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Control-relevant modeling in drug delivery

Robert S. Parker[a,*], Francis J. Doyle III[b]

[a]*Department of Chemical and Petroleum Engineering, 1249 Benedum Hall, University of Pittsburgh, Pittsburgh, PA 15261, USA*
[b]*Department of Chemical Engineering, University of Delaware, Newark, DE 19716, USA*

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Abstract

The development of control-relevant models for a variety of biomedical engineering drug delivery problems is reviewed in this paper. A summary of each control problem is followed by a review of relevant patient models from literature, an examination of the control approaches taken to solve the problem, and a discussion of the control-relevance of the models used in each case. The areas examined are regulating the depth of anesthesia, blood pressure control, optimal cancer chemotherapy, regulation of cardiac assist devices, and insulin delivery to diabetic patients. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Anesthesia; Biomedical engineering; Blood pressure; Cancer chemotherapy; Diabetes; Compartmental model; Pharmacokinetic model; Model identification; Insulin delivery; Process control; Toxicity

Contents

*Corresponding author. Tel.: +1-412-624-7364; fax: +1-412-624-9639.
E-mail address: rparker@engrng.pitt.edu (R.S. Parker).

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1. Introduction

The development of mathematical models of complex chemical and biological systems has advanced considerably in the last decade with the advent of advanced computing platforms, coupled with the availability of data from novel sensors. The predictive properties of such models makes them ideally suited for the simulation of novel operating regimes, and for the development of model-based control schemes. The development of high fidelity models is especially useful in the medical arena where the model may be simulated forward in time to predict the time-course and effect of a drug dose on a patient, or may be employed directly in an optimized controlled drug delivery regimen. As discussed recently in a perspective by Stokes [1] and demonstrated by a press release from Entelos and Bayer AG [2], the availability of a fundamentally-derived patient simulator can speed the drug discovery and development process by allowing hundreds or even thousands of simulations to be performed in the time of a single animal experiment.

For models that are used to predict patient behavior, this detailed modeling approach works well. Although the model structures typically contain large numbers of parameters and differential equations, as well as nonlinearities common to biological processes [3–6], numerical integration is computationally inexpensive, and detailed models can yield accurate predictions. It is when these models are to be used for other purposes, such as treating a disease state via drug delivery, that one must examine the issue of control-relevance. A key issue here is that the performance of model-based control systems is directly linked to model accuracy [7]. A block diagram for a typical model-based control scheme is shown in Fig. 1.

Examples of two levels of model complexity are shown in Figs. 2 and 3. Fig. 2 shows a schematic of glucose-insulin dynamics in the diabetic patient, based on a low-order model. A detailed pharmacokinetic/pharmacodynamic model of glucose-insulin behavior developed using compartmental modeling techniques is given in Fig. 3. While the schematic in Fig. 2 can be represented using as few as three differential equations, each compartment of Fig. 3 contains at least two differential equations, one each for glucose and insulin. For comparison, the nonlinear model resulting from the approach in Fig. 3 contains 19 total differential equations [4,6]. Another key issue in model construction is the identification of model coefficients. Parameters for low- or reduced-order models are easy to calculate from a moderate data set, and on-line parameter adaptation for patient individualization is relatively straightforward to implement. These models are

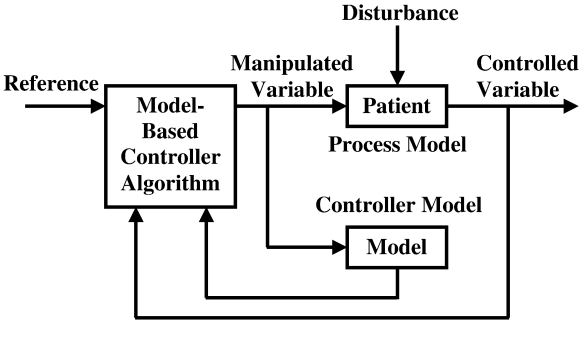

Fig. 1. Generic block diagram for a model-based controller.

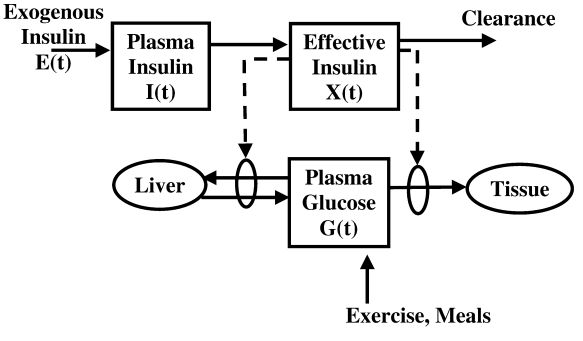

Fig. 2. Schematic of a low-order glucose-insulin model, such as the 'Minimal Model' of Bergman et al. [86].

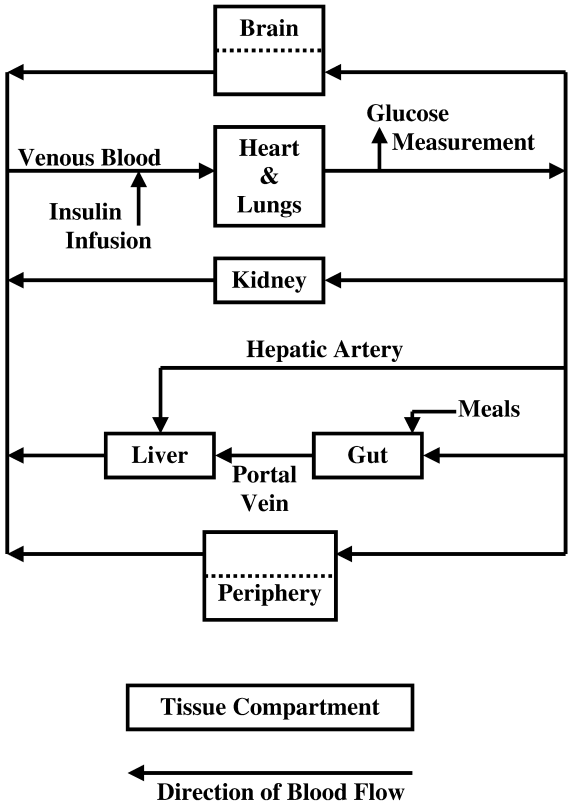

Fig. 3. Detailed compartmental (pharmacokinetic/pharmacodynamic) model of glucose-insulin interactions (from Refs. [4,6,105,118]).

