From Chemical Plants to Clinical Patients: Process Control Applications in Biomedicine

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Abstract
In recent times, there has been a convergence and interaction between the age-long principles of chemical process control (hitherto exclusive to the world of man-made industrial chemical process plants) and the life sciences (particularly biomedicine). This review article presents some examples of application areas in biomedicine where process dynamics and control, as a sub-discipline of process engineering, is being utilized to save human lives. It especially focuses on the extension of the chemical engineer's "process" and "system" to embrace parts of the human body or microbial cells. The aim of the article is to make the reader appreciate how the traditional chemical engineering tools of process dynamics and control can be applied newly to biomedical problems. This is to stir the readers' mind to explore other exciting ways of applying control engineering knowledge to solve modern healthcare challenges. The review was conducted under three broad application headings: medical device engineering applications, industrial-scale production of therapeutic substances and elucidatory investigations into complex physiologies.

Keywords: Medical Devices, Anaesthesia, Biomedicine, Healthcare, Process Systems, Bioengineering

1. Introduction

Centuries of engineering practice have seen the profession transform many facets of human life viz-a-viz food and drinks, transportation, communications, and the environment. In contemporary times, its influence has transcended these traditional domains to include medicine. While many may think that engineering and the life or medical sciences have nothing in common, trends since the dusk of the last century are indicative of a rapid convergence of the two disciplines.

Process control, as a sub-discipline of process engineering, has grown in relevance in biomedicine today. Whilst past centuries might not have seen much of process engineers' involvement in medical practice, there exists now, no barrier to the cross-disciplinary interaction of ideas and innovations ongoing between these vast scientific disciplines. The deployment of classical chemical engineering tools in chemical kinetics, fluid mechanics and control theory to medical problems, continues to transform the face of modern healthcare.

Khoo (1999), writing from the perspective of physiological application, defines a control system as "a collection of interconnected components that can be made to achieve the desired response in the face of external disturbances". Typically, two types of control mechanisms or problems exist: servo and regulatory. A servo control problem seeks to make a process output track a dynamic set-point. A regulator's objective, on the other hand, is to keep the process output within desired limits in the face of dynamic influences or disturbances.

Regulatory control is frequently encountered in physiology and biomedicine. The human body is replete with regulatory control systems. The regulation of body temperature (also known as thermoregulation), the maintenance of blood sugar concentration within consistent limits (glycaemic control) and balancing of salt and water concentrations in the body (osmoregulation), are few examples.

Fig. 1 depicts a general control engineering perspective for a closed-loop process. In the cases described in this review, most of the times, the "plant" represents the human body or sections of it which may vary in scale: from the cell to tissue to organ to the whole-body systems.

More than anything else, control engineering's relatively recent and rising impact in the diverse healthcare disciplines has brought to fore the versatility and indispensability of its age-long principles in the modern world. So far, process engineers' interdisciplinary activities in medicine can be reviewed in three broad areas: medical device engineering, industrial-scale production of therapeutic substances and elucidatory physiological modelling research. In these three broad areas, we see the applications of control engineering and the use of its analytical tools for the welfare of patients.

2. Medical Device Engineering

The development of medical equipment primarily registers the presence of engineering in medicine. The gadgets range from instrumentation devices such as the blood glucose sensor, life-support facilities like the cardiopulmonary bypass machine, to therapeutic aids like the insulin pump and the hemodialyzer (artificial kidney). The application of control engineering principles to a number of prominent medical issues has led to the design of some of these machines. For futuristic research recommendations and tutorial purposes, we will consider three examples.

2.1 The Artificial Pancreas

Closed-loop medical devices are innovative solutions by engineers which utilize automatic controllers to aid patients in certain life functions or assist clinicians in performing their duties. These gadgets abound in diverse disease management cases. An example is in diabetes care. As at 2015, an estimated 415 million people in the world are living with diabetes (Ortmann et. al., 2017). This alarming statistics calls for intervention, not only from medical researchers but also from collaborating engineers, to improve the health of the patients.

In drug administration for diabetes care and management, an ongoing technological development for type 1 diabetes care and management is the “artificial pancreas”. The artificial pancreas uses a closed-loop system, illustrated in Fig. 2. It is conceived as a technology which would automatically respond to blood glucose changes by providing the required amount of insulin in the same manner the biological pancreas would have done. In recent years, this idea has attracted many control engineering interventions in a bid to develop a medical equipment to meet this need. The continuous supply of glucose concentration data “informs” the decision system (controller) on the insulin action to prescribe in a closed-loop online fashion.

