***Supplemental Digital Content* 1**

**Closed-Loop Vasopressor Controller**

 The closed-loop vasopressor controller was developed in Microsoft Visual C (Microsoft Corp, Redmond WA) and has three component layers which determine the drug rate. These layers are a diagnostic layer (collecting, screening, and processing the incoming data), a prescriptive layer (whereby the processed data is converted into an error signal), and a treatment layer (where the error signal prescription is converted into a treatment dose).

The data collection and management layer collects incoming vital signs data as well as current controller output (the drug rate). Incoming vital signs may be captured from advanced hemodynamic monitors or directly from the arterial blood pressure waveform. This layer then filters the data for obvious error (values > 300 during arterial line flushes, etc), stores the values, and calculates additional real-time derived values like an infinite-impulse response low-pass filter (IIRLPF) MAP using the same methodology as Görges and colleagues in their report of an online system identification methodology.1 Compared to using a straight average MAP over time, the IIRLPF value remains robust to noise in the input data, but more rapidly trends change in MAP value compared to a straight time-averaged value.

 The second controller layer is a proportional-integral-derivative (PID) control layer which uses the IIRLPF MAP as input, compares this to the user-defined MAP target, and outputs an adjustment control value. The proportional and derivative errors are dampened in a run-time user-configurable region above and below the target MAP referred to as ‘tolerance zones’ in which blood pressure error is corrected less aggressively. These regions are designed to allow the user to designate the preferred direction of error from target. For example, the system may be configured to target a MAP of 70, but to prefer error to be above target when it occurs.

Finally, the PID calculated adjustment value is then passed to the final layer of the controller, a rules-based component that takes the adjustment control value and converts it into a drug dose change specific to the vasopressor being infused. The rules component also includes run-time configurable infusion rate limits (upper and lower) to restrict the range of dose the controller may titrate within, and dose-changes-per-minute limits to accommodate infusion pump capability limits where needed, as well as input sources that do time-averaging of output vital signs.

Reference:

1. Gorges, M., D.R. Westenskow, K. Kuck and J.A. Orr, A tool predicting future mean arterial blood pressure values improves the titration of vasoactive drugs. J Clin Monit Comput, 2010. 24(3): p. 223-35.