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REVIEW ARTICLE

Intelligent automated drug administration and therapy: future of healthcare

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Abstract

In the twenty-first century, the collaboration of control engineering and the healthcare sector has matured to some extent; however, the future will have promising opportunities, vast applications, and some challenges. Due to advancements in processing speed, the closed-loop administration of drugs has gained popularity for critically ill patients in intensive care units and routine life such as personalized drug delivery or implantable therapeutic devices. For developing a closed-loop drug delivery system, the control system works with a group of technologies like sensors, micromachining, wireless technologies, and pharmaceuticals. Recently, the integration of artificial intelligence techniques such as fuzzy logic, neural network, and reinforcement learning with the closed-loop drug delivery systems has brought their applications closer to fully intelligent automatic healthcare systems. This review's main objectives are to discuss the current developments, possibilities, and future visions in closed-loop drug delivery systems, for providing treatment to patients suffering from chronic diseases. It summarizes the present insight of closed-loop drug delivery/therapy for diabetes, gastrointestinal tract disease, cancer, anesthesia administration, cardiac ailments, and neurological disorders, from a perspective to show the research in the area of control theory.

Keywords Closed-loop control · Drug delivery · Control system · Biological systems · Insulin therapy · Cancer treatment · GI tract · Neurological disorders · Cardiac ailments

Introduction

Over the last few decades, there have been significant advancements in the field of electronics, wireless communication technologies, bioengineering, computational intelligence, and automation, which generate unlimited possibilities in the field of healthcare. Another significant engineering area, namely, the control system, has become an integral part of healthcare applications such as robotic surgery, image-guided therapy, life-support systems, closed-loop drug delivery, and automated and implantable devices. One of the significant challenges in the healthcare field is the requirement of dedicated medical staff to observe the patient for administrating the drug during various medical conditions such as surgery, post-surgery recovery, or critically ill conditions. In emergency conditions such as a pandemic, it is difficult for the caregivers and clinicians to reach each patient; therefore, the automated drug delivery plays a crucial role in reducing the unnecessary load on clinicians and nurses in routine emergencies. Moreover, people have become more aware of their health nowadays, and they prefer their personalized medical devices, which provide feedback about their health condition daily.

With medical research progressions, new drugs have also been developing to treat various human diseases. The conventional drug administration methods are either oral or infusion, which distributes the administered medicine

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to the whole body. Unfortunately, this kind of distribution may damage the body's healthy tissues and cells [1]. The most suitable way of administering medicine or drugs should follow the five norms, such as the right patient, right dose amount, right route, proper timing, and right drug [2]. Different drugs do not have the same effects on other patients due to intra-patient variability and drug dose. Due to the intra-patient pharmacokinetics and pharmacodynamic effects of the administered drug, some drugs may show their immediate response, and others may take some time to show their effectiveness. Despite the broad therapeutic view of many medications approved by the Food and Drug Administration (FDA), some drugs have a limited therapeutic range, such as chemotherapeutic drugs, for cancer treatment to limit the side effects [2]. Hence, clinicians require a method to administer medicine in a controlled manner.

The open-loop drug delivery has been a classical method for administering the drug to patients, a prescheduled and controlled drug release. Recently, closed-loop control has gained popularity in the medical sector because of its ability to maintain drug concentration to regulate the physiological parameters within desired limits using a feedback element. Despite several other advantages, the closed-loop systems can keep the constant physiological parameters even in disturbances and can compensate for the interpatient variability to a more considerable extent [3]. For many years, the focus of researchers has been on closed-loop anesthesia administration and continuous glucose sensing [4]. Still, most of the presently available delivery systems cannot provide an exact dose of a therapeutic compound to the desired organ within a particular time interval [5]. An automated drug administration system is a pre-programmed drug delivery system with minimum human interference. The drug dose is administered via electronic or mechanical instrumentation systems like microprocessors with features such as adjusting the dose amount as per required set point, drug concentration, and plasma drug concentration [6].

Any drug delivery system's goal is to provide the therapeutic effects of drug administrations by limiting its side effects. For instance, the anesthesia drug administration is of two types, i.e., bolus dose (delivered with a handheld syringe) and continuous infusion (using an infusion pump). Another popular category of anesthetic drug infusion is a target-controlled infusion. In this, the physician works with a computer for drug infusion. The computer-computed drug can be delivered by either bolus or infusion to obtain the desired concentration. It instructs the infusion pump to infuse the calculated amount of medication; the computer continuously computes the amount of drug present in the tissue and its influence on the amount of drug for obtaining the target concentration using the pharmacokinetics model the drug used and host patient covariate. The surgical stimulation varies faster during the surgery, which requires precise and rapid administration of the dose. However, the traditional infusion techniques cannot perform effectively in these varying conditions; therefore, the target-controlled infusion using pharmacokinetic models would provide a potential solution to the physicians for more precise anesthetics administration [7]. The closed-loop systems perform better than the open-loop systems for drug administration for conditions such as vasopressor therapy, fluid resuscitation, and anesthesia administration. These systems have several advantages like prevention from over-dosage, reduction in physiological variability, and relaxation to caregivers [8]. The safety and efficacy of each drug depend on drug-related factors such as administration route, patient characteristics, disease status, dose regimen, pharmacokinetics, and pharmacodynamic characteristics of the drug [9]. Moreover, electronics and pharmaceuticals' collaboration has generated drug delivery devices to enhance patient choice and upgraded patient adherence to the therapy [10].

In recent times, the microelectromechanical systems (MEMS) technologies are rapidly developing and provide small device's mass production. Several advancements in infusion devices that can sense, mix, pump, and control fluidic volumes such as bio-capsules, microneedles, and implantable pumps have been reported in the literature. These drug delivery systems mainly use three components, i.e., drug reservoir (chamber), release mechanism, and packing. The medicine/drug is delivered to the human body's desired location using different actuation mechanisms to ensure accuracy and reliability. These systems can also be used with microvalves and microsensors and develop a feedback control loop [11]. Therefore, these devices open new possibilities in closed-loop drug delivery; for example, an effective real-time closed-loop insulin delivery device has been possible due to modernizations in the field of subcutaneous insulin infusion pumps and real-time glucose monitoring sensor [12].

The control algorithm is a significant factor in closed-loop–based medical therapy. It is still a developing field that reduces intra-patient variability issues [2]. For designing any closed-loop system, an efficient control algorithm is a prime and essential requirement. For control applications, a proportional-integral-derivative (PID) controller is the first choice for the process and healthcare sectors. The advanced control algorithm, such as optimal control or model predictive control (MPC), is considered for healthcare applications [13]. The inter-patient variability is one of the hurdles in the closed-loop drug delivery systems. Frequent changes in pharmacodynamic-pharmacokinetic model parameters cause difficulty in implementing a standard controller that could work over many patients. The problems also increased by uncertainties that occurred by variations in the host patient's model characteristics during a clinical procedure [14]. Therefore, the adaptive and online controllers could be a possible solution for the closed-loop drug delivery mechanism of biological systems.

In this era, the artificial intelligence (AI) techniques showed their potential to provide advanced data prediction and analysis and develop personalized medicine. The AI-based control techniques such as fuzzy logic control (FLC) [15, 16], neural network [17], and reinforcement learning [18] have been gaining popularity among researchers. The FLC approach is a promising and model-free approach [19]. The MD-Logic Artificial Pancreas System for type-1 diabetes uses FLC for obtaining the lines of reasoning of the diabetes expert. In 2015, Medtronic received this system's license worldwide with a clear vision of using AI-based techniques in their future closed-loop control devices [20]. Recently, the use of machine learning approaches seems a long-running business in the medical sector. For example, the machine-learning algorithm has been in service to suggest a suitable action for the real-time physiological waveform data in the operation theatre, and its collaboration with patient demographic obtained from electronic health record system, and it could allow the real-time information on the bedside system as a support for clinical decisions. The clinician, performing anesthesia administration, uses several hemodynamic measuring devices and electronic recording systems. The machine learning–based systems would provide personalized medical care to the patients in a proper manner [21]. The quality of healthcare systems has been improved with additional machine-learning algorithms and AI techniques [22]. Moreover, integrating areas such as information technology, artificial neural network, and wireless communication can lead to smart drug delivery devices to overshadow the limitations of conventional therapeutic techniques [23].

The advancements in the field of medical, ultra-low-power computing, sensing techniques, and networking have revolutionized the area of implantable and wearable medical devices such as insulin therapy, deep brain stimulation, cardiac pacing, intrathecal drug delivery, defibrillation, and many others. In general, these devices communicate to external diagnostic tools to form a personal healthcare device, using wireless technologies [24]. The personalized physiological medicine would become a significant part of intensive care unit applications [25]. The Internet of Things (IoT) has a substantial role in the implementation of personalized monitoring systems. Moreover, smart syringes and pills are gaining popularity in the smart healthcare domain [26]. The IoT provides users the capability to plan daily, and it communicates, both wirelessly and physically, with real-world devices such as smartphones and tablets [22]. Therefore, the collaboration of IoT with the healthcare sector helps develop technologies to provide medical assistance to every person at ease and automate healthcare services.

There have been considerable developments in closed-loop glucose control for insulin delivery and closed-loop anesthesia administration, which results in fully functional closed-loop therapy for clinical use. However, a fully automatic closed-loop insulin therapy is still under investigation. These advancements have laid a base for innovations in other medical areas that require closed-loop control applications. Here, the authors present a thorough and rapid review of the most widely used closed-loop drug delivery administration system for diabetes, anesthesia, cardiovascular system, gastrointestinal tract, cancer treatment, and neurological disease, with a broader perspective of control theory applications. Further, the limitation of present schemes and future visions for the development of fully closed-loop drug delivery or therapeutic devices have also been reported.

Basic scheme of closed-loop drug administration

In this section, the essential components of a closed-loop drug delivery system designed to treat any disease are presented. A closed-loop drug delivery system has three parts: sensor, actuator, and an effective control strategy. One typical example of this is to bring the glucose level concentration within its desirable limit by infusing a precise amount of insulin dose using an insulin infusion pump. Another example is administering specific doses for chemotherapy treatment for cancer patients and, similarly, anesthetics dosage during surgery. For a closed-loop feedback system, the critical challenge is to provide an efficient control in the presence of several perturbations such as different patient sensitivities, external disturbances, or noise effects. The communication interface, such as a wireless communication device that can communicate with a mobile, microcomputer, or some built-in mechanism, is also essential for personalized devices. A brief description of the closed-loop drug delivery system components is presented in the following subsections, as shown in Fig. 1.

