

Closed-Loop Strategies for Patient Care Systems

Ronald Pauldine, MD, George Beck, BS, RRT, Jose Salinas, PhD, and David W. Kaczka, MD, PhD

Military operations, mass casualty events, and remote work sites present unique challenges to providers of immediate medical care, who may lack the necessary skills for optimal clinical management. Moreover, the number of patients in these scenarios may overwhelm available health care resources. Recent applications of closed-loop control (CLC) techniques to critical care medicine may offer possible solutions for such environments. Here, feedback of a monitored variable or group of variables is used to control the

state or output of a dynamic system. Some potential advantages of CLC in patient management include limiting task saturation when there is simultaneous demand for cognitive and active clinical intervention, improving quality of care through optimization of the titration of medications, conserving limited consumable supplies, preventing secondary insults in traumatic brain injury, shortening the duration of mechanical ventilation, and achieving appropriate goal-directed resuscitation. The uses of CLC systems in critical care

medicine have been increasingly explored across a wide range of therapeutic modalities. This review will provide an overview of control system theory as applied to critical care medicine that must be considered in the design of autonomous CLC systems, and introduce a number of clinical applications under development in the context of deployment of such applications to austere environments.

Key Words: Closed-loop, Critical care medicine, Mass casualty.

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Current health care delivery paradigms rely on provider-directed care, in which a physician or another health care provider assumes responsibility for patient evaluation and management of therapeutic interventions. Unfortunately, such a model cannot always be extended to remote areas or environments where lifesaving interventions and continuous life support are required. For example, military operations, mass casualty events, and remote work sites on earth and in space present unique circumstances in which available health care providers may lack the skills necessary for optimal patient management, or the number of patients may overwhelm available resources. Under extreme circumstances, health care providers may attempt interventions of questionable benefit that significantly exceed their clinical expertise, and in so doing compromise that what is considered standard of care in normal environments. In these situations, life support systems that augment care by acting autonomously or by providing decision support may have the potential to improve outcome.

Closed-loop control (CLC) uses feedback to control the state or output of a dynamic system.¹ Such systems are common in our everyday life and remain largely unnoticed

while controlling home temperature, the speed of automobiles, or the output from power plants. However, their use in critical care medicine remains limited. Despite the limited acceptance of CLC in the clinical arena, various therapeutic applications have been successfully demonstrated.^{2–6} Potential benefits of CLC are (1) quicker continuous intervention compared with intermittent caregiver intervention, (2) consistent treatment based on physiology and proven algorithms, (3) continued, appropriate ventilator operation in the absence of a skilled caregiver,⁷ and (4) the conservation of consumable resources. In emergency care, CLC may be critical to the success of care provided in mass casualty and military scenarios where caregivers have a limited skill set or victims outnumber attendants. This review will present the concepts that must be considered in the design of autonomous control systems and introduce a number of clinical applications under development in the context of their applications in austere environments.

FEEDBACK CONTROL SYSTEMS: AN OVERVIEW

The tools of linear systems and control theory provide a framework for understanding: how a physical process or system achieves a desired outcome and the cause-and-effect relationship between the input to a system and its corresponding output. The input can be considered a variable under direct control, which the system uses to regulate the output, whereas the output is a desired or observed response, which can either be a single variable or a combination of variables depending on the system under consideration. A physiologic example of such a relationship is that between the minute volume of a mechanical ventilator and the resulting arterial CO₂ tension (Paco₂) of a patient. When the patient is underventilated, Paco₂ will rise, whereas if he is hyperventilated, Paco₂ will fall. This type of cause-and-effect relationship is an example of an open-loop system. A critical feature of open-loop systems is that they do not use

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From the Department of Anesthesiology and Critical Care Medicine (R.P.), Johns Hopkins Bayview Medical Center, Baltimore, Maryland; Impact Instrumentation Inc. (G.B.), West Caldwell, New Jersey; Trauma Information Systems Development (J.S.), US Army Institute of Surgical Research, Fort Sam Houston, Texas; and Department of Anesthesiology and Critical Care Medicine, Department of Biomedical Engineering (D.W.K.), The Johns Hopkins University, Baltimore, Maryland.

