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Principles of Physiologic Closed-Loop Controllers in Neuromodulation

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ABSTRACT

Rationale: As neurostimulation devices increasingly incorporate closed-loop functionality, the greater design complexity brings additional requirements for risk management and special considerations to optimize benefit. This manuscript creates a common framework on which all current and planned neuromodulation-based physiologic closed-loop controllers (PCLCs) can be mapped, including integration of the "Technical Considerations of Medical Devices with Physiologic Closed-Loop Control Technology" guidance published in 2023 by the United States Food and Drug Administration, a classification of feedback (reactive) and feedforward (predictive) biomarkers, and control systems theory.

Results and Conclusions: We explain risk management in the context of this framework and illustrate its applications for three exemplary technologies. This manuscript serves as guidance to the emerging field of PCLCs in neuromodulation, mitigating risk through standardized nomenclature and a systematic outline for rigorous device development, testing, and implementation.

Keywords: Algorithm, closed-loop control, neurostimulation, technology

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INTRODUCTION

Our approach to defining key terms used in the control of neuromodulation devices is to follow the 2023 Food and Drug Administration (FDA) "Technical Considerations for Medical Devices with Physiologic Closed-Loop Control Technology," which references the International Electrotechnical Commission (IEC) 60601-1-10 requirements for medical electrical equipment. The definitions used here should be understood as further limited only to the context of applications in neuromodulation control. We also strove to maintain continuity between definitions in the glossary by[1] and risk management paradigms outlined in,[2] but we have expanded on both studies to include specific applications. This tutorial aims to provide a useful resource for stakeholders across the device development pipeline, from physicians, scientists, and engineers to patients and the public, to understand how best to apply physiologic closed-loop controllers (PCLCs) to their indication such that it works predictably, successfully mitigates risk, and improves therapy efficacy.

A PCLC, as defined by IEC60601-1-10, is a medical device or system that automatically adjusts or maintains a physiologic variable(s) through delivery or removal of energy (eg, electric) or matter (eg, drugs, or liquid or gas considered as a medical device) using feedback from a physiologic-measuring sensor.

PCLCs rely on proper integration of biomarkers, or objective measurements that meaningfully reflect a physiologic state/process, disease process, or response to a therapeutic intervention. The evolution of PCLCs in neuromodulation is positioned at the convergence of stimulation and sensing technologies and increasingly sophisticated control algorithms, including leveraging artificial intelligence (AI), representing a significant shift toward truly personalized and adaptive therapies. Recent advances in control algorithms have enabled the development of more sensitive, accurate, and reliable biomarkers—both reactive and predictive—that enhance real-time decision-making capabilities of neuromodulation systems. For instance, the integration of machine learning methods for feature extraction and classification has substantially improved the detection and predictive accuracy of critical physiologic states, such as seizure onsets or pain exacerbations, facilitating timely and precise intervention adjustments.

A critical frontier in the field is the expansion of closed-loop neuromodulation from primarily reactive systems toward fully autonomous adaptive therapies leveraging predictive AI. Emerging capabilities such as multimodal sensor integration, real-time edge computing, and deep learning are enabling closed-loop systems not only to respond to immediate physiologic signals but also to anticipate clinical needs on the basis of patterns discerned from longitudinal data. Innovations such as evoked compound action potential (ECAP)-adjusted spinal cord stimulation (SCS) illustrate how neural biomarkers can directly drive dynamic adjustments in stimulation dose to maintain therapeutic efficacy despite physiologic variability, significantly improving patient outcomes and device usability.[3] Moreover, adaptive deep brain stimulation (DBS) systems that modulate therapy based on beta band power in Parkinson's disease (PD) indicate the clinical viability of major loop PCLCs to continuously adapt to disease-specific neurophysiologic states.

STIMULATION DOSE

Stimulation "dose" is defined as those aspects of technology that affect ways energy is applied to the body[4]:

1. "amplitude" of the stimulation, which is the peak intensity, whether voltage-controlled (expressed in volts) or current-controlled (expressed in amperes)
2. "waveform" and "timing" of the stimulation, which spans duration of therapy application, the interval between treatments, and how intensity changes during treatment (such as "frequency" and "pulse duration")
3. "Location" is where energy enters the body. Location refers here only to the relevant interface between the device and body (not all device parts). For electrical stimulation, location is the size, shape, and placement of electrodes with respect to the target neural tissue. Changing location can therefore change the energy requirements in (1) and (2).

Neuromodulation dose and the properties of the body together determine which cells are exposed to what energy, which in turn drives the outcome of neuromodulation. In this sense, two devices that provide an identical dose to the target neural tissue are indistinguishable to the body—they are the same in the therapeutic responses they produce. Device parameters outside dose, such as its user interface and battery life, certainly matter but are not part of the therapeutic dose. Therefore, when we personalize neuromodulation dose, we adjust only amplitude, location, or waveform/timing.

Similarly to pharmacokinetic dose responses, the relationship between the amplitude and waveform of the electrical stimulation and the response of the target tissue may be nonlinear or nonmonotonic. For example, stimulation that depends on neural activation must exceed the activation threshold to have benefit, and stimulation below that value will not be efficacious. Stimulation may affect the body through multiple mechanisms, including longer-term neuroplasticity processes, which can have beneficial or counterproductive components. The dose/response relationship for each of these mechanisms should be established to determine how to provide predominantly beneficial, and preferably optimal, therapy.

Each neuromodulation device is designed to provide a limited range (set) of neuromodulation doses, and limits its range of dose parameters on the basis of technology (eg, hardware limitations), the use-case (intended use), and safety standards[5–7] (eg, limiting charge density to below that which could cause tissue damage). This does not mean it is advisable to try any dose available from a given device; for example, some doses may be painful or activate areas outside the target (ie, we assume stimulation is perfectly selective of the target area, but dose is simply greatest in the target and decreases with distance from the electrodes, potentially activating other areas). A single neuromodulation device may allow a few or many possible doses—that is, combinations of amplitude, location, and waveform/timing. Given too many dose possibilities to practically test and a cost to testing ineffective doses (eg, lost time, side effects), there must be a therapy technique or algorithm to search for and select a preferred neuromodulation dose regimen. The effects that changing dose parameters have on neurons in time and space remain an active area of investigation for many disease types.

Although adaptive pharmaceutical devices do exist, such as the artificial pancreas, a combination of a constant-glucose monitor and an insulin pump, which allows blood-sugar control using feedback,[8] individualized therapy with most drugs is limited to coarse adjustment of amount (eg, number of pills) or timing (eg, morning and evening). Neuromodulation devices are inherently

designed to allow dynamic, real-time dose adjustment. This allows therapy to be personalized, even on a treatment-by-treatment basis. Dose can be adjusted midtreatment because there is an instant corresponding change in energy in the body. The pharmacokinetics of drug delivery are sluggish by comparison. However, the exact time relationship between energy delivery and symptom reduction varies by indication, and some conditions (eg, depression, epilepsy[9]) may require weeks or months for therapeutic effects from neuromodulation to be observed.

By adjusting stimulation location, neuromodulation can deliver energy to one or several neural targets, in contrast to systematically distributed drugs. Changing stimulation location allows engaging distinct regions of the nervous system that are implicated in disease etiology or its control. A device location may be changed by moving electrodes, for example, adjusting a transcutaneous electrical nerve stimulation device over a painful body region. In situations in which a device has several electrodes already placed, stimulation location may be changed by selecting which contacts are activated—which is the case for implanted devices.

Thus, neuromodulation devices are adjustable in real time and with specificity in both time and region. When dose is adjusted for an individual, it is personalized. The selection of one of the many possible doses relies on biomarkers measured from individuals. The next two sections describe how biomarkers are used in personalized neuromodulation dose tuning, including classifying distinct approaches and classes of biomarkers.

MANUAL VS AUTOMATIC DOSE ADJUSTMENT

The traditional strategy for neuromodulation is to set certain fixed stimulation parameters, monitor the patient's symptoms, and manually change the settings during clinical visits as needed. This "manual loop" is considered "human in the loop:" all changes to therapy are implemented directly by a clinician, nurse, or, to a limited extent, the patient. There is no automated "control policy" embedded on the device. Stimulation parameters are programmed on the basis of clinician or patient input, and changes in behavior are reported by a patient through self-report or in a clinical examination. If available, complementary monitoring sensors (eg, electrophysiology) indicate whether any changes to the physiology result. Changes to either physiology or behavior are fed back to and interpreted by the "human in the loop" to update or keep fixed the stimulation dose. This method often sets long-term stimulation parameters (for use over weeks/months) on single snapshots in time (eg, determined on a clinical examination or programming day) but has limited ability to adjust stimulation dose on an ongoing and short-term basis. In addition to the clinician, the "human in the loop" can include the patient, who is provided with a programmer with limited control on dose (eg, on/off, intensity) as preset by the clinician.

Newer devices, with automated loops, will detect, predict, and react to state changes in the physiologic system, as shown in Figure 1. This "automated loop" still involves a "human on the loop" who monitors its operation: A clinician sets the initial conditions of the loop (set point, dose, stimulation parameter limits, and basic control rules), but the device has the capacity to make changes to the stimulation dose while the loop is running without necessary intervention from the clinical team. In this case, changes in the physiologic variable are directly compared with a target, or "setpoint," and the difference, or "error," is fed back to the algorithmic control to react and change stimulation parameters. Devices may measure and adapt to physiologic data (biomarkers) or nonphysiologic data (eg, time of day, battery level). Devices may respond to the current state of the measured variable or a predicted future state. Among biomarkers, we later explain the distinction between those used in feedback and feed-forward control. Automated loops also include "fallback modes," which begin in response to unexpected values from any of the feedback or feedforward signals, and emergency stops. The "human on the loop" also can include the patient, with important but restricted programming capabilities.

Moving from a manual to an automated loop does not reduce the level of responsibility of human members of the clinical team, but it has the potential to reduce their frequency of interaction. Although in both manual and automated loops, the clinician is responsible for configuring sensors, selecting biomarkers, and monitoring for alerts, the crux of the difference between the two approaches is the way therapy is changed over time. In a manual loop, the role of the clinical team involves selecting and troubleshooting the exact dose and stimulation paradigm, including stimulation location, time, frequency, pulse width, and waveform (usually a variation of a rectangular pulse) to optimize therapeutic dose. Because disease symptoms fluctuate with time, the provider and patient select a predetermined follow-up frequency to adjust these stimulation settings as needed. In an automated loop, however, the clinical team sets the initial stimulation paradigm, and this paradigm then adjusts stimulation dose in an automated fashion over time. The provider, however, remains required to set limits on the stimulation parameters, configure algorithm control policy parameters, and meet regularly with the patient to ensure optimal delivery of therapy. Human involvement also would be required if an entirely new stimulation paradigm were desired, or if an automatic mode were stopped for any reason. Thus, the use of an automated loop does not reduce the role of the clinical team or lessen the imperativeness that they maintain a good mental model of the automated processes at work. The IEC 62366 defines mental models as "how users think the system behaves vs how it actually behaves," and IEC 60601-1-10 Section 4.2.2 requires the designer to "ensure that the user interface communicates the control system's current state, mode, and intent in a way that matches the operator's mental model." For this reason, each of the practical PCLC examples, later, includes a schematic of the basics of the mental model for that application, building on the general framework in Figure 1, with individual differences outlined in Table 1.

TYPES OF BIOMARKERS

Automatic control relies on feedback ("reactive") biomarkers and/or feedforward ("predictive") biomarkers. In this section, biomarker types are explained on the basis of a prior framework and analysis.[10] Biomarkers, as considered here, are specifically used to adjust stimulation dose and are part of control loops for dose optimization. The nature of the biomarker affects the way it is used in a loop. Through the inclusion of both feedback and feedforward variables, we expand beyond the IEC 60601-1-10 definition of a PCLC "command variable" as purely feedback against a "comparing element."