To achieve this goal, a mathematical model describing the dynamic glucose-insulin process is usually the starting point for most control engineering interventions. The commonest model employed to describe the glucose-insulin dynamics is the Bergmann minimal model developed in 1979 to describe insulin kinetics during Intravenous Glucose Tolerance Test (IVGTT). It has now gained much popularity with modern modifications existing. It is a three-state dynamic model relating the blood glucose concentration, G to the plasma insulin concentration, Y.

$$G'(t)=-p_1(G(t)-G_b)-X(t)G(t)+h(t) \quad (1)$$

$$X'(t)=-p_2X(t)+p_3(Y(t)-Y_b) \quad (2)$$

$$Y'(t)=-p_4Y(t)-X(t)G(t)+\frac{i(t)}{V} \quad (3)$$

In terms of the deviation variables g = G-G_b and y =Y-Y_b, with the subscript b denoting the basal concentrations, and assuming that the state variable X is slow so that $X'(t)=0$,

$$g'(t)=-p_1g(t)-\frac{p_3}{p_2}G_by(t)-\frac{p_3}{p_2}y(t)g(t)+h(t) \quad (4)$$

$$y'(t)=-p_4y(t)-p_4Y_b+\frac{i(t)}{V} \quad (5)$$

With such a model as the Bergmann model, various types of controllers are being used to close the loop and substitute for the use of the biological pancreas: from the conventional PID to the more sophisticated model-based predictive controllers. Some reviews (Sparacino et al., 2010; Bequette, 2010) have identified the need to improve the mathematical algorithms and tools utilized for the analysis of continuous glucose data in real time in order to achieve the goal of a safe, cheap, simple and smart artificial pancreas. Such tools assist to predict future glucose concentrations ahead of time, and forewarns of impending hyperglycaemia or hypoglycaemia.

In the same vein, the automation of insulin delivery needs accurate optimal control infusion algorithm. Therefore, model predictive controllers (MPC), reputed to be among the best control algorithms, have been employed for insulin infusion (Parker et al., 1996; 1999; Hovorka et. al., 2004; Ionescu and DeKeyser, 2005).

Model predictive control applications to automated drug delivery in the treatment of type 1 diabetes in which insulin is administered to control high blood glucose concentrations is an active research area. MPC has recently been employed as the controller or decision system for the artificial pancreas. In the works of Patra and Rout (2016), Cao et. al. (2017) and Ortmann et. al. (2017), MPC algorithms were applied to the regulation of glucose-insulin dynamics in type 1 diabetes. A more recent study by Messori et. al. (2018) evaluates the effectiveness of MPC for the artificial pancreas taking into consideration inter-patient variability. The work contains the result of an in silico trial.

Despite the promising use of MPC, it is computationally demanding especially for a nonlinear process during the on-line optimization procedure. Researchers are working to overcome this drawback. Dua et. al. (2006) employed a novel parametric programming approach in their MPC algorithm. Chakrabarty et. al. (2018) attempted an event-triggered MPC algorithm which aims at saving energy used up by the iterative computations of the MPC controller. For the artificial pancreas technology to be commercially and easily available for type 1 diabetes patients, this computational energy consumption must be resolved. There is, therefore, room for more novel control algorithms. Nonlinear model predictive control (NMPC) algorithms utilizing automatic differentiation (AD) could be developed in order to overcome the computational drawback often encountered with MPC. NMPC algorithms utilizing AD techniques have been proposed and previously applied to nonlinear industrial systems (Cao, 2005; Cao and Chen, 2009). The artificial pancreas would, therefore, benefit from these new and promising control algorithms.

2.2 The Hemodialyzer

Renal failure is a condition describing the malfunctioning of the kidney(s). One of the major functions of the kidneys is their excretory role in getting rid of metabolic waste products contained in the blood through filtration and eventual excretion in urine. These toxic wastes build up in the blood during kidney failure, portending death for the sufferer. One key strategy employed clinically to save patients is to have a kidney transplant. An alternative solution however is the use of an artificial kidney - an in vitro device which selectively removes metabolic wastes from the blood through the use of a semi-permeable membrane via a process known as dialysis.

The design of this device generates a number of chemical engineering problems: the selection of suitable membrane material, the choice of geometric configuration for stacking the membrane, the determination of flow pattern and rate for the dialysate, amidst safety considerations among others (Mistry and Udani, 2006). Control engineering issues would also normally arise in the operation of an artificial kidney.

2.3 The Pump Oxygenator

Coronary occlusion, the obstruction of the arteries supplying blood to the heart muscles, is one of the leading causes of death in the western world; it is a precursor to killers like cardiac arrest and stroke. The coronary artery bypass graft is a surgical procedure by which the obstructions or atherosclerotic plaques in the coronary arteries are bridged by a vein graft. During this open-heart procedure, the heart does not pump efficiently, hence the need for a device which can help restore normal blood flow and oxygen to the heart. This device is known as the cardiopulmonary bypass machine or the pump oxygenator whose development has involved help from chemical engineers in designing special blood filters to delay clotting thereby saving the blood platelets, and the heat exchangers employed in it to cool and re-warm the blood, among others (Mistry and Udani, 2006).