Address for reprints: Ronald Pauldine, MD, Department of Anesthesiology and Critical Care Medicine, A3W-387, Johns Hopkins Bayview Medical Center, Baltimore, MD; email: rpauldi1@jhmi.edu.

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feedback to regulate the output, only the relationship between the input and the system. Typically, open-loop systems are calibrated to achieve a desired output based on a given input. This results in a very simple relationship but one that is not capable of adjusting to disturbances to the system. To design an open-loop controller that functions to specifications all the time, the design engineer would be required to have complete knowledge of the system and be assured that there are no unforeseen disturbances to the system. Given their simplicity and inability to react to changes in the environment, open-loop systems find limited practical or autonomous applications in patient care.

Closed-loop systems, alternatively, use feedback related to the actual output of the system to make adjustments to the actuating input.¹ In this arrangement, a feedback controller monitors the output and adjusts the input as necessary to maintain the desired output. This feedback minimizes the impact of disturbances to the overall system and provides the ability to maintain the desired response. This is accomplished by the regular comparison of the desired system response to the actual system response. This difference between the desired and actual responses (or error signal) is then used to adjust the output so that the difference is minimized. A typical feedback control system is illustrated in Figure 1. Here, the actual system response as measured by a sensor is continuously fed back to the system and compared with the desired system response. The difference is processed by a controller that makes appropriate adjustments to an actuating input to the plant or process under control. An example of such an arrangement applied to a patient system would be the automatic adjustment of inspired oxygen of a ventilator (F_{IO_2}) to maintain a desired level of oxygen saturation as measured from a pulse oximeter (S_{PO_2}). Here, the desired system response is the predetermined S_{PO_2} value, the error signal is the difference between the desired and actual S_{PO_2} , the controller is the algorithm or relationship that determines what change needs to be made to the F_{IO_2} to achieve the desired output, the plant or process is an F_{IO_2} regulating device (such as a blender), and the sensor is the pulse oximeter, which provides the S_{PO_2} feedback signal.

For closed-loop systems, there are several ways a controller determines what changes need to be made to the actuating input to the plant (or process). Specifically, how a controller responds to the differences between the desired system response and the actual measured response must be considered when evaluating CLC systems. Systems that seek to reduce the difference between the desired response and the

measured response are called negative feedback controllers.¹ Negative controllers seek equilibrium at or closely around the desired response, by producing an actuating signal that is opposite the deviation of the measured response from the desired response. If the measured response is greater than the desired response, then, the control signal seeks to reduce the measure value back to the set point. The benefits of negative control are precise control toward a stable equilibrium and an ability to maintain equilibrium in the face of changing physiologic conditions.

The simplest example of control is proportional control where the control effort is proportional to the error between the desired response and the measured response. As the error gets larger, the controller exerts a greater influence in an attempt to achieve the desired response. An example of proportional control is how a driver steers a car. If the driver is where he wants to be on the road, there is very little correction (steering) done. When he wants to turn (i.e., the current position is significantly different from his desired position), he applies significant correction. A limitation of proportional controllers is that they can oscillate between extremes if there is not sufficient damping in the control system. In this simple example, the steering mechanism's tendency to go straight acts as a damping force to the operator's steering corrections. Because of the inherent lack of damping and the associated risk of oscillation, simple proportional controllers have limited use in patient care systems.⁸ Alternatively, a proportion-integral-derivative controller produces an actuating signal that is proportional not only to the error signal, but also to its derivative and integral. Thus, proportion-integral-derivative controllers act in a way similar to the way an actual clinician would approach control of a medical system. For example, when an anesthesiologist acts as a controller, he must consider the history of his efforts to maintain anesthesia (integral component) as well as how quickly any discrepancies occur between his efforts to maintain appropriate oxygenation, ventilation, and anesthetic depth with the actual condition of the patient (derivative component).