"Reactive biomarkers" (also called responsive biomarkers) are measures of physiologic activity that are expected to respond

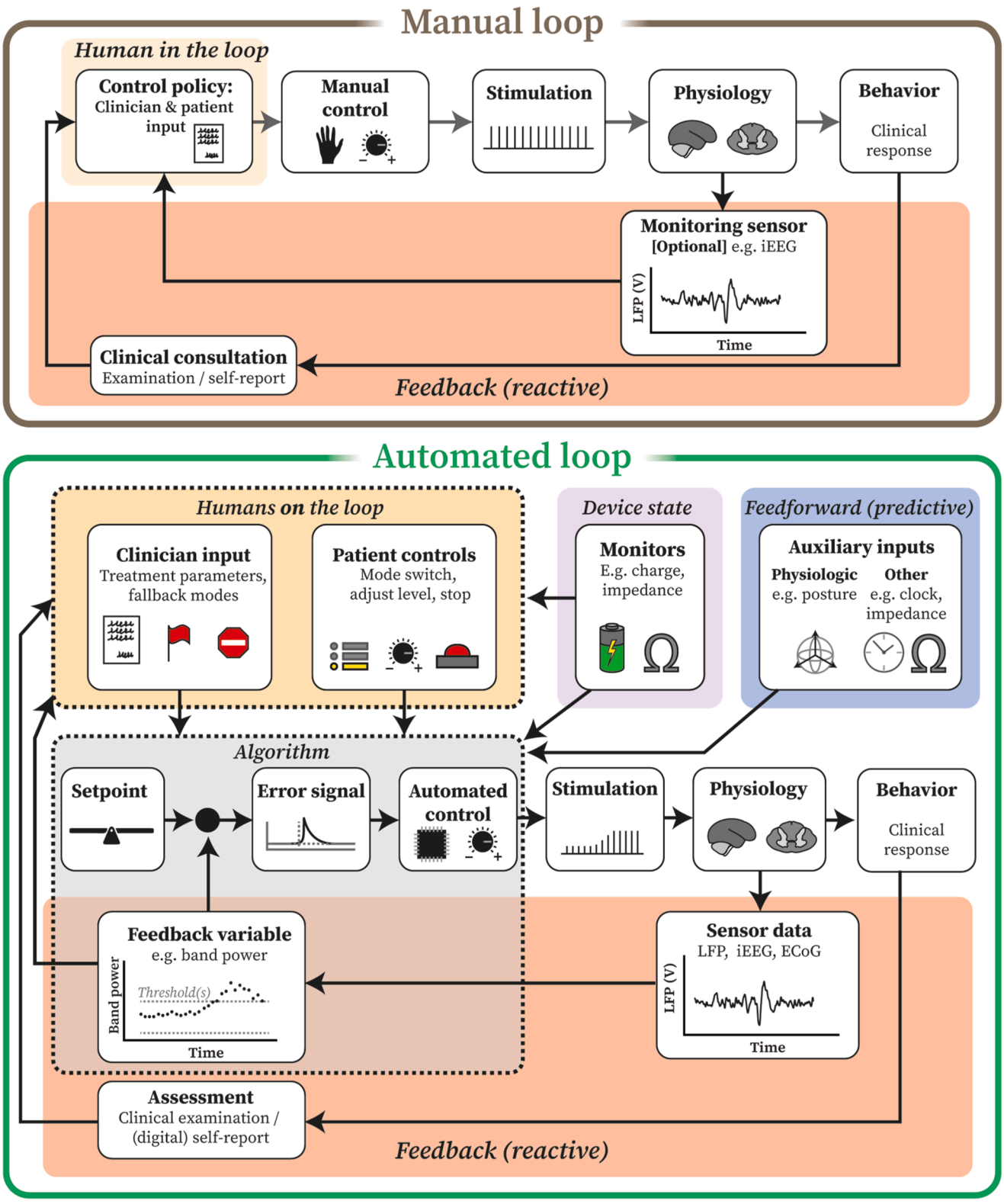

Figure 1. PCLCs can be either manual or automated loops depending on the level of human involvement: whether the actuator is fully controlled by the human in the loop (manual loop) or whether the actuator runs automatically within human input guidelines and periodic monitoring of device logs and alerts to ensure proper running (automatic loop). Clinicians input all the rules for the algorithm box, including (as represented by respective icons in the automated loop) stimulation limits, flags, and fallback modes. Patients may be able to switch programs manually, fine-tune amplitudes, or activate emergency stops to stimulation. Automated PCLCs allow incorporation of more flexible algorithms and more complex variable integration (ie, both feedback and feedforward elements) while also monitoring device state (eg, battery life, electrode integrity). The icon in the setpoint box is a seesaw; representing values may appear on either side of the one desired value. Icons in the automated control box are an integrated circuit and a tuning dial, representing internal processing on the device to determine the

directly to stimulation and can therefore inform adjustments to the stimulation paradigm. For example, if the reactive biomarker is in the desired range compared with a setpoint, the stimulation dose would maintain a constant level. Conversely, if the reactive biomarker is not in the desired range compared with a "setpoint," the stimulation dose would be changed according to a prespecified control policy. Once a new dose is selected, changes in the reactive biomarker continue to be monitored. Reactive biomarkers can be broadly separated into three types. "Type 1" reactive biomarkers are clinical response surrogates: durable responses to dose, which track changes to primary clinical outcomes and are sustained after stimulation is off (eg, a recorded brain state that correlates with targeted disease severity). "Type 2" reactive biomarkers typically concern the mechanism of action; they measure an acute change in the body's response to dose (eg, a brain state that changes transiently when an effective treatment is delivered). "Type 3" reactive biomarkers are instant, electrodynamic changes that measure energy delivered to the tissue (eg, the electric field generated in a brain target during a stimulus pulse).

Whichever type of reactive biomarker is used, it is important to characterize the dose response curve (Fig. 2), paying special awareness to what may cause differences from the ideal response (Fig. 2a) in offset, gain (change in biomarker per change in stimulation amplitude; Fig. 2b), noise, and tonicity (Fig. 2c). One also should consider the time scale, or longevity, of the effect and whether there is a time delay, or phase lag, for the effect to occur. Figure 2d to f shows examples of dose response curves from SCS and from DBS for PD, highlighting how these factors affect the region of operation (usable stimulation amplitudes) for a given device and application. A special consideration here is that most physiologic systems are only linear time invariant (LTI) on certain scales. This will be further explained in the SCS use case, later, but it is raised here to highlight (1) there are applications in which nonlinearities are observable enough to affect design considerations not just on a population basis but a patient-to-patient basis, and (2) it is prudent to define a region of interest/operation that avoids such edge cases. Selecting a region of operation within these "stability margins" will ensure the system acts consistently and predictably. Our scope is to provide common definitions and explanations at the tutorial level to learn about the field; more nuanced, application-specific considerations are beyond the scope of this manuscript.

"Predictive biomarkers" are measures of physiologic activity or anatomy that are not expected to directly respond to stimulation. Predictive biomarkers can be measured before stimulation starts or during stimulation (eg, genetics [DYT-1] can predict dystonia response).[14,15] Stimulation dose is adjusted on the basis of predictive biomarker without the expectation the predictive biomarker will change. For example, stimulation intensity may be changed on the basis of subject posture without the expectation that posture will be influenced by stimulation. Predictive biomarkers may be "gates" that determine the timing of dose delivery (eg, syncing stimulation pulses to breathing). Alternatively, predictive biomarkers may be "playback" of a specific signal feature that provides information on whether stimulation dose and location are optimized. Predictive biomarkers may be considered "neuronavigation" if they provide information on the position of neuroanatomy in relation to dose delivery—thus, fluoroscopy is considered a neuronavigation biomarker predictive of effectiveness of dose delivery. Evoked responses to test stimulation also can be used as predictive biomarkers that may indicate change in brain excitability or brain state (eg, sleep or wake status) and would then provide information on how stimulation dose should or should not be altered. Predictive biomarkers may be measured once or repeatedly.

It is important to note these are simplified categories of biomarkers based on how they are used,[10] such that the same biomarker may be used in one system as reactive (feedback) and in another as predictive (feedforward). Some biomarkers may have overlapping characteristics among types, and some PCLCs may actuate on the basis of multiple biomarker inputs. There could be any number of combinations of short-term, durable, reactive, and predictive biomarkers monitored operating on any number of timescales (ie, latency to response, settling time). For this reason, a hierarchy of biomarkers (ie, an explicit definition of biomarker priority) and how a device responds to each of them (ie, the control hierarchy) are a critical design consideration. Implicit in our definition is that factors not measured or not used in a PCLC are not biomarkers as previously defined (eg, a lead migration that is not observed or not responded to).

Finally, we clarify that systems may measure physiologic or device parameters that are not used to adjust stimulation dose. These are not biomarkers as previously defined for the purpose of this guidance. These may include monitoring device state (eg, battery charge), detecting faults (eg, in a lead or a sensor), or clinical assessments that are not directly used to adjust dose (eg, medical inclusion criteria, a clinical trial outcome measure). These measures are important for device and intervention design (and, in some cases such as battery charge, they are explicitly integrated in our framework), but our task of explaining biomarker use in PCLCs depends on considering measurements that are used in the PCLC.

"MAJOR" VS "MINOR" LOOP CONTROL

Neuromodulation PCLCs can operate with different hierarchies of feedback control for appropriate titration of parameters such as stimulation amplitude, pulse width, and frequency. Control systems engineers refer to these hierarchies as "major loop" control, which operates around the entire system under control, and "minor loop" control, which closes the loop around a subcomponent. Each control method can provide therapy improvements. An example of major loop control is to sense a signal directly associated with a disease state—such as elevated beta band power, a pathophysiologic marker of PD—and adjust the therapy in response to changes in this signal[16] (the later example supplies more details). There are many types of control response, including but not limited to those explained in the use cases, later (bang-bang control, dual threshold control, and proportional integral derivative). Similarly, a PCLC can leverage minor loop control, reacting to a signal not strictly associated with a disease state but

stimulus change. Similarly, manual control has a hand and a tuning dial because a human must be involved to change stimulation. The icons in the physiology block represent the brain and spinal cord, respectively, as the key areas of interest for neuromodulation. All other icons are labeled explicitly within the figure. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Key Components of an Automated Loop for Three Different Applications.

Automated loop variable	Responsive neurostimulation for epilepsy	DBS for P D	SCS for chronic pain
Clinician input	Treatment parameters, fallback modes	Treatment parameters, fallback modes	Treatment parameters, fallback modes
Patient controls	Therapy stop	Mode switch, adjust level, stop	Mode switch, adjust level, stop
Device state (monitors)	Battery charge, electrode impedance	Battery charge, electrode impedance	Battery charge, electrode impedance
Feedforward (auxiliary sensors)	Nonphysiologic: magnet swipe	Auxiliary inputs: time of day, tissue impedance	Disturbance: posture change, cough, heartbeat
Setpoint	Dynamic criterion	Beta target	ECAP target
Error signal	Difference from dynamic criterion	Difference from target	Difference from target
Automated control	Bang-bang control	Bang-bang or dual threshold control	Proportional-integral-derivative, threshold
Stimulation	Short-term stimulation burst on/off	Amplitude adjustment	SCS pulse amplitude adjustment
Physiology	Sensing from brain	Sensing from brain	Sensing from spinal cord
Behavior	Seizure count and severity	Symptoms: bradykinesia, tremor, freezing	Pain experience (pain relief, quality of life)
Sensor data	iEEG, ECoG	iEEG	Aβ fiber ECAP
Assessment	Clinical examination/(digital) self-report	Clinical examination/(digital) self-report	Clinical examination/(digital) self-report
Feedback variable	Half-wave, line length, area	Beta power	ECAP amplitude

still important to maintain the integrity of the system. For example, in SCS systems, minor loop feedback can help automatically optimize parameters by making the system more immune to variations in the tissue-electrode interface. Owing to postoperative maturation of the electrode-tissue interface and spinal cord motion with postural shifts, the number of activated fibers resulting from the stimulation can shift over time and during activities of daily living.[17,18]

The circuits of implanted devices often have a mechanism to measure the current or charge delivered in the face of impedance fluctuations, for example, by monitoring the current across a reference resistor against an expected voltage. In its simplest form, such constant-current stimulators that adapt the output voltage on the basis of feedback from these impedance measurements are using minor loop control; in this case, the improved immunity to impedance variations can stabilize the charge delivery not as a PCLC but as an important subcomponent of the PCLC design. More advanced technologic mitigations for number of activated fibers variability now include posture-responsive stimulation circuitry using evoked potential measurements and feedback control systems[3,19] (the later example supplies more details). Although minor loop control does not use a symptom biomarker as the feedback control variable, positive therapeutic impact may nevertheless be realized through their incorporation, particularly in the context of system automation and therapy optimization relevant to dose consistency. For long-term therapy roadmaps, researchers continue to explore direct pain biomarkers,[20] which might one day enable a major loop control around a primary symptom of interest.