Sensor

A suitable sensor plays a significant role in designing any closed-loop system used to measure the physiological parameters. It is the feedback element of closed-loop control systems used for sensing the output variables. The drug delivery systems with micropumps incorporate the closed-loop feedback systems that enable the pump to perform, monitor, and increase the efficacy of therapies provided to the user. The control over a delivery profile can be possible with the insertion of physical sensors to the system that generates the information for pressure,

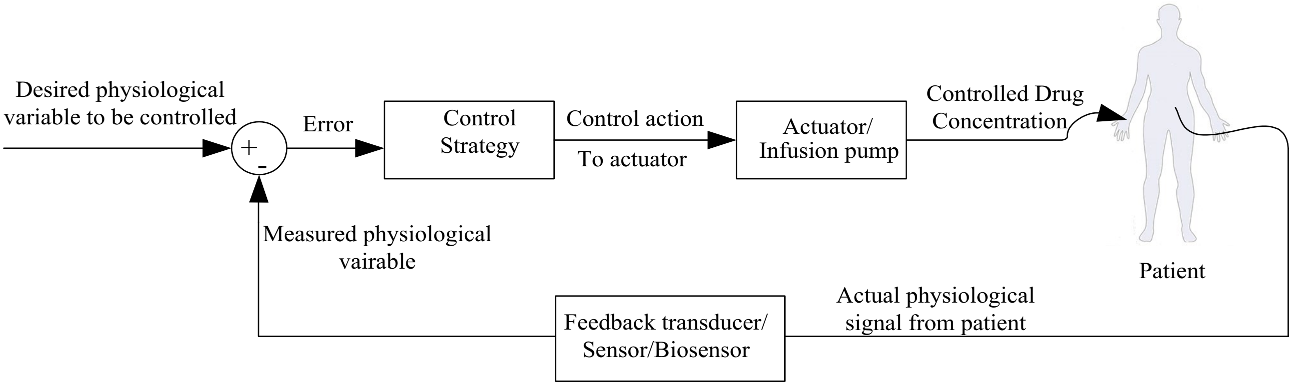


Fig. 1 Basic block diagram of closed-loop drug delivery administration

flow rate, forward delays, and real-time status of the micropump [27].

For glucose measurement, mainly three glucose-sensing techniques are invasive, minimally invasive, and non-invasive [28]. The advancements in closed-loop insulin therapy are ignited with the development of sensors such as Medtronic (Cygnus) [13]. As per [29], the traditional biochemical invasive technique is painful. It involves drawing small blood from the human body and determining the glucose level via the blood sample's biochemical analysis. The minimally invasive method is less painful and available in portable glucometers wherein the pricking of a finger is to be done to get a drop of blood. Other minimally invasive techniques include fluorescent sensor technique and microdialysis probe, and their procedure is also painful.

Therefore, developing painless and non-invasive glucose measurement methods with high reliability and good accuracy is needed. Non-invasive glucose sensing techniques are far-infrared spectroscopy, near-infrared (NIR) spectroscopy, impedance spectroscopy, and many others [29].

Due to advancements in high sensitivity, miniaturized design, and effectiveness properties of electronics detectors, the effective analytical method in detecting infectious agents and the development of personalized medicine have been cited. A biosensor is used to detect an analyte that binds a biological component of the body to a physiological detector. The transducer can be of optical, electrochemical, or thermal type [30]. Another class of sensors is the implantable biosensors that can deliver continuous data on the levels of a target analyte and monitor the changes in analyte levels over a while without any interference from the patient or physician. For example, a continuous glucose-monitoring system for the long-term use (more than 90 days), Eversense, Senseonics Inc., has been in the market which uses an implantable glucose-monitoring sensor, wearable smart transmitter, and a mobile app for the display of real-time measurement. The long-term implantable sensors also reduce the risk of sensor damage [31].

Electrochemical glucose sensors played a significant breakthrough in insulin therapy for a diabetic person [32]. Sheybani et al. presented the implementation, fabrication, and description of a completely integrated, electrochemical-based drug tracking system. It has some significant features such as real-time tracking of drug delivery, detection of leaks, and blockage present in the pump system [33]. The electrochemical aptamer-based switching sensor recently received significant popularity for real-time sensing of different small molecules and biological analytes [34]. Another promising area for transdermal biosensing is the use of microneedles, which provide minimally invasive and easy-to-use technology. In recent years, Abbott developed the FreeStyle Libre® Flash Glucose Monitoring system, consisting of a tiny glucose-sensor to be worn under the skin and connected with a water-resistant plastic on the body patch. It has real-time glucose monitoring, trend evaluation, comprehensive reports, and glucose monitoring for 14 days [35]. With the continued advancements in fabrications and MEMS, the development of new and improved sensors could be possible, and it is also the need for the state-of-art healthcare sector.

Infusion pump or actuator

It is one of the developed components of the closed-loop control system for medical applications. A drug administration system usually consists of a small, electronic-controlled personal mechanical pump that provides the patients' drug infusion via subcutaneous or intravascular catheters. The state-of-art infusion pumps have high precision, low flow rate, battery power, app-based small form factor, and integrated wireless control mechanism. The commercially available continuous infusion pumps are for insulin therapy for diabetes control and viable for future works. The present-day insulin pumps are a small pager size, with an insulin reservoir, a small battery-operated motor connected to the computer control mechanism, and a subcutaneous infusion system via cannula and tubing system [1]. Despite the time-lag issue in the control system, closed-loop therapies use subcutaneous pumps due to their features, such as higher ease to the users [36].

An infusion pump, in general, is used to administer the drug to the patient body. In 1999, Kwok et al. presented their experience in implementing a computerized drug delivery system to control mean arterial pressure wherein the IVAC 570 infusion pump was used [37]. Cobo et al. developed an implantable micropump with small-form factor features and wirelessly controlled to administer the drug for cancer treatment in small animals such as rodents. The commercially available pumps for mice are Primetech, Alzet pump, and iPrecio pump. The presented pump uses a low-power electrolysis actuator to dodge heavy implanted batteries [27].

The clinical insulin pumps are widely used due to their accuracy, predictivity, easy-use, and insulin bolus dose calculation based on user-input data. However, these pumps have some issues, such as tubing being used to deliver the insulin, which can catch or detach. Therefore, patch pumps have been developed with advanced characteristics like lightweight, smaller in size, readily adhere to place, disposable (entirely or partially), and no tubing for infusion. Though there are several advantages of patch pumps, some problems are still associated with their use, such as pump size, poor adherence, and controller requirement [38]. The insulin patch systems are based on the cannula to deliver the drug to the skin, but the cannula insertion is a painful procedure, and the risk of infection is enhanced [1]. The scientists in patch pumps have resolved some issues by involving control components. The OmniPod® Insulin Management System, Insulet Corp., MA, was the first patch pump promoted in the USA, consisting of a pod, which is to be replaced every 3 days, and a personal Diabetes Manager is required [38]. Layne et al. presented an extensive review of the development and latest advancements in Pod and Personal Diabetes Manager used for insulin therapy [39]. Cengiz et al. demonstrated an excellent review of the results and future challenges in insulin pumps [40].

As per [40], there would be increased use in real-time continuous glucose monitoring for better glycemic control to cut the risk of hypoglycemia and result in a fully automatic artificial pancreas. Moreover, ultra-fast acting insulin pumps are the prospects of closed-loop insulin therapy. Another promising technology for drug delivery in closed-loop systems is with microchip drug delivery implants in which an array of specifically addressable and sealed drug reservoirs with drugs [1]. Various implantable on-demand drug delivery devices have also been investigated for neurological disorders. In 2018, Dagdeviren et al. developed an implantable, miniaturized, remotely controlled neural drug delivery system that can perform dynamic adjustment of the treatment with precise spatial accuracy. It was reported that this developed system was capable of modulating the local neuronal activity in small rodents and large animal models and enabled feedback control by recording the neural activity simultaneously [41]. Therefore, it is an open area for researchers to develop small and efficient actuators or infusion pumps with advanced features.

Control strategy

The control strategy/algorithm is the heart of the closed-loop drug delivery system. It takes the input from the feedback sensor and calculates the required drug concentration as per the patient's physiological condition. The appropriate control signal, then actuates the drug infusion pump to deliver the necessary amount of drug to the patient whenever requires. In general, the control system acts as an intermediate connection between the biosensor and the drug infusion mechanism. It helps in translating the sensor readings into the instructions for drug delivery. The control system can be a personal computer, a laptop, a smartphone, or a built-in unit [36]. The smartphone seems a perfect choice for incorporating a control system due to its wireless features. Dexcom (San Diego, CA) and Abbott Laboratories (Lake Bluff, IL) developed implantable glucose biosensors and operated them with the smartphone with Bluetooth and NFC protocols. Moreover, the Minimed® 670G (Medtronic, 2017) uses the control system with an insulin pump tied to the patient via a catheter, and the communication with implanted biosensor is purely wirelessly [36].

For many years, PID controllers are the prime choice for control engineers even in the medical field because of their unparalleled advantages, such as various methods for tuning control parameters, acceptable performance, and simple implementation [42]. Chee et al. presented an expert PID control approach for the patient's blood glucose regulation in intensive care units. The combination of the concept of expert systems and traditional PID controller is applied with clinical sliding table techniques [43]. The conventional PID controller and MPC approach are the two commonly used pump-controlling approaches in the closed-loop systems [38]. The PID controllers are unresponsive to the time delay associated with the subcutaneous glucose monitoring and insulin infusion route. Due to limitations of classical PID controller, the MPC approach has been gaining popularity due to its features: reduction in time-lags associated with subcutaneous glucose monitoring and insulin delivery as a personalized model adapts to an excellent extent to individual glucose dynamics; a model learns from daily life activities and optimizes its response to a subsequent meal; the model-based control strategy allows the use of meal- or hypoglycemia-sensing approach [44]. Several authors have recently used the MPC approach for insulin therapy to regulate blood glucose [12, 45, 46]. Other most commonly used control approaches are optimal control, sliding mode control (SMC), and FLC [47, 48], artificial neural network [49], and H-infinity control approach [50]. The detailed description of various control approaches for different drug administration system is presented in subsequent sections . However, the control theory is a growing engineering area to solve complex real-world problems, even for the healthcare sector.

