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EDITORIAL

Smart Sensors for Maintaining Physiologic Homeostasis

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Introduction

A smart sensor can be defined as a device that measures the environment, converts the input into a signal, and interfaces with a well-programmed controller.[1] The controller then automatically calculates and delivers a control signal to an actuator that determines a quantity of output from the actuator.[2] If the actuator is commanded to maintain physiologic homeostasis, then the system is known as a closed-loop system.

Artificial intelligence is the branch of computer science concerned with making computers behave like humans. Artificial intelligence includes expert systems that are computers programmed to make decisions in real-life situations.[3] A smart sensor uses artificial intelligence to maintain physiologic homeostasis.

A smart sensor integrated with an actuator is known as a smart transducer. A closed-loop system can contain multiple smart transducers that control separate processes side by side, or else multiple sensors can aggregate input to determine a single type of actuator output. Transducers can interact with microprocessors, instrumentation systems, or control networks. Institute of Electrical and Electronics Engineers 1451, a family of smart transducer interface standards, describes a set of open, common, network-independent communication interfaces for these interactions, which can allow transducer data to pass through a common set of interfaces within systems or networks by either wire or wireless means.[4]

Closed-Loop Medical Devices

Devices facilitating actions that could be considered the practice of medicine without a license have traditionally not been cleared by the Food and Drug Administration (FDA). When might automatic closed-loop control by a device be appropriate and accepted both by the medical and regulatory communities? A computer can perform better than a human to make a medical decision and carry out an automatic prespecified response in three situations, and these types of situations are the most promising for the development of smart sensor-controlled medical systems. These situations are listed in **Table 1**.

Table 1.
Features of Situations Where Smart Sensors Can Make and Carry Out a Decision Better than a Human

1.	A complex problem that requires a computer to solve and maintain constancy
2.	Skilled decision makers are not available
3.	Instant response to the situation is needed, and there is insufficient time available to contact an expert to interpret the input

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Abbreviations: (FDA) Food and Drug Administration, (ICD) implantable cardiac defibrillator, (VF) ventricular fibrillation, (VT) ventricular tachycardia

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At least eight different types of closed-loop medical devices are currently being developed or are already approved containing smart sensors coupled to actuators for maintaining physiologic homeostasis. These types of devices are listed in **Table 2**. Three of the systems are approved for use in the United States and Europe, one is approved for use in Europe, and four are investigational, including the artificial pancreas, which is a major focus of interest in the diabetes technology community. The following eight sections describe each of the eight types of smart sensor-driven closed-loop systems for maintaining physiologic homeostasis.

Table 2.
Eight Devices or Systems Using Smart Sensors to Maintain Physiologic Homeostasis

Types of devices approved by the FDA and CE for these purposes.
1. Cardiac pacemaker
2. Implantable cardiac defibrillator
3. Closed-loop mechanical ventilator
Type of device cleared by CE but not approved by the FDA for this purpose.
4. Computer-assisted personal sedation system
Types of devices not approved by the FDA for these purposes.
5. Artificial pancreas
6. Brachytherapy insertion system for prostate cancer
7. Blood pressure controller for surgery
8. Smart insulin

Cardiac Pacemaker

The purpose of a cardiac pacemaker is to maintain an adequate heart rate, either because the heart's native pacemaker is not fast enough or because there is a block in the heart's electrical conduction system.[5] The smart sensor of a pacemaker contains one or more electrodes that are introduced transvenously into one or more heart chambers. The actuator component of the system is the same set of electrodes that can deliver a pacing impulse. The components of the pacemaker that integrate the sensor and actuator are as follows: (1) an amplifier to process electrode information and (2) a computer to decide when to pace. A battery is also part of the system. Pacing is typically in one of two modes: on demand or dynamic. On-demand pacing is the established function of a pacemaker. If a pacemaker fails to sense a heartbeat within a specified beat-to-beat interval, then the pacemaker will stimulate the heart with an electric pulse. Dynamic pacing is rarely performed, but this closed-loop process for controlling heart rate uses multiple inputs besides heart rate. These inputs include the amount of physical activity performed as measured by an accelerometer,[6] the amount of metabolic activity as measured by myocardial vibration,[7] or myocardial contractility based on right ventricular impedance, which reflects autonomic innervation to the heart.[8] When cardiac pacing is needed, then there is usually no time to transmit an abnormal rhythm and call upon a health care professional to interpret the rhythm. Therefore, an automatic closed-loop system to maintain a physiologic heart rate is desirable.