RISK MITIGATION

A key takeaway from the FDA guidance and the 60601-1-10 framework is the critical need for proper risk mitigation at each step of the loop (as described in Fig. 3), including variable logging. The first step is to have an intuitive mental model through which to understand the patient transfer element, or the relationship between the physiologic signal sensed and the electrical stimulation delivered, especially in comparison with the steady-state value of the physiologic variable, as previously described (Fig. 2). This mental model includes items already described in addition to which levels of stimulation are safe or unsafe. This information helps set functional risk mitigation parameters such as physiologic sensing limits and stimulation limits. The next step is to be mindful of the possibility that a device malfunctions or an unexpected artifact is encountered as a person with an implant interacts with their environment. The FDA guidance warns against several pitfalls of PCLC implementation, specifically complacency, loss of situational awareness, automation bias, and skill degradation.[21]

The likelihood of failure from either complacency or loss of situational awareness is reduced by implementation of proper monitoring (eg, logs, alerts) and setting of entrance and exit criteria (Fig. 3). It is important to consider every possible failure mode, to monitor data that could indicate such failures (eg, impedance, device temperature), to alert when human intervention may be necessary, and to plan for the next appropriate action to take for each failure mode. In such cases that a failure mode is encountered that meets the loop's exit criteria (evidence such that it is unclear whether appropriate adaptive stimulation is being provided), an automated PCLC should switch to a fallback mode (eg, a stimulation setting within the safe, therapeutic range that

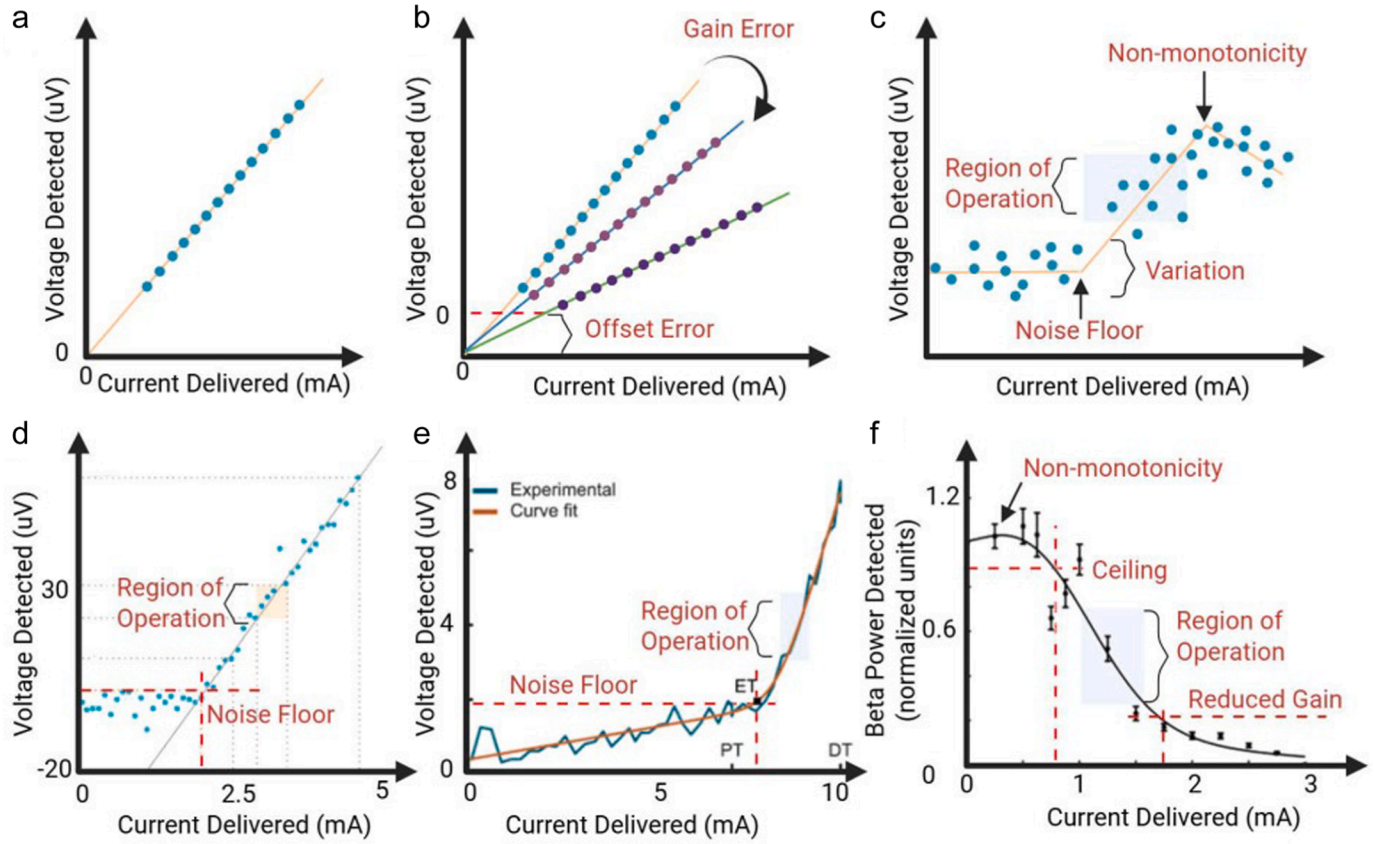

Figure 2. Biomarker design considerations. a. Ideal, noiseless, monotonic dose response. b. Schematic of incorporation of offset error and gain error. c. Schematic of incorporation of noise, variation, and nonmonotonicity. d and e. Adaptations of data from Saluda (d) and Medtronic[11] (e), highlighting general similarities of different devices, although they may still have different variability and dose response. f. Adaptation of a figure modeling beta dose response,[12] based on real data from patients with PD,[13] highlighting that some biomarkers may decrease with dose, and gain is not constant. In this case, there is decreasing biomarker reduction with increased amplitude at approximately 1.75 mA. [Color figure can be viewed at www.neuromodulationjournal.org]

does not change with the biomarker). A fallback mode may, in some cases, mean turning stimulation off or reverting to manual control. Whichever fallback mode is initiated, it should continue operating until the next time a log indicates that the failure mode has been resolved and the loop's entrance criteria is met. In some cases, a fallback mode may be initiated by the patient or physician (eg, by a magnet swipe) during a clinical visit (eg, while they undergo imaging) or other instance when a specific, sustained setting is required. Although not all failure modes can be prevented, their likelihood of occurrence and potential impact on therapy delivery are reduced.

The likelihood of failure from either automation bias or skill degradation is further reduced by proper verification and validation testing. Because human physiology is dynamic, all settings are subject to both inter- and intrapatient variation, including the value of the setpoint. System settings should be verified to accommodate this dynamic range and have proper monitoring in place to alert whether something is outside this expected range or requires human intervention. It is the clinician's job, as the human on the loop, to check monitors and logs to ensure devices remain operating within the expected range. Introducing automation into therapy delivery introduces inherent risks given the PCLC performs a task on the basis of on a sensed variable, without a human in the loop. Although the performance characteristics can and should be verified with in silico, in vitro, and/or preclinical models, clinical examinations should be conducted to assess the clinical value and risk profile of the technology. The clinician needs to understand how the device operates when it encounters a failure mode once deployed, not just when it is operating under ideal conditions.

Risk will never truly be reduced to zero, but implementation of good risk mitigation measures can come close. In the unfortunate case that an adverse event does occur, good monitoring and logging will aid in forming reports for the FDA and other regulatory bodies to review. These records are instrumental in identifying design deficiencies that lead to faults, and allow timely design improvements. Clinicians using these devices should be able to put these logs into the context of their mental model of the system and work to prevent repeating the adverse event in the future.

PRACTICAL EXAMPLES

In the following sections, we discuss three practical examples of FDA-approved PCLCs used commercially. We explain the motivating principles and physiology, mental model, biomarkers for automated control, risk mitigation strategies, and practical implementation and performance metrics. These are simplified descriptions of the major components and loops of each use case, but it should be remembered that any number of minor loops also could be operating.

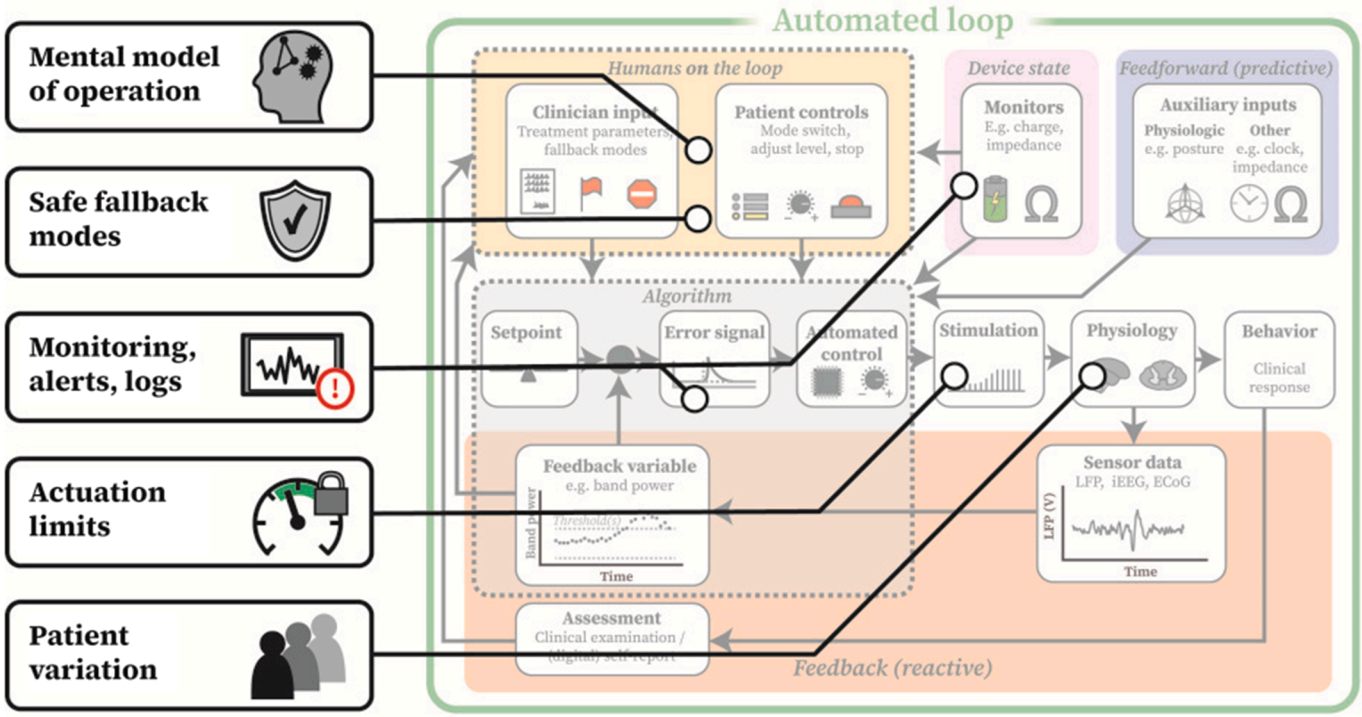

Figure 3. Risk must be mitigated at every step of PCLC implementation. In automated loops, the user sets actuation limits and safe fallback modes with appropriate monitoring, alerts, and logs to flag any time the system violates the mental model of operation, conflicts with assumptions about physiologic limits, or otherwise requires human intervention (eg, battery charge). [Color figure can be viewed at www.neuromodulationjournal.org]

Use Case: Responsive Neural Stimulation

This example introduces the NeuroPace RNS® System (NeuroPace, Mountain View, CA), the first PCLC device for responsive neurostimulation approved by the FDA for neuromodulation to treat drug-resistant epilepsy in 2013, which hereafter will be referred to as the "responsive neurostimulator." The responsive neurostimulator delivers targeted neural stimulation in response to physiologic changes detected in the intracranial electroencephalography (iEEG) or electrocorticography (ECoG) signals. Figure 4 adapts the general PCLC block diagram introduced in Figure 1 to this use case, illustrating how specific variables from the responsive neurostimulator map onto the generic framework.

Motivation and Mental Model: Delivering Dose Responsive to a Biomarker for Epilepsy

The mental model behind responsive neurostimulation therapy assumes that stimulation, when delivered near seizure onset, may interrupt or shorten seizure duration, reduce the likelihood of subsequent seizures, or both. Early evidence supporting this mental model came from Lesser et al,[22] who showed that brief bursts of electrical stimulation could terminate afterdischarges triggered by cortical stimulation in humans. The control loop described here has a bang-bang output, meaning one of two discrete stimulation states: on or off. The responsive neurostimulator also supports two advanced responsive-stimulation paradigms: (1) frequency-adaptive stimulation, which automatically adjusts the burst frequency on the basis of the detected iEEG signal, and (2) phase-synchronized stimulation, in which stimulation is delivered at a specified phase of the iEEG signal in the detection channel. Notably, adaptive stimulation with the responsive neurostimulator system remains responsive therapy. It allows automatic adjustment of the frequency of the responsive stimuli depending on the detected signal; this is differentiated from the continuous stimulation automated loop (also often called adaptive stimulation) for other systems and applications.