3. Commercial Production of Therapeutic Substances

Besides developing closed-loop clinical gadgets, control engineers also help to make important healthcare substances, such as drugs and vaccines, available in very large quantities. Often, microbial and mammalian cells are employed industrially to produce proteins, hormones, vitamins and antibiotics. Examples abound: the microbe *Penicillium notatum* is used in the production of penicillin, a popular antibiotic; the hormone insulin, employed for the treatment of diabetes mellitus, is harvested in large amounts from the culture media of certain genetically-engineered bacteria; and certain mammalian cells are used to produce complex therapeutic proteins such as monoclonal antibodies. Vessels where the biochemical conversions yielding these products occur are called bioreactors. The duty to design such reactors and other ancillary equipment in the most hygienic, efficient and economical manner is the specialty of biochemical engineers. Therefore, issues bordering on effective scale-up operation— agitation requirements, optimum conditions of temperature and pH, cells' oxygen demand and the like, are the usual concerns which these engineers try to resolve.

Besides the design considerations, process engineers use mathematical modelling, dynamic analyses and controller design principles as found in traditional process engineering practice, to optimize the operation of these large-scale biochemical processes for the benefit of patients. Here, we see the traditional process control engineering in application to the biotechnology field. Of particular note here, because of its relevance to the theme of this article, is that the process systems to be controlled are cell cultures in large vessels.

For instance, in Kager et al. (2020), a nonlinear model predictive controller (MPC) was implemented in a Penicillium chrysogenum fed-batch process and compared to a PI(D) and an open-loop feedback control scheme, referenced as model-based control (MBC). The controllers were used to maintain predefined set-points of biomass specific glucose uptake rates, product precursor and nitrogen concentrations by manipulating the glucose, precursor and nitrogen feeds. It was discovered that, in comparison to PI(D) and MBC, the MPC efficiently avoided formation of by-products, which resulted in efficient substrate utilization and an overall product gain of 14%.

Process control has also been of importance in the vast production of antibodies. In a recent work by Feidl et al. (2020), it was demonstrated that despite significant process disturbances and drifts, a robust process design and the supervisory control enabled constant (optimum) process performance and consistent product quality in the integrated continuous manufacturing of antibodies. In an earlier work, Anilkumar et al. (2017) carried out an offline and online multi-objective control of a fed-batch bioreactor for the induced foreign protein production by recombinant bacteria using model predictive control (MPC).

Furthermore, researchers are also deploying automatic process control technologies for large-scale cell processing where closed-loop automated systems are used to effectively eliminate the laborious manual processes of buffer exchange and product concentration involved in the commercial-scale manufacturing of products for gene and cell-based therapies. Li et al. (2019) described a newly-developed cell processing device that is suitable for small- to medium-scale cell processing and aims to bridge the gap between manual processing and large-scale automation. Rafiq and Thomas (2016) also reviewed the evolving role of automation in process development and manufacture of cell and gene-based therapies.

4. Elucidatory Investigations Into Complex Physiologies

In addition to their feats in the vast production of therapeutics and design of medical devices, chemical engineers are also assisting medical researchers to gain understanding of normal and diseased physiological processes. They are building mathematical and numerical models of parts and whole sections of the cardiovascular, respiratory, hormonal, digestive and skeletal systems. In biomechanics, they combine the traditional partial differential equations of fluid flow and solid mechanics to describe the flow of blood in diseased vessels, attempt to simulate the heart's action, and study the movement of muscles and skeletal structures. While some simulate the effect of inhaled pollutants through the lungs, others develop mathematical equations for the growth and spread of cancer cells. A few also venture to look at the control action of drugs. Working with other applied physical scientists, chemical engineers are actively involved in interdisciplinary engagements of computational biology, medical imaging, biorheology, biomedical process control, mathematical physiology, drug metabolism and so on.

Biomedical process control is aiding clinicians' understanding of normal and pathological physiologies: from diagnostics to therapeutics, from the ICU to the home and outpatient care settings. Here, the "process" paradigm has shifted from the chemical plants to include whole or parts of "the patient" for control analyses and design.

4.1 Control in Anaesthesia and Surgery

Anaesthesia is the practice of painless surgery which has left an indelible imprint in medical history and still holds a major importance in modern-day medicine. A reason for this is apparent. The level of pain experienced during surgery before the invention of effective anaesthesia can only be left to imagination. Tales of surgical occurrences in the pre-anaesthesia era give an inkling of, not only the physical pain, but also of the shock and emotional suffering involved. So important was the invention of anaesthesia!

