Abstract

The treatment of combat casualties frequently involves infusion of multiple drugs (e.g. sedatives, opioids and vasopressors) in addition to fluid resuscitation. Usually, fluid resuscitation is performed first to restore the patient's volume state, followed by the infusion of drugs that can optimize the hemodynamics and/or relief the pain. In some circumstances, however, fluid and drugs must be infused simultaneously. Simultaneous administration of fluid and intravenous drugs presents a practical challenge related to the interactions between them. On one hand, fluid infused dilutes the drugs by lowering its plasma concentration, thereby weakening the drugs' intended clinical effects. On the other hand, the clinical effects of the intravenously administered drugs on the hemodynamics can interfere with the therapeutic goal of fluid resuscitation. Yet, the vast majority of existing work on closed-loop control of fluid resuscitation and intravenous drug infusion has focused on either fluid resuscitation or intravenous drug infusion alone, while methodologies and algorithms applicable to simultaneous administration of fluid and intravenous drugs have not been rigorously investigated.

In the context of control engineering, this problem might be simply considered as a multivariable control problem. Nevertheless, the intricacy and nonlinearity in the system dynamics, in conjunction with limited sensor measurements makes this problem highly challenging. Hence, our work to analyze the conflicts between multiple treatments and to develop algorithmic framework to overcome such conflicts can represent a major leap toward the realization of complex automated medical care in the future, which can make a significant impact on human wellbeing. The main objective of this thesis is to investigate on de-conflicting management of fluid resuscitation and medication infusion, which is in twofold: first and foremost, to develop a mechanistic understanding of the interactions and

interferences between the two treatments and second, to come up with novel solutions to address the challenges.

To achieve the first goal of this project, we developed an integrated mathematical model of cardiovascular system and pharmacokinetics-pharmacodynamics (PK-PD) model of drugs. This study involves constructing the model based on current knowledge of physiology, isolated and interactive drug effects, parameter identification using real-world data to verify and validate the model, rigorously analyzing the results to demonstrate that multiple medical treatments can endanger the safety of patient care unless the treatments are properly controlled.

To accomplish the second goal, we designed a strategy that realizes a safety assurance control of multiple treatments. This study involves model-based hemodynamic monitoring, robust nonlinear dynamic feedback control, safety assurance control design and treatment target mediation. In terms of controller design, we used a 2-degree of freedom PID controller for fluid loop, and an absolute stability guaranteed PID controller based on circle criterion and linear matrix inequalities (LMI) for drug loops.

This dissertation considers a 2-input 2-output model (fluid resuscitation and propofol sedation), as well as a more sophisticated 3-input 2-output model (fluid resuscitation and propofol sedation with PHP vasopressor treatment) for case study. It turned out that the proposed methods worked well on both models. In addition, having more inputs provides more flexibility in terms of controller design.