Biomarkers for Automated Control

The responsive neurostimulator comprises an implantable neurostimulator and leads, a patient remote monitor, a clinician programmer, and cloud-based data storage always accessible to authorized clinicians or researchers through any internet-connected smart device (Fig. 5). The implanted device continuously analyses iEEG/ECoG signals and applies up to three seizure detection tools using patient-specific half-wave, line length, and area (area-under-the-curve) algorithms configured for early seizure detection.[24,25] These tools can be applied to one or two iEEG/ECoG channels individually or in combination with logical operators (eg, OR, AND). When any selected feature exceeds its programmed threshold (fixed or variable threshold, Fig. 4), it serves as a biomarker of epileptiform activity or an imminent seizure and triggers stimulation. We categorize these features as type 1 reactive biomarkers, given our mental model[22] relies on them as surrogate metrics of the primary clinical outcome, seizure likelihood; however, they share characteristics with type 2 reactive biomarkers because the stimulation delivered causes a short-term change that may eventually become a durable change. The responsive neurostimulator uses a hybrid setpoint strategy: adaptive or fixed threshold for line length and area, and fixed threshold for half-

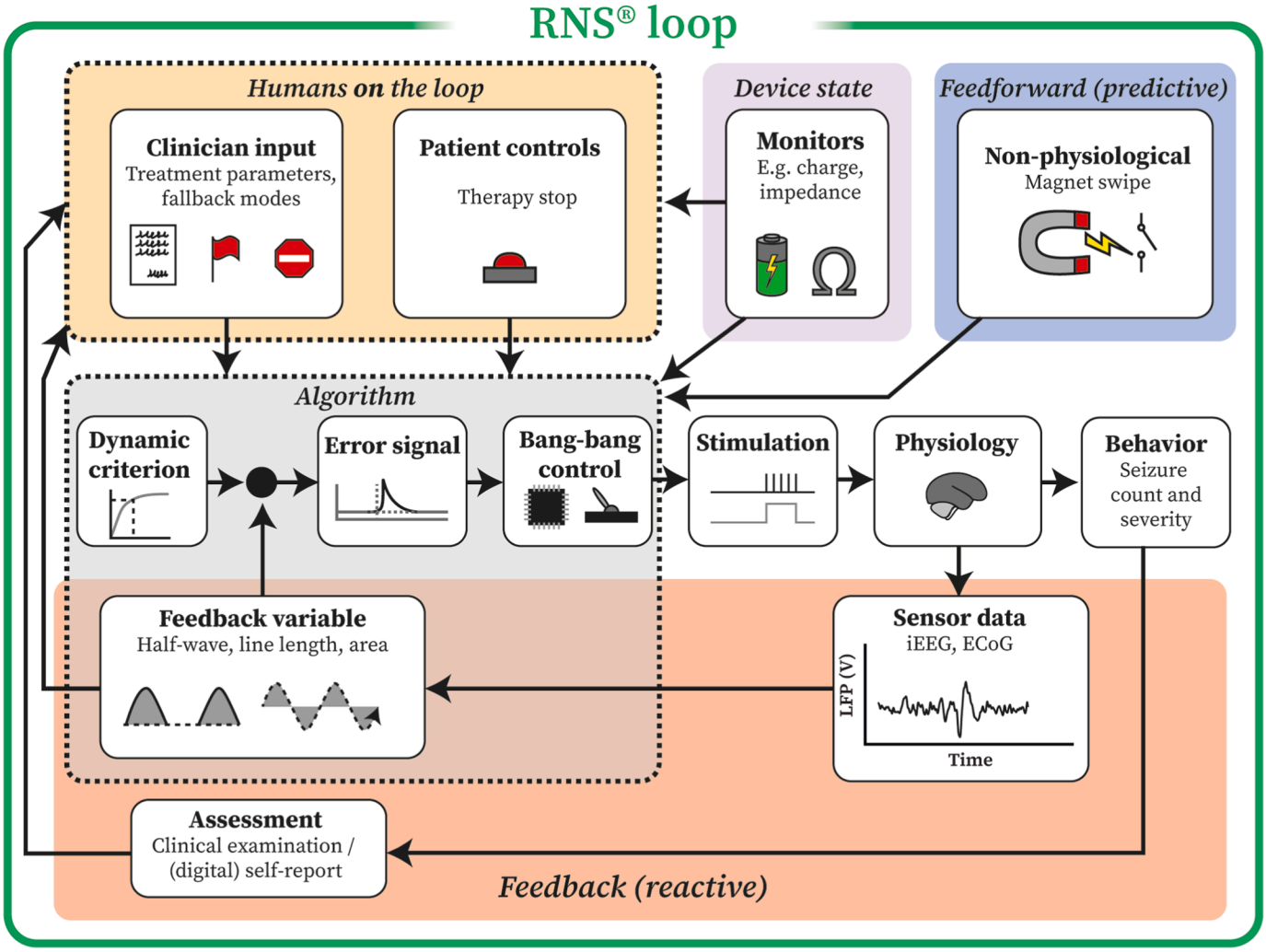

Figure 4. Block diagram of a general PCLC system, adapted to the specific examples of the variables used in this case study of responsive neural stimulation for treatment of epilepsy. In this case, patient controls are limited to emergency stops or iEEG storage initiated by a magnet swipe. Instead of a stationary setpoint, there are several dynamic criteria that influence the stimulation control. Monitors, including event logs, help inform future algorithm adjustments. Icons carried over from Figure 1 retain their meaning. Setpoint has changed from a seesaw to a curve on an axis to represent a range of expected values given a range of inputs. The tuning dial in the control box has been replaced by a switch because there are only two discrete stimulation states, not a continuous range. All other new icons are named explicitly in the figure. Table 1 presents a comparison with other applications. RNS, responsive neurostimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

wave. Adaptive thresholds are continuously updated on the basis of a long-term baseline window compared with the window used to compute the short-term line length or area, which helps maintain sensitivity while minimizing false detections. Initial validation of these biomarkers was conducted using clinical data from the Emory University data base, which was later integrated into the IEEE EEG portal data base.[26] This validation formed part of the presubmission materials required by the FDA for Investigational Device Exemption approval of the responsive neurostimulator feasibility study.[27]

Risk Mitigation Strategies for an Epilepsy PCLC

The system architecture incorporates hierarchical layers of control (Fig. 5). The embedded layer, housed in the implant, corresponds to the automatic loop in Figure 4 that manages detection and therapy delivery using a bang-bang control policy, effectively running the PCLC algorithm to ensure immediate responses to physiologic changes. The two upper layers (monitoring and data base layers) are manually operated and map to the humans on the loop block in Figure 4. Each layer communicates upward by providing data and downward by enforcing safeguards against risks and hazards while enabling flexibility for future system enhancements. Because data are gathered from multiple implantable neurostimulators across patients, AI-driven analyses at the data base layer can be used to design monitoring algorithms that detect and warn of potential hazards, thereby reducing patient risk.[23] These algorithms may evolve into autonomous PCLC algorithms operating at the higher layers, typically with longer response times but relying on robust computing power that is not feasible at the implant level (embedded layer, Fig. 5). Researchers can update the implantable device's closed-loop control policy at

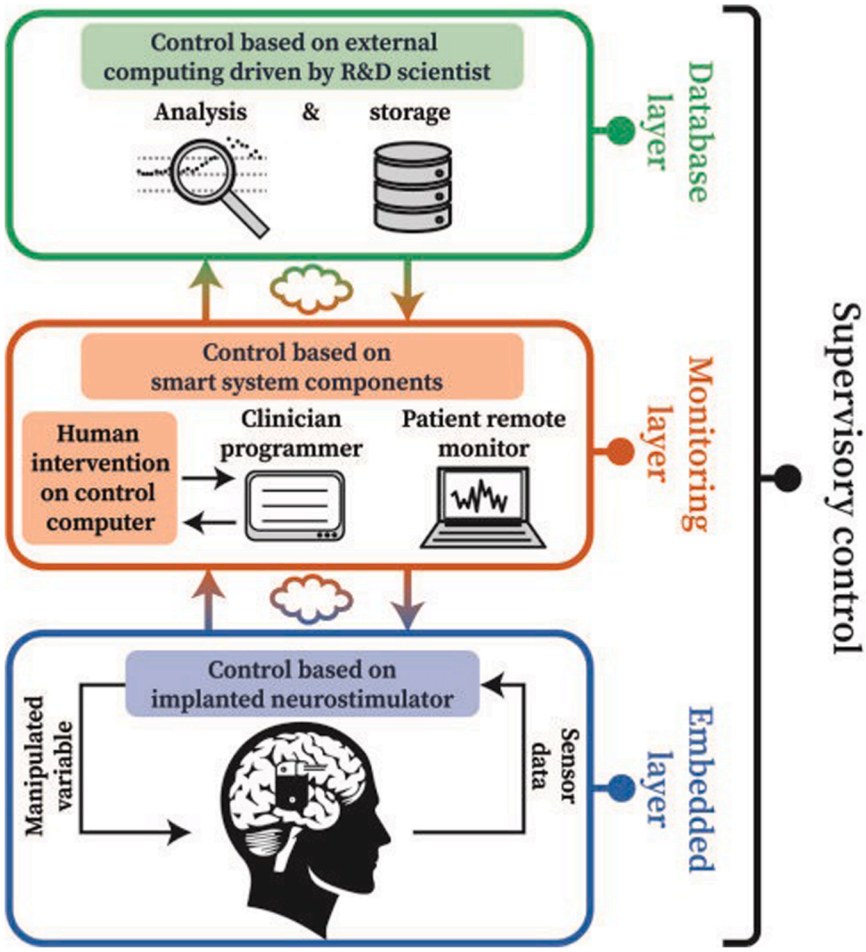

Figure 5. Example of robust and versatile PCLC system three-layer functionality (adapted from[23]). [Color figure can be viewed at www.neuromodulationjournal.org]

the data base layer using all the data received from multiple devices to improve the PCLC algorithm and deploy it through the monitoring layer to the implantable device, effectively enhancing control for periods spanning hours, days, or months as the learnings and implementation updates are executed.

A key feature of the system is its safety-oriented design. As part of the embedded layer (Fig. 5) or algorithm block (Fig. 4), the system includes a manual safety override mode that allows patients to temporarily suspend therapy by placing a magnet within 1 inch of the implant, provided this capability is not disabled during programming.[28,29] Therapy automatically resumes once the magnet is removed.

For each event detected, the system enforces a safety limit by restricting stimulation to a maximum of five consecutive "therapies" per stimulation "event" while the detection flag remains active.[28,29] In this case, each therapy comprises one or two bursts, and if two bursts are configured, they are delivered consecutively with no intervening delay.[29] This controlled stimulation strategy is designed to minimize the risk of overstimulation. If the detection flag remains active after the maximum number of therapies has been delivered, stimulation is suspended and will not resume until the detection flag resets (typically indicating the end of the seizure event) and a new detection occurs.[29] In addition to a limit on the number of therapies per episode, the number of stimulation episodes per day is limited to a user-configurable maximum.

The responsive neurostimulator incorporates several automated fallback modes to ensure patient safety in the event of critical faults. These include the end-of-service (EOS) reset, triggered when battery voltage falls below the safe threshold, causing the device to suspend therapy, detections, and all measurements. The general neurostimulator reset occurs if the system detects an unrecoverable internal error or reaches EOS, placing the device in a nontherapeutic state until reprogrammed or replaced. Moreover, a direct current-leak reset is automatically initiated in response to electrosurgical interference, suspending all therapy and detections until clinical reprogramming is performed. Each of these states represents a fallback mode characterized by fault-driven, autonomous transitions to a predefined safe configuration.[28,29]

Practical Implementation and Performance

The responsive neurostimulator was one of the first neuromodulation platforms to integrate a secure cloud-hosted patient data management system (PDMS), enabling ongoing research and algorithm refinement[30–32] with the potential to update the system in the future, through a population-level data base for

optimization.[23] The neurostimulator's onboard memory stores up to 53 minutes of iEEG data, with smart prioritization triggers to prevent overwriting critical recordings. It also stores 28 days of hourly event counts, reflecting clinical changes and cyclic patterns (circadian and multidien), and one to two days of time-stamped event records, providing a detailed record of episode times and durations. Patients and caregivers can transfer data to the remote monitor post event to ensure physiologic data retention. These stored data support offline analysis and tuning of detection parameters. Users can simulate detection changes and visualize their effect on event classification through the PDMS platform, accessible through any connected device.[28]

The system supports two depth or cortical strip leads (four contacts each), allowing targeted stimulation in one or both brain hemispheres. Although it lacks independent current sources per contact, which can lead to uneven charge distribution across variable impedances, it remains clinically effective. These design trade-offs reflect a balance among miniaturization, power constraints, and safety, all while delivering therapeutic performance across multiple seizure focus sites or network nodes. Good feedback ensures stimulation adjustments until therapy works, making the operational performance of individual subcomponents less critical. Location of the implantable pulse generators (IPG) also is important when considering susceptibility to cardiac artifact. For example, the responsive neurostimulator is unique in that its cranially mounted design makes it less susceptible to these than systems with pectoral-mounted IPGs.[33,34]

System performance has been tracked over time, with the most recent published abstract describing results from a prospective, multicenter, multiyear, postapproval study.[35] In the full, currently in-press article, the authors report that 343 participants were enrolled, and 324 were implanted; 307 completed one year; 289 completed two years, and 271 completed three years, representing the intent-to-treat cohort at each timepoint.[36] The published abstract indicates that 255 participants with available seizure outcome data in the prespecified 30-to-36−month window contributed to the primary effectiveness end point, with an overall seizure reduction of 82%: 90% in patients with neocortical onset and 73.5% in those with mesial temporal lobe epilepsy.[35]

What's Next?

To our knowledge, the responsive neurostimulator sets a foundational precedent as the first closed-loop neuromodulation device indicating that physiologic responsive therapy can be safely and effectively implemented in patients. Its combination of continuous physiologic monitoring, cloud-integrated analytics, and AI-driven personalization has created a feedback-rich ecosystem for nurturing ongoing therapy improvements in the future.[31,32]

Looking forward, as AI and automation capabilities grow, therapies such as the responsive neurostimulator underscore the importance of modular architecture with data storage capabilities to support incremental innovation. The medical industry benefits from platforms that enable rapid iteration, such as that in Figure 5, which allows components to evolve independently without requiring simultaneous development and is aligned with the PCLC framework we introduce here in Figure 1. Modular designs with relative component independence and architectural versatility enable greater integration flexibility, scalability, and adaptation to new clinical insights, market demands, and regulatory requirements. This strategy not only facilitates iterative advancement across device generations but also mitigates technical and business risks.