Anaesthesia can be defined as "the lack of response and recall to noxious stimuli" (Nunes et al., 2007a). There are usually three components that characterize general anaesthesia (Yelneedi et al., 2009): hypnosis (lack of consciousness), analgesia (lack of pain perception), and muscle relaxation (lack of movement). Anaesthetists (or anaesthesiologists) utilize certain drugs to maintain each of these components. Hypnotics, analgesics and muscle relaxants are used respectively. Hypnotics help to induce unconsciousness and memory loss (amnesia) during surgery which is important to the success of surgical procedure. Monitoring the depth of consciousness (also known as depth of anaesthesia or depth of hypnosis) of the patient and effectively administering the hypnotic drug (which may be inhalational or intravenous) is very crucial to the success of surgery. Isoflurane and propofol are commonly administered inhalational and intravenous anaesthetics respectively while the Bispectral Index (BIS) is the commonly used measuring indicator for the depth of consciousness.

Automatic control in anaesthetic drug delivery has become necessary due to a number of reasons, topmost of which is the need for improved patient safety and care. It is evident that utmost care and caution is required in the administration of anaesthetic drugs and the maintenance of its key phases. Anaesthetists are often multi-tasked physicians who attend to a number of overwhelming anaesthesia issues during the procedure. Automatic administration of the drugs would, no doubt, provide support for them in their multiple patient monitoring and drug administration duties and thus reduce the chances of human error. Furthermore, it takes a good automatic system to combine simultaneously the multiple constraints and requirements arising in anaesthesia practice. The quantity of drugs that is safe to administer is bounded; the desired concentration of the drug in the blood must be within certain limits for the patient to be safe. Also, the patient's depth of unconsciousness must be kept within an operative range. The foregoing issues necessitate the design of automatic controllers for anaesthesia. Much of these control needs and benefits are covered in Fig. 3 (Oshin, 2016).

There has been observed development in the utilization of automatic controllers in general anaesthesia especially with the use of target-controlled infusion (TCI) systems. Despite the current level of accomplishment, there are still needs calling for advanced control technology interventions. TCI systems are open-loop mechanisms that require the intervention of anaesthetists to "close the loop" doing little to relieve their excessive burden. Traditional feedback control systems like the on-off, P, PI and PID have also proved useful but often lack the framework to rigidly enforce constraints. Model predictive control (MPC), reputed to be the most widely used industrial control technology (Bequette, 2003), have also been introduced in recent years to address the spotted control challenges in anaesthesia. Although many of these controllers originally evolved to be applied to vast petrochemical plants (Bequette and Doyle, 2001), their application to anaesthesia where the chemical plant is now the clinical patient, is rather young and developing.

Just as it is required for a typical process plant, the application of control and dynamic studies in medicine requires the use of a model of the system. In this case, this is the patient model. The physiological process involving an anaesthetic dose is typically described by a linear dynamic system of equations and a nonlinear static relation known as the Sigmoidal Hill Model. Drug mass balances are written based on "compartments" often representing the blood, body or tissues "lumped" into "perfectly-mixed volumes" in the same manner that stirred tanks are employed to depict chemical processes. This theoretical modelling paradigm is known as compartmental modelling. Standard compartmental models describing the relationship between anaesthetic (drug) inputs and patient output indicators (like the Bispectral index, BIS) often consists of two interacting parts: a pharmacokinetic (PK) compartment model and a pharmacodynamic (PD) model (Beck et al., 2007). The model of the BIS response to propofol infusion is a PK-PD model depicted schematically in Fig. 4.

The PK-PD propofol hypnosis model is a type of Wiener model. The PK component of the model, as well as the first-order time-lag equation, collectively form a system of linear dynamic equations represented by equation 6. This is in series with the nonlinear static Hill equation 7.

$$\begin{bmatrix} \dot{C}_1 \\ \dot{C}_2 \\ \dot{C}_3 \\ \dot{C}_e \end{bmatrix} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21}\frac{V_2}{V_1} & k_{31}\frac{V_3}{V_1} & 0 \\ k_{12}\frac{V_1}{V_2} & -k_{21} & 0 & 0 \\ k_{13}\frac{V_1}{V_3} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix} \begin{bmatrix} C_1 \\ C_2 \\ C_3 \\ C_e \end{bmatrix} + \begin{bmatrix} \frac{w}{\bar{k}V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} u \end{bmatrix} \tag{6}$$

$$BIS = BIS_0 \frac{EC_{50}^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}} \tag{7}$$

The first attempt at achieving automatic control of the depth of anaesthesia was made by Bickford (1950). Subsequent collaborative works in the decade appeared in Soltero et al. (1951) and Kiersey et al. (1954). Bickford and his colleagues demonstrated the use of automatic control to administer intravenous thiopental and liquid ether to human patients. They utilized the EEG output as a feedback signal to the device which administered the drug in proportional mode.

Now numerous detailed design of PID, nonlinear MPC and linear MPC controllers and simulations for propofol anaesthesia under surgical clinical conditions of induction and maintenance phases in anaesthesia can be found in literature (Oshin, 2016; Yelneedi et. al., 2009; Ionescu et. al., 2008; Nino et. al., 2009). The induction phase of anaesthesia is the first phase which covers the period from the start of the anaesthetic infusion to the period when unconsciousness is achieved prior to surgery. Once a patient has been successfully induced into unconsciousness prior to surgery, it is the goal of anaesthesia to also keep him in that pain-insensitive state while the surgical procedure lasts. This is the maintenance phase. There is a last phase, known as the awaking phase, which is a postoperative period covering when the anaesthetic infusion stops to the period when the patient fully regains consciousness.