Even more closely related to human behavior are so-called fuzzy logic controllers, which allow for some uncertainty to be incorporated into a feedback control system rather than assuming behavior based on deterministic mathematical models. For example, the error between the actual and desired system response is "fuzzified" by partitioning it into a number of overlapping fuzzy sets, each having an amplitude reflecting how strongly a particular value of the error belongs

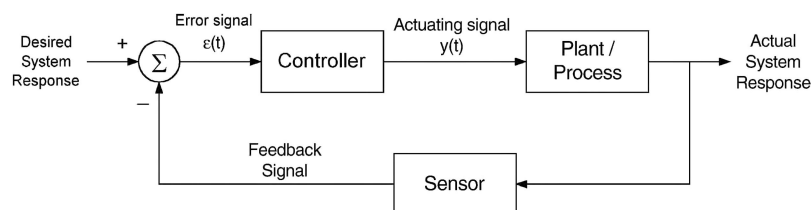


Fig. 1. Example closed-loop control system. Modified from Kaczka and Beck,²⁰ with permission.

to the set. A rule table can then be constructed based on these sets, which may incorporate the level of the error, with some other conditions of the patient's physiology. The controller then adjusts the desired settings according to some ad hoc criteria.^{9,10}

Closely akin to fuzzy logic controllers are decision tables, which are powerful facilities for expressing complex procedures, programs, and control strategies.¹¹ Decision tables provide a mechanism whereby large quantities of data can be condensed into an easily interpreted and manipulated form. Their use evolved from truth tables developed to demonstrate possible outcomes in multivariable problems.¹² Compared with conventional rule-based expert systems, decision tables are more amenable to modification. Unlike software-based systems, the entries in decision tables are readily available for inspection and manipulation.¹³ One of the simplest constructs for control is a rule which takes the form IF (some condition[s]), THEN (some action[s]). Given this, the user is able to apply the rule and act to all circumstances where the conditional clause IF... is met. Decision tables are rule sets. A decision table is therefore a matrix that associates a set of decision variables with a set of actions.¹⁴ Decision variables may include patient symptoms, physical examination findings, and laboratory results. Actions can include therapeutic interventions or directions to obtain additional clinical data.

One drawback of the arrangement of Figure 1 is the assumption of system stationarity or time invariance. That is, the properties of plant or process do not change over time. In these situations, adaptive control techniques become quite useful.¹⁵ For example, an interventional process applied to an injured patient who is resuscitated over time may require a control system that can adapt to his changing physiology. Adaptive control provides a mechanism to compensate for time-varying parameters in a predetermined fashion as dictated by the operating conditions. Adaptive control techniques require a set of parameters that can be adjusted algorithmically to guarantee stability during changes of the system and provide convergence as the underlying model changes over time.

Adaptive control can be classified into feedforward and feedback adaptive control methods.¹⁶ Feedback adaptive control uses an adjustment mechanism that is updated from the results of the controller output, the resulting changes in the plant or process, and the time-varying parameters expected by the model of the system. Outputs of the adjustment mechanism are new sets of controller parameters that provide better convergence and stability as the underlying process changes over time. Feed-forward adaptive control works jointly with feedback control systems to provide an additional layer of control by modifying the control effort of the feedback control mechanism based on a measured disturbance in the system. In the example of a resuscitation system, a change in a patient's intravenous infusion rate would generate a change in the output of the controller before the output variables are measured based on the expected change of the target. These control techniques provide a natural control

mechanism for implementation in patient care systems. As a patient's physiology changes during recovery, adaptive control systems will provide a better and more robust control technique for adapting to the changing parameters of the patient.

CLINICAL APPLICATIONS OF CLC: EXAMPLES AND CONSIDERATIONS

The possibilities for application of closed-loop technology in clinical practice are wide ranging. Potential advantages include limiting task saturation when there is simultaneous demand for cognitive and active clinical intervention, improving quality of care through optimization of the titration of medications, conserving limited consumable supplies, preventing secondary insults in traumatic brain injury, shortening duration of mechanical ventilation, and achieving appropriate goal directed resuscitation.^{17,18} Challenges in the successful implementation of these strategies include the fact that any such system must take into consideration the complexity of the system under control (the patient), the ability to accurately measure the controlled variable(s) (the sensors), and the reliability of the controlled variable(s) to accurately reflect the true physiologic goal or set point targeted as well as the validity of controller algorithms to address the measured variable correctly.¹⁹ These examples may be considered in the context of the discussion above outlining theories of CLC.