Use Case: PD Adaptive Regulation

Motivation and Mental Model: Stabilizing Dose With Regulation of a Biomarker

DBS is a well-established therapeutic approach for alleviating the motor symptoms associated with PD.[37,38] Despite its efficacy, however, patients often continue to experience moment-to-moment symptom fluctuations. These fluctuations can be attributed to changes in physical activity, medication state (particularly with agents such as levodopa), and circadian rhythms. Importantly, these variations are reflected in the neural local field potentials (LFPs) recorded from the brain, which show clear alignment with the patient's sleep-wake cycle[39] and contribute significantly to signal variability.

The ability to record neural signals directly from implanted stimulation electrodes presents an opportunity to apply a PCLC to DBS systems. In accordance with the principles of IEC 60601-1-10, this kind of control system could provide real-time responsiveness to the patient's changing physiologic state. Although patient-operated controllers are currently used to manually adjust stimulation amplitude, this method is limited by its practicality. Regular manual adjustment, particularly during nighttime or sleep, places a considerable burden on the patient and may fail to adequately respond to symptom variability. Furthermore, clinical adjustments made during routine visits are inherently limited by their infrequent and static nature, and some bursts occur on time scales (seconds) too fast on which to respond. These limitations underscore the need for a more dynamic, automated approach to DBS delivery. As illustrated in Figure 6, the mental model of an automated loop for PD is to regulate the physiologic biomarker analogously to a home thermostat.

Biomarkers for Automated Control

LFPs are biopotential measurements of change in charge within the extracellular space, representing the summation of synaptic activity in the population of neurons around the recording contacts. LFPs recorded from the electrodes provide a window into the brain's ongoing activity, making them ideal candidates for use as biomarkers in adaptive systems. These signals, representing aggregate neural activity, can serve as both reactive (type 2) and predictive biomarkers. Among the most common metrics used are the spectral energy levels within specific frequency bands. Specifically, increased power in the beta band (approximately 13–30 Hz) has been associated with bradykinesia and hypokinetic states, whereas increased gamma band activity (~55–75 Hz) is linked to dyskinesia and more active motor states.[40,41] Moreover, the gamma band can entrain to the half harmonic of the stimulation frequency (eg, 65 Hz when using 130-Hz stimulation), offering a potentially stable and reliable reactive biomarker.[42,43] As we have described, multiple morphologies of gamma band have been attributed to PD, including but not limited to broadband, finely tuned, and entrained biomarkers. What each of these means mechanistically and how best to apply them within a classifier remain an active area of research.

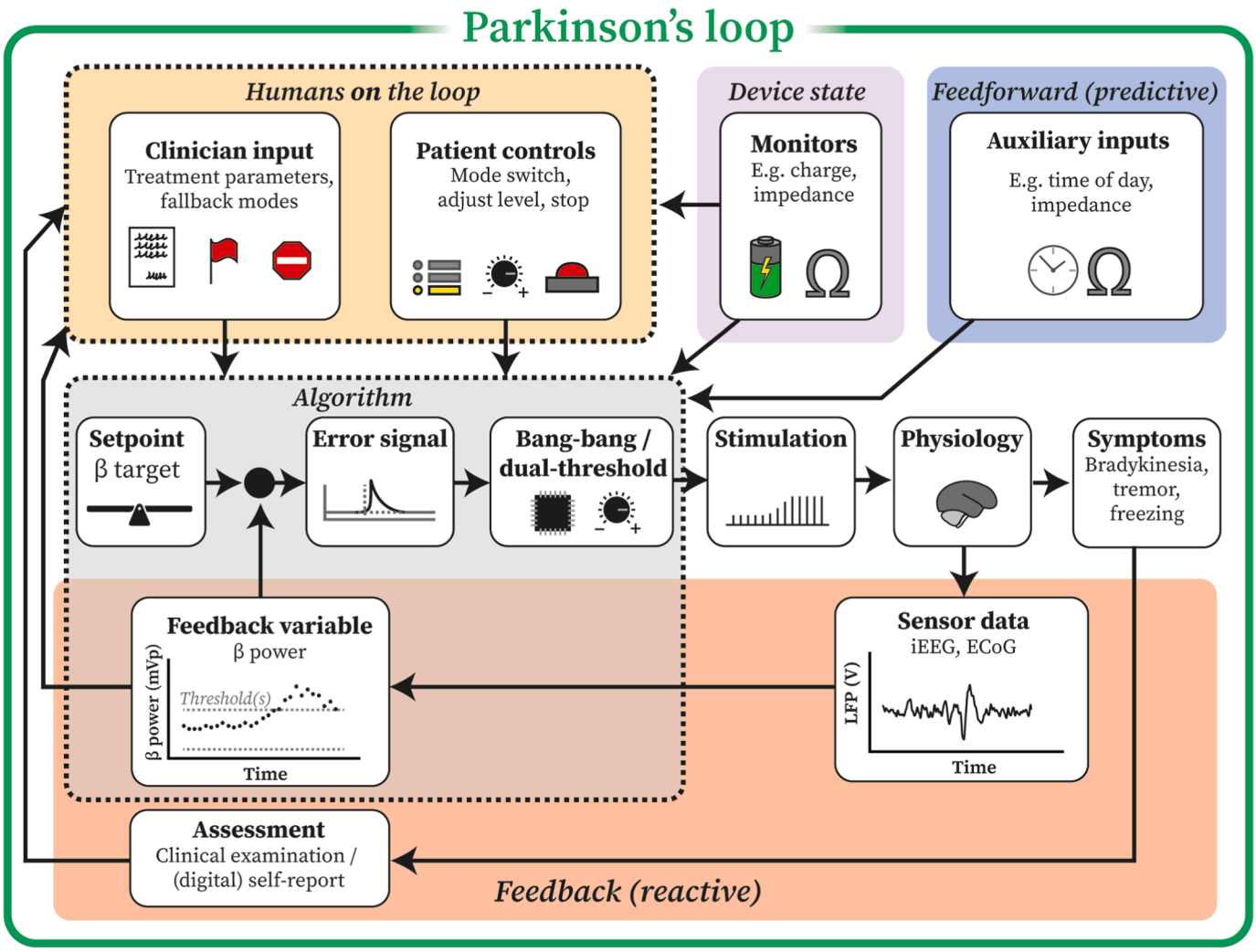

Figure 6. Block diagram of a general PCLC system, adapted to the specific examples of the variables used in this case study of DBS for the treatment of PD. Beta power is the classic reactive biomarker for a PD application, but other auxiliary inputs could be useful as predictive variables. Icons carried over from Figure 1 retain their meaning. All other new icons are named explicitly in the figure. Table 1 presents a comparison with other applications. [Color figure can be viewed at www.neuromodulationjournal.org]

Although reactive biomarkers are widely studied, predictive biomarkers offer untapped potential. For example, circadian fluctuations in neural signals are highly predictable and can be leveraged for anticipatory adjustments in stimulation. This mirrors strategies used in epilepsy treatment[44] (eg, vagus nerve stimulation, albeit for avoiding side effects of sleep apnea at night[45]) and offers a parallel path for PD care. By incorporating a real-time clock into the DBS system, it becomes possible to synchronize stimulation patterns with the patient's chronotype and expected symptom patterns throughout the day.[46] In doing so, the system can deliver tailored therapy that proactively addresses symptom exacerbations before they manifest. Similarly, adaptive control during sleep could be modulated to account for overlapping signal features such as sleep spindles that may otherwise confound beta-based biomarkers.

Risk Mitigation Strategies for a PD PCLC

Developing a robust PCLC demands careful attention to risk mitigation strategies. Neural signals used for control are exceedingly small, typically in the range of 1mV root mean square. This makes them vulnerable to contamination by cardiac artifacts and stimulation interference, both of which can compromise signal integrity. Cardiac interference often overlaps with the beta frequency band, whereas stimulation artifacts can saturate amplifiers and lead to a failure of the control algorithm. In these scenarios, the adaptive system may default to continuous stimulation, as a fallback mode, effectively reverting to the established open-loop mode of therapy.

Several strategies are used to mitigate these risks. Proximity of the implant location to the heart plays a crucial role, and choosing a location further away, preferably on the right side of the body, reduces susceptibility to cardiac artifacts.[34] Similarly, careful design of the signal acquisition chain and interleaving of stimulation and sensing functions help prevent amplifier saturation. In alignment with 60601-1-10, additional safeguards include the implementation of safe bounds for stimulation amplitude and the ability to disengage the adaptive algorithm if it fails to operate correctly. These measures ensure that even in the presence of faults, the system remains within a clinically acceptable and safe operating regime.

As was noted in Figure 2f, increasing stimulation amplitude does not always lead to a decrease in symptoms, nor is the magnitude of dose response constant across stimulation amplitudes. This is possible because other characteristics of stimulation, such as pulse width, also influence physiologic response to stimulation[47] (eg, fiber recruitment depends on charge duration and fiber diameter). Conversely, more obvious nonmonotonic behavior is observed in PD during hippocampal stimulation—when, if stimulation exceeds an upper limit, suppression is no longer achieved, and it becomes possible to trigger an afterdischarge and worsened symptoms.[48] Users can mitigate the risk of operating within stimulation doses that exacerbate symptoms using postimplant symptom titration to identify a patient's dose limits: the dose above which symptoms decrease and the dose above which side effects are observed.

Practical Implementation and Performance

The journey from concept to clinical application has involved several key studies. The initial demonstration of adaptive DBS (aDBS) used a single-threshold "bang-bang" controller that increased or decreased stimulation on the basis of a real-time reading of beta activity.[49,50] This simple reactive approach proved effective in early trials and laid the foundation for more sophisticated control schemes. Subsequent models introduced dual-threshold algorithms, which incorporate upper and lower bounds for neural activity. This dual threshold, "homeostatic" approach reduces unnecessary switching and provides a more homeostatic mode of regulation. Other strategies have explored the use of entrained gamma signals as alternative or complementary biomarkers. These signals, tied to a fixed frequency relative to the stimulation frequency, are less susceptible to cardiac noise and offer a consistent reference point for control. Proportional control methods also have emerged, wherein stimulation levels are scaled in real time according to the magnitude of the beta signal, allowing more nuanced modulation of therapy. Newronika has an ongoing, double-blind trial with crossover (NCT04681534) directly comparing PD outcomes with aDBS and those with continuous DBS (cDBS), but the results are not yet available.

A recent pivotal trial[51–53] directly compared single-threshold and dual-threshold adaptive controllers with standard cDBS. A key trial outcome metric was the amount of therapeutic "On" vs "Off" time—when On time refers to periods of adequate symptom control, and Off time denotes time with persistent symptoms. The study achieved its primary outcome, revealing that both aDBS approaches maintained similar levels of therapeutic On time without troublesome dyskinesia (associated with overstimulation). In terms of raw benefit, the dual-threshold controller yielded a statistically significant and clinically meaningful improvement of +1.3 hours in daily On time and −1.6 hours in Off time compared with standard DBS.[54] When participants were able to select their preferred method of the options tested, improvements were +1.4 hours in daily On time and −1.7 hours in Off time compared with standard DBS.[55] Importantly, adverse events were comparable across all treatment modalities, and most participants elected to continue with adaptive stimulation during long-term follow-up.

What's Next?

Although the performance gains were moderate, with reduction in total electrical energy delivered by aDBS compared with cDBS (15% for the single-threshold approach and 13% for the dual threshold approach, neither of which was statistically significant[54]), a significantly improved therapy On time with aDBS marks a significant step forward in the clinical translation of PCLC systems for PD. With regulatory approvals now in place, future work will focus on refining control algorithms and integrating additional signal features. A particularly promising direction involves the implementation of predictive, time-based hierarchical control algorithms that differentiate between daytime and nighttime operation.[46,56] This not only has the potential to reduce side effects during sleep but also may contribute to long-term improvements in sleep architecture, which could have disease-modifying implications.

In conclusion, applying PCLC principles to DBS therapy for PD represents a promising evolution in care. By responding in real time to the patient's neurophysiologic state and incorporating safeguards aligned with international safety standards, such systems offer the potential for more personalized, effective, and safer therapy.

Use Case: ECAPs in SCS for Pain

Motivation and Mental Model: Stabilizing Dose With Regulation of a Biomarker

An ECAP is a biopotential originating from several activated fibers; this biopotential is elicited by a suprathreshold stimulating pulse. The dorsal spinal ECAP is characterized by a triphasic biopotential resulting from the synchronous activation of dorsal column Aβ fibers in response to an electrical stimulus (Fig. 7). The relative size of the ECAP (rather than absolute) is considered to reflect the number of activated fibers; all other factors being constant, as the percentage of axons activated increases from 0% to 100%, the measured ECAP response will increase monotonically from 0mV to a relative maximum.

ECAPs may be used to measure the number of activated fibers from (each) SCS stimulus pulse or to measure the changing state of the nervous system (spinal cord) as influenced by the SCS therapy—in the latter case test, ECAP stimuli may be interleaved with the therapeutic SCS stimuli.[57,58] These uses may not be independent. The presence (or absence) of an ECAP is not considered a clinical biomarker of pain or a necessary or sufficient condition for pain relief. A stimulation artifact is not an ECAP. A closed-loop SCS system using ECAPs is any system in which the stimulation output is adjusted automatically on the basis of measured ECAPs—any such system is PCLC. One such method is to identify a target ECAP level and then adjust stimulation amplitude to maintain the ECAPs at or near the target level (Fig. 8).