It is clear from the foregoing, that process modelling, dynamics and control theory can be extended to a surgery patient. The goal of this application is to aid clinicians' understudying of the patient for safety reasons and to end up with improved care outcomes.

4.2 Control in Cancer Treatment

In order to investigate the poorly-understood cancer process, in recent times, control engineering has found applications in cancer treatment protocol design (Parker, 2007). Chemotherapy treatment protocols are being designed using optimal control theory. The entire treatment plan acts as a closed-loop system with the treatment design algorithm closing the loop as the controller.

As found in all drug administration instances (like in the anaesthesia case above), the pharmacokinetic (PK) and pharmacodynamic (PD) models of the patient which quantitatively describe the effects of the actions of the chemotherapy drugs on the patient, are needed to enable the design of the control algorithm. Model-based control strategies, like the MPC, optimizes the desired therapeutic objectives in a feedback fashion using desired PK-PD profiles as reference trajectories to arrive at treatment plans or schedules which are specific to the patient.

A most recent idea proposed by the author and which is a current research undertaking is the use of process dynamic modelling methods and control theory to characterize cancer cell movement. The research aims to develop a comprehensive mathematical model that would aid in the understanding and understudying of the biological phenomenon of cell migration as it relates to cancer. As a tool, the model would assist medical researchers in the oncology field to simulate methodologies and means to forestall cancer cell migration.

It is further envisaged that the application of control engineering methods to elucidate the regulatory process of cancer cell migration would lead to a useful mathematical model which besides serving as a tool for the studying of the process of migration of cancerous cells, would also be useful as a clinical aid to simulate cancer cells' apoptosis in silico and guide biological researchers on how to implement the programmed cell death of the cancerous cells.
In other words, it is envisioned that the mathematical depiction of the complex biochemical and biomechanical cell migration regulatory processes with conventional closed-loop automatic control engineering methods and techniques would lead to a mitigation plan to contain the menace of the spreading of the cells. Such mathematical and control description is amenable to dynamic studies, stability studies, and other engineering modifications which may be of benefit to the understudying of the real-life biological phenomena.

Furthermore, it is projected that as a clinical tool, the mathematical model and resulting simulator from such modelling and control adventures at the early stages of cancer diagnostics, would assist medical researchers in the oncology field to also plan ahead methodologies and protocols to forestall the further progression or spreading of cancerous cells.

5. Conclusion

Control engineers' collaborative work with health experts is one that will not lay still as greater challenges are destined for the future. Besides the applications described in this review, some other challenges and opportunities in biomedical process control were identified in Morari and Gentilini (2001); and Doyle et. al. (2007). Again, the future life of control engineers in health can be projected to include aiding in the growing of new organs via tissue engineering. More applications, other than the ones covered in this review, may be encountered in the future by process engineers, in our daily experiences and relations with medical researchers.

In response to the present and potential medical challenges for control engineers, educators are rebuilding existing curricula or creating entirely new ones which would suitably equip emergent process control engineers to handle these present and future interdisciplinary challenges. Introductory courses on biological processes are now taught to undergraduates in many engineering programmes; and at the graduate level, specialised degrees in interdisciplinary engineering and biomedical research are offered by these departments in several colleges where an independent engineering department devoted to this is non-existent. All these are being done in a bid to race with the tides of the profession. Great grounds are still awaiting the control engineering touch in medicine; onus is laid on us to look into the future and take giant strides!