Much of the state of the art knowledge in application of closed-loop technology in patient care comes from the areas of mechanical ventilation²⁰ and administration of general anesthetic agents.¹⁹ The goals of mechanical ventilation are maintaining alveolar ventilation, unloading the respiratory muscles, preventing end-expiratory collapse (by use of positive end-expiratory pressure), and providing a respirable gas mixture that maintains oxygenation.²¹ Initial efforts focused on maintaining adequate ventilation using feedback from exhaled gas.^{5,6,22,23} This was driven by the physiologic relationship between alveolar ventilation and ETCO_2 and the ease of measuring exhaled gas. As arterial blood gas machines became available, investigators evaluated algorithms for ventilation, oxygenation and positive end-expiratory pressure control.^{13,24} In addition to the measured physiologic parameters, a number of studies have demonstrated the benefit of minimizing patient's work of breathing using feedback based on continuously measured respiratory mechanics.²⁵ Reliable pulse oximetry has helped many authors demonstrate the ability to maintain an adequate SpO_2 level by controlling FiO_2 .^{26,27}

Anesthetic applications have focused on refinement of target controlled infusion (TCI) technology. Traditional target controlled infusions have primarily used titration of sedative hypnotic agents through algorithms based on mathematical modeling of the pharmacokinetics of the administered agent, whereas closed-loop applications have taken the process further by integrating various physiologic measures such as hypnotic depth as clinical targets.²⁸ TCI systems are open loop systems that use a pharmacokinetic model algorithm with operator input

of variables such as age, gender, height, and weight to control an infusion device to maintain a target plasma concentration of a given drug as predicted by the specific algorithm.²⁹ The pharmacokinetic models are generally derived from relatively small numbers of healthy subjects, and there is significant variability in pharmacokinetics between individuals; therefore, inaccuracies in the model as applied to a specific patient are likely. This means that the predicted or set concentration may vary considerably from the actual plasma concentration but the algorithm will still adjust the infusion rate to maintain stable plasma levels at a set level. Because the operator can change the target to a clinically desired effect, the controller will be effective in maintaining a clinically effective concentration of drug. TCI devices have been in wide spread use in the delivery of general anesthetics throughout the world with the notable exception of the United States.³⁰ A number of publications support the efficacy and safety of these devices in a variety of clinical situations.^{29,31,32} In considering the application of this technology to general anesthesia, it is important to understand that different medications target different components of the anesthetic such as hypnosis, analgesia, and muscle relaxation. Agents may behave synergistically and have pharmacodynamic effects beyond the intended clinical effect such as cardiovascular or respiratory depression. Closed-loop systems refine the concept further by providing feedback based on a target effect to automatically adjust the controller. This provides the ability to address population variability as well as provide adaptive control by incorporating systems that respond to individual patient responses to a specific medication and respond to changing clinical conditions over time. The consideration of how to measure appropriate physiologic targets over a wide range of normal and abnormal patient conditions within the context of an often hostile environment reveals some of the challenges in designing CLC patient care systems for use in austere settings. Closed-loop applications in general anesthesia have focused on use of electroencephalogram data in various formats as a target for titration of hypnotic agents such as propofol by automated controllers.^{33–35} These include bispectral index, electroencephalographic entropy, and auditory evoked potentials.³⁶ These measurements have been shown to correlate with changes in consciousness but depth of anesthesia is not directly measurable and considerable debate remains as to what accurately defines depth of anesthesia. Closed-loop systems using bispectral index score (BIS) are the best studied to date with a number of publications documenting efficacy. BIS is calculated by a proprietary algorithm that performs multivariate analysis of the bifrontal electroencephalogram using a weighted sum of subparameters including spectral frequency, a bispectral measure, and a measure of burst suppression. The analysis yields a dimensionless number ranging from 0 to 100 with levels from 90 to 100 representing a fully awake state, 60 to 70 and 40 to 60 indicating light and moderate sedation, respectively, and values less than 40 suggesting deep to excessive hypnosis.³⁷ BIS is sensitive to multiple artifacts including muscle movement and has been best studied in patients under general anesthesia with