Biomarker for Automated Control: ECAP

Both the generation (neuronal activation) and detection of ECAPs depend on a range of factors, including stimulation dose, measurement methods (eg, recording configuration, signal processing, noise), and subject condition (eg, posture). Some of these factors, such as postural dependence of the distance between the SCS electrodes and the spinal cord, may be leveraged. For example, a change in posture might cause a change in ECAP amplitude, which is then used to adjust the stimulation amplitude. ECAP can be leveraged as a type 2 reactive biomarker (reflecting engagement of mechanisms of therapy action) of spinal cord activation to deliver closed-loop therapy, and our generic schematic for an automated loop can be applied to chronic pain management (Fig. 8). A PCLC system may then be used to maintain the amplitude of the ECAP at a target setpoint by varying the stimulus charge on the next output pulse (Fig. 7).

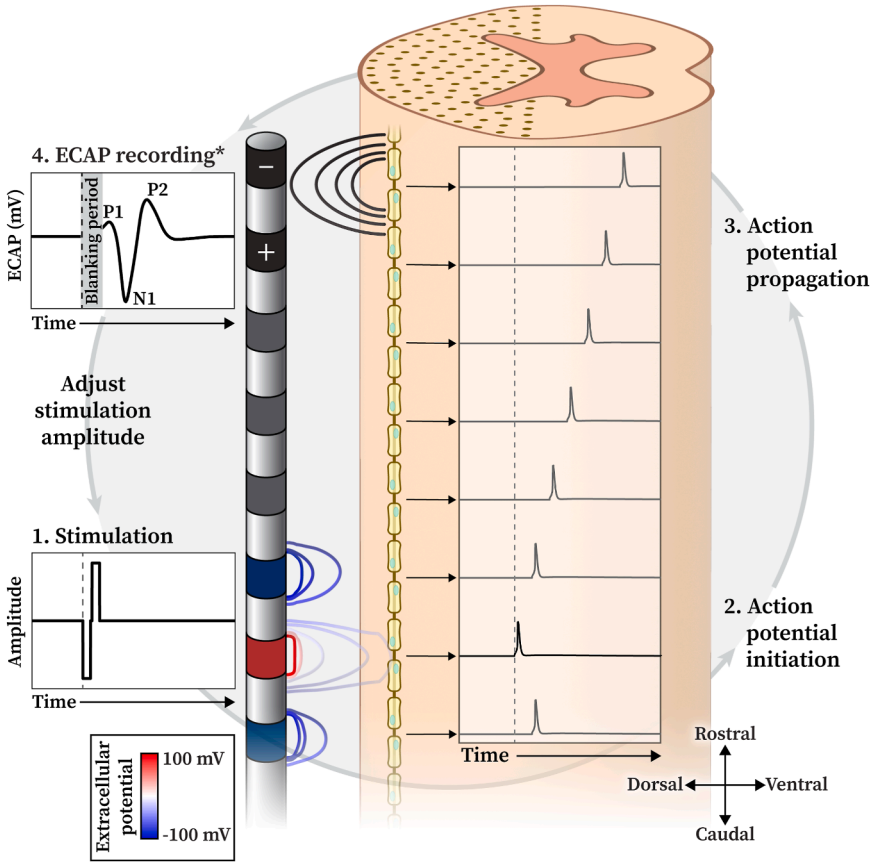

Figure 7. PCLC approach to SCS for chronic pain treatment. Depiction of the spinal cord and epidurally placed electrodes, indicating (1) the applied stimulation pulse, (2) action potential generation within the dorsal spinal cord (only a single axon is shown for clarity), (3) action potential propagation along the spinal cord, and (4) bipolar ECAP recording for automatically adjusting the next stimulus pulse amplitude. *Importantly, the ECAP represents the summation of action potentials from all active fibers passing by the recording electrodes, rather than the single fiber shown here. Various stimulation configurations (eg, bipole, guarded cathode) and recording (eg, adjacent or spaced electrodes) configurations can be used provided there is sufficient distance between them to allow clear separation between the stimulation artifact and neural response. (Reproduced from.[12]) [Color figure can be viewed at www.neuromodulationjournal.org]

This ECAP biomarker serves as a good example for pragmatic design of a PCLC when physiologic interfaces are often variable and nonlinear. As a type 2 biomarker, care must be applied when considering ECAP-controlled PCLC SCS for improved dose consistency. In particular, the characteristics of the sensed ECAP can be influenced by the relative position of the stimulating and recording electrode motion with respect to the spinal cord (Fig. 7). An increase in spacing between an SCS lead and the cord, for instance, yields a smaller ECAP amplitude for two reasons; when a fixed charge is output from a stimulation electrode, less stimulation energy is coupled from the stimulation electrode to the spinal cord (a smaller number of fibers are activated), and a larger component of the evoked biopotential is shunted to the CSF at the recording electrodes (a smaller sensed ECAP amplitude). These factors manifest as differences in the offset and gain of the dose response curves (Fig. 2) for different postures (eg, Fig. 7 in[11] and Fig. 8 in[59]). Together, these factors mean that a constant ECAP amplitude does not necessarily imply a constant degree of neural activation across multiple postures (eg, a higher degree of activation is required to achieve a target ECAP amplitude for larger distances between the recording electrodes and the spinal cord).[11,59] From an intuitive perspective, the change in distance between the spinal cord and the recording electrode introduces an "offset" and "gain error" per Figure 2b. The designer must consider how this source of error might affect the design of their feedback approach. Although not negligible, in this example of ECAP-controlled SCS, the relative impact of variations in offset and gain is lower than the inherent variation in stimulation-induced neural activation noted with manual-loop SCS, which is how the control loop can still yield a net benefit despite the measurement error.[59]

In the parlance of control theory, the ECAP sensor is not strictly LTI, but in practice, most physiologic processes and real-world systems can only be approximated as LTI inside a specific operating window. A common design method is to "linearize" the model for the system around a specific operating point as an approximation (eg "the region of interest," Fig. 2c). Given non-LTI feedback systems can underperform, for example, with a response that oscillates about the control setpoint or otherwise causes an undesired output, the validity of the linear approximation over the operational range of the system should be justified for the control scheme used. Recognizing the limitations of the feedback control variable, such as those previously described, is an important consideration for all manner of robust PCLC design and use. Designs using these biomarkers often require a degree of pragmatism, but the limitations of the required assumptions (eg, linearization about an operating point) and suitable

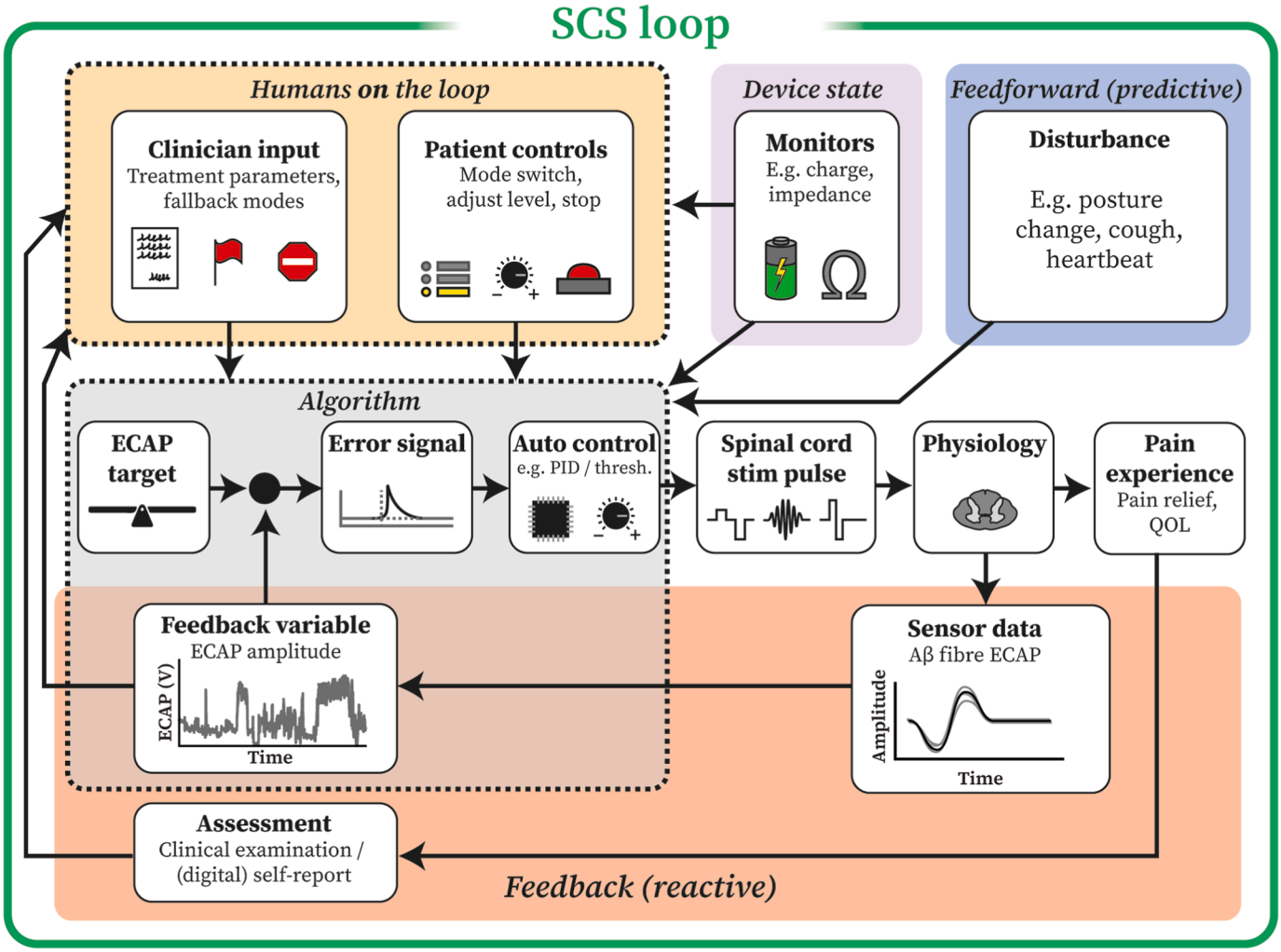

Figure 8. Block diagram of a general PCLC system, adapted to the specific examples of the variables used in this case study of SCS for chronic pain treatment. The ECAP is used as a type 2 reactive biomarker, and changes in posture, among other disturbances) are leveraged as predictive biomarkers. Icons carried over from Figure 1 retain their meaning. There are three icons in the SCS pulse box to indicate the variety of stimulation types that may be used. Table 1 presents a comparison with other applications. PID, proportional integral derivative; QOL, quality of life; stim, stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

risk mitigations for extending outside the "linear range" must be considered carefully in the context of use.

Risk Mitigation Strategies for a Pain PCLC

Although the clinician and patient work together during clinical consultation to set appropriate stimulation limits, this system can run freely without continuous clinician involvement. If the patient's experience of their pain does not meet expectations, or worsens, another visit to their clinician can be initiated to adjust parameters further. Any changes in the patient model over time are important to consider; in this case study, data have been published to confirm the long-term stability of the ECAP characteristics and the efficacy of the therapy designed to maintain the ECAP at a target level.[60] Stability of the ECAP at a target level does not imply, however, that the patient is receiving a consistent level of neural activation, for the reasons previously given, and the approximations for the biomarker use should be factored into the design. Special consideration also should be taken to ensure side effects are minimized with the given parameter sets. Specifications should relate to the dose/response relationship of the effect to be optimized or the side effect to be minimized. For example, with a closed-loop system during a cough, the stimulation may exceed the patient's comfort level for continuous stimulation, but if the loop responds quickly enough, the event is not uncomfortable.

An important consideration for the design of a PCLC for SCS is when to implement monitoring of trust checks, or periodic checking of logs that no failure modes or algorithm exit criteria have been encountered and that the system is still operating within assumptions of the mental model. Failure of trust checks should generate an alert and usually should trigger a fallback mode. Regarding the sensor, one must consider sources of noise that disrupt the integrity of the ECAP, such as stimulation artifact, amplifier saturation limits, amplifier noise, broken conductors, or external interference such as airport scanners. A PCLC SCS system should carefully consider how to report or respond to

physiologically impossible measurements, such as a negative ECAP amplitude, for instance. If such an event does occur, the PCLC designer should consider what actions to take or not take on them. Regarding the automated control actuator, one must consider the effects of current and voltage compliance limits, resolution (step size), timing resolution and accuracy of the output waveform, tissue encapsulation, and conductor integrity. Moreover, care must be taken that, for example, stimulus artifacts, electrical noise in the ECAP recording system, and environmental noise (such as theft detectors and induction cooktops) do not adversely affect the ability of the loop to maintain the specified level of neural activation.

When trust checks fail, the designer must consider the appropriate strategy to deploy. If external noise is detected that might compromise the ECAP amplitude estimation, the system may revert to manual-loop (fixed output stimulation) mode. In this case, the choice of current setting must be made, including factors such as using a last known good state, maintaining therapy, and usability considerations such as alerting the user to the device now being in manual mode. Design choices also must be made to decide entrance criteria (eg, duration for which trust checks pass) and appropriate behavior on reentering the automated mode (eg, which ECAP target setting to maintain).

