Personalized Closed-Loop Medication Therapeutic Systems in Medical CPS: An Ultimate Solution to Goal-Directed Therapy

Ramin Bighamian[1], Andrew T. Reisner[2], and Jin-Oh Hahn[1]

[1]University of Maryland, College Park 20742 [2]Massachusetts General Hospital, Boston 02114

1- Introduction: Necessity of Effective Therapy

- In today's clinical practice, medication dose is adjusted by human clinicians. Statistical results from 150 patients receiving vasopressors show that about 25% of MAP per hour is either too low or too high due to inefficient dose administration (Fig. 1-2).

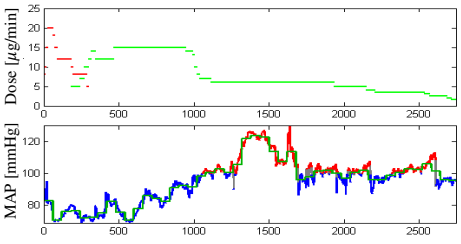

Figure 1: MAP overshoot due to large rise in vasopressor dose

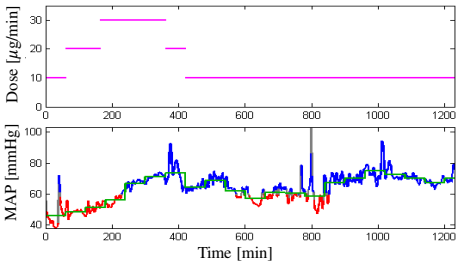

Figure 2: Failed wean due to large drop in vasopressor dose

- Another complicating factor in dose adjustment is the substantial individual variability in the physiologic responses to medication therapy (Fig. 3).

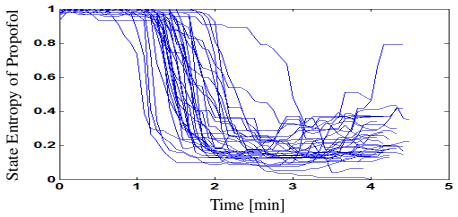

Figure 3: Diversity in depth of anesthesia response to propofol

2- Why Closed-Loop Therapy?

- 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.
- 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.

3- Challenges: Challenges in Closed-Loop Therapy

- A survey published in 2011 showed that, for example, goal-directed closed-loop therapy is used by only 5.4% of anesthesiologists in the United States, indicating that there are a number of key challenges:
- ✓ The control systems must be robust against individual variability in dose-response behaviors.
- ✓ The validation of technology is not trivial, if not impossible. 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 (Fig. 4).

Figure 4: Major applications suffering from immature sensor technology

4- Solution: Adaptive Closed-Loop Control

- To relax stringent performance-robustness trade-off, a hybrid mixing-dose-response-physiologic model (Fig. 5) is proposed, which incorporates:
- ✓ A low-order mixing model to imitate the real-time distribution of medication at the site of drug action.
- ✓ Phenomenological (empirical) dose-response models to dictate physiological mechanisms of receptor effects to medication as a function of dose.
- ✓ A physiologic model to translate the agent's actions into the ultimate clinical responses that are available to measure in real-time.

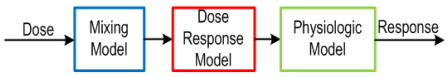

Figure 5: A hybrid mixing-dose-response-physiologic model

Proposed Model's Characteristics

- ✓ Regarding the large inter-individual variability in dose-response, this hybrid model can be readily adapted to each patient with sufficiently close simulated responses to the real-world phenomena.
- ✓ An appropriate balance between complexity and fidelity of the model results in high-fidelity model-based simulation test beds to be utilized to expedite validation.
- ✓ This model represents a "virtual sensor" that can be a solution to overcome current technological limitation of sensor technologies in closed-loop therapy (Fig. 6).

5- Representative Applications of Closed-Loop Therapeutic Systems

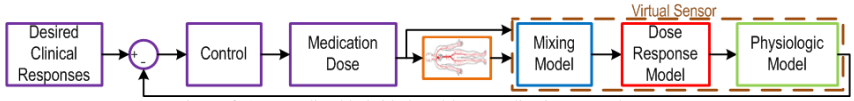

Figure 6: A generalized hybrid closed-loop medication control system

5.1- Personalized Control/Prediction of Vasopressor Infusion Response

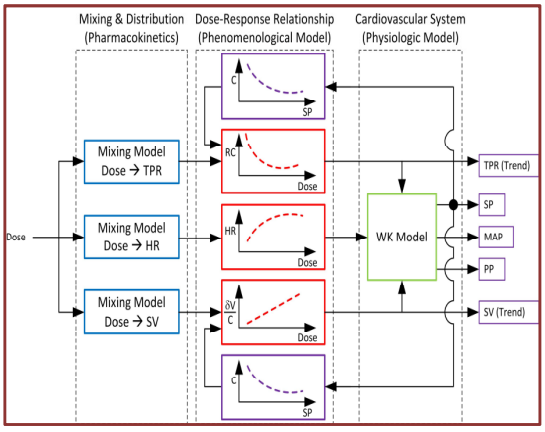

Figure 7: Hybrid model to reproduce responses to vasopressor infusion doses

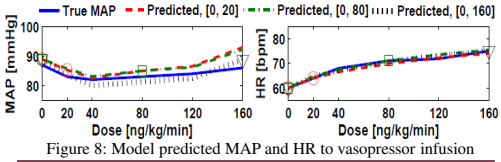

Figure 8: Model predicted MAP and HR to vasopressor infusion

5.2- Personalized Fluid Resuscitation

Desired Fluid [ml]	Actual Fluid [ml]	Fluid Error [%]
1527+/-449	1579+/-437	1.12+/-4.75

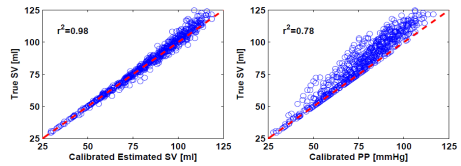

Figure 9: Correlation between true BV vs. estimated BV and PP