References

1. Anilkumar M., Padhiyar N., Moudgalya K. (2017), “Multi-objective control of a fed-batch bioreactor using shrinking horizon MPC: a case study”, Proceedings of the 6th International Symposium on Advanced Control of Industrial Processes, May 28-31, 2017, Taipei, Taiwan, pp. 25-30
2. Bird R. B., Stewart W. E., Lightfoot E. N. (2002), Transport Phenomena, 2nd ed., John Wiley & Sons, p. iv
3. Beck C., Lin H.-H., Bloom M. (2007), "Modeling and control of anesthetic pharmacodynamics", Biology and Control Theory: Current Challenges, Lecture Notes in Control and Information Sciences, Vol. 357, Springer-Verlag, Berlin, Heidelberg, pp. 263-289
4. Bequette B. W. (2010), "Continuous glucose monitoring: Real-time algorithms for calibration, filtering, and alarms", Journal of Diabetes Science and Technology, Vol. 4, No. 2, pp. 404-418
5. Bequette B. W. (2003), Process Control: Modeling, Design and Simulation, Prentice Hall, New Jersey, USA
6. Bickford R. G. (1950), "Automatic electroencephalographic control of general anesthesia", Electroencephalography and Clinical Neurophysiology, Vol. 2, No. 1-4, pp. 93-96
7. Cao Y. (2005), "A formulation of nonlinear model predictive control using automatic differentiation", Journal of Process Control, Vol. 15, pp. 851-858
8. Cao Y., Chen W.-H. (2009), “Automatic differentiation based nonlinear model predictive control of satellites using magneto-torquers”, Proceedings of the 4th IEEE Conference on Industrial Electronics and Applications (ICIEA 2009), May 25-27, 2009, Xi’an, China, pp. 913-918
9. Cao Z., Gondhalekar R., Dassau E., Doyle F. J. (2017), "Extremum seeking control for personalized zone adaptation in model predictive control for type 1 diabetes", IEEE Transactions on Biomedical Engineering, Dec. 2017, pp. 1-1
10. Chakrabarty A., Zavitsanou S., Doyle F. J., Dassau E. (2018), "Event-triggered model predictive control for embedded artificial pancreas systems", IEEE Transactions on Biomedical Engineering, Vol. 65, No. 3, pp. 575-586

11. Doyle F., Jovanovic L., Seborg D., Parker R. S., Bequette B. W., Jeffrey A. M., Xia X., Craig I. K., McAvoy T. (2007), “A tutorial on biomedical process control”, Journal of Process Control, Vol. 17, pp. 571-594
12. Dua P., Doyle F. J., Pistikopoulos E. N. (2006), "Model-based blood glucose control for type 1 diabetes vial parametric programming", IEEE Transactions on Biomedical Engineering, Vol. 53, no. 8, pp. 1478-1491
13. Feidl F., Vogg S., Wolf M., Podobnik M., Ruggeri C., Ulmer N., Walchli R., Souquet J., Broly H., Butte A., Morbidelli M. (2020), “Process-wide control and automation of an integrated continuous manufacturing platform for antibodies”, Biotechnology & Bioengineering, Vol. 117, pp. 1367-1380
14. Hovorka R., Canonico V., Chassin L. J., Haueter U., Massi-Benedetti M., Orsini-Federici M., Pieber T. R., Schaller H. C., Schaupp L., Vering T., Wilinska M. E. (2004), "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes", Physiological Measurement, Vol. 25, No. 4, pp. 905-920
15. Ionescu C., De Keyser R. (2005), "EPSAC predictive control of blood glucose level in type I diabetic patients", Proceedings of the 44th IEEE Conference on Decision and Control, and the European Control Conference, CDC-ECC '05, December 12-15, 2005, Seville, Spain, pp. 4845-4850
16. Ionescu C. M., Keyser R. D., Torrico B. C., Smet T. D., Struys M. M. R. F., Normey-Rico J. E. (2008), "Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia", IEEE Transactions on Biomedical Engineering, Vol. 55, No. 9, pp. 2161-2170
17. Kager J., Tuveri A., Ulonska S., Kroll P., Herwig C. (2020), “Experimental verification and comparison of model predictive, PID and model inversion control in a Penicillium chrysogenum fed-batch process”, Process Biochemistry, Vol. 90, pp. 1-11
18. Khoo M. C. K. (1999), "Physiological Control Systems: Analysis, Simulation and Estimation", Wiley, New York
19. Kiersey D. K., Faulconer A., Bickford R. G. (1954), "Automatic electroencephalographic control of thiopental anaesthesia", Anaesthesiology, Vol. 15, No. 4, pp. 356-364
20. Li A., Wilson S., Fitzpatrick I., Barabadi M., Chan S. T., Krause M., Kusuma G. D., James D., Lim R. (2019), “Automated counterflow centrifugal system for small-scale cell processing”, Journal of Visualized Experiments, Vol. 154, e60423
21. Messori M., Incremona G. P., Cobelli C., Magni L. (2018), "Individualized model predictive control for the artificial pancreas: In silico evaluation of closed-loop glucose control", IEEE Control Systems Magazine, Vol. 38, No. 1, pp. 86-104
22. Mistry M., Udani S. (2006), "Just what the doctor ordered", The Chemical Engineer, No. 778, pp. 54-55
23. Morari M., Gentilini A. (2001), "Challenges and opportunities in process control: Biomedical processes", AIChE Journal, Vol. 47, No. 10, pp. 2140-2143
24. Niño J., De Keyser R., Syafiie S., Ionescu C., Struys M. (2009), "EPSAC-controlled anesthesia with online gain adaptation", International Journal of Adaptive Control and Signal Processing, Vol. 23, No. 5, pp. 455-471