typically less accurate than fundamentally derived models in the predictive sense. In generating fundamental models using compartmental or pharmacokinetic/pharmacodynamic techniques, coefficients are usually taken from available literature data, and this precludes systematic individualization to patients without a detailed sensitivity analysis of the model and comparison to patient data.

Control-relevant modeling aims to trade-off the detailed complexity and predictive capacity of fundamentally derived models versus the need for a model structure suitable for controller design, with the knowledge that the simpler model does not fully characterize the process [8,9]. Model complexity is a significant consideration in the development of a model for control design. Intrinsic to any model-based control scheme is an effective model inversion, determining the inputs which yield a suitable output. For example, a large number of coupled nonlinear ordinary differential equations (ODEs) may admit straightforward integration on a modest PC computer, however, the inverse problem associated with the controller calculation may be a computationally intractable problem. Another critical issue for control-relevant modeling is the capture of dynamic behavior in the bandwidth regime of the controlled response [10,11]. In fact, one can often tolerate a large amount of mismatch in an open-loop simulation response without sacrificing significant performance loss in the closed-loop, provided the correct frequency range is captured in the model. This is a subtle issue, since many modelers will place a heavy emphasis on capturing the steady-state response of a patient, when in fact simple integral control action can tolerate up to 100% error in the system steady-state gain [7]. Of course, the concept of bandwidth is tightly connected to the desired speed of response and other performance objectives, so this may require iterations between control design and model development. In the chemical process literature, the concept of control-relevance has been applied in areas such as model identification [8,9,12–14], parameter estimation [15,16], and model structure selection [17–20].

The following sections will examine the development of mathematical models and model-based control algorithms for a variety of disease or patient states requiring drug delivery.

2. Automatic regulation of hemodynamic variables

2.1. The drug delivery problem

The management of critical care patients in a surgical environment has attracted a considerable level of interest from the control community, with an intent of automated regulation of key patient variables. The patient variables which are typically monitored are the mean arterial pressure and cardiac output, however, more recently the depth of anesthesia has become a focal point for measurement, modeling, and control. The drugs that have been employed in regulating such hemodynamic variables include sodium nitroprusside, dopamine, phenylep-

hrine, nitroglycerin, and propofol. Some of the earliest work on blood pressure control involved empirical tuning of proportional-integral (PI) controllers using first-order-plus-time-delay models [21], while the more recent work in this area (for example, see Refs. [22,23]) employs more sophisticated modeling approaches including multiple linear models and detailed non-linear compartment models. As with any control problem, the degree of patient modeling required is dictated by the controlled performance specifications, the specific control architecture, and the availability of patient data.

In this section, we will review a number of modeling approaches in the broad area of hemodynamic variable regulation, including the area of anesthesia control. Broadly speaking, one could categorize the modeling approaches as low order empirical, multiple linear model, or detailed fundamental. An additional descriptor for the low order empirical models is the possibility of on-line adaptation of model parameters to capture patient variability.

2.2. Mean arterial blood pressure control

One of the earliest detailed mathematical models of blood pressure is described in Ref. [24]. One of the key conclusions of that study was that multivariable interactions were intrinsic to the system, and simple scalar analysis was of limited value. A related detailed circulatory model is described in Ref. [25]. That model is comprised of 38 nonlinear differential equations, including flow relationships between compartments, compartment balances for the two drugs under consideration, pressure-flow relationships, and drug effect relationships. A particularly interesting component of that model is the inclusion of a nonlinear baroreceptor reflex term which accounts for the natural tendency to regulate blood pressure on a beat-to-beat basis [26]. The model was originally developed to relate sodium nitroprusside and dopamine effects to mean arterial pressure and cardiac output. Recent extensions to the original model include provisions for phenylephrine, nitroglycerin, and propofol infusion, as well as pulmonary arterial pressure and propofol blood concentration as modeled outputs [23].

An important technical consideration in the use of such a model for control purposes is the pitfall associated with a simple Jacobian linearization of the full nonlinear model to yield a simplified linear model. In Ref. [27], the authors point out that steady-state in such a pulsatile circulatory model would correspond to the volumes and flowrates at the end of diastole. Such an approximation would yield accurate heartbeat-to-heartbeat dynamics for the model states, but would provide limited information on the mean arterial pressure and cardiac output which are calculated through integration over the heartbeat cycle. The authors suggest a step-response formulation that eliminates this technical problem.

A number of authors propose empirical techniques for model development, which consists of identifying the patient model directly from the available data [21,28–32]. The early work of Slate et al. [21] involved the identification of a first-order model relating sodium nitroprusside to blood pressure. The final form of the model was comprised of two separate first-order-plus-time-delay terms, one for the injection effect (delay of 30 s) and one for the recirculation effect (delay of 45 s). The model was identified using a pseudo-random binary signal (PRBS) which provides rich data for subsequent model fitting. The model was employed in a PI control algorithm, and tested in simulation. A discrete first-order model was considered in Ref. [29], in which least-squares regression was applied to experimental data to yield the model coefficients. An adaptive extension of Slate's model is presented in Ref. [32], which allows one to manage intra- and inter-patient variability.