anesthetic techniques including neuromuscular blockade. Our interest here is the potential to apply this technology to austere settings including the prehospital or transport environment. One application where such technology is particularly appealing is in the realm of long haul transport of critically ill patients where maintaining adequate sedation and analgesia is an important consideration. While there is a paucity of data in this arena, evaluation of BIS in the intensive care unit provides a framework to discuss some of the challenges in developing these systems for use in this demanding milieu. Problems to be addressed include how to model the profound alterations in pharmacokinetics present in many patients with critical illness or injury and the ability to measure target values such as state of hypnosis. BIS algorithms have not been validated in critically ill patients and studies have suggested problems with muscle movement artifact and temperature instability.^{38–40} Other concerns include interference from electrical equipment, power supplies, and patient manipulation. In critically ill patients requiring neuromuscular blockade, BIS may be more useful as a significant source of artifact is eliminated.⁴¹ The limitations in the patient transport environment are obvious given the frequent presence of vibration, movement, and temperature instability. In addition to the infusion of hypnotic agents, closed-loop technology has been studied in titration of neuromuscular blockers using automated train of four monitoring to adjust the infusion.^{42–45} Titration of vasoactive agents has also been achieved with closed-loop technology in the settings of cardiac surgery, neurosurgery, and critical illness.^{46–48} The development of improved sensors for glucose monitoring has resulted in attempts at using closed-loop systems for glycemic control.^{49,50}

Despite the technological challenges, closed-loop technology has a number of potential advantages that may be attractive to those working in the prehospital or patient transport environment. Studies in intrahospital and interhospital transport suggest relatively common errors in management resulting in secondary insult in patients with traumatic brain injury including problems with ventilator management and hemodynamic control.^{51–55} Automated titration of ventilation could have a positive impact in this important area. Conservation of consumable resources such as oxygen is important in long haul transport and has been a factor in untoward events in the aeromedical transport of military casualties.⁵⁶ In this environment, multiple patients may require ventilator support or simple oxygen therapy. Depending on the aircraft used and the specific onboard oxygen supply and delivery system, oxygen supply may be critical. Preliminary studies suggest that automated control of inspired oxygen concentration results in a more rapid downward titration compared with manual control and an implicit advantage in oxygen supply conservation.⁵⁷ Closed-loop technology has been applied to experimental scenarios including hemorrhagic shock and burn resuscitation with encouraging results.¹⁷ The challenges in developing systems to handle sedation and analgesia have been outlined above.

Currently, application of closed-loop technology in clinical patient care remains experimental. Concerns have been raised in a number of areas that mandate rigorous testing and validation of each specific application. Issues include the considerable pharmacokinetic and pharmacodynamic variability in patient responses to a given drug concentration. These differences can in part be handled by adaptive controllers. Infusion of anesthetic agents, sedatives, and analgesics must consider the interplay between the specific agents, the given effect on the controlled variables or measured surrogates and untoward effects on other systems such as cardiovascular or respiratory depression that may occur. This has clear implications for the design of useful algorithms and adds considerable complexity to the system. Other criticisms have centered on the effect of expanding technologic complexity on the user. In the view of some critics, complexity introduces a greater likelihood of system failure, potentially shifts operator tasks to concentrate at specific times during care with a net effect of intense periods of peak work followed by lulls in workload that may actually degrade overall performance, and perhaps more importantly introduces concerns regarding the interface between automated control and return of manual control to the operator. Return to manual control may be particularly problematic in scenarios where the automated control system is constructed in such a way that the controller compensates for severe alterations in physiology with normalization of important clinical data points in a manner that the controller intervention is unrecognized by the operator until the compensation fails and the patient condition declares itself through rapid and potentially unrecoverable clinical deterioration.⁵⁸ This again has clear implications for the construction of algorithms that can handle complex clinical interactions and provide smooth return to manual control when indicated.

CONCLUSION

The application of closed-loop technology in a variety of patient management systems has the potential to improve patient care throughout a wide range of conventional and unconventional clinical settings including austere prehospital scenarios, the transport environment including intrahospital and interfacility patient movement, the operating theater, and into the intensive care unit. Further work is needed to develop robust and accurate sensors, controllers, and algorithms with testing of each specific application in commonly encountered as well as extreme clinical circumstances with a focus on evaluating the safety and reliability as well as the clinical efficacy of such systems.

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