Implantable Cardiac Defibrillator

An implantable cardiac defibrillator (ICD) is a battery-powered electrical impulse generator that is implanted in patients who are at risk of sudden cardiac death due to ventricular fibrillation (VF) and ventricular tachycardia (VT). The device detects a cardiac arrhythmia and corrects it by delivering a jolt of electricity.[9] An ICD is used to treat two types of dangerous heart rhythms: VF, which is an unsynchronized and very dangerous rhythm producing cardiac arrest, and VT, which is a synchronized and dangerous rhythm that can lead to dangerous rhythm that can lead to ventricular fibrillation. Where a pacemaker speeds up a slow rhythm, an ICD slows a rapid rhythm of VT or VF. An ICD can deliver any of the following: (1) antitachycardia pacing for VT; (2) low-energy cardioversion for VT; or (3) high-energy defibrillation for VF.[10] As with a cardiac pacemaker, the sensor and actuator are the same electrodes. When antitachycardia pacing, cardioversion, or defibrillation is needed, then there is usually no time to transmit the abnormal rhythm and call upon a health care professional to interpret the rhythm, so an automatic closed-loop system to maintain a physiologic cardiac rhythm is desirable.

Closed-Loop Mechanical Ventilation

Mechanical ventilation devices are necessary for patients who are too weak to breathe for themselves. These systems require regular adjustment of settings, such as the minute ventilation volume, the tidal volume of each assisted breath, and the maximum pressure permitted per assisted breath. Closed-loop mechanical ventilation systems were developed for specific settings to facilitate automatic sensor-driven adjustments in ventilator settings for safe assisted control of a patient's ventilator-assisted breathing. There are two types of closed-loop mechanical

ventilation: adaptive support ventilation and intelligent targeting ventilation. Adaptive support ventilation is a decision support mode of ventilator control that delivers assisted or controlled breathing cycles to minimize the work of breathing.[11,12] This method uses closed-loop control to reach a minute ventilation target by adjusting the applied pressure, the inspiratory/expiratory time ratios, and the respiratory rate. This method may be useful for weaning a patient from a ventilator when the patient is strong enough to trigger the ventilator. Adaptive support ventilation decreases the number of adjustments in ventilatory settings by the hospital staff. This method might reduce the risk of errors in the settings and might speed up the weaning process from a ventilator. Intelligent target ventilation is a rules-based expert system that uses predefined ranges for spontaneous breathing frequency, tidal volume, and end-tidal carbon dioxide concentrations to adjust the inspiratory pressure and maintain the patient in what is referred to as a respiratory zone of comfort.[13] This method works well for weaning. The sensors in this type of ventilator system measure respiratory parameters, and integrated bellows deliver the breaths. A closed-loop respiratory system is useful when skilled respiratory therapy or physician decision makers are not available for frequent adjustments of the ventilatory settings.

Computer-Assisted Personal Sedation

During endoscopic procedures, mild sedation is administered. The current standard of care is to administer both a benzodiazepine and an opioid. There has been interest in development of a safe closed-loop system to administer propofol, which is a sedative.[14] A nurse or gastroenterologist would manage the device. With such a system in place, an anesthesiologist would not be needed for endoscopic anesthesia, which would save money. Compared to the currently used anesthetic agents in endoscopic centers, propofol might increase the quality of sedation and hasten recovery. Furthermore, if the sedation recovery period can be shortened, then there is a potential for greater throughput of patients at the center. In rare cases, however, propofol sedation has been reported to cause such side effects as excessive sedation or temporary respiratory depression. The package label of propofol limits its use to "persons trained in the administration of general anesthesia,"[15] which would appear to restrict nonanesthesiologists from administering the drug.