25. Nunes C. S., Mendonça T., Brás S., Ferreira D. A., Amorim P. (2007a), "Modeling anesthetic drugs' pharmacodynamic interaction on the bispectral index of the EEG: The influence of heart rate", Proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, August 23-26, 2007, Lyon, France, pp. 6479-6482
26. O'Hara D. A., Bogen D. K., Noordergraaf A. (1992), "The use of computers for controlling the delivery of anesthesia", Anesthesiology, Vol. 77, No. 3, pp. 563-581
27. Ortmann L., Shi D., Dassau E., Doyle F. J., Leonhardt S., Misgeld B. J. E. (2017), "Gaussian process-based model predictive control of blood glucose for patients with type 1 diabetes mellitus," 11th Asian Control Conference (ASCC), December 17-20, 2017, Gold Coast, QLD, Australia, pp. 1092-1097
28. Oshin T. A. (2016), "Automation in anaesthesia", Lambert Academic Publishing, Saarbrucken, Germany
29. Parker R. S., Doyle F. J., Harting J. E., Peppas N. A. (1996), "Model predictive control for infusion pump insulin delivery", Proceedings of the 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, October 31-November 3, 1996, Amsterdam, The Netherlands, pp.1822-1823
30. Parker R. S., Doyle F. J., Peppas N. A. (1999), "A model-based algorithm for blood glucose control in type I diabetic patients", IEEE Transactions on Biomedical Engineering, Vol. 46, No. 2, pp. 148-157
31. Parker R. S. (2007), "Modelling for anti-cancer chemotherapy design", Journal of Process Control, Vol. 17, pp. 576-582
32. Patra A. K., Rout P. K. (2016), "Adaptive continuous-time model predictive controller for implantable insulin delivery system in Type I diabetic patient", Optimal Control Applications and Methods, Vol. 38, No. 2, pp. 184-204
33. Rafiq Q., Thomas, R. (2016), "The evolving role of automation in process development and manufacture of cell and gene-based therapies", Cell and Gene Therapy Insights, Vol. 2, No. 4, pp. 473-479
34. Soltero D. E., Faulconer A., Bickford R. G. (1951), "The clinical application of automatic anesthesia.", Anesthesiology, Vol. 12, No. 5, pp. 574-582
35. Sparacino G., Facchinetti A., Cobelli C. (2010), "Smart continuous glucose monitoring sensors: on-line signal processing issues", Sensors, Vol. 10, pp. 6751-6772
36. Yelneedi S., Samavedham L., Rangaiah G. P. (2009), "Advanced control strategies for the regulation of hypnosis with propofol", Industrial and Engineering Chemistry Research, Vol. 48, No. 8, pp. 3880-3897

