Closed-Loop Medication Therapeutic Systems: An Ultimate Solution to Deliver Goal-Directed Therapy

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The tasks of medical science fall into three categories. The first is to understand disease biology. The second is to find effective therapies. And the last is to ensure that those therapies are delivered effectively. This third category, which is perhaps the most important for clinical outcomes, has been almost ignored by research funders, government, and academia.

The delivery of effective treatment to critically ill patients requires adequate administration of medications to resuscitate (e.g., by maintaining circulation against blood loss) and stabilize (e.g., by mitigating pain due to injury) the patient. In today's clinical practice, medication dose is adjusted by human clinicians. A complicating factor is that medications typically exert undesired side effects if its dose deviates out of safe range (which is typically very narrow). So, they can be either beneficial or detrimental to the recovery: both over-dosing and under-dosing can adversely affect outcome. The second complicating factor is that there is a substantial individual variability in the physiologic responses to medication therapy. Therefore, standard clinical practice is to iteratively and empirically adjust the medication dose in a given patient, seeking to maximize the desired beneficial effects relative to the deleterious side effects. So, the standard practice suffers from two main limitations: (i) caregivers may fail to notice when a medication dose must be adjusted to meet resuscitation goals, and (ii) caregivers may not always select optimal dose changes in case dose changes are required, leading to patients subject to suboptimal therapy or pronounced side effects.

Closed-loop systems can ensure the delivery of effective therapy by addressing the abovementioned challenges. It is anticipated that automated closed-loop systems may be superior to human clinicians particularly when clinicians are in short supply, pressed for time, or overwhelmed by many patients. These systems are always vigilant and never distracted by other obligations. Furthermore, they employ careful and exacting computations, whereas a clinician often resorts to subjective ad hoc estimations to make clinical decisions. Studies have shown that human brain has difficulty in simultaneously processing more than 5 variables. Unfortunately, this is what a clinician's brain is subject to when closely monitoring and treating a number of patients, since it is supposed to make many therapeutic decisions based on a limited number of clinical variables from each patient. Thus, in theory, a well-designed automated closed-loop medication control system could help clinicians make superior adjustments to medication doses, avoiding dangerous delays in noticing the need for adjustments, and avoiding dose adjustments that are far from being optimal.

Closed-loop control of medication administration has received great attention during recent decades. A multitude of algorithms have been reported on insulin control in diabetes, control of anesthetics and opioids, and fluid treatment against blood loss. Despite this level of effort, a survey published in 2011 showed that the footprint of goal-directed closed-loop therapy in the realm of critical patient care is still negligible. For example, goal-directed closed-loop therapy is used by only 5.4% of anesthesiologists in the United States. This indicates that there are still a number of key challenges that today's technology must address:

- The control systems must be robust against individual variability in dose-response behaviors. In many of the control systems reported in the literature, the robustness aspect is not considered rigorously, or even if it is considered, a simple and rudimentary approach of sacrificing the system's performance to achieve reasonable level of robustness is taken. The effort to personalize control algorithm is relatively rare, which is due, at least in part, to the prevalent use of traditional pharmacological models as control design models, which does not offer an ideal platform for real-time adaptive personalization.
- The validation of technology is not trivial, if not impossible. The closed-loop medication control systems are intended for human use. However, the validation in humans is not practical due to ethical reasons.

- Sensor technologies are not fully mature yet, which limits the deployment and widespread acceptance of medication control systems. For example, subcutaneous glucose monitors exhibit significant time delay with respect to the blood glucose level; sensors applicable to analgesia control do not exist; all the endpoints currently used in closed-loop fluid treatment suffer from critical drawbacks. Even for the sensors used in current clinical care, the credibility of the measurement quality is still an open challenge. For instance, blood pressure waveform measurements are commonly corrupted and distorted by signal artifacts and noises. Using the measurements with unknown creditability can make a drastic impact on the performance of closed-loop control systems.

In order to resolve the abovementioned challenges, we contend that a patient-individualized adaptive closed-loop control algorithm must be developed to relax stringent performance-robustness trade-off, by reducing the uncertainty in the dose-response model with real-time model updating. To this aim, new dose-response models must be developed that do not require any measurements not available in real-time (such as blood medication concentration). For this purpose, a hybrid mixing-dose-response-physiologic model can be conceived, which incorporates 1) a low-order mixing model to imitate the real-time distribution of medication dose at its site of action (thus not necessitating the measurement of medication concentration), 2) a phenomenological (empirical) dose-response model to dictate physiological mechanisms of receptor effects to medication as a function of medication dose, and 3) a physiologic model to translate the actions of the medication into the ultimate clinical responses that are available to measure in real-time. This model has the following characteristics:

- Due to the large inter-individual variability in dose-response, this hybrid model must be individualized to yield optimal therapy. Noting that physiologic dose-response relationship is highly complex, a judicious balance between model complexity and fidelity must be made. Appropriate integration of empirical and physics-based models can ensure that model parameters can be easily adapted to each patient, and as well, model-predicted clinical responses are accurate. This simple but high-fidelity hybrid model can then be readily adopted to design reliable, high-performance closed-loop medication control systems.
- Implementing hybrid dose-response models with appropriate balance between complexity and fidelity can enable the development of high-fidelity model-based simulation test beds, which can be employed to expedite validation, translation and deployment of closed-loop medication control systems.
- By virtue of simplicity, the hybrid models can be used as “virtual sensors” in closed-loop medication control systems, which can amend the limited sensor technologies currently available (Figure 1). These virtual sensors are designed to infer unmeasured, internal dose-response mechanisms from readily measured clinical responses, thereby providing the closed-loop control systems with comprehensive physiologic state of the patient. This can in turn lead to improved strategies for control of medication infusion. For example, model-based pulse wave analysis can be used with blood pressure waveform measurements to infer cardiac output, stroke volume and vascular resistance (which are important parameters for hemodynamic control but cannot be easily measured). Also, automated intelligent sensors to differentiate real from artifact-corrupted physiologic measurements can enhance the safety of closed-loop control systems by rejecting low-quality measurements in making control computations.

It is anticipated that successful exploitation of the above opportunities by the CPS community may be a vital step towards the development and widespread deployment of technologies that can ultimately perform personalized, closed-loop wholly automated control of medication administration.

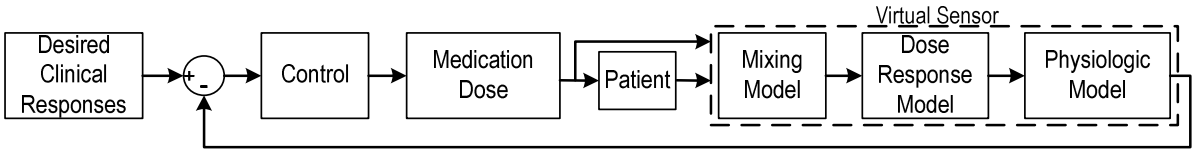

Figure 1: Hybrid Model-Based Closed-Loop Medication Control System