Usability and user understanding of the operating state of the PCLC should be factored into the design of user interfaces. In this SCS example, the user (usually the clinician) is provided with a real-time trace of the measured signals from the patient (the raw ECAP trace), the estimated ECAP amplitude, the target setpoint, and the stimulation current. This approach allows the user to validate, through real-time visual confirmation, that the loop is sufficiently responsive to postural changes (eg, the ECAP amplitude time trace does not take multiple seconds to recover to the target setpoint), and to ensure the loop is not configured to overshoot the target setpoint (eg, the ECAP amplitude time trace is oscillating about the target). Thus, the user can build a mental model of the relationship between patient movement and PCLC configuration while actively minimizing risk.

Practical Implementation and Performance

Responsiveness of the PCLC to changes in patient state or ECAP amplitude target setpoint is an important factor in the design of this approach toward PCLC SCS. In SCS, daily activities cause significant variability in the electrode-spinal cord distance. This is illustrated in the "Fixed-output, manual loop" plots of Figure 9, where a fixed output current yields large deviations in dorsal column fiber activation. When a PCLC is deployed to maintain a target ECAP amplitude, the stimulation current must change significantly to cater for the postural changes ("automated-loop" plots of Fig. 9). Standard control system metrics such as response time, settling time, overshoot, and steady-state deviation should be specified and verified but with a caveat that some of these control system metrics, for example, "settling time," might assume the system is LTI, and the approximations for this simplified model might warrant alternative metrics depending on the context of use. It is recommended that these parameters be described in terms relevant to the patient; for example, if our goal is to ensure that the PCLC can effectively respond to the sudden change in electrode-spinal cord distance generated by a cough, the designer should characterize the expected rate of state change of a cough across a representative population of patients and design the system to respond in a timeframe that neutralizes the impact of this change, or if these data are not available, consider the worst-case situation.

What's Next?

As with many PCLC systems, the physiologic variable in this case study (the ECAP) is not a direct biomarker of the disease state being treated (chronic pain), but rather a type 2, reactive biomarker (a proxy for the number of dorsal columns fibers activated by the stimulus pulse) to assist in SCS during some circumstances. Although the ability to record ECAPs is well established,[62] lessons continue to be learned through patients implanted with either of the two commercial devices currently leveraging ECAPs in SCS-based pain management.[3,60,63,64] As experience widens, several areas of enhancement are possible: improved sensing to better discriminate signal from noise; compensating for movement of the measurement electrodes; improved supervisory functions to ensure therapy fallback modes are used more rarely; and a more detailed understanding of the relationship of ECAP (dose) to pain relief (response) across patient etiologies, anatomical variation, and inclusive of relevant demographic information. Stimulation adjustments also may be performed on a pulse-by-pulse basis when needed as part of the minor loop fine tuning a system with a major loop controlled by one of the emerging "markers of pain."[20] Recognizing the biophysical basis of the spinal ECAP, ECAP-adjusted PCLC technology has recently been introduced as a tool to help mitigate the number of activated fibers variability intrinsic to all manner of SCS. Although potentially relevant to many neuromodulation modalities—such as sacral neuromodulation[65,66]—this PCLC technology is particularly useful with SCS owing to the mobility of the spinal cord and associated changes in the number of activated fibers with activity and postural shifts.[11] Amplitude changes in the ECAP resulting from spinal cord motion may be used as a control signal to inform stimulation adjustments that yield a more consistent number of activated fibres[58,67] and therefore a more predictable response to therapy.

As a field, it also is important to keep searching for a more direct correlate of pain relief, in particular a reactive type 1 biomarker that directly correlates with the patient's subjective feeling of pain. The bidirectional systems that enable DBS for PD are being applied to explore these biomarkers and their applications in pilot research studies,[68] which more directly close the feedback loop on the clinical symptom of interest.

Future Use Case: Type 3 Biomarkers

Because type 3 biomarkers measure only energy deposition in the tissue (and not physiologic) response, they may meet the PCLC requirement "for adjusts or maintains a physiologic variable(s) through delivery or removal of energy (e.g., electric)" but not "using feedback from a *physiologic*-measuring sensor." Nonetheless, a clear and complete rubric of markers used to regulate closed-loop neuromodulation is needed to classify type 3. There is emerging research into the relevance of type 3 markers for therapy. For example, brain impedance (as opposed to simply electrode impedance) for different indications, particularly in epilepsy,[69] might prove useful for assessing brain state and adjusting therapy. Impedance metrics are especially useful in concert with well-defined stimulation circuits, and the variance over time and in response to stimulation is a potentially useful measure to confirm stimulation was delivered to the target tissue.[70]

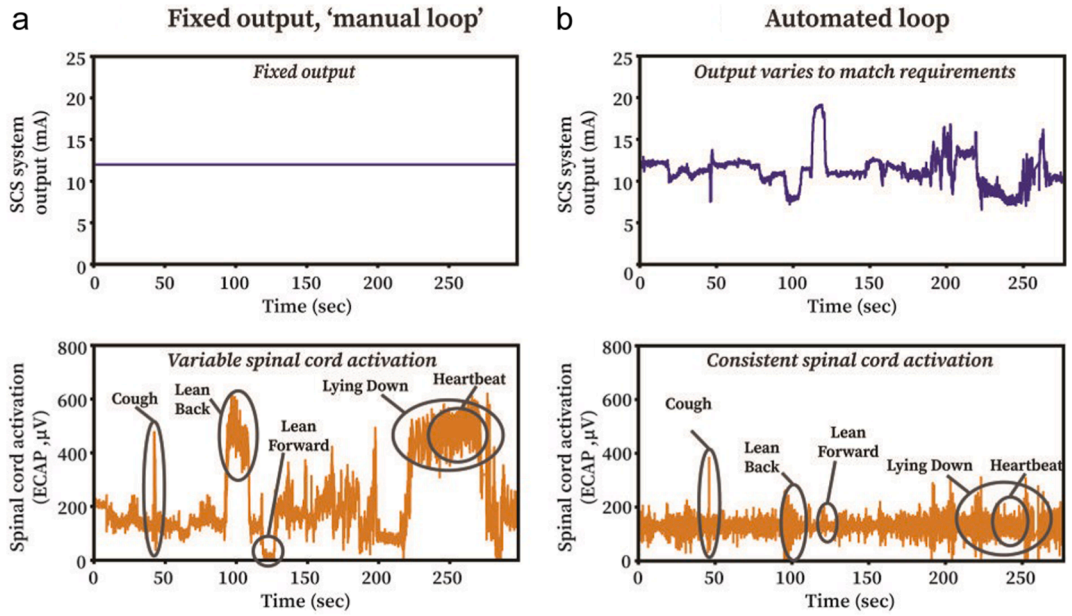

Figure 9. Fixed-output, manual-loop SCS (a) vs automated-loop SCS (b). Patient's involuntary physiologic and voluntary movements change the separation between the electrode and the spinal cord. Panel a plots: Fixed-output, manual-loop SCS delivers a fixed output of stimulation current, which leads to a variable level of dorsal column fiber activation during typical daily activities. Panel b plots: In automated-loop SCS, the stimulation current is automatically adjusted in real time using feedback of the measured neurophysiologic response to stimulation to maintain the target response. (Reproduced from.[61]) sec, seconds. [Color figure can be viewed at www.neuromodulationjournal.org]

ADVANCED TOPICS IN PCLCS FOR NEUROMODULATION

Training Embedded Algorithms

There is continued interest in algorithms to enable adaptive neurostimulation therapy. The development of automated-loop algorithms requires consideration of the embedded nature of the neurostimulation systems, in which onboard computational and memory resources are limited. First, training algorithms requires collection of data to accurately estimate the relationship between biomarkers and symptom severity (eg, beta band and tremor or bradykinesia in PD) or different neural states (eg, sleep/wake). Owing to the dynamic nature of the nervous system, in which physiology varies according to diurnal and longer duration cycles, or the potentially infrequent occurrence of symptoms for different disorders (eg, seizures in epilepsy), sufficient longitudinal data must be gathered to estimate biomarkers accurately and to characterize their behavior overtime for good algorithm performance. Key items necessary for training supervised learning algorithms are labeled data sets and known ground truths, both of which may be harder to obtain for some indications than others (a binary, objective seizure/nonseizure state label for an epilepsy indication vs a gradient of subjective severities for a pain indication may be considered). Continuous data streaming is not desirable for primary cell devices, given this leads to quicker depletion of the device battery and subsequent need for battery replacement surgeries to avoid therapy loss. Rechargeable devices mitigate this concern; however, their battery limits the duration they can continuously stream without recharge. Neurostimulation devices may include limited onboard memory to capture data for later download; however, use of this requires careful consideration of what data should be captured for later download from the device. As such, there is a need to efficiently capture data so that it can be used for algorithm development. This may be achieved through intermittent download of data recorded to the device embedded memory (for later labeling by trained clinicians) or through external measurement systems and machine learning algorithms for symptom and/or neural state detection to identify periods when data downloading should be triggered. Many PCLCs operate as part of a hierarchical system (Fig. 5) that allows computationally compact algorithms to be embedded on implanted devices but guided by computationally complex algorithms on external devices. In this way, once sufficient data are acquired, algorithm training can be conducted off the device to identify optimal algorithm parameters to track the biomarker of interest. The said parameters can then be validated on an in silico model of the disease state[71] or fed directly back to the implanted device for implementation of the trained algorithm in the closed-loop system. Although the intermediary step in silico is not mandatory, it is useful from a patient safety point of view to ensure selected parameters do not interact with known elements of the system in a way that defies the mental model of the system.

Incorporation of AI

Although available devices do not have embedded AI capabilities, it is important to consider how AI fits into existing hierarchically distributed systems and how these will eventually converge. As neuromodulation systems evolve to include sophisticated AI capabilities, it becomes essential to separate the intelligent decision-making components from the safety-critical and infrastructure systems. A modular design paradigm can facilitate this separation by establishing clear boundaries among the following:

1. "device management": core functions such as signal acquisition, stimulation delivery, power management, and hardware diagnostics;
2. "safety and risk management": regulatory-compliant layers that handle fallback modes, automated control actuator bounds, physiologic signal integrity, and alarm systems per International Organization for Standardization 60601-1-10;
3. "intelligence layer": algorithmic or AI-based systems responsible for interpreting longitudinal data, optimizing stimulation strategies, and personalizing care over time.

This layered approach not only improves system resilience and maintainability but also enables incremental upgrades of AI modules without compromising regulatory certification of the base device infrastructure.

In line with the FDA's recommendations for Software as a Medical Device (SaMD), particularly in AI and machine learning (ML) contexts, modularity allows (1) "locked base functionality" with traceable version control, meaning the algorithm always generates the same output given the same inputs and does not learn from consecutive uses; (2) "AI model" updates under a prespecified change control protocol (eg, the FDA's Predetermined Change Control Plan [PCCP]); (3) "explainability-by-design," when algorithms provide traceable decision paths, allowing clinicians to maintain situational awareness and avoid automation bias; and (4) "postmarket performance monitoring" through cloud-aggregated data dashboards.

For safety-critical tasks such as seizure detection or posture-adaptive spinal stimulation, real-time physiologic signal interpretation must occur on-device using edge AI deployed between "edge devices" (eg, sensors, smart phones, and anything else within a specified internet of things), and there is no FDA-approved device using edge AI on the IPG itself. In contrast, noncritical operations, such as retraining models or refining long-term control policies, can be delegated to cloud-based frameworks. This division allows regulatory decoupling, in which only validated edge components require full clinical certification, whereas cloud components may continue evolving under controlled protocols.

As AI components become more deeply integrated into PCLC systems, robust risk mitigation and performance monitoring mechanisms must be embedded throughout the device lifecycle. Regulatory authorities such as the FDA emphasize the importance of model traceability, training data provenance, and ongoing postmarket surveillance to ensure that AI driven decisions remain safe, effective, and unbiased over time. Continuous monitoring is particularly critical for models that adapt or are retrained post deployment. These models must be evaluated against clinically meaningful performance thresholds, and degradation in model accuracy should automatically trigger alerts, human review, or reversion to validated fallback modes. Incorporating confidence scoring, out-of-distribution detection, and real-time audit trails can further reduce the risk of automation bias or silent failure. Such practices empower the human on the loop and align with the regulatory frameworks such as the FDA's "Good Machine Learning Practice" principles[72] and proposed Total Product Lifecycle approach for AI/ML-based SaMD.

Successfully transitioning to modular, AI-enabled PCLC systems requires a systems engineering mindset that embeds safety, usability, and regulatory traceability across all levels of the technology stack. Intelligent systems should remain assistive—not autonomous—unless explicitly validated for autonomous control. Decoupling AI from safety-critical infrastructure enables more rapid innovation, robust oversight, and greater adaptability to clinical demands across diverse patient populations, ultimately yielding better and more quickly trained embedded algorithms.

LOOKING AHEAD: LESSONS FROM ADVANCED PCLCS IN DIABETES

The most mature and widely used PCLCs are automated insulin delivery (AID) systems (previously known as artificial pancreas device systems[73,74]). More than a million people around the world who live with insulin-requiring diabetes depend on these systems to maintain blood glucose in a safe range. AID systems work by sensing blood glucose with a continuous glucose monitor (CGM), deciding how much insulin to deliver with a PCLC algorithm, and acting to deliver the insulin with an insulin pump.