In Ref. [30], a simple scalar model from nitroprusside (input) to mean arterial pressure (output) is developed, using an ARMAX (Auto Regressive Moving Average eXogenous input) time series model. Two elements which bear noting include the use of a noise model to more accurately capture unmodeled (noise) effects, and the use of a least-squares update to provide on-line adaptation of model parameters. The models were employed in a generalized predictive control (GPC) algorithm and tested experimentally with mongrel dogs. Similar modeling approaches are reported in Refs. [28,31].

While adaptation is one form of compromise between detailed nonlinear approaches and simple linear models, an alternative approach is the formula-

tion of a finite number of multiple linear models which can be 'selected' in particular regimes of the patient's variables. Such an approach is described in, for example, Refs. [33–35]. The results in the blood pressure control literature range in complexity from eight models [33] to 36 models [36]. Using the 'bank' of models that are collected, one can design a corresponding 'bank' of controllers that will be active in selected ranges of the patient's variable space. There are two important considerations in the development of a multiple model patient description. First, the procedure for collecting individual patient models must be determined. One could use local approximations of a detailed nonlinear model, as is done in Ref. [35], or combine empirical models collected over different regimes [33]. The former allows the possibility of significant model reduction. The second question is the procedure for 'switching' between models. In some cases, such as empirical studies, the conditions of model validity may be well defined in terms of input variables (drug delivery rate) or output variables (pressure) and a suitable schedule for switching is straightforward. A more theoretically detailed approach is described in Ref. [35] using the recursive Bayes theorem for computing model weights. A model predictive control (MPC) algorithm which employs multiple models is detailed in Refs. [35,36]. The use of MPC allows for rigorous constraint handling. A potential drawback of the multiple model approach is the need for an increasing number of models as the number of drugs and operating regimes increases. The current trend in computational power suggests that this consideration may not be critical.

2.3. Issues for anesthesia control

There are a number of additional issues one must consider in the development of a controller to automate anesthesia. The key distinction, compared to scalar blood pressure control, is the incorporation of variables to denote anesthetic effects, often referred to as the depth of anesthesia. From a medical standpoint, the depth of anesthesia consists of a range of patient responses including: hypnosis, amnesia, analgesia, and muscle relaxation [37]. The primary challenge in modeling such a system is the determination of measurable quantities which reflect these conditions. Some candidates include mean arterial blood pressure, heart rate, electroencephalogram (EEG), and evoked potential (EP).

In Ref. [38], a detailed pharmacokinetic model is simplified by linearization and discretization to yield a linear model for the prediction of the effect of alfentanil on both anesthetic and side-effects. The primary objective is to deliver the minimum amount of drug required to prevent movement, and the secondary objective is to minimize transient concentrations such that undesirable side-effects, such as muscle rigidity, are avoided. An open-loop algorithm was developed, and simulations suggested reasonable performance.

A number of model-based anesthesia control studies, including clinical trials, have been published by Glattfelder and co-workers [22,37,39]. A methodical modeling study is described in great depth in Refs. [37,39], the pertinent details of which are summarized here. The overall system model employed in their research consists of three sub-models: a patient model (pharmacokinetic and hemodynamic effects of anesthetic), a breathing model, and the hemodynamic effect of surgical stimulants. They use detailed physiological models for anesthetic drug effects and interactions, the respiratory system, and the effect of disturbances (stimulants) [37]. The ensuing model is linearized and reduced to yield a more computationally tractable formulation.

An important additional consideration, detailed in Ref. [22], is the determination of the appropriate disturbance models for surgical stimuli during a procedure. These would typically include incision, intubation, laryngoscopy, and trapezius squeeze. They employ an empirical Box-Jenkins model, justified by observations that the effects of surgical stimulation and anesthetics appear to be linear. An observer-based state feedback regulator and a model predictive controller are synthesized, and the results of clinical trials are reported in Ref. [39]

2.4. Fuzzy models for control of blood pressure and anesthesia

An alternative to either the empirical or fundamental modeling and control approaches described above is the construct of fuzzy set theory models and the corresponding rule-based controllers. In this frame-

work, one considers a very coarse categorization of both system response and the resultant control action. In the context of blood pressure control, one might consider the following simple rule: 'if the mean arterial pressure is a little above setpoint, slightly increase the SNP infusion rate' [40]. Such a modeling framework requires little in the way of formal model development, obviating the need for both extensive data records and detailed physical understanding. Of course, the tradeoff is that the achievable performance from such a scheme is inherently limited. On the other hand, some fuzzy rule-based systems can accurately capture human responses and thus can be used to mimic the open-loop behavior of a surgeon or anesthesiologist.

Several studies have reported combinations of fuzzy and adaptive methods for the regulation of blood pressure and anesthesia [39,41–43]. The degree of algorithm complexity varies from the kind of simple rules described above, comprising a so-called expert system, to more complicated 'fuzzy engines' which switch in different control algorithms (P, PI, PID) and/or controller algorithm parameters (e.g. gain) depending on the patient behavior or error in tracking a physiological variable. In effect, the underlying model in such schemes is a composite of several regime-defined behaviors, which also distinguishes the approach from classical rule-based methods which do not typically allow such multiplicity in membership functions. A formal framework for the analysis and synthesis of such fuzzy-logic based controllers is the multiple-model framework described earlier, where the membership function concept translates directly.

3. Delivery of chemotherapeutic agents in cancer

3.1. The drug delivery problem

Cancerous tumors, left unchecked, will increase in size until they ultimately kill the patient. One approach to cancer treatment is the delivery of chemotherapeutic agents designed to eradicate cancer cells. The selection of drug doses and delivery schedules is a challenging process relying on a series of trial-and-error procedures that establish the mean toxic dose (MTD) and effective treatment regimen for each drug of interest. The development of effective treatments is made more complicated by the incomplete knowledge of pharmacodynamic effect of the cytotoxic agents on tumors related to intertumor and interpatient variability. Through the use of mathematical models, a more systematic approach to drug treatment regimen development is possible.