Four gastroenterology and hepatology societies evaluated the safety, efficacy, economic impact, and training issues for gastroenterologists and other nonanesthesiologists (who are usually nurses) involved in the administration of propofol for gastrointestinal endoscopy. They concluded that profolol is safe for use by nonanesthesiologists if "it is administered by a team of individuals who have received training specific to the administration of propofol."[16]

A computer-assisted personalized sedation system called SEDASYS has been developed to integrate propofol delivery with patient monitoring so that endoscopist/nurse teams can safely administer propofol for routine esophagogastroduodenoscopy and colonoscopy.[17] The system is intended for mild-to-moderate sedation, but not deep sedation. SEDASYS has the capability to do the following: (1) integrate patient monitoring with propofol delivery and oxygen delivery; (2) monitor pulse oximetry, capnometry, the electrocardiogram, and noninvasive blood pressure; and (3) react to an automated responsiveness monitor, which measures a patient's response to mild auditory and tactile stimuli at regular intervals. SEDASYS calculates and delivers a loading dose of propofol as well as a maintenance dose of propofol selected by the physician. The device then controls the oxygen flow rate to maintain oxygenation. By integrating physiologic measurements, it will prevent oversedation. The system will slow anesthetic delivery for a decreased respiratory rate or a decreased oxygen saturation, but not for an abnormal pulse or blood pressure or an increased carbon dioxide level. In a multicenter unblinded trial of SEDASYS, which compared current standard of care with SEDASYS administered by endoscopist/nurse teams, the SEDASYS system resulted in less hypoxia, improved patient and clinician satisfaction, faster recovery, as well as no serious adverse events.[18]

On October 26, 2010, the FDA elected to not approve SEDASYS for three reasons: (1) no data had been submitted comparing outcomes using this product between anesthesiologist and nonanesthesiologist users; (2) no evidence was submitted that a proposed training program for the product would mitigate anesthetic risks; and (3) there was evidence of deeper-than-intended sedation in some subjects with this product.[19] The manufacturer is appealing this decision, and the FDA has elected to appoint a new independent advisory panel to reconsider the SEDASYS clinical trial data and application. This case reflects the scrutiny that a sensor-powered closed-loop system can be subject to by the FDA. For closed-loop systems such as this one, the agency's tolerance of any design flaws in protocols or any adverse outcomes might, in part, hinge on whether the product is perceived by the agency to address clinical situations where (1) a complex

problem requires a computer to solve; (2) skilled decision makers are not available; or (3) an instant response to the situation is needed and there is insufficient time available to contact an expert to interpret the input, even if such a system provides documented clinical benefits to study subjects and increased satisfaction by study subjects and clinicians compared with current therapy. This system has CE Mark approval.

Artificial Pancreas

An artificial pancreas can be defined as a device that contains only synthetic materials and substitutes for an endocrine pancreas by sensing the blood glucose level, determining the amount of insulin needed, and then automatically delivering an appropriate amount of insulin.[20] The main components of this closed-loop system are as follows: (1) a continuous glucose monitor, which serves as a smart sensor; (2) an insulin pump, which serves as an actuator; and (3) a controller with artificial intelligence software to link the two arms of the system. At least five different types of inputs can be gleaned from the glucose monitor, including the following: (1) absolute glucose level data points; (2) blood glucose calibration data; (3) direction of change of glycemia data; (4) rate of change of glycemia data; and (5) predictive modeled data as to where the glucose level is headed. Current artificial pancreas systems are limited by a need for better sensors, faster onset of action of insulin, and better software algorithms. Remote wireless monitoring of sensor input and actuator output, intended to enable a health care professional at a central station to troubleshoot or even assume control, will probably become part of these systems eventually.[21] The FDA is expected to provide guidance in the near future on appropriate targets for safety and effectiveness of closed-loop systems.[22] The appeal of such a device when it is time to apply for regulatory approval is that it will be able to make numerous decisions every day for insulin dosing when skilled decision makers, such as physicians or nurses, are not available.

