaptive?), and the potential inability to a priori provide bounds on device performance for all individuals, may cause device rejection unless all possible failure modes are characterized and evaluated in significant detail. A secondary technical concern is the inherent variability or uncertainty encountered in a clinical patient population, which is typically greater than 100% (parametrically). A final complicating factor is economics. The price of a device is both market and development cost driven. Devices are often too expensive for the vast majority of patients; lack of insurance coverage may make it impossible to realize profitable sales volumes.

The regulatory approval process and the economics of the healthcare system are probably the greatest barriers and are also the least technical in nature.

Conclusions

All of the opportunities discussed in this section are effectively worthless in the medical arena if they cannot be translated to clinical practice. This fact simply highlights (1) the need to communicate more effectively the strengths and weaknesses of control tools and calculations with noncontrol experts, and (2) the requirement that interfaces for any or all of the aforementioned tools be constructed such that the tools can be deployed in a clinical environment by conventional healthcare providers such as nurses.

Finally, to underscore the importance of the promise of biological systems as a target domain for the controls community, we note that three of the National Academy of Engineering Grand Challenges [36] have direct relevance for control systems technology in medicine:

- Engineer better medicines. Engineers are developing new systems to use genetic information, sense small changes in the body, assess new drugs, and deliver vaccines.
- Advance health informatics. Stronger health information systems not only improve everyday medical visits, but they are essential to countering pandemics and biological or chemical attacks.
- Reverse-engineer the brain. For decades, some of engineering's best minds have focused their thinking skills on how to create thinking machines—computers capable of emulating human intelligence.

Selected recommendations for research in the control of biological systems:

- Success in the development of the artificial pancreas, and of other closed-loop biomedical devices, will be contingent on the development of robust, verifiable advanced control algorithms.
- Algorithms for controlled drug delivery are an exciting research opportunity; advances are needed to characterize and to accommodate the considerable intrapatient as well as interpatient variability that exists in disease (and healthy) populations.
- Biological control and diagnostic applications require modeling and system identification approaches that integrate structure determination, parameter estimation, and model verification—and human understandability of generated models is an important criterion.

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