3.2. Models for tumor growth

A primary motivation for the development of tumor growth models is the development of optimal chemotherapy profiles. These approaches generally assume that a method for continuous delivery of drug to the patient is available. The modeling approaches to cancer chemotherapy can be classified into two major groups: lumped parameter models and cell-cycle models [3,44,45]. Lumped parameter models define tumor growth on the macroscopic scale, in terms of cell count and selected tumor- or patient-dependent parameters. Examples of lumped parameter modeling equations are the logistic, exponential (Malthusian), Bertalanffy, and Gompertz, and the Gompertz equation has been used to model tumor growth as studies have shown it captures the clinical tumor data most accurately [3,45–49]. Each model is based on a growth function, a continuous monotonically-increasing function describing the increase per unit time in tumor cell count (or equivalently, tumor size) [45]. The Gompertz model of tumor growth is given by [45]:

$$\dot{N} = \lambda_G N \ln \frac{\theta}{N}$$

$$\lambda_G = \frac{1}{\tau} \ln \left[\frac{\ln \frac{\theta}{N_0}}{\ln \frac{\theta}{2N_0}} \right]$$

Here, the number of tumor cells is given by N, and λ_G is the growth rate constant, with doubling time, τ, plateau population, θ, and initial tumor population, N_0. These model forms are advantageous for controller design purposes due to their low order and monotonic behavior in terms of cell growth, and individualizability to patients [3,45,46,49]. One potential shortcoming for these model types is the

assumption of a homogeneously growing cell population in the tumor, which may not be the case. Also, many chemotherapeutic drugs are cell-cycle specific, meaning that their toxic effects are targeted to cells in particular stages of growth. In these cases, the more detailed class of cell-cycle models may prove more useful for control studies.

Cell-cycle models describe cancer tumor behavior based on the number of cells in a given stage of the cell cycle, as shown in Fig. 4 [50]: resting; RNA and protein synthesis; DNA synthesis; construction of mitotic apparatus; or mitosis. These models provide greater insight to the cellular behaviors of the cancer tumor, at the expense of increased complexity since each cell-cycle stage is governed by its own differential equation [50]:

$$\dot{X}_{G0} = -(T_{G0} + d_{G0})X_{G0}(t) + 2rT_M X_M(t)$$
$$\dot{X}_{G1} = -(T_{G1} + d_{G1})X_{G1}(t) + 2(1-r)T_M X_M(t)$$
$$\dot{X}_S = -(T_S + d_S)X_S(t) + T_{G1}X_{G1}(t)$$
$$\dot{X}_{G2} = -(T_{G2} + d_{G2})X_{G2}(t) + T_S X_S(t)$$
$$\dot{X}_M = -(T_M + d_M)X_M(t) + T_{G2}X_{G2}(t)$$

Here the number of cells in a particular stage is given by X_i, the transition rate between stages is T_i, the death rate for cells in a particular stage is d_i, and of the cells that undergo mitosis, r enter the resting stage and $(1-r)$ return to the RNA/protein synthesis stage. The above model formulation assumes that each stage is subdivided into only one compartment. A shortcoming of this modeling approach is the inability to determine the exact number of cells in, and the transition rate of cells between, the various stages of the cell-cycle, as direct measurements of the tumor cells are not available. Despite the lack of parameter identifiability, approximate models of cell-cycle behavior have been constructed using linear differential equations [3,50,51], and these models are useful for analysis purposes. As an additional benefit, models of this class can handle the effects of cell-cycle specific drugs, for example the breast cancer drug paclitaxel, for effectiveness against a given tumor. For tumors where good estimates of model parameters are possible, this model structure offers distinct advantages based on its additional detail.

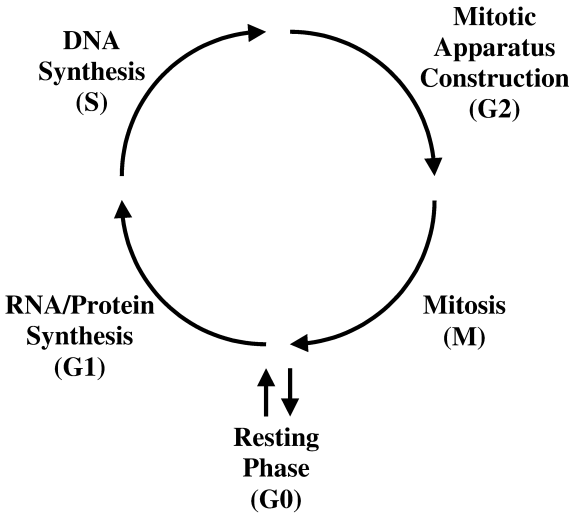

Fig. 4. Cell-cycle model of tissue growth, as employed in cancer tumor growth modeling (adapted from Refs. [3,50]).

Intermediate levels of model complexity and more detailed tumor growth models are both possible. Bajzer et al. [44] developed a second-order nonlinear dynamic model capable of capturing spontaneous tumor regression. The Oncology Thinking Cap [49] uses the Gompertz model to describe tumor growth, but allows for many more complicated tumor behaviors such as tumor heterogeneity and spatial variations within the tumor, different tumor types, cellular behaviors (e.g. sensitivity to various treatments), micro- and macro- environments, and many other factors through statistical techniques and Monte Carlo simulation.

