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Journal of Process Control 17 (2007) 571–594
JOURNAL OF PROCESS CONTROL
www.elsevier.com/locate/jprocont

A tutorial on biomedical process control

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Received 13 February 2006; received in revised form 15 January 2007; accepted 16 January 2007

Abstract

This paper presents a tutorial on five typical applications within the area of biomedical process control. The specific applications discussed include: control of insulin administration for treating diabetes mellitus, dynamic modeling for anti-cancer chemotherapy regimen design, modeling and control of drug infusion in critical care, structured treatment interruptions: a control mathematical approach to AIDS protocol design, and dynamic modeling and control of the anticoagulant drug heparin. The objective of the tutorial is to illustrate the rich and important set of problems within the biomedical area that process control engineers can contribute to solving. Solution to these problems can have a significant medical as well as economic impact.

Keywords: Model based control; Dynamic modeling; Optimization; Constraints; Parameter estimation; Drug delivery; Pharmacokinetics; Anticoagulation; Chemotherapy; Diabetes; HIV/AIDS therapy; Critical care

1. Introduction

The application of dynamic modeling and advanced control techniques in the process industries has increased significantly over the last two decades. Model predictive control received a key boost from Shell's publication of their dynamic matrix control methodology [1]. An important driver for the use of model based control was the economic benefits that it achieved. Although the application of advanced control continues to increase in the process industries, the field is beginning to show signs of maturing. As a result researchers are looking at new application areas, for example in the bioprocess area and applications to more complex systems, such as those involving liquid and solid phases. One excellent area to which advanced process control can be applied is the biomedical area. Biomedical process control is rich with interesting and challenging problems. When a physician administers a drug he/she is basically acting as a control engineer. The physician's goal is to achieve a therapeutic objective, and their manipulated variable is typically the drug delivery schedule that they prescribe.

To facilitate process control researchers considering the biomedical process control area, this paper gives a tutorial on this subject. In the tutorial five typical biomedical control applications written by five different groups of authors are discussed. **These five applications were not chosen to give complete coverage of the field of biomedical process control. Rather they were chosen as specific examples of the types of biomedical control research that are being carried out today.** Each section of the tutorial is self contained and it contains literature references to the problem addresses. The specific application areas addressed involve:

Control of insulin for treating diabetes mellitus by Frank Doyle Lois Jovanovic and Dale Seborg
Modeling for anti-cancer chemotherapy design by Robert S. Parker
Modeling and control of drug infusion in critical care by B. Wayne Bequette
Structured treatment interruptions: A control mathematical approach to AIDS protocol design by Annah M. Jeffrey, Xiaohua Xia, and Ian K. Craig
Modeling and control of the anticoagulant drug heparin by Thomas McAvoy

Model based control of biological systems requires the same components as in other process control application domains; sensing of key process variables, a process model

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doi:10.1016/j.jprocont.2007.01.006

and actuators with sufficient authority to influence the controlled variables. As always, plant understanding is key. Biological systems in general are distributed parameter, stochastic, nonlinear, time varying dynamical systems. Process models are often derived from first principles by domain experts, such as theoretical biologists. In some cases data driven models are used. Biological systems tend to exhibit multi-compartmental interactions that are usually not well understood and as a result, the interactions cannot be accurately modeled mathematically. Control engineers have to convert these models into a form that is suitable for controller design. This conversion requires a certain basic understanding of the process that can be somewhat difficult for engineers to obtain, but is well worth the effort.

Most process variables in biological systems can only be measured online, if at all, under clinically controlled conditions such as in a hospital. In many cases measurements are only available at discrete intervals with long associated dead-times. Sensor accuracy has the potential to hinder effective control of the process variables. For example, in Section 4 of this paper, the currently available (off-line) assays cannot detect viral loads below 50 copies per mL of plasma (20 for ultra sensitive assays). Drugs are often the only actuators available to manipulate controlled variables in biological systems. For accurate control a good actuator model is also required as the control signal used is the drug efficacy and not the number of pills. This means that, the dosage to end point efficacy relationship has to be clearly defined for each drug. In cases where more than one drug is used to treat the same condition, then consideration has to be made for issues such as drug–drug interactions as well as the combined efficacy. Lastly design of drug dosing regimens should be done using clinically driven criteria.

Although the five application areas discussed in this paper are diverse they have a number of elements in common. They all involve the use of dynamic models and they deal with problems whose solution will yield significant economic benefits as well as improved quality of life through better therapy. All five problems involve the use of advanced control, particularly model based and optimization based control. Further dynamic models for most of the biomedical applications discussed show a great deal of variability from patient to patient and methods to deal with this variability have to be incorporated into the solution to each problem. Clearly, there are some problems in the biomedical area that lend themselves to data based modeling. The fact that this tutorial does not consider these problems should not be interpreted as indicating their lack of importance.

The biomedical process control area is one that has great growth potential, and one for which the tools used by process control engineers directly apply. However, the biomedical control field has its difficulties as well. One obvious difficulty involves the safety of any proposed new strategy for delivering a drug. If there is any question about the safety of a new drug policy then the policy will not be used. There is the issue of the medical and engineering communities being open to what the other community has to offer. It is important for both engineers and physicians to find collaborators with whom they are able to work effectively. There is also a communication issue since engineers and physicians tend to use different terminology and come at problems from different perspectives. For example engineers talk about lumped parameter systems and physicians use the term compartment models. In spite of these difficulties, the biomedical process control holds tremendous promise. The area is rich with interesting, important and challenging problems, and it is hoped that this tutorial paper will stimulate process control engineers to look further into it.

Reference

[1] C.R. Cutler, B.L. Ramaker, Dynamic matrix control – a computer control algorithm, Joint Automatic Control Conf., San Francisco, CA, 1980.

doi:10.1016/j.jprocont.2007.01.012

I. Glucose control strategies for treating type 1 diabetes mellitus

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1. Introduction

Type 1 diabetes mellitus is a disease characterized by complete pancreatic β-cell insufficiency. The only treatment is with subcutaneous or intravenous insulin injections, traditionally administered in an open-loop manner. Without insulin treatment, these patients die. Insulin was discovered in 1921, and although now it has been purified and manufactured by recombinant DNA technology, one still must individualize the treatment to mimic normal physiology in order to prevent the complications of hyper- and hypoglycemia (elevated glucose levels, and low glucose levels, respectively). The literature documents [1–3] the strong correlation between hyperglycemic excursions and the increase the risk of complications. The Diabetes Control and Complications trial [1] was the landmark study of 1440 type 1 diabetic people randomized into two treatment wings: intensive insulin delivery and standard care. Those people who had mean blood glucose concentrations below 110 mg/dl (glycosylated hemoglobin levels less than 6.0%) had no increase risk for retinopathy, nephropathy and peripheral vascular disease. Those patients who had ele-