ABSTRACT TITLE: STATISTICAL COMPARISON OF COMPARTMENTAL PROPOFOL PHARMACOKINETIC MODELS FOR DESIGNING COMPUTER-CONTROLLED INFUSION SYSTEMS

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Introduction: Target controlled infusion (TCI) systems and physiological closed-loop controlled (PCLC) infusion systems for propofol delivery rely on pharmacokinetic (PK) models to customize infusion rates for patients. More than 15 adult propofol PK models have been published [1]; all are three-compartment models that use different formulae to generate population parameters from biometric information (e.g. sex, age, weight, height) and report different amounts of additional inter-individual variability. There is no consensus on which model is the most accurate. Furthermore, no study has systematically compared propofol PK predictions from the different models to characterize the effect of model choice on TCI and PCLC system performance.

Methods: We treat the compartmental PK models as dynamical systems and perform control-theoretic statistical analyses of system properties that are important for TCI and PCLC systems. We demonstrate our approach by analyzing the predicted steady-state plasma concentration and frequency response of seven representative propofol PK models for 100,000 simulated patients. The selected models are: Marsh-Adult (i.e. Diprifusor), Schnider, Schuttler, Eleveld (2014), Eleveld (2018), Barr, and Smuskiewicz. These models are widely-used for TCI and PCLC systems, and represent the diversity of approaches and patient populations in which in PK studies of propofol have been conducted.

Results: Our results show that given the same patient, propofol PK predicted by different models can be quite different (Fig 1A). This suggests that the performance of TCI systems—which use exact predictions of compartmental drug concentrations to design infusion profiles—is very sensitive to model choice. We also show with a global sensitivity analysis that biometric information only explains a small fraction of the variability in predicted concentrations for all models (Fig 1B). The remaining variability comes from additional inter-individual variability that cannot be easily known for individuals and accounted for when designing TCI infusions profiles. Finally, our frequency response results show that the PK behavior for all simulated patients predicted by all seven models, considering both biometric-based and unexplained inter-individual variability, are approximately stable first-order systems (Fig 1C). This suggests that is possible to design robust controllers for PCLC systems that are safe and perform well for all models regardless of which model is most accurate.

Conclusion: We have shown that using control-theoretic statistical analysis to characterize systematically compartmental PK models can significant inform the design of computer-controlled infusion systems. The inability for TCI systems to reduce sufficiently PK variability has been a key factor that has prevented their regulatory approval in the United States [2]. Our results provide evidence for why this is an unrealistic demand for TCI systems and suggest that PCLC systems can perform better. In this study, we have only scratched the surface of possible applications of control theory in combination with advanced statistical methods in pharmacology. We conjecture that further cross-fertilization of ideas from these fields will improve our understanding of drug action, design of computer-controlled infusion systems, and as a consequence, patient care.

References

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