3.3. Chemotherapy drug pharmacokinetics

The response of the tumor to therapy is governed by the pharmacokinetics and pharmacodynamics of the chemotherapy drug. As measurements of the drug concentration within the tumor are difficult to make, the effective concentration is usually assumed to be equal to that in the blood plasma. A popular approach to pharmacokinetic modeling of chemotherapy drugs uses the ADAPT (or ADAPT II) software program [52,53]. The software identifies the parameters for compartment-based models of drug behavior from concentration profile data, and also provides a simulation engine for the comparison of the identified model response to the actual patient

data. This technique has been used by Egorin and co-authors to develop a three-compartment model of paclitaxel pharmacokinetics from clinical data [54]. The resulting compartmental model is given by:

$$\dot{x_1} = -\left[\left(\frac{V_1V_T}{V_1K_T + x_1} + \frac{V_1V_C}{V_1K_C + x_1} + k_{13}\right)x_1\right] + k_{21}x_2 + k_{31}x_3 + I$$

$$\dot{x_2} = \frac{V_1V_T}{V_1K_T + x_1}x_1 - k_{21}x_2\dot{x_3} = k_{13}x_1 - k_{31}x_3$$

Drug compartment concentrations, x_i, are dependent on the central compartment volume, V_1, the rate constants for drug transport between compartments, k_{ij}, the maximum velocities for clearance, V_C, and transport, V_T, and the concentrations associated with $\frac{1}{2}$ the maximum velocity of clearance, K_C, and transport, K_T. Unlike many cancer chemotherapy drugs, the pharmacokinetics of paclitaxel are nonlinear [55], as seen from the Michaelis-Menten relationships in the above model. The presence of this nonlinear behavior may require some degree of nonlinear compensation in a corresponding controller, thus motivating a control-relevant model of drug kinetics. Another software package, NONMEM [56], can also be used to fit clinical data to compartmental models. Karlsson et al. used this package to fit models for the saturable distribution of paclitaxel in patients [57,58] as well as the pharmacodynamics of white blood cells in response to a paclitaxel dose [57]. Network thermodynamics models, as described by White and Mikulecky [59], and physiologically based pharmacokinetic models for in vivo drug behavior [60,61] require more effort construct and more and different drug and tissue data to identify (when the model parameters are uniquely identifiable). Like the cell-cycle models of tumor growth, however, they offer a greater degree of physical understanding. As evidenced by the latter citations, this modeling technique has applications beyond cancer therapy.

3.4. Cancer chemotherapy treatment issues

The determination of optimal drug delivery profiles for cancer patients is a multifaceted problem. One complication is the poor understanding of drug pharmacodynamics — the effect of the drug on tumor response. For cycle-non-specific drugs, assuming that there is no time-dependent variation in drug sensitivity (concentration×time of exposure= toxicity), the tumor cell death kinetics can be modeled as a linear function of the tumor size (N) and of the drug concentration (x_1) [62]. This is a reasonable approximation of the tumor behavior, and is commonly used in simulation studies [45,50,63–66]. This simplifies both the modeling and controller synthesis problems. When necessary, more complicated expressions for cell kill such as the Michaelis-Menten equation used by Asachenkov et al. can be employed [3]. Some drugs, such as paclitaxel, are cycle-specific [67]. This means that they attack patient and tumor cells in a particular phase of the cell-cycle. For the purposes of modeling treatment by these types of drugs, a cell-cycle model will offer significant advantages since the cell death kill term can be localized within the model. Examples of cell-cycle specific chemotherapy studies are those of Webb [68,69] and Panetta and Adam [70].

Additional complications must be modeled when delivering chemotherapeutic agents to cancer patients. Chemotherapeutic drugs are, by definition, toxic to the patient, so toxicity effects to healthy tissues should be included in a patient model. One common effect is leukopenia, a reduction in white blood cell count of the patient after treatment [57,71]. Through the modeling of this effect, optimal delivery profiles can be constructed to minimize the degree of leukopenia observed in patients while maintaining efficacy of treatment. In modeling toxicity, the method of delivery must also be considered [3,72]. The delivery of chemotherapeutic agents via bolus versus continuous infusion can lead to differences in both toxicity to the patient and efficacy of treatment [54]. Under the assumption that model accuracy is coupled to achievable performance [7], patient-drug models that include saturable drug kinetics [73], drug resistance [74], and cycle-specific tumor behavior [68–70,75] can lead to improved therapies. More complicated modeling issues result when a single drug is insufficient to elicit a pharmacodynamic response from the tumor, for example when the tumor is resistant to the chemotherapeutic drug [76]. A further consideration is the sequence effect, where the pharmacokinetics, and possibly pharmacodynamics, of tumor drugs vary based on

the order in which they are given. Several studies have attempted to address these issues in either a modeling or optimal treatment framework [50,65,77–79]. A final complication in modeling chemotherapeutic agent delivery is the heterogeneity that may exist within cancerous tumors. A recent review on drug delivery to solid tumors highlighted the issues in spatial variations within the tumor, such as blood flow and the related drug delivery, and also the need for dynamic understanding regarding cell-kill kinetics and toxicity to the patient [80]. Depending on the level of pharmacodynamic understanding and the mechanism of drug action, control-relevant choices can be made regarding tumor growth and pharmacokinetic models.

4. Insulin delivery to type I diabetic patients

4.1. The drug delivery problem

Type I, or insulin dependent, diabetes mellitus is a disease characterized by insufficient pancreatic insulin secretion. This results in wide variations in the patient's blood glucose concentrations. Most of the long-term health problems related to diabetes are a result of the loss of metabolic regulation. To stabilize this condition, exogenous insulin is required. Current medical recommendations for insulin therapy [81,82] recommend three to four daily glucose measurements, and an equivalent number of subcutaneous insulin injections. An alternative approach is to deliver insulin continuously, either subcutaneously or intravenously, using a closed-loop device. Ideally, a glucose sensor [83] would sample blood glucose concentration and pass this information to a glucose control algorithm. The algorithm would calculate an insulin delivery rate designed to keep the patient under metabolic control, and a signal would drive a mechanical pump to deliver the desired amount of insulin. This section will highlight the various issues faced in modeling the human glucose-insulin system and the insulin delivery problem.