Communication interface

Wireless technologies are a prominent part of smart healthcare systems. Various wireless techniques such as Bluetooth, 6LoWPAN, radiofrequency, and Wi-Fi are commonly used in healthcare networks to communicate and exchange information. The state-of-art computing devices use devices such as smartphones, personal digital assistants, tablets, and supercomputers. The memory of devices significantly accounts for smart healthcare devices, as information needs to be stored [22]. The integration of IoT with intelligent healthcare provides a platform to make these devices automated. These devices' essential components are sensors, actuators, a local area network, the Internet, and the cloud [22]. A schematic diagram of closed-loop drug administration or therapy for different biological ailments such as cancer, cardiac problems, GI tract diseases, and others is shown in Fig. 2.

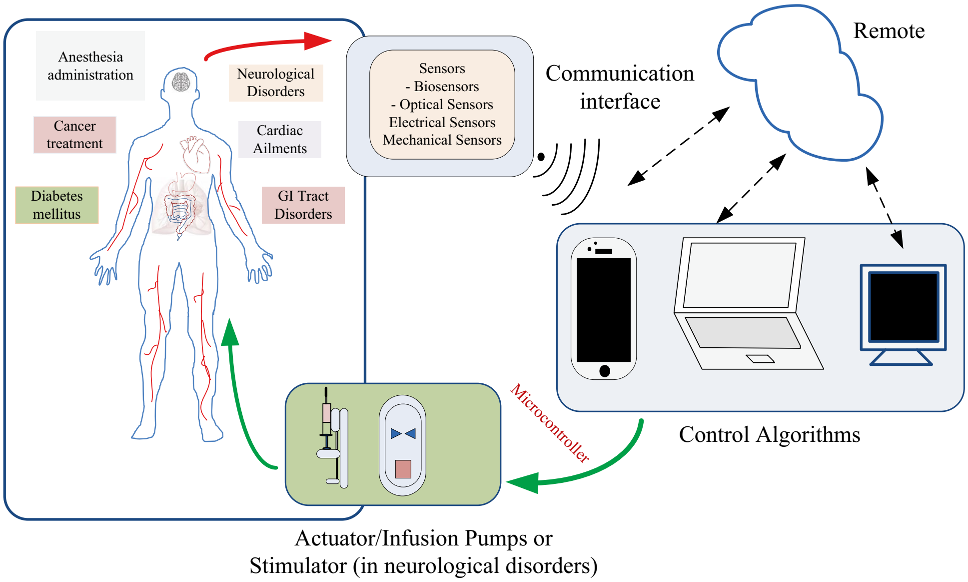
Developed techniques for closed-loop control of different biological systems

In this section, different healthcare areas in which the closed-loop drug delivery techniques/therapies have created radical changes are discussed. The advancements, current research, challenges, and future scope in the field of closed-loop drug delivery systems/therapies are cited in the following subsection:

Closed-loop diabetic control and insulin delivery

As per [51], it is reported by the International Diabetes Federation that the estimated number of diabetic patients would grow to 642 million in 2040 as compared with approximately 415 million patients in the year 2015. It is reported that there are mainly three types of diabetes, such as type-1 diabetes, gestational diabetes, and type-2 diabetes, which are identified by a high level of blood glucose, i.e., hyperglycemia. Several methods, such as insulin pen, pump, and syringe, are used for insulin delivery to the user. However, subcutaneous injection is widely used due to its advantages, such as high absorption capability, cost-effectiveness, and delivery efficacy. Administration of frequent injection can cause pain and infections to the patients. The sub-optimum delivery of insulin can cause hypoglycemia, resulting in behavioral and cognitive disturbances, brain damage, coma, and even death. Therefore, researchers have been working in different insulin delivery areas such as non-invasive, controllable administration, oral, nasal, and transdermal delivery [51]. The use of painless needles, such as microneedle patches, has been fabricated for transdermal insulin administration with thin and short features to minimize the pain [52].

Fig. 2 A schematic diagram for closed-loop control of different biological ailments



In general, type-1 diabetes is an autoimmune state that primarily affects the pancreatic beta islet cells and can cause insulin deficiency and hyperglycemia in the host body [53]. As per [54, 55], the population with Type-1 diabetic patients has been increased by 3–5% per year to 1.1 million worldwide from 2000 to 2019. For diabetic patients, one of the leading standard solutions to cope with impaired beta-cell function is pancreas implantation or preplacement of islets. However, due to limited resources, no perfect technique has been developed for supplying sufficient function beta-cells. Therefore, the best option for diabetic patients is to use closed-loop control [56]. The basic design of closed-loop insulin therapy for regulating the blood glucose level is shown in Fig. 3.

Since 1950, the closed-loop drug delivery system has been an area of research for many scientists. In 1980, Miles Laboratories was the one who received premarket approval for its device named as BIOSTATARTM system, which is used to control the blood glucose levels by insulin infusion for the diabetic person [57]. As the validations are under observation, the closed-loop artificial pancreas has become one of the most potent options for diabetic patients [58]. With the advancement, the artificial pancreas may become a completely automated and closed-loop system having a glucose monitoring facility, insulin infusion pump, and a suitable controller [22].

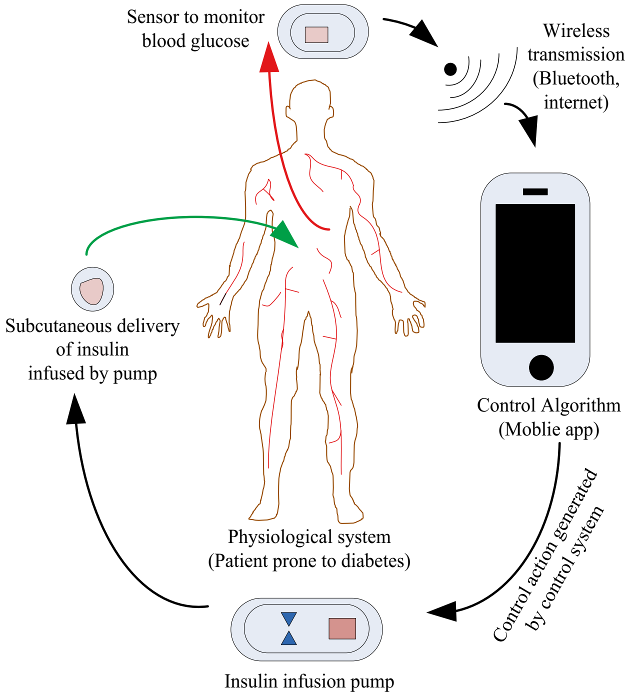


Fig. 3 Basic block diagram of a closed-loop control strategy for insulin delivery

Various control techniques such as classical PID [59], H-infinity [60], MPC approach [61], SMC [62], FLC [63], and neural network [64] have successfully been developed for closed-loop control. Over time, the most commonly used control approaches have been traditional PID and MPC approach. The PID controller cannot work effectively in disturbances; therefore, the model-based approach MPC can be utilized [65]. Dudde and Vering investigated the use of an MPC approach for automated insulin delivery [61]. Kaveh and shtessel proposed the SMC applied to regulate the blood glucose level in diabetic persons [66]. Yasini et al. presented an H-infinity controller-based technique for a type-1 diabetic patient to regulate the blood glucose level [67]. Borrello et al. presented a nonlinear compartment model for observing the difficulties faced during treatment with patients having different patient sensitivities at the intensive care unit, wherein 15 different sets of patient parameters are used [68]. Zavitsanou et al. investigated an individualized optimal insulin delivery using a control strategy with patient-specific model-predictive control, a personalized scheduling strategy, a state estimator, and open-loop optimization formulation related to patient-specified process models and bounds [69]. Emami et al. explored different mathematical models that describe the relationship between endogenous glucose production and glucagon and insulin level in the subject [70]. Del Favero et al. presented an outpatient study to investigate postprandial glucose regulation in artificial pancreas using MPC strategy [71]. Cao et al. presented an extreme seeking control strategy for developing personalized zone adaptation features in the MPC approach for patients with type 1 diabetes [72].

Further, Shi et al. proposed a control penalty adaptation strategy for zone MPC for artificial pancreas using the predicted glucose and its rate. The robustness and performance of the proposed adaptive control strategy were carried out on 100 adult cohort of FDA-approved UVA/Padova simulator, and tested against conventional zone MPC strategy [73]. Percival et al. presented a multi-parametric MPC for subcutaneous insulin delivery for individuals with type-1 diabetes. These control approaches were efficient, robust toward insulin sensitivity variations, and minimum burden for the patient [12].

In recent times, the AI-based control approaches, such as FLC and neural networks, have also been investigated to regulate the blood glucose level for diabetic patients. As per [20, 74], most of the ICU-based glucose monitor controllers are mathematically driven and based on traditional PID controller or MPC approach. In this, an AI-based control approach is suggested to achieve better regulation of glucose. Asadi and Nekoukar presented an adaptive fuzzy integral SMC technique for glucose regulation wherein system dynamics are obtained online using fuzzy logic systems [65]. In 2012, Yasini et al. also presented a fuzzy logic-based closed-loop control system to regulate blood glucose [74]. Wang et al. developed a collaborative control approach with particle swarm optimization and the MPC approach to identify the model online and automatically optimize insulin drug rate design [75]. Trajanoski and Wach implemented and evaluated a simulation study of neural predictive control approach for closed-loop control of glucose using subcutaneous tissue glucose sensing and subcutaneous infusion of monomeric insulin analogs [76]. Song et al. presented the learning-type model predictive control for artificial pancreas by an unannounced meal for patients with type-1 diabetes to emphasize the performance and safety concern [77]. Canete et al. presented an artificial neural network–based technique to obtain patient dynamics identification and blood glucose regulation. For this study, a Lispro infusion subcutaneous pump and subcutaneous glucose monitor were used to get the clinical datasets for diabetic patients under treatment[49]. Further, an in silico and ad hoc artificial neural network model was obtained for every patient to find the insulin-glucose relation [49]. Daskalaki et al. investigated an actor-critic learning control-based adaptive approach for regulating glucose in patients with type-1 diabetes under the treatment of sensor-augmented pump therapy [47]. In 2016, Grosman et al. investigated the effectiveness and safety features of Medtronic's hybrid closed-loop system for the patient with type-1 diabetes in a supervised outpatient manner [78].

