Closed-Loop Vasopressor Controller Robustness Against Variability in Pharmacokinetics, Pharmacodynamics, and Infusion Line Delay

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Background: There is growing evidence that intraoperative hypotension, both cumulative time and degree, is associated with increased morbidity and mortality post-operatively. In the ICU, treatment of hypotension has long been a priority in patient management. In both settings, vasopressor drips are frequently used to maintain mean arterial pressure, but our own research has shown that titration of these drips is frequently suboptimal, with 30% of time spent > 20mm Hg above reasonable target MAP and 10% of time spend >10mm below reasonable target MAP. Automatic titration is a task easily managed by computer, and we have successfully demonstrated the feasibility of a novel closed-loop controller for this task. Individual patients may exhibit differences in both dose response and drug elimination, however, so safe performance of such a system must be demonstrated across a plausible range of possible pharmacokinetics and pharmacodynamics. We sought to establish whether the current controller would still operate safely given such variability.

Methods: Using a previously established and validated physiologic simulation model, we modified the response to a generic alpha-agonist agent modeled after phenylephrine to include randomization of: 1) Potency, with a range of 1/5x to 3x typical response. The drug was modeled with a convex response curve (decreasing impact with increasing dose) and a median-dose for 50% full potential effect (MD50) inflection point of 625 micrograms as baseline, with a range of 150 – 1500 in the randomization. 2) Drug clinical effect half-time. Baseline was set to 150 seconds, with randomization range set from 90 to 300 seconds. 3) Infusion delay: 0 to 60 seconds between 'infusion' of a dose and clinical effect. The closed-loop controller was run on a separate laptop using the network to communicate dose to the simulator and receive back vital signs data in return. 500 Monte Carlo runs per condition were used as a reasonable sample to assess overall performance. Performance across the runs was compared to no management and management in the "optimal" PK/PD patient (MD50=625, half-time of 150s, 10s infusion line delay). A 30-minute 3-stage sepsis/vasodilatory scenario was used as the testing condition. Controller target was set to 70mm Hg, with 'acceptable' performance permitted from 68-75 mmHg.

Results: Performance results for each condition are shown in Table 1. Spaghetti plots of mean arterial pressure over time are shown in Figure 1. Higher infusion line-lag was found to be the biggest contributor to overshoot, and low patient responsiveness the largest contributor to undershoot.

Discussion: The controller remained stable in all runs (convergent on target over time). Performance degradation was relatively minor in the Variable condition, with most error coming from being over-target.

Table 1: Results of Simulations

	Study Condition		
	No Treatment	Ideal	Variable PK/PD
Under Target	1770 ± 0	497 ± 108	488 ± 225
Over Target	0 ± 0	146 ± 46	234 ± 208
Under or Over	1770 ± 0	643 ± 148	682 ± 300
Major Err (> ±10)	1456 ± 337	157 ± 72	172 ± 95

Figure 1: Spaghetti Plots of MAP over 30-minute Simulation Scenarios