4.2. Modeling glucose-insulin interactions

A wide variety of models have been used to capture the glucose and insulin dynamics in diabetic patients since the early modeling results of Bolie [84], nearly 40 years ago. A similar model structure, containing two linear differential equations describing glucose and insulin dynamics, was employed by Ackerman et al. [85]. Although these four-parameter models oversimplified the actual patient behaviors, they were easily identified from available data.

An early example of a control-relevant model was the development of the 'Minimal' model by Bergman et al. [86], given by the following equations:

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b$$
$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 I(t)$$
$$\frac{dI(t)}{dt} = E(t) - nI(t)$$

This three-state model describes plasma glucose, $G(t)$, dynamics based on plasma insulin, $I(t)$, and insulin concentration in a remote compartment, $X(t)$. Insulin is assumed to be delivered only through exogenous means, $E(t)$, and the parameters, P_i and n, are characterized to individual patients. The basal glucose concentration is given by G_b. A schematic of this model is shown in Fig. 2. By design, this lumped representation of glucose-insulin behavior used the minimum number of compartments and parameters to accurately capture the patient response. Bilinear coupling of glucose and insulin terms increased the accuracy of the model, but did still allowed straightforward computation, including inversion. Several studies in the literature [87,88] have documented shortcomings in this model, however. Quon et al. [87] performed a frequently sampled intravenous glucose tolerance test (FSIVGTT) and compared the effect of basal insulin delivery with the insulin delivery provided by the Biostator (which mimics healthy-patient insulin secretion). It was found that the minimal model overestimates the ability of glucose to facilitate its own uptake and underestimates the contribution of elevated insulin levels. A study by Weber et al. [88] provided a method for improving minimal model parameter estimates from FSIVGTTs by increasing the time window of data used in the initial identification, and combining this with a second FSIVGTT data set obtained while the norepinephrine levels of the human subject were elevated. This resulted in a decrease in parameter

fractional standard deviations, their performance metric. Finegood and Tzur [89] concur with Quon et al. [87] that the minimal modeling method has shortcomings, but differ in their analysis. The former find that care must be taken in estimating glucose effectiveness on its own disposal for subjects with varying levels of insulin secretion, while the insulin contribution may or may not alter glucose uptake.

Another low-order structured model of the glucose-insulin system was developed by Salzsieder and co-authors [90,91]. The resulting four-state linear model contained glucose and insulin effects, as well as a net body glucose balance. Parameters in the model were identified from data and validated for dogs [90–92] as well as humans [93–95]. This model was successful at capturing steady state behavior as well as slow process dynamics. Faster dynamics were not accurately captured, but this may be due to characteristics of the test sequence rather than shortcomings in the model structure [92].

Among the first models to include physiological detail, in terms of organ-derived model divisions, were the models by Tiran and co-authors [96,97]. These models were also among the first to include nonlinear effects in the description of glucose metabolism. The increased complexity allowed for a description of glucose and insulin throughout the body, rather than the lumped approximation taken by earlier authors [98]. Cobelli and co-authors have developed detailed models of glucose and insulin dynamics [99–102]. Key contributions of these models are the inclusion of glucagon effects, which stimulate glucose release, and the use of threshold functions (hyperbolic tangents) to describe the saturation behaviors seen in biological sensing (e.g. hepatic glucose production). Without presenting the entire model, the key behaviors can be observed in the glucagon submodel [100]:

$$\dot{u}_2 = -0.086u_2 + 2.35H_7(u_{13})M_7(x_1)$$

$$H_7(u_{13}) = 0.5\{1 - \tanh \times [6.86 \times 10^{-4}((u_{13} - u_{13_b}) + 99.2)]\}$$

$$M_7(x_1) = 0.5\{1 - \tanh[0.03((x_1 - x_{1_b}) + 40)]\}$$

The glucagon concentration in plasma and interstitial fluids, u_2, is a function of the plasma/extracellular fluid glucose concentration, x_1, and the interstitial fluid insulin concentration, u_{13}. The threshold behavior of glucagon release is clearly demonstrated through the H and M functions. Note that the threshold functions are dependent on the deviation between the concentration of insulin or glucose and its respective basal value. A detailed modeling study was presented by Puckett [5]. The body was accurately modeled as a two-blood-pool system representing insulin and glucose concentration because the time scale of interest was much greater than the tissue equilibration times. Unfortunately, this structure neglects any high-frequency dynamics that may exist in, or occur to, the system.

A physiologically-based compartmental model of glucose and insulin dynamics, shown in Fig. 3, was developed by Guyton et al. [103], extended by Sorensen et al. [6,104], and further extended by Parker et al. [4,105]. This model treated glucose and insulin separately, with coupling through metabolic effects (e.g. multiplicative terms for glucose effect and insulin effect on glucose uptake) utilizing threshold functions similar to those of Cobelli et al. [99]. A lumped whole-body representation for glucagon was included to complete the glucose-insulin system model with counter-regulation. The primary drawback of detailed physiological models is the identification of individual patient parameters. In these cases, a ‘nominal’ patient is often developed, based on mean values of literature data. A detailed sensitivity analysis can identify parameters that could dramatically affect closed-loop performance, and these model parameters should be customized either through off-line or on-line estimation from data.

4.3. Subcutaneous tissue modeling issues

The most common method for insulin delivery to diabetic patients is subcutaneous injection because of its inherent ease of management and greater safety compared to an intravenous approach. One of the major issues with subcutaneous insulin delivery is the need to model not only the physiological behaviors described above, but also the kinetics of subcutaneous insulin. A recent review by Nucci and Cobelli [106] compares and contrasts six models of subcutaneous insulin kinetics. These approaches ranged from simple compartmental models [107–

110] and empirically-derived low-order models [111] to highly complex physiologically-based models that explicitly capture behaviors such as insulin binding and conversion between the hexameric, dimeric, and monomeric insulin states [112–114]. A key issue faced by the subcutaneous insulin kinetics models reviewed in Ref. [106], especially those with less complicated structure, is the dependence on insulin preparation (monomeric, NPH, lente, ultralente) due to their widely varying release behavior. Although the complex models generally offer better predictive performance, the utility of these models in a controller would be limited because of their size (e.g. the model of Ref. [113] requires the solution of 31 nonlinear differential equations).