Several authors have also implemented dedicated control strategies for closed-loop control of blood glucose levels for diabetic patients. Kato et al. presented a drug release system based on converting chemical energy, glucose, and mechanical energy or pressure. The unique feature of this technique is that it utilizes the organic engine technique, which does not require any kind of power source [79]. Patek et al. proposed a three-layer modular configuration for diabetes control, consisting of a continuous safety system, sensor and pump interface module, and a real-time control system with post-meal insulin infusion features recommendation for regulating hyperglycemia and safety for the prevention of hypoglycemia [80]. Jacobs et al. implemented a fully automatic artificial pancreas design that takes the glucose readings from two sensors and delivers insulin and glucagon to the patient without any human intervention [81].

Similarly, Moscardö et al. presented a dual-hormone control approach for glucagon- and insulin-coordinated delivery with a multi-input single-output plant [82]. Berián et al. proposed a wearable insulin delivery system that lowers the computation requirements and energy consumption without harming the computation needs [83]. Ruan et al. investigated a hierarchical model to develop a relation between subcutaneous insulin administration and the carbohydrate intake for continuous glucose monitoring for 12 weeks with a daily variability [84]. Tschaikner et al. developed a novel diabetic treatment device with a commercially available continuous glucose sensing and insulin infusion design via a single-skin insertion site [85]. Tauschmann et al. investigated the effectiveness of sensor (enhanced Enlite Medtronic MiniMed, Northridge, CA) life for overnight closed-loop control. The closed-loop glucose monitoring accuracy varies with sensor life, such as the least accurate on day 1 of sensor insertion in the host body [86]. Several authors have presented extensive reviews on developing different technologies and glucose monitoring advancements for diabetes [87–90]. Bally et al. reported a closed-loop system approach to improve glucose control in patients suffering from type-2 undergoing non-critical care [91]. Turksoy et al. presented a system that collaborates hypoglycemia early alarm system with the artificial pancreas controller, which integrates multivariable technique to provide information for glycemic control during exercise and sleep to prevent the danger of hypoglycemia. This system does not need any patient information, such as exercise announcements, meals, and preprandial insulin bolus during closed-loop studies [92].

Some examples of closed-loop glucose monitoring devices are Dexcom SEVEN PLUS (DexCom Inc, USA), MiniMed (Medtronic, USA), and FreeStyle Navigator (Abbot Laboratories, USA) [93]. The first commercial MiniMed closed-loop glucose monitoring system was limited for clinical use only. This device was planted under the skin and saved 3 days of data from downloading and analyzing blood glucose levels [36]. In 2017, the FDA approved MiniMed® 670G for sale, facilitating the closed-loop control of basal glucose with a closed-loop glucose sensor and a wearable insulin pump. The available device acts as a hybrid closed-loop system wherein the user's role is specified for manually delivering meal boluses, inputs about diet and exercise, and calibration of sensor data 2–4 times/day. Therefore, the requirement of an entirely closed-loop system has still been a hotspot for researchers and scientists. Recently, the collaborative approaches have been adopted by firms such as Dexom and Tandem Diabetes Care, Abbott, and Bigfoot Biomedical, as well as Senseonics and Roche, to jointly investigate the closed-loop system for the next few years [36]. Therefore, the design and development of closed-loop control of insulin therapy is still an open problem for control engineers and other scientific community.

The closed-loop artificial pancreas requires a control algorithm to deliver an appropriate amount of insulin to keep the blood glucose level within safe limits. However, a suitable controller's development requires accurate mathematical modeling, a significant and emerging research area for the past few years [94]. Despite significant advancements, researchers have still been looking for a solution to improve the components. Advanced insulin pumps have been used for efficient diabetic control [95]. Other technical specifications for closed-loop systems such as insulin pumps can be smaller in size, advanced safety characteristics, and adequate energy efficiency. Further improvements in closed-loop glucose monitoring could be in supervising algorithms and possible miniaturization of glucose sensors to enhance the patient's ease or make it implantable for long-term use.

Closed-loop control and drug administration in cardiac ailments

Despite significant advancements in the field of cardiac assist devices (CAD), the use of control systems and modeling concepts are comparatively newer concepts added to this area [96, 97]. For a prosthetic blood pump, the control techniques imitate the human heart's typical local response due to cardiac output requirements. The current devices, such as artificial hearts and ventricular assist devices, employed simple control techniques for obtaining the operation at a fixed rate for pulsatile flow pump or fixed speed for continuous flow pumps [97]. The first CAD device, namely Baxter/Novacor left ventricular assist device (LVAD), obtained FDA approval in 1998 [98]. The present-age pacemakers also consist of an analog sense amplifier, output circuit, a telemetry system, and a controller using a microcontroller. Moreover, the implantable pulse generators or cardiac pacemakers also developed real-time sensing skills to detect and monitor intracardiac signal events [99]. As per [100], several control possibilities, such as adaptive PID control, FLC approach, and fuzzy logic PID techniques have already been developed to design cardiac pacemakers. Shi also investigated an intelligent control method based on the fuzzy PID approach for the cardiac pacemaker system [101]. In 2018, Karar presented an adaptive backstepping controller for improving the dual-sensor pacemaker's performance for controlling the heart rate using a radial basis function neural network [102]. The diagnosis of coronary artery disease is a significant measure for patients suffering from cardiac disorders. Therefore, pharmacological stress testing is one of the alternatives to exercise stress testing. A closed-loop drug-device system was implemented for the diagnosis of CAD wherein drug catecholamine; arbutamine was infused intravenously to enhance the heart rate and cardiac contractility to generate symptoms of ischemia [103].

Another most significant cardiac system area that has been evolved, in recent times, with the advancements in control theory, is the mean arterial blood pressure (MABP). It is one of the most significant hemodynamic parameters of the human body. It should remain within stable limits in various clinical conditions such as anesthesia administration, cardiac surgery, and post-surgery recovery as post-operative hypertension leads to severe problems like cerebrovascular problems, disruption of vascular suture lines, and bleeding [104]. The most commonly used fast-acting vasodilator drug is sodium nitroprusside (SNP) to lower blood pressure. The prime requirement to deliver its precise and accurate dose automatic control of MABP seems a better option during critical situations. Though several researchers have been working toward automatic MABP control, it does not seem an easy option for the control engineers due to some issues such as time-varying uncertainties, time-delay, and modeling uncertainties of the SNP dose-model response [105]. Over the years, various control schemes have been proposed for automated regulation of the MABP for drug infusion—such as PID controllers, adaptive controller [106], model reference adaptive control [107], robust multiple model adaptive control [108], FLC [109–111], MPC [112], fractional order control [113], neural network [114], and reinforcement learning [115]. Kwok et al. presented a computerized drug delivery system for the automatic regulation of MABP using SNP infusion. The control algorithm comprises long-range predictive control with a collaboration of a finite horizon and infinite horizon optimization terms. The control algorithm works adaptively using recursive control relevant identification for the proposed long-range predictive control approach [116]. Polycarpou and Conway presented an adaptive neural network method for modeling and closed-loop control of MABP via SNP drug infusion, wherein an indirect model reference adaptive control approach using neural network is developed [117]. In 1992, Ying et al. investigated a closed-loop control for MABP regulation in post-surgical patients via SNP drug infusion using a fuzzy-PI controller [118]. Treesatayapun presented a self-adjustable multi-input fuzzy rule emulated network approach and its learning method for automated control regulation of MABP for intravenous SNP drug delivery [119]. Gao and Er presented an adaptive control and modeling scheme with a generalized fuzzy neural network to control blood pressure via SNP infusion. The feedforward generalized NN was applied with a linear feedback control approach [120]. Tafreshi et al. presented a robotic tilt table for early mobility by modulating the body inclination and automatic leg movement to control the heart rate and blood pressure using an intelligent self-learning FLC scheme [121]. In 2020, Sharma et al. investigated an interval type-2 FLC approach to control MABP for SNP drug infusion. The results are compared with FLC-PID control and traditional PID control approaches. Moreover, the optimal control parameter values were obtained with the cuckoo search algorithm. The future perspective in blood pressure regulation explores new adaptive and intelligent control algorithms, designing cost-effective hardware, and exploring efficient sensing technologies [122]. Therefore, it is evident that the new research studies have been going on design and development of closed-loop controlled drug delivery to control the MABP for different clinical conditions to improve the persons' quality of life in critical care units during surgery.

As per [108, 123], the only commercial device named IVAC titrator (IVAC corporation, San Diego, CA, USA) was available in the market till 2012, and later discontinued from the market. The IVAC TITRATOR system was the only closed-loop SNP drug delivery device that received the FDA's premarket approval to regulate blood pressure following the cardiovascular surgeries [97]. It was removed from the market due to reasons such as not advanced computer-interface technology, no reliable communication standards presented at that time, used customized blood pressure sensor that was not easy to use, high price, and unclear effect of reduced variabilities patient outcomes. However, with new communication standards and advancements in the microprocessor-based pump techniques, a closed-loop MABP system could improve the market [123]. Moreover, in this era of IoT, wireless technologies, AI-based control approaches, and MEMS technologies, it seems possible to occupy the market with cost-effective and reliable automated, even implantable, blood pressure systems that could improve patients' life quality and possibly remove the workload of caregivers and clinicians.