Over the past two decades, AID systems have progressed from in-clinic, laptop-based research setups[75] to fully ambulatory systems integrating components from multiple sponsors. In parallel, the commercial-regulatory ecosystem has transformed, offering lessons—and warnings—that other PCLCs would be wise to heed.

Early AID systems were developed following prospective FDA guidance,[74] commercialized by a single sponsor,[76] and reviewed by the FDA as class III[77] medical devices. High costs, intellectual property thickets, and specialized knowledge have grown to the point where it is now too difficult and expensive for a single sponsor to develop all three components: CGM, algorithm, and insulin pump. Today, AID systems include components provided by multiple sponsors. Each component is reviewed as a class II device with special controls.[78]

Integrated CGM (iCGM) and interoperable automated glycemic controller (IAGC) devices require clinical validation data gathered through a pivotal trial, typically comprising hundreds of subjects for three months. Once a new iCGM or IAGC has been cleared through the 510(k) pathway to be substantially equivalent to the predicate de novo device, they may be integrated into an AID system without additional regulatory review if a clear PCCP[79] is in place. Alternate controller enabled infusion pumps (ACE) pumps only require bench testing and human factors validation. All AID systems currently marketed in the United States embed the control algorithm directly in the firmware of the insulin pump.

Some of the challenges faced by the iCGM/IAGC/ACE pump pathway are described in the breakout box, later (Fig. 10). Although there are many other challenges, we have highlighted those most translatable to PCLC development and deployment in the neuromodulation space.

Various challenges remain with this class II iCGM/IAGC/ACE pump pathway, and as a result,

> "It has never been more difficult to launch an insulin pump, CGM, or AID system in the United States. Technical, commercial, and regulatory constraints affect the development and FDA review of AID systems, which must be developed for people from all socioeconomic groups. Cost, risk, and uncertainty of the commercial-regulatory pathway make it very difficult for innovators to participate. They lack access to venture capital and pump or CGM partners. Interoperable AID system development will benefit from an updated, harmonised

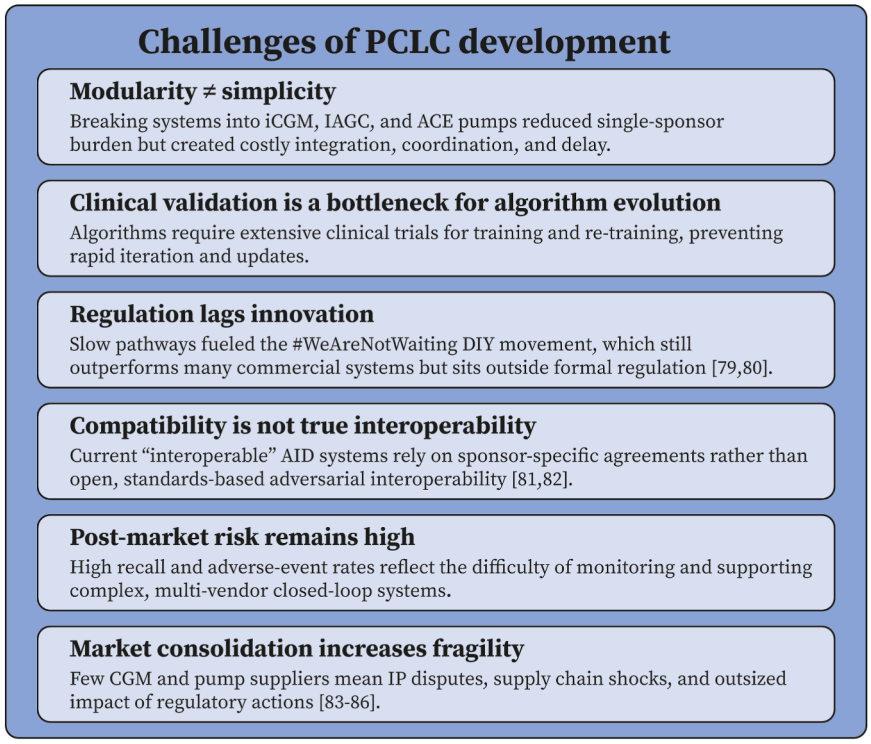

Figure 10. The field of neuromodulation can learn a lot from the deployment of PCLCs for diabetes. Although this is very high level, and not nearly inclusive of all potential lessons learned, the key takeaway is the work does not stop after commercialization, and developers should consider ways inventions will fit in the health care ecosystem after approval for commercial use.[80–88] DIY, do it yourself; IP, intellectual property. [Color figure can be viewed at www.neuromodulationjournal.org]

and transparent commercial-regulatory pathway. Institute of Electrical and Electronics Engineers (IEEE) 11073 and Bluetooth secure plug-and-play interoperability standards will foster true 'competitive compatibility.' Alternative evidence generation methods, such as simulation, post-market feedback loops, and FDA acceptance of PRO and RWE studies, would accelerate access to the benefits of AID."[89]

PCLC developers in the neuromodulation space can learn from the experiences of diabetes device developers and avoid pitfalls through early consideration of standards, strategic leverage of modular design, and in silico methods for rapid algorithm validation.

Innovation and Future Directions

Looking ahead, we hope our framework will allow more devices to incorporate automated loops, permitting the generation of direct comparisons of the effects of manual and automated control (eg, on symptoms, side effects, and adverse events, in addition to clinical time spent programming devices), which will determine standard of care. Moreover, sooner than we think, neuromodulation systems will increasingly integrate multilayered AI-driven architectures—encompassing implant-level embedded controls, external programmable interfaces, and cloud-based analytics—to enable ongoing refinement and personalization of therapy. This hierarchical control architecture, exemplified by systems such as the responsive neurostimulator, offers a scalable model for managing complexity and adaptability, allowing devices to evolve continuously through updates driven by patient-specific data and aggregated population insights. As regulatory frameworks evolve alongside these technologies, ensuring validation and safety of dynamic algorithmic updates will become paramount. Ultimately, the fusion of advanced AI with physiologic closed-loop neuromodulation presents a transformative potential, setting the stage for precision neurologic care capable of real-time, autonomous optimization tailored uniquely to each patient's evolving clinical landscape. This article may potentially be applicable and useful (on an ad hoc basis) beyond the domain of official PCLC devices, such as for brain computer interfaces and other devices that use various forms of human-in-the-loop control or automated control based on nonphysiologic variables. By encouraging researchers and device developers to leverage and apply the PCLC guidance/standards to adjacent device areas, it is hoped we can lay the groundwork for future expansion of the FDA Guidance and IEC 60601-1-10 standard to officially include a broader scope of devices.

SUMMARY CHECKLIST AND CONCLUSIONS

In this work, we have distilled all neurostimulation systems into either manual or automated loops. We have favored these terms over open-loop and closed-loop to instead differentiate on the basis of level of human involvement, or whether the human is more in the loop (directly adjusting settings) or on the loop (monitoring logs and alerts to ensure proper function). We have provided a generic flowchart (Fig. 1) of the components of an automated loop, including opportunities for risk management, and have mapped three examples to this framework. Our intention is that those engineers, physicians, patients, and others using PCLCs use this flowchart and the checklist in Figure 11 to ensure good device design and usage. Key points are to know one's biomarker and

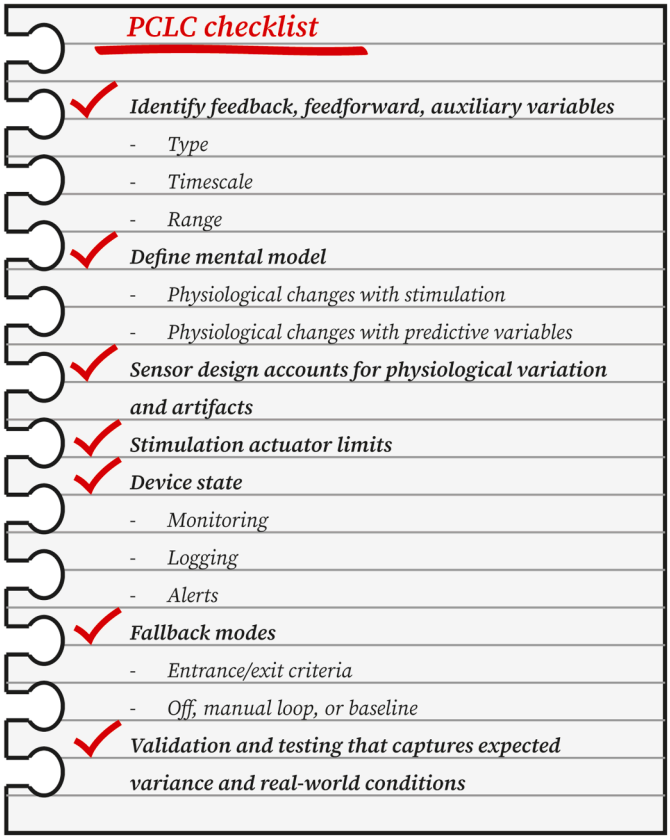

Figure 11. Following this checklist will help PCLC developers thoughtfully design safe and effective devices. Although this is very high level, each point has many subcomponents discussed at length in the text. [Color figure can be viewed at www.neuromodulationjournal.org]

sensor, have a sound mental model of the algorithm and automated control actuator, validate user design and safety features, and provide adequate checks to avoid complacency and skill degradation.

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Authorship Statements

Victoria S. Marks prepared and compiled the manuscript with senior guidance from Scott F. Lempka, Marom Bikson, and Tim J. Denison. Joram J. van Rheede prepared figures and provided textual feedback. Dario J. Englot contributed to the automated loops section. Dean M. Karantonis, Rosana Esteller, David Dinsmoor, Peter Single, Robert S. Raike, and Tim J. Denison provided initial drafts of each practical application of PCLCs. John E. Fleming, Pierre-François D'Haese, and Lane Desborough contributed text to advanced topics in PCLC application, namely, embedded algorithms, AI, and diabetes, respectively. Barrett Larson provided text for the innovations and future directions sections. Richard North, Lawrence Poree, and Pierre-François D'Haese secured the support of the Institute of Neuromodulation and championed working groups at conferences to facilitate collaboration across multiple continents and many time zones. Given their role as *Neuromodulation* Editorial Board Members, Drs. Richard North, Lawrence Poree and Scott Lempka (Section Editor), were not involved in the peer-review of this article and did not have access to information regarding its peer-review. Full responsibility for the editorial process for this article was delgated to another journal editor. All authors approved the final manuscript.

Conflict of Interest

Victoria S. Marks was a paid intern at Medtronic, Inc and a paid consultant at Amber Therapeutics. Joram J. van Rheede has received speaker fees from Medtronic, Inc and is a paid consultant at Amber Therapeutics. Dean M. Karantonis and Peter Single are employees and shareholders of Saluda Medical. Rosana Esteller was employed by NeuroPace from 2000 to 2016, where she led pivotal advancements in sensing technologies, closed-loop algorithms, and automated detection systems, and contributed to the execution of clinical trials. Scott F. Lempka has received research support from Abbott Neuromodulation, Medtronic PLC, Neuromodulation Specialists, LLC, and Presidio Medical, Inc; is a shareholder in CereGate, Neuronoff, Inc, and Presidio Medical Inc; and is a scientific advisory board member of CereGate and Presidio Medical, Inc. Tim J. Denison is chief engineer and has shares at Amber Therapeutics, and is director at Onward Medical and a nonexecutive chairman at Mint Neuro. The remaining authors reported no conflict of interest.

Although this document was prepared with the Food and Drug Administration (FDA) regulations on physiologic closed loop controllers in mind, no employees of the FDA were involved in the drafting of this document, nor does it serve as any official guidance document. All commentary and advice are based on the authors' experiences and interpretations of the field.

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COMMENTS

I strongly believe that PCLC in neuromodulation is the long-term future of the therapy. If that is indeed the case, we all need to share the correct language, definitions, basic understandings, and safety concerns to make this mainstream. This study is a seminal foundation document along that path. This article will stand the test of time and should be read by everybody not within 12 months of retirement.

I have learned a lot from reading this article and learned more by reading around the subject to embed the relevant subject parts of the report. The authors are to be truly congratulated on the successful herding of cats and wrestling this into fruition.

The seamlessness, lack of voluntary attention to therapy adjustment, and improved outcomes are reasons many patients never want to go back from an insulin pump to the "old ways." We also are starting to observe that in neuromodulation, and we are only at the very beginning of that journey. Imagine a device that anticipates, autocorrects, and averts the major symptoms produced from CNS/PNS dysfunction. To call that a gamechanger would be an understatement. I look forward to seeing where this journey takes us.

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I hope you enjoy reading this article as much as I did reviewing it: "Principles of Physiologic Closed-Loop Controllers in Neuromodulation." This represents a high point in our field. The knowledge gained, the challenges faced, and the likely future directions explained will give the reader great optimism. Our journal represents a broad church of science. This article brings different neuromodulation fields together—spine, brain, and diabetes. There is some caution that the burden of development may be hampered by regulation, data protection, and high cost. Collaboration is key.

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