In addition to the sensitivity to insulin preparation, subcutaneous insulin delivery is complicated by inter- and intra-patient variability as observed by Puckett and Lightfoot [109]. They encountered time dependent gain and dynamics variations in insulin uptake from subcutaneous depots. With the recent advances in insulin preparations, such as monomeric or Lyspro insulins, it appears that the subcutaneous delivery route does not pose the challenges to glucose control that are common with slower insulin preparations. The limitation currently present would instead be based on the construction of an accurate and robust model for insulin kinetics.

Subcutaneous sensing of glucose is a desirable method of measurement, because it is less invasive than intravenous sensing techniques. However, the modeling of subcutaneous glucose behavior is necessary for control purposes, as the subcutaneous concentration will lag the bloodstream concentration, and it may also demonstrate a measurement bias. Models for subcutaneous glucose concentration, and for the prediction of blood glucose concentration from subcutaneous data, have been developed by Bonnecaze and co-authors [115,116]. They have demonstrated that reasonable estimates of the blood glucose concentration can be constructed from subcutaneous measurements, although their sampling interval was 30 s — faster than typical sensors operate. Although performance of a closed-loop device would be reduced by the subcutaneous sensing of glucose due to the slower dynamics, this measurement is much more accessible than intravenous glucose concentration.

4.4. Empirical and fuzzy modeling approaches

An alternative to the high fidelity physiologically-based models developed above is the use of empirical structures to accurately capture relevant input-output relationships. Typically, the model structure is chosen to facilitate either model-based controller design or parameter estimation. A modeling study by Bremer and Gough [117] posed the question, ‘‘Can present and future blood glucose values be predicted from recent blood glucose history?’’ Using autocorrelation functions, it was demonstrated that short-term predictions of glucose concentration could be accurate under certain conditions. A linear time-series model was developed from simulated insulin-glucose (input-output) data by Parker et al. [118,119]:

$$y(k) = \sum_{i=1}^{M} h(i)u(k-i)$$

Here, changes in the glucose concentration, $y(k)$, were assumed to be related to the sum of past insulin delivery rates, $u(k-i)$, weighted by the coefficients $h(i)$, over a horizon of length M. Although the actual relationship is nonlinear, a linear representation was chosen to facilitate controller design. When it is necessary to capture more complicated behaviors, more detailed model structures can be employed. A nonlinear neural network model of blood glucose concentration was identified from subcutaneous glucose sensor and subcutaneous insulin delivery data by Trajanoski et al. [120,121]. An issue in empirical model development is the trade-off between model accuracy and model parsimony. While detailed nonlinear models may offer better predictive accuracy, it is often at the expense of (significantly) increased data requirements for model generation.

Fuzzy models, as introduced in Section 2.4, have also been used for the modeling and control of blood glucose concentration in diabetic patients. Bellazzi et al. [122] developed a fuzzy model using qualitative simulation and a priori interaction information in the form of fuzzy rules. Bleckert et al. [123] used statistical techniques to develop a stochastic linear differential equation model of glucose-insulin metabolism, which can be interpreted as having fuzzy distributions for the parameter estimates. The a

posteriori probability distributions were then used to establish an optimal control policy for a simulated patient. Optimal control based on a fuzzy patient model was presented by Lim and Teo [124]. The result is a robust method for computing a single insulin injection in the presence of parameter uncertainty, although the underlying patient model is a modified form of Ackerman [85].

4.5. Issues in glucose concentration control

A variety of control algorithms have been applied to the glucose control problem, ranging from classical feedback techniques like proportional-integral-derivative (PID) control [94,125,126] and pole-placement [90] to model predictive control (MPC) [118,121]. A full analysis of these algorithms can be found in a review by Parker et al. [127]. In the context of modeling for drug delivery, certain behaviors should be included in control-relevant models.

Two potential insulin delivery strategies are possible for treating diabetes: intravenous and subcutaneous (including intraperitoneal). The former is advantageous because delivered insulin is immediately dispersed throughout the body in a lossless fashion, and it can be targeted to particular tissues based on catheter placement. As demonstrated by Cobelli and Mari [100], portal vein insulin delivery more accurately matched healthy patient blood glucose profiles, and was able to better restore the physiological glucose balance when compared to peripheral insulin delivery. The use of the subcutaneous route would require the synthesis of a more complicated model, to capture the change in dynamics, and also a less aggressive control algorithm due to the delivery location induced delay in insulin availability.

From a performance perspective, several issues must be addressed. Based on the sampling rate of a controller, which will be at least partially determined by sensor dynamics [128], limitations on model size and structure (nonlinear vs. linear) will need to be enforced so that the inversion computation will be completed within the available time. Adaptation of the patient model on-line has been shown to improve performance [92,127], but this will lead to constraints on the model parameterization. On the other hand, fixed structure controllers are intuitively more appealing, and when the patient model is linear about a particular operating condition, H_∞ controller synthesis techniques can be used to guarantee a certain degree of performance [105,129]. An ideal control-relevant model of a type I diabetic patient, therefore, would be individualized and easily adjustable, with a model structure facilitating controller design and straightforward to analyze performance characteristics.

5. Modeling for cardiac assist devices

Although not specifically a drug delivery problem, we include a review of control-relevant modeling of cardiac devices in this section. The rich history of device design, including advanced modeling and controller development, motivate its inclusion in this review paper.