Closed-loop drug delivery in GI tract disorders

The diseases such as small intestine tumors, obscure gastrointestinal, and Crohn's disease are related to the body's gastrointestinal system. These chronic diseases demand the targeted delivery of doses for their treatment. The controlled-drug delivery systems infuse the continuous release of medication at a particular position of the gastrointestinal tract [124]. There has been increased research in targeted and reliable drug delivery for gastrointestinal systems nowadays. One solution to detect and diagnose the mentioned pathologies associated with the GI tract is the wireless capsule endoscope [125]. Several authors have worked toward developing an efficient capsule endoscope (CE) for the past few years. In 2000, Meron produced an M2A capsule endoscope, Given Imaging, Yoqneam, Israel [126], which was used to examine the small intestine because the traditional endoscope could not travel the total length of the GI tract. This CE has a video imager, light source, transmitter, and batteries in a small 11 × 26-cm^3 plastic cylindrical container, and it is propelled by the natural driven by peristalsis [127].

Another device by Olympus America (Allentown, PA) was approved by the FDA to provide an image of the small intestinal mucosa. Later, the M2A capsule was named the PillCam SB (PSB) and obtained the FDA's approval for clinical use after its small trial with push enteroscopy [128]. Some other CE also includes MicroCam (IntroMedia, Korea) and OMOM (Chongqing Jinshan Science and Technology Co Ltd., China). These available CE technologies suffer from one issue, i.e., using the natural peristalsis of the digestive system, which can be a reason to miss some disease lesions [129]. Despite several advancements, the wireless CE was used for the diagnostic purpose; therefore, CE for providing treatment to GI tract pathologies was a significant concern. Therefore, several researchers developed some innovative devices for providing regional drug delivery, and these are IntelliCap by Philips Electronics, Enterion capsule (Phaeton Research), and InteliSite (Innovative Devices LLC). The delivery techniques employed in these devices cannot direct the particular pathogen, and the drug would spread over a small portion of lumen due to the peristaltic movement. They do not have any mechanism to stop the action and hold a particular position [130]. As per [131], the foremost therapeutic wireless capsule endoscope was developed to treat the GI tract bleeding using a clip-releasing mechanism. In 2011, Ciuti et al. presented an extensive review of wireless capsule endoscopy and swallowable devices for diagnostic and therapeutic applications [132]. Various authors have also worked in computer-aided detection methods for capsule endoscopy to diagnose GI tract pathologies [133, 134].

One of the commercially available capsules named Enterion™ can deliver solutions and powders to particular GI tract locations, wherein the capsule site can be obtained using gamma scintigraphy. However, the device cannot perform as an intelligent device to release a particular drug [135]. Woods and Constandinou presented a targeted delivery of dose in a confined tubular environment, and it integrates a holding mechanism for CE [130]. InelliCap® (Medimetrics along with Philips) is the first intelligent, electronic, oral, compact, and drug capsule for providing minimally invasive targeted delivery in the GI tract. It has built-in intelligence with temperature and pH sensor, and communication is done by wireless radio frequency technique. It provides personalized drug delivery at a specified time and place and is monitored by a personal computer [136]. It consists of a fully biocompatible covering, drug reservoir, a microfluidic pump-controlled embedded microprocessor for pumping action, wireless trans-receiver, on-board battery, and actuated medicine dispensing, and an electronic system with pH and temperature sensor [136]. The CE requires its inherent locomotion for its active control to provide an adequate diagnosis. In 2015, Lee at al presented a study for an active locomotive intestinal capsule endoscope system wherein the driving system was based on the externally electromagnetic actuation system [137].

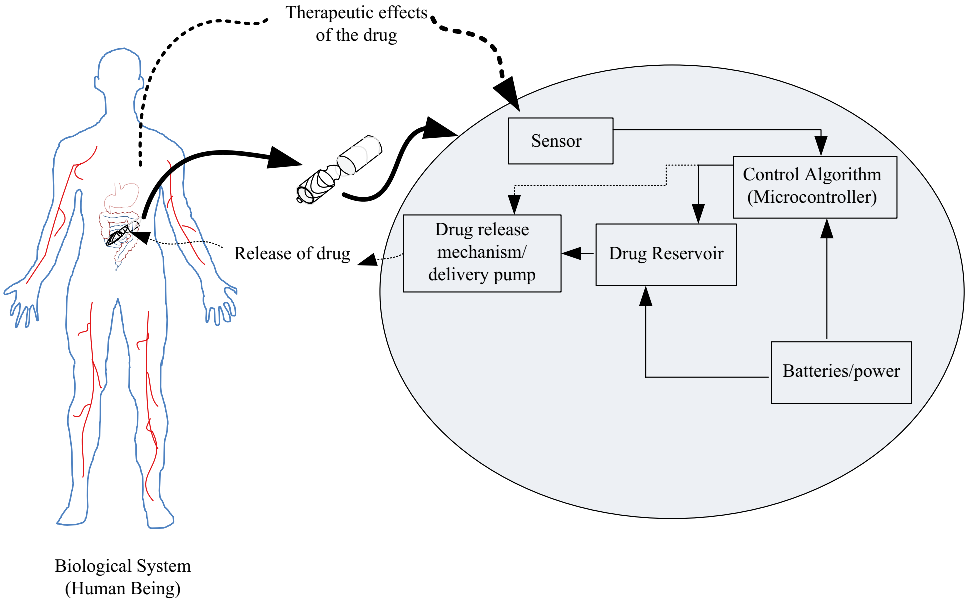
Similarly, Le et al., in 2016, presented a soft magnet material–based drug delivery module with active locomotive intestinal capsule endoscopy to develop features such as positioning control and drug release [129]. Fontana et al. presented a spherical-shaped wireless capsule endoscope using a magnet actuation technique for reporting colorectal cancer [138]. A therapeutic wireless capsule endoscopy using photodynamic therapy was developed to treat Helicobacter Pylori [139]. Leung et al. investigated a therapeutic technique using a balloon tamponade effect for treating GI hemorrhage. The inflatable balloon was used to stop GI tract bleeding by generating pressure between the GI wall at the lesion [140].

Swallowable pills are gaining popularity for drug administration because the oral administration of the drug is preferred for its low cost and massive patient acceptance [141]. Smart pills are beneficial for handling locally activated disease and gastrointestinal diseases like esophageal cancer, gastroesophageal reflex, and irritable bowel syndrome [142]. Capsule endoscopy devices have embedded cameras, data transfer, and a coin battery. Earlier, these endoscopic pills have locomotion with natural peristalsis motion of GI, which has limitations such as the incapability to stop and control and danger of capsule retention in the tract. Therefore, several researchers have been working toward adding locomotion means to the endoscope capsule. In [143], an extensive review of current locomotion techniques is available and their features like speed, size, power, temperature, and mobility mechanism. A basic scheme of closed-loop drug administration for the GI tract disorders using swallowable pills or capsules is shown in Fig. 4.

A capsule robot has been developed as the enhanced capsule endoscope, capable of active locomotion, i.e., the capsule robot can stop at different intestinal portions to perform a biopsy and drug delivery and can move backward and forward for diagnosis of mass lesions. Gao et al., in 2016, presented a motor-based capsule robot for exploring the GI tract, which is a small device and has a wireless power transmission method. Thus, the active locomotion is obtained with an inchworm mechanism having two expanding tools at each end with a central extensor [144]. In 2019, Guo et al. presented a release mechanism for drug delivery and remotely controlled the flow rate of drugs, quantity to be released, and release time of the drug. The drug delivery capsule to be administered to the GI tract consists of a shell, a release mechanism having two permanent magnets and a solenoid, batteries, and a control system module [124]. Hassan and Haque presented a real-time computerized bleeding detection method for wireless capsule endoscopy. The features are obtained using the normalized gray level co-occurrence matrix method, and the support vector machine was used for classification [145].

Goffredo et al. developed a small pill for local drug administration on gastrointestinal tissue. It consists of a miniature electrolytic pump. Its actuation principle is based on the electron of the water-based solution parted from the drug tank using an elastic membrane [146]. In 2019, Luo et al. developed a gastrointestinal artificial intelligence diagnostic system for providing a diagnostic tool for gastrointestinal cancer with the analysis of images obtained from clinical endoscopes [147]. In 2020, Saito et al. presented a deep learning–based detection method that can automatically detect different types of lesions in wireless capsule endoscopy images. In this work, a convolution neural network was trained with images captured of small bowels from various institutions and developed a model capable of automatically detecting lesions [148]. In 2020, Soffer et al. presented a detailed systematic review of the implementation and demonstrated deep learning techniques for wireless capsule endoscopy [149]. Therefore, the recent research of closed-loop control of therapeutic solutions to the GI tract diseases has been developing efficient actuators and advanced AI-based control strategies. It offers limitless opportunities in the near future.

Fig. 4 Basic block diagram of a closed-loop control strategy for GI tract disorders using swallowable pills



Real-time control of drug administration for cancer treatment

As per research, around 8 million people die from chronic cancer disease worldwide, and proper technologies can avoid about one-third of these unfortunate diseases [150].

Cancer has been a worldwide issue for researchers, engineers, and physicians in the present age. Cancer encompasses the uncontrolled and unregulated growth of abnormal cells, which are termed as tumors. These tumors can attack the surrounding tissues of the body, and travel to different body parts and, ultimately, it causes the death of the patient if it is not cured on time. The most common cancer generation causes external and internal factors, such as tobacco consumption, unhealthy diet, mutations, and immune conditions [151]. The formation of the tumor is due to the imbalance in cell proliferation and apoptosis. Moreover, this kind of proliferation of cancerous cells is exponential. Over the prolonged sequence of events and unsuitable treatment, this cell imbalance results in cancer cells' continuous growth that causes the death of cancer patients [152].

Different techniques such as chemotherapy, surgery, radiotherapy, hormone therapy, or immunotherapy or their combination have been available for the treatment of cancer disease. Among these approaches, chemotherapy treatment is the most regularly used for treating the person who has cancer. The chemotherapy approach's critical objective is to abolish the abnormal cancer cells after completing the treatment session [153]. However, the appropriate treatment using chemotherapeutic drugs has not yet been discovered, which can only destroy the tumor cells [154]. In 1995, liposomal doxorubicin was the foremost anti-cancer drug that got approval from the FDA [155]. As per [156], the main objectives of these radiations and chemotherapy therapies are to destroy the cancerous cells as the tumor cells are more prone to the cancer drugs and techniques due to their growth at a faster speed compared with healthy cells in adults. Despite several advancements for patient survival with these methods, the researchers have been working in the field of novel therapeutic targets, alternate dose route, and targeted delivery to enhance patients' quality of life and survival time [156].