Brachytherapy Insertion System for Prostate Cancer

Brachytherapy for prostate cancer therapy refers to permanent placement of radioactive seeds into the prostate under ultrasound guidance.[23] There is up to a 30% failure rate with current needle insertion technology. Improper placement can require reinsertions to situate seeds properly, or else the patient is at risk of greater radiation toxicity and a lower rate of cure. The current three-stage workflow for prostate brachytherapy consists of the following: (1) acquiring an image set of the patient anatomy; (2) determining the best location for the radioactive seeds; and (3) delivering the seeds via needles through the perineum into the prostate. A magnetic-resonance-controlled robot has been developed in a pilot project to implant radioactive seeds extremely close to target locations.[21] This technology is equipped to utilize two novel imaging methods: magnetic resonance imaging and magnetic resonance spectroscopy. These imaging modalities can identify, respectively, areas of cancer by their tissue properties and local concentrations of choline, which is produced by prostate cancer. The magnetic resonance images may prove to be superior to ultrasound for localizing cancer. The smart sensor in this case is the magnetic images, and the actuator is the linked robotic biopsying device. To the extent that improved seed placement is due to computerized imaging and needle localization technology, this technology might be favorably received by regulatory bodies if the safety and effectiveness profiles can be demonstrated to be reasonable.

Blood Pressure Control for Surgery

Closed-loop control of blood pressure during surgery could improve the safety of surgeries. Closed-loop systems have been proposed to treat low blood pressure with medications that raise blood pressure and to treat elevated blood pressure with medications that lower blood pressure. Both types of system use artificial intelligence applied to continuous automatic noninvasive blood pressure cuff measurements of blood pressure. Automatic blood pressure cuffs are the system's sensors, and computer-controlled infusion pumps are the system's actuators. Computer-controlled vasopressor infusions have been reported to successfully treat hypotension in intensive care patients and during spinal anesthesia for caesarean sections.[24] Computer-controlled infusions of nitroprusside[25] and opioids[26] have been reported to treat hypotension successfully in surgical patients. No such system is currently approved for clinical use. Closed-loop control of hypovolemia with fluid infusion to maintain a target blood pressure level has also been proposed.[27] The attraction of these systems is not so much that maintaining a target blood pressure is too difficult a task for health care professionals or that these professionals are in short supply in a hospital, but rather that these systems can respond immediately to input, and sometimes blood pressure perturbations require immediate correction.

Smart Insulin

Stimuli-responsive insulin, also known as smart insulin, requires synthesis of a polymer that senses environmental changes and then undergoes structural changes resulting in release of insulin. These smart insulin polymers undergo self-regulated drug release according to need.[28,29] Unlike classical closed-loop systems, these materials do not contain a specific sensor or a specific actuator. The insulin itself or a gel surrounding the insulin is both the sensor and the actuator. This is a unique mechanism of closed-loop control of self-actuation, which is unlike the other systems in this article. No smart insulin product is commercially available. These smart drug delivery systems are both a drug and a device and will need to demonstrate benefit in both categories.

Conclusions

Smart sensors coupled to actuators can achieve physiologic homeostasis. Closed-loop systems that apply artificial intelligence to maintain physiologic homeostasis of cardiovascular and respiratory processes are currently available. Additional closed-loop systems to achieve physiologic homeostasis of blood glucose, blood pressure, and proper localization of brachytherapy needle localization are under development. Smart sensors and control systems for actuators are becoming increasingly sophisticated. Closed-loop systems are an attractive method for automatic and accurate maintenance of physiologic homeostasis without any need to wait for summoning a health care professional to assess the situation and make a therapeutic decision. Translating smart sensor research into actual products will require approval by regulatory agencies. These agencies have made it clear that they will demand clear demonstration of safety from any smart-sensor-controlled system where the physician is taken out of the treatment loop.

Disclosures:

Dr. Klonoff is a consultant for C8 Medisensors, Inc.; Insuline Medical Ltd.; LifeScan, Inc.; Medtronic Diabetes; Merck; and Roche Diagnostics.

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