5.1. The drug delivery problem

In the area of cardiac assist devices, there has been a relatively long history of device development, although the application of advanced control theory and process modeling has been a recent occurrence (see for example Refs. [130–134]). The first of such implantable devices to receive approval by the FDA (1998) is the Baxter/Novacor Left Ventricular Assist Device (LVAD). A schematic of the blood flow problem is shown in Fig. 5. In effect, cardiac assist

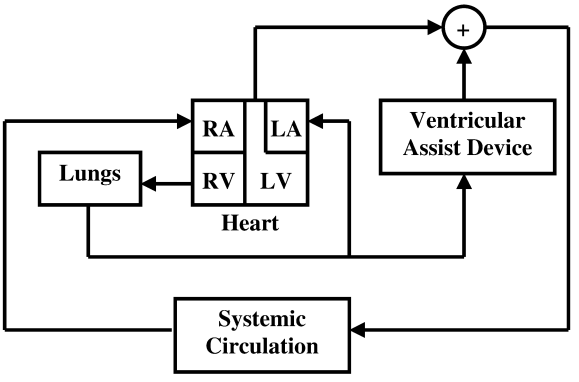

Fig. 5. Schematic of the blood flow pattern in a patient with a left ventricular assist device.

devices are mechanical pumps which provide 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' (e.g. level of exercise, emotion, posture, etc.). Clearly, the 'ideal' device would mimic the body's own mechanisms for maintaining cardiac output at target levels, however, the current devices on the market are rather primitive in terms of automation, requiring the patient to adjust setpoints directly [131].

5.2. Control-relevant model development

There are a number of approaches to modeling the cardiac system for the purpose of control design, ranging from reduced order circulatory models [135–138] and simple pump models [130,131], to more detailed circulation models [132,133].

A widely used system-level model consists of resistance, capacitance, and diode elements in a simple circuit analog, and captures the pulsatile behavior that results from the action of the left ventricle [135–138]. In such a circuit model, the voltage is analogous to pressure and the current is an analog for flow. Such a simple model can be used to simulate both a healthy cardiac response [136,137] as well as a reduced cardiac response [134] which would necessitate some form of cardiac assist device.

A mechanical pump model is presented in Refs. [130,131] as the basis for both estimating key cardiovascular parameters, as well as formulating key performance indices for controller design. The overall cardiac output is the sum of the pump flow and the natural heart flow. The former is calculated from a simple pump model relating speed and current to flow, while the latter is inferred from cardiac contractility and flow pulsatility. The data presented in Ref. [131] suggest that flow can be estimated to a high degree of precision, and the dynamics of the pressure response are also reproduced accurately. The overall performance index that is formulated in Ref. [130] involves the calculation of several physiologic indices that indicate the onset of suction in the pumps, as well as the more standard measures for cardiac output and pressure. In effect, the authors use data-driven calculations to infer the onset of pump suction, yielding an augmented model.

A more detailed model, intended for control design applications, has been recently developed at the University of Utah (the so-called Utah Circulation Model (UCM) [132,133]). It is a classic compartment model, consisting of a network of lumped nodes. Each node is characterized by a resistance, compliance, pressure, and blood volume. The most elementary version of the model contains four heart valves and seven blocks: left heart, right heart, pulmonary circulation (arterial and venous), systemic circulation, vena cava, and aorta. This compartment model is augmented with an axial flow VAD model to yield the overall system model. Preliminary studies using a modified proportional-integral (PI) controller indicated reasonable performance in simulation.

6. Summary

When treating human diseases, the overall goal is to cure or manage the disease while minimizing the negative impact of side-effects associated with therapy. Often, automation of the drug delivery process can result in improved consistency of delivery and more effective therapy. A natural response to this is the use of control engineering tools on biomedical drug delivery problems. A key component in the development of an advanced model-based control algorithm is the underlying patient model. Given the volume of work devoted to modeling biological processes, from the relatively simple lumped-parameter approximations of tumor growth [3] to the complex nonlinear models for insulin kinetics [112], there is clearly no general purpose method for selecting a model structure or parameterization. The focus of this review has been on the control-relevance of process models developed for ventricular assist devices, hemodynamic variable control, cancer tumor growth and chemotherapy, and insulin delivery to diabetic patients.

In the current work, a control-relevant model is one that has: (i) predictive capability in terms of the process input-output behavior; and (ii) utility in performing on-line calculations for control or optimization purposes. Given the range of characteristic

times in the biomedical problems summarized here, from seconds in the ventricular assist device to weeks in cancer chemotherapy, there is a degree of problem-specificity evident. Calculations using a more complicated model of cancer chemotherapy, for instance, would be possible because they would not need to be completed in the approximately 5–10-min interval required in glucose concentration control. If one accepts the idea that controller performance is directly associated with model accuracy, a working hypothesis would be to use the most detailed model necessary to achieve predictive accuracy, provided that the resulting control computation can be completed in the available time. However, computational performance is not the sole issue in controller and model selection.

One issue that complicates biomedical control and modeling problems, perhaps more than chemical process control, is the significant inter- and intrapatient variability observed. Therefore, a key component in a control system for drug delivery is an adaptive element. Although it is more difficult to guarantee stability and performance levels for these systems than for static control algorithms, the ability of the algorithm to individualize to a patient's specific behaviors may lead to remarkable performance improvements [127].

The state of current clinical practice varies with respect to the four major topic areas surveyed above. Ventricular assist devices are currently in use, as are continuous infusion insulin pumps, although the latter are generally not implemented in closed-loop mode. Blood pressure and anesthesia control are in the clinical trial stage, and the use of models in cancer chemotherapy is currently limited to analysis rather than control. Given the ongoing improvement in computational power and techniques, the potential impact of process control approaches to biomedical problems will increase. The key component in the synthesis of successful strategies for disease treatment, however, is the development of control-relevant models for drug delivery.

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