During the chemotherapy sessions, the chemotherapeutic drug is injected into the body to kill the tumor or cancer cells. These drugs are administrated into the body through some veins or by some oral means. It is a known fact that chemotherapeutic agents are harmful. It is crucial to administer the drug as per the specific schedule, and a particular amount as the drug as the inappropriate dose can lead to killing healthy cells [157]. Therefore, it is the prime requirement for cancer chemotherapy to inject an appropriate amount of drugs on a scheduled time into the patient body. Over the years, several techniques [158–161] have been proposed for drug administration for cancer treatment, which is mainly in open-loop control manners such as numerical methods based on analytical gradient [158], direct search algorithm and systematic search region contraction [159], modified optimal control for the cancer drug scheduling using adaptive elitist population-based genetic algorithm [160], and optimal control technique for cancer drug scheduling using memetic algorithm [161]. The methods described above [158–161] are working in an open-loop manner. On the other hand, the closed-loop control systems are robust and accurate in the presence of disturbances and non-linearities; therefore, a closed-loop drug delivery system can be used to improve the performance of chemotherapy treatment [162]. For developing the control-based drug delivery techniques in cancer chemotherapy, a validated mathematical of the tumor with suitable parameters and risk factors is the prime requirement [163].

In recent times, many control engineers have been working toward developing a closed-loop control strategy for cancer drug administration and scheduling to work efficiently, even in the presence of perturbations or uncertainties. Some of the prominent control techniques developed, in recent years, for cancer drug administration are PID [164], I-PD controller [165], FLC [166], two degrees of freedom PID [167], adaptive fuzzy back-stepping control [168], learning-based control [169], adaptive control [170], closed-loop optimal control [171], interval type-2 FLC [172], MPC [173, 174], reinforcement learning control [175], sliding mode control (SMC) [163], super-twisting SMC [176], internal model control [153], and H-∞ controller [177]. For testing the developed drug, the clinical trials are the prime requirements to start using patients. However, the protocols for finding the optimal drug dose for cancer treatment are usually based on the host's physical attributes such as sex, body weight, age, and body surface area. However, these factors do not account for pharmacokinetics and pharmacokinetics changes related to different patients [178]. However, the drug dose and scheduled time of the drug to be administrated to the patient under treatment is one of the significant issues in chemotherapy treatment. Any nonconformity in the administered chemotherapeutic drug can affect the loss of efficacy (under-dosing) or toxicity (due to over-dosing) of the drug [179]. Therefore, a clear and narrow range of drugs is to be administrated to provide an effective and reliable treatment for any cancer patient. In 2017, Rokhforoz et al. investigated an extended Kalman filter observer-based robust approach for the cancer drug delivery to simultaneously control different cells such as normal, tumor, and immune cells [180]. The controller's stability is also established in the validated model's parameter uncertainties without considering the enhanced drug-toxicity level during the drug injection in treatment sessions [180]. In 2018, Zhan et al. presented an extensive review of currently developed computational models for drug transport in cancer tumors and other drug delivery methods such as nanoparticle-based–mediated drug delivery and convection-enhanced drug delivery [181]. In 2019, Khalili and Vatankhah investigated an optimal trajectory using the steepest descent method, and the adaptive control approach is used for drug delivery in cancer chemotherapy. The stability analysis of closed-loop drug delivery is obtained using the Lyapunov theory and Barbalat lemma [182]. In 2020, Shindi et al. presented an approach that combines optimal control theory with the multi-objective swarm and evolutionary algorithms to find the optimal drug for cancer therapy [183]. In 2018, Pandey et al. presented a study on PID-based control strategy for drug concentration control in cancer treatment [184]. In 2019, Pachauri et al. investigated a modified fractional order internal model control scheme for the closed-loop drug scheduling of cancer treatment [153] . Panjwani et al. presented a study on the optimal drug scheduling using a two-degree of freedom fractional order PID control scheme for chemotherapy [185]. FLC can use the expert's knowledge for the development of automated drug delivery [186, 187]. All of these works are simulation studies and are model-based approaches and are lacking clinical trials. Before testing a chemotherapeutic drug on a patient, it needs to pass the appropriate clinical trials in order to incorporate the effects of all real-world uncertainties, disturbances, and pharmacokinetic and pharmacodynamic differences between individuals.

The MEMS technology has revolutionized the area of personalized devices and is mentioned for use in cancer treatment. Song et al. presented a MEMS device made up of polydimethylsiloxane, and it contains a doxorubicin drug with a remarkable effect on the pancreatic cancer cell lines [188]. Karar et al. presented a closed-loop FLC approach to control intravenous cancer drug administration using intuitionistic fuzzy sets and optimization techniques, namely, invasive weed optimization [162], considering clinically applicable safety constraints. For this method, the proposed controllers' parameter is optimal and adaptive for controlling the drug concentration. Future work involves using progressive patient models with side effects of cancerous drug administration like autoimmune and destroying healthy cells. Furthermore, the real-time pre-clinical studies with the developed controller in animals are the ultimate future goal of this work. The basic scheme for closed-loop administration of chemotherapeutic agents for clinical trials is shown in Fig. 5.

In 2017, Mage et al. proposed a real-time generalized closed-loop drug administration for chemotherapeutic agents. They demonstrated a stable and protracted feedback-based closed-loop control system in live rats and rabbits for the drug doxorubicin using an aptamer-based biosensor [179]. This work provides a possibility for real-time controlled drug delivery for chemotherapeutic agents for human clinical trials. However, in this study, a simple PID controller was implemented in real time, which calculates the output rate of drug infusion by comparing the measured output *in vivo* concentration to the reference set-point. As per [179], the faster control of drug administration can be obtained by improvement in the control algorithms. To account for the real-world non-linearities and self-adaption to pharmacokinetics changes from patient-to-patient and avoid manual re-tuning of the controller, the advanced control approaches such as model predictive control could be a better alternative for real-time control of chemotherapeutic agents. Moreover, AI-based control techniques would also provide adequate control for closed-loop drug administration for cancer treatment.

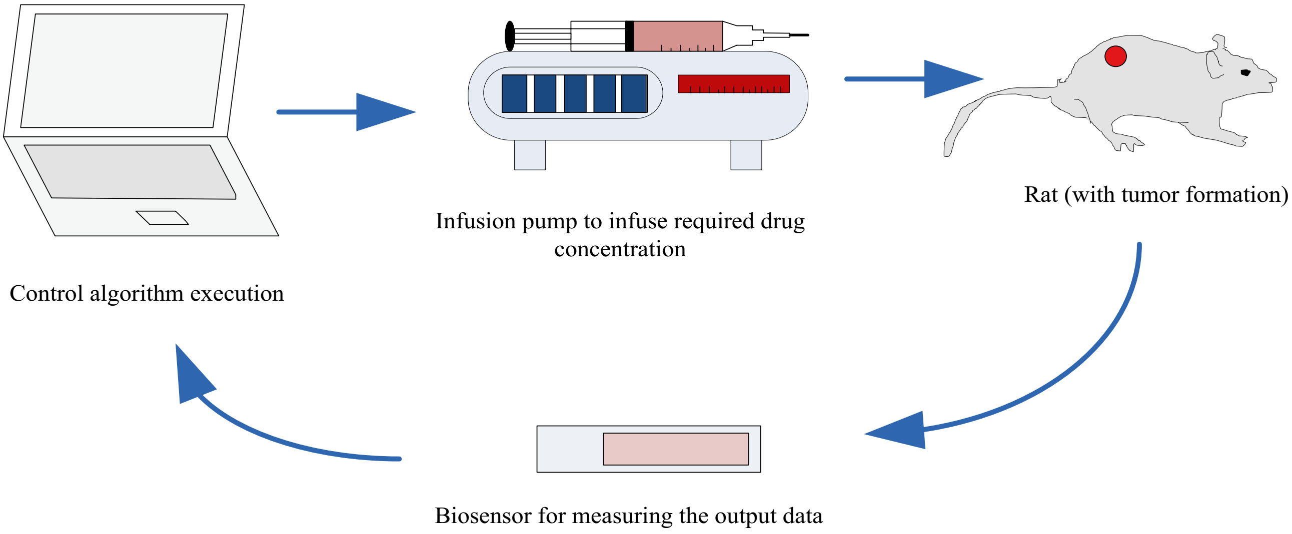


Fig. 5 The basic scheme of the closed-loop cancer treatment

Closed-loop administrating and controlling of anesthesia

As per literature, general anesthesia means loss of response toward noxious stimuli using the drugs. Anesthesia administration is done with three types of medicines: muscle relaxation drug, hypnotic drug, and analgesic drug. Propofol and remifentanil are short-acting drugs that cause hypnosis and analgesia. The efficacy of a closed-loop anesthesia system, in general, depends on the control variables; therefore, suitable set-points need to be selected for three components of general anesthesia such as analgesia, hypnosis, and neuromuscular blockade [189]. The anesthesiologists are bound to monitor and regulate the parameters such as respiratory and hemodynamic systems and clinical signs of appropriate analgesia and hypnosis, to estimate the depth of anesthesia. Therefore, a clinically validated and numerically processed-electroencephalograph (EEG) termed as the bispectral index (BIS) is used as the indicator for the depth of hypnosis, which measures the degree of depression in the brain [190]. BIS enumerates the relationship among underlying sinusoidal components of the EEG and BIS. It has been a guidance source for observing hypnosis in different closed-loop systems with several advantages: increased hemodynamic stability, fast recovery of patients, decreased anesthesia consumption, and overall effective hypnotic control to manual anesthesia control [191].

The anesthesia drugs administered to the patients have a severe side effect on the patient's system, like cardiorespiratory suppression. As the anesthesiologists or ICU caretakers are not aware of the pain, a drug's infusion is administered manually. Therefore, the closed-loop systems have gained popularity over open-loop or manual drug delivery systems due to their advantages such as appropriate time and range of administrated anesthesia, reduced burden of low-level tasks to anesthesiologists, improved patient safety, and improved quality of care for patients by decreasing the variability in the clinical application of drug [192]. Until today, the anesthesia is administered manually by an anesthesiologist or physician at ICU based on continuous visual tracking of the patient's brain activity on the EEG or indirect measurement parameters such as muscle tone or heart rate monitoring. One of the advancements is in the brain-machine interface. The brain activity is monitored automatically, and based on these real-time neural activities, the anesthesia drug infusion rate is adjusted [193].