Figures

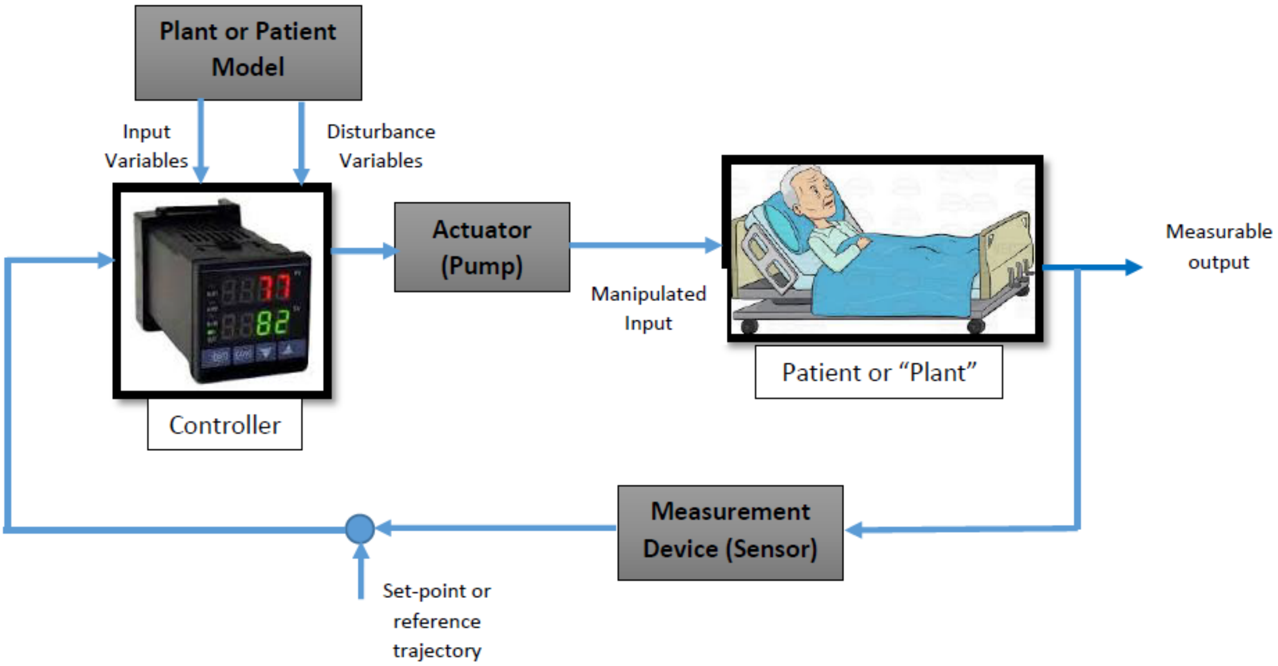

Fig. 1: Schematic of a closed-loop feedback process

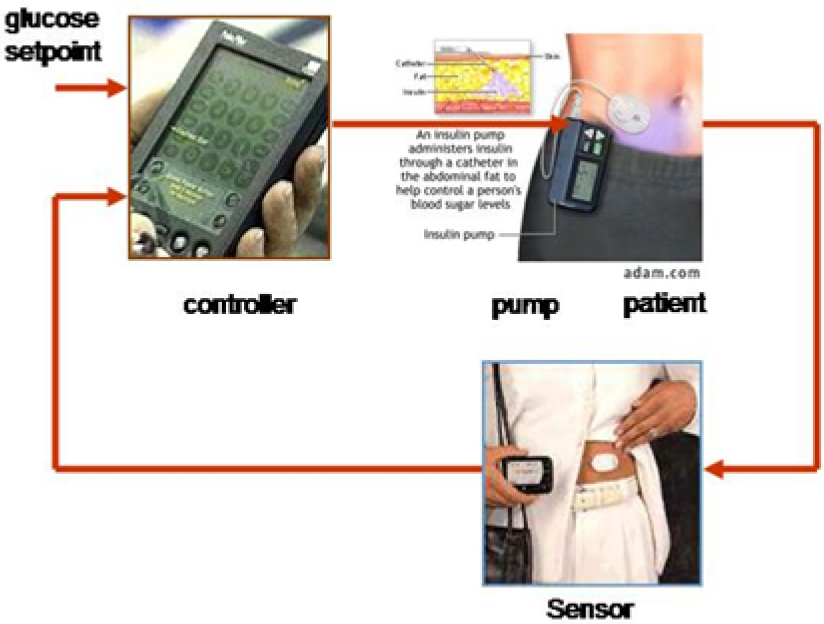

Fig. 2: The artificial pancreas is illustrated (Bequette, 2010)

The patient is the process as the controller regulates the blood glucose level (output signal) measured by the sensor in a closed-loop fashion by prescribing the amount of insulin (input signal) to the actuator (pump).

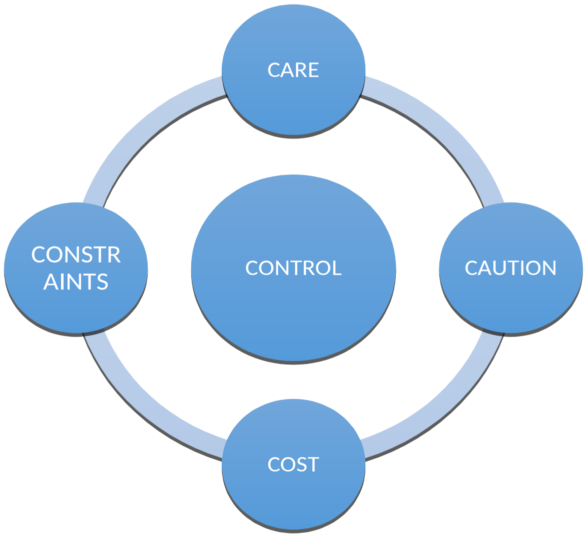

Fig. 3: Control engineering concerns in anaesthesia revolve around patient care, cautionary procedures, optimized surgical cost and other safety constraints

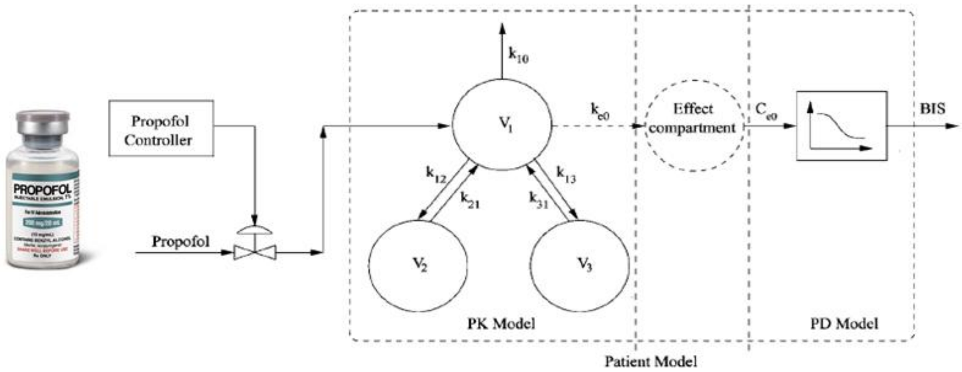

Fig. 4: A schematic of the PK-PD model of propofol hypnosis