In recent times, several efforts have been made for administrating anesthesia to patients in a closed-loop manner, as shown in Fig. 6. Still, no concluding technique has developed in real-time clinical practice. The main reason for not adopting any method is due to legal regulations [194]. For a closed-loop control of the anesthetic drug, the feedback report of the clinical effect must adapt the anesthetic drug concentration continuously to optimize the drug administration to the user to improve safety [195]. Therefore, the safety of the patient under anesthesia administration is a prime concern for the clinicians. Myers et al. proposed a study on automated drug delivery for the propofol to total intravenous anesthesia administration. A closed-loop PI controller delivers organic molecules such as propofol with an experimental flow system model and electrochemical biosensor [196]. Ngan Kee et al. investigated a study on closed-loop computer-controlled phenylephrine administration for the regulation of blood pressure of 53 patients with spinal anesthesia for elective caesarean section wherein the simplified on-off algorithm was employed to infuse phenylephrine intravenously [197].

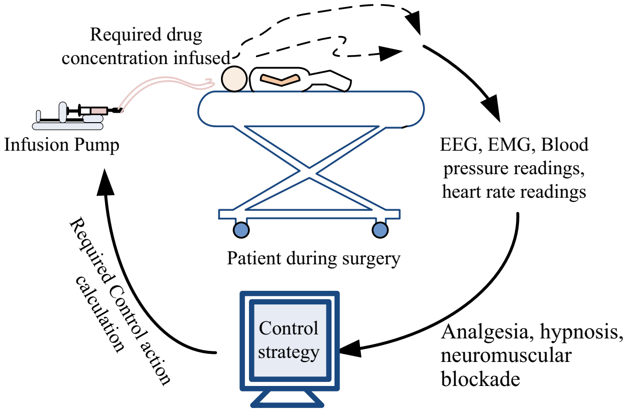


Fig. 6 Basic scheme of the closed-loop control for anesthesia administration

Gentilini et al. investigated a computerized-controlled intravenous infusion of opiate alfentanil to maintain the mean arterial pressure and drug concentration in plasma wherein the MABP is obtained invasively using a catheter cannula, and the plasma concentration is estimated using a pharmacokinetic model. The control approach used for the closed-loop control system was the explicit MPC approach [198]. Soltesz et al. presented a convex-optimization-based PID control approach to control the infusion rate of anesthetic drug propofol. The controller designed is formulated on different identified patient models, relating the EEG-based consciousness with infusion rate [199]. Agrawal et al. investigated a fuzzy PID control approach for quantifying the isoflurane drug to be administered to the patient to regulate the set anesthetic depth [200]. Borera et al. presented an adaptive neural network filter–based reinforcement learning control approach for propofol hypnosis using the BIS of EEG as a controlled parameter [201]. Zaouter et al. proposed an automatic anesthesia mechanism for closed-loop delivery of intravenous anesthetic drugs during the cardiac surgical procedure with cardiopulmonary bypass wherein the drug delivery robot embeds all three parts of general anesthesia, i.e., analgesia, hypnosis, and muscle relaxation [202]. Caruso et al. investigated the issue related to drug administration in the spontaneously breathing patient and implemented a solution for improving patient safety [203]. In 2019, Yousefi et al. presented a safety system for the plasma, target site concentrations, and blood pressure of the patient within the safety limits during closed-loop anesthesia administration propofol [204]. In 2019, Medvedev et al. presented a PID-based control for closed-loop anesthesia administration for neuromuscular blockade [14]. In 2020, Savoca et al. instigated a physiologically based pharmacokinetics-pharmacodynamic simulation study on quantification of cardiovascular risk of the high-risk patients who underwent closed-loop anesthesia administration to see the outcome of the hemodynamic changes on the variable depth of hypnosis [205]. The works cited to show that the closed-loop control of anesthesia administration has been an active research area. However, it still requires approval for human use in a truly controlled manner.

Closed-loop control in neurological diseases

In neurology, the closed-loop control systems are used for movement disorders, epileptic seizures, cognitive recovery after brain injury, and strokes' supervision. The closed-loop system consists of a sensing system, data transmitter, data processer, and corrective response for the output loop [206]. Over the past two decades, neurostimulation has become an efficient therapeutic method for treating tremors for patients suffering from neurodisorders after US FDA approves deep brain stimulation (DBS) therapy in 1997 [207]. DBS is a powerful therapeutic technique for Parkinson's disease, essential tremor [208], and dystonia [209]. Parkinson's disease is a neurodegenerative disease associated with movement disorders. As per [210], around 6.3 million patients worldwide have Parkinson's disease, and it will rise to 9 million by the year 2030. The worst thing is that its cause is unknown, and remedies are not available; therefore, medication and deep brain stimulation are the only way to reduce the symptoms. The only way for patients who do not respond to medication is DBS, though it has side effects.

The levodopa is the most commonly used and effective Parkinson's disease medicine that passes into neurons and then gets converted into dopamine [211]. In [212], Araujo et al. presented an in vitro closed-loop control system using a PID controller for maintaining the brain dopamine concentration. In [213], real-time closed-loop control of the subcutaneous levodopa drug infusion pump is developed for regulating the steady concentrations of plasma levodopa. Though the better approach is to control the plasma dopamine level instead of plasma levodopa, a closed-loop PID-controlled strategy for conventional Duodopa pump for optimal delivery of levodopa in the presence of disturbances, intra-patient, and inter-patient variability [210], wherein the PID controller was tuned by Ziegler-Nicholas method and particle swarm optimization to see the effectiveness of the control strategy.

Over the last two decades, open-loop DBS has proven to be a valuable and useful therapeutic option for patients with Parkinson's disease, essential tremor, or dystonia whose motor symptoms cannot be controlled by drug therapy alone. After the success of open-loop DBS for movement impairments, the closed-loop DBS seems a promising technology that can suppress the side effects of stimulation, thereby improving the efficacy of the system [209]. A closed-loop system generates stimulation efficiently only when the motor function is found abnormal. Progressions in implantable technology are directed to implantable closed-loop neurostimulation systems that continuously sense physiological signals and adjust the response as per detected signal [209]. Fleming et al. presented a new rule-tuning technique for obtaining the PI controller parameters for targeting pathological duration beta-band oscillatory activities within the clinical constraints. The proposed PI controller outperformed the clinically presented on-off controller and dual-threshold closed-loop amplitude control techniques [214]. Some other advantages of closed-loop responsive stimulation are low neurostimulator replacement and enhanced battery life and optimal neurostimulator settings with physiological signals as biomarkers to evoke the stimulation [215, 216]. Therefore, many researchers and engineers have been developing efficient and reliable neurostimulation devices to improve patients' lives suffering from neurological disorders.

As per [209], an entirely implantable closed-loop DBS device named as Activa PC+S neurostimulator (Medtronic) has been designed for the trial use, which is developed

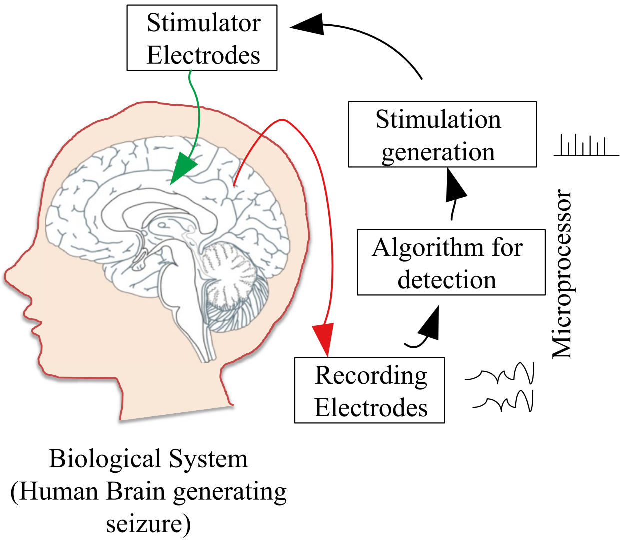


Fig. 7 The basic scheme of the closed-loop stimulation for epilepsy treatment

with Activa PC neurostimulator with features such as added sensing, detection, and stimulation. However, in the development of closed-loop concurrent sensing and detection where the stimulation and sensing both are performed via the same leads, the technical hurdles involve the separation of stimulation signal from the desired motion.

Another promising area of closed-loop control for neurological disorders includes treating epilepsy, as shown in Fig. 7. As per [217], around 1% of the population worldwide is affected by epilepsy disease. Among a third of epilepsy, the suffering person does not respond well to present medication, and the patient for those surgeries is not applicable. The only option for controlling this disease is neurostimulation that improves the quality of life of epileptic patients. The current treatment options for preventing epileptic seizures have been using electrical stimulation or continuous drug delivery, which leads to exposure of the brain and body of the patient to an unnecessary risk of adverse effects [218]. For the past years, open-loop neurostimulation was the only option for epileptic patients. However, a new hope has flourished with the medical approval of the closed-loop vagal nerve stimulation and responsive neural stimulation [217]. Presently, the neurostimulation therapies, namely, open-loop vagus nerve stimulation (VNS Therapy Cyberonics, Houston, TX, USA) and closed-loop responsive cortical stimulation (RNS System, NeuroPace, Mountain View, CA, USA), are approved by the US FDA as a therapeutic aid for the epilepsy disease [209]. In [219], closed-loop responsive stimulation has emerged as an attractive concept. This closed-loop method responds shortly after the onset of a seizure, and it would provide the therapy to early seizure termination to prevent the evolution of disability seizure. Ramgopal et al. presented an extensive review of seizure detection and prediction methods for it, and their integration in a closed-loop warning system for epilepsy is also summarized [206].

One of the options available for patients with generalized epilepsy disease is closed-loop brain stimulation [220]. The Responsive Neurostimulator (RNS®) system is the first FDA-approved closed-loop device [220]. An RNS device consists of a neurostimulator implanted in the cranium, recording strip leads, and stimulating cortical strip leads. In a closed-loop manner, the stimulator generates responsive electrical stimulation to seizure foci whenever atypical electrocorticographic activity is noticed. The neurostimulator is capable of sensing, recording, and continuously monitoring electrographic activities. Other parts included in the system are a programmer for the clinician, an internet-based database for storage, and a remote monitor for the patient. The detection algorithm techniques used are optimized and effective to perform real-time detection with the limitations of present implantable methods such as processing and restricted power capabilities [209]. RNS device is an implantable method which determines the seizure onset and triggers the focal electrical stimulation to suppress the seizures. It uses electrodes to record, process, and transmit the EEG signals for the input algorithm [221]. Salam et al. presented a drug-delivery technique for treating epilepsy using the embedded electrodes to observe the seizures wherein a micromechanical pump was used to deliver the drug stored in a refillable reservoir placed under the scalp. This device comprises asynchronous seizure detection, a neural signal amplifier, hybrid subdural electrodes, and a micropump drug delivery system [222]. Selvaraj et al. investigated the efficacy of the closed-loop optogenetic PI controller for seizure detection [223].

In 2013, the NeuroPace RNS system, a closed-loop device, obtained FDA approval as a therapeutic aid for a drug-resistant epileptic seizure. It showed the median decrease in seizure frequency by 53% in 2 years and, later on, after 6 years, a 72% reduction was reported [224, 225]. It uses an on-board processor, four recording channels with bi-directional leads for stimulating and recording, and offline analysis storage. It uses a pattern detection method for stimulation. However, the detection and simulation parameters are adapted as recommended by the manufacturer; hence, the optimized therapeutic response for a genuinely personalized device is hindered due to limited knowledge about the therapeutic method of action, stimulation, and detection parameters [220]. Therefore, these challenges must be handled carefully to attain the maximum benefits of a closed-loop device for drug-resistant epilepsy. The advanced methods like bottom-up informatics, employing machine learning and brute-force combinatorics-based approach, open up unlimited bright opportunities to develop an enhanced personalized strategy, explain the optimal parameters, and less clinical load [220].

The first FDA-approved closed-loop neurostimulation device uses simple threshold-based techniques. New approaches, such as machine learning for early seizure detection, will provide room for new closed-loop tools and improved low power implant hardware [218]. In [218], comparatively more recent deep-learning techniques, namely, convolution neural network, were used to implement the automatic seizure detection.

The minimization of the device is also required for designing an implantable device. It is reported that these deep-learning approaches can help in developing new low-power hardware for closed-loop devices for handling neurological disease. The long-term variabilities in the signal properties and seizures are the concerns that are to be addressed; therefore, it is essential to involve experts from different zones, such as machine learning, signal processing, clinicians, and hardware design futuristic neurostimulation device [218].

Future visions and limitations

The world is evolving fast with technology, and so is drug delivery and healthcare. Consumers are already monitoring their health statistics using a cellphone, digital watches, and portable electronic devices. Some of the popular health parameters are heart rate, blood pressure, oxygen levels, and temperature. With many companies already offering remote medical services through the internet and connected devices for health checks and surgeries, doctors and patients find the new technology useful and time-saving. The gap is still present when doctors want to deliver controlled medication to their patients remotely. With advancements in IoT technology, remotely controlled drug delivery can take an edge in the current scenario of automated drug delivery. Besides, integrating control algorithms with microfluidics and lab-on-a-chip will take a front seat in controlled drug delivery shortly.

The present age of digital electronics, nanomedicine, and wireless technology demands individualized drug delivery systems in the healthcare sector. The patients want to learn about their fitness and physiological measures daily; therefore, the future lies in the advanced drug therapeutic systems, which could be free from the frequent clinic visits and easily readable by the patient himself or some guardian/physician at a remote location. For instance, the present technological advancements created a paradigm shift in closed-loop delivery systems where the need for attendant/caregiver is omitted for administrating precise and timely anesthesia dosage to the patient during surgery. As of now, the life of a diabetic person has improved with particular closed-loop insulin therapy daily. Similarly, in the future, cancer treatment could be carried out more effectively and with fewer side effects with the closed-loop drug administration. Some other fields, such as gastrointestinal tract disease, blood pressure control, and cardiovascular disorders, are also benefitted from these advanced drug delivery techniques. The closed-loop control techniques also helped the persons suffering from neurological conditions such as Parkinson's disease and epilepsy. Some implantable devices also use these advanced closed-loop and wireless technologies to provide early diagnosis and comfortable treatment regularly. Healthcare technology has been integrated with closed-loop systems for developing friendly and individualized medical devices for different biological applications. For long-term use and therapy with closed-loop devices, these devices are essential to provide continual biocompatibility. Therefore, a complete validation of materials and efficient elimination of toxic substances must be carried out [226]. New monitors/actuators may also be developed to design improved closed-loop drug delivery systems explicitly for widespread metabolic diseases [226]. With the advancements in computational speed, intelligent controllers need to be investigated for future work. Different optimization could be explored for tuning of controller parameters. The adaptive controllers to handle the real world's nonlinearities and the pharmacokinetic conditions of other individuals could be integrated into the closed-loop drug delivery devices.

Despite several advantages, the advanced technology comes with some countable limitations which must be considered while using the closed-loop drug delivery systems. The inaccurate or false readings of the sensor can lead to untimely or improper drug dosage, which can risk the patient's life. Another issue is with implantable devices as the material used should be biocompatible and safe. One of the significant challenges is the short life-time and power consumption issues of batteries used in this electronics-based closed-loop and implantable devices [6]. To avoid the danger associated with recharging of battery or low-power issues for IoT healthcare devices, one of the options is to recharge the battery of the coordinator node at short intervals. Hence, an efficient energy-aware security solution is essential for these devices [227]. The state-of-art drug delivery implantable devices use power long-life batteries as these devices require power only in milliwatts, and voltage ranges are about 1 volt or above. Energy harvesting is one of the best options for resolving power issues, though a wireless electromagnetic system has security and range issues. Therefore, biological energy harvesting for power requirements has been gaining popularity these days [228]. In [229], a self-powered iontophoretic transdermal drug delivery wearable system was presented and regulated using the energy harvested by the biomechanical motions. Therefore, it is also an open research area for the researchers to develop self-powered or biologically harvested energy-based implantable devices.

Cost-effective and needleless healthcare devices have been the aim of researchers for many years [22]. However, smart healthcare methods using IoT and the user's enhanced quality of life can be easily dominated by compromised security issues. Intelligent healthcare systems are prone to security attacks such as interruption of service, manipulating original data, forging messaging, and producing a false impression. It is a challenging job for the software engineers to offer a comprehensive solution to the dynamic security updates of the systems. For instance, attacks on a wirelessly controlled insulin delivery system can overtake the entire insulin pump control and can cause deadly consequences to the user/patient. Moreover, the data's confidentiality and integrity containing personal information about patients or users is another challenge in smart healthcare devices. The attack on individual wireless devices can be avoided by implementing strict medical security to these systems. Cryptography is one of the most commonly used methods for securing wirelessly transmitted data and avoiding unauthorized access to personalized settings [24].

Furthermore, security attacks can be avoided by two different approaches, such as rolling code protocols and body-coupled communication. The rolling code encoder approach is considered the most vigorous cryptographic protocol. The generation of random rolling codes avoids the device's dependency on a particular device's personal area network each time. The body-coupled communication protocol–based security model decreases the signal strength, and it is almost impossible to breach the security without physical contact with the patient [22].

Another hurdle in this regard is that the low cost of smart healthcare devices' design results in the processor with slow speed and low onboard memory; therefore, it seems complicated to integrate additional security mechanisms [24]. Present-day engineers need to develop further measures to handle threats and secure the essential information at both the developer and user end [22]. The limitations in developing continuous chemical sensors also need to be resolved by the constant development of chemical sensors [4].

Machine learning and AI techniques have become hot research areas in the present age, especially healthcare technologies. Using these techniques, the personalized and intelligent administration of drugs would be available as a futuristic technique wherein the patient response to a particular pharmacological agent would be more precisely predicted than with the present-age devices. Therefore, more sophisticated analytics with machine learning would result in interaction between different closed-loop systems [218]. Furthermore, the use of AI-based control techniques is the future of closed-loop drug delivery or implantable devices. Finally, the full potential of 3D printing in drug delivery, for example, 3D tablets, has yet to realize its full potential in automated drug delivery. The present paper briefly reviews the application of IoT in an automated drug delivery system. However, a detailed review of these dimensions of drug delivery can benefit future researchers extensively in the future.

The IoT applications could be integrated to develop intelligent real-time monitoring and interacting systems, for personalized healthcare of the disabled and elderly people, even at their home [230]. Therefore, the long-term vision and future success of the growing closed-loop therapeutic system can be achieved by collaborative efforts of healthcare professionals, engineers, researchers, industry, and the user.

Concluding remarks

This review summarizes the collaborative efforts of control theory with the healthcare sector to develop a patient-friendly closed-loop drug administration system and an efficient implantable system. The healthcare sector is a vast field to work within it. This review explores the concept of automated drug delivery systems/therapies for providing treatments for various ailments such as neurological disorder, cancer, diabetes, GI tract diseases, cardiac conditions, and anesthesia administration during surgery. The development of a fully automatic implantable device requires different techniques such as MEMS technology, wireless communication or IoT techniques, control theory, bio-engineering, artificial intelligence, and some others. The research in the field of automated insulin delivery is quite matured till now. However, there is still room to improve the design to enhance the ease and reach the device to the mass population with cost-effectiveness. Moreover, biological control systems require appropriate modeling and system identification to establish pharmacokinetics-pharmacodynamics relations. Therefore, it is equally essential to simulate the mathematical models and apply control techniques for designing an efficient closed-loop drug therapy for clinical trials, and ultimately to launch it in the market.

In recent times, AI techniques open immense opportunities to develop optimal, miniaturized, implantable, and intelligent drug delivery systems to improve the quality of life of the patients suffering from different diseases and reduce the workload of caregivers. The integration of advanced, self-adaptive, and intelligent control techniques with presently developed automated devices could make these devices "an intelligent and automated friend" to the patients suffering from different ailments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate. It is a review paper. The paper does not contain any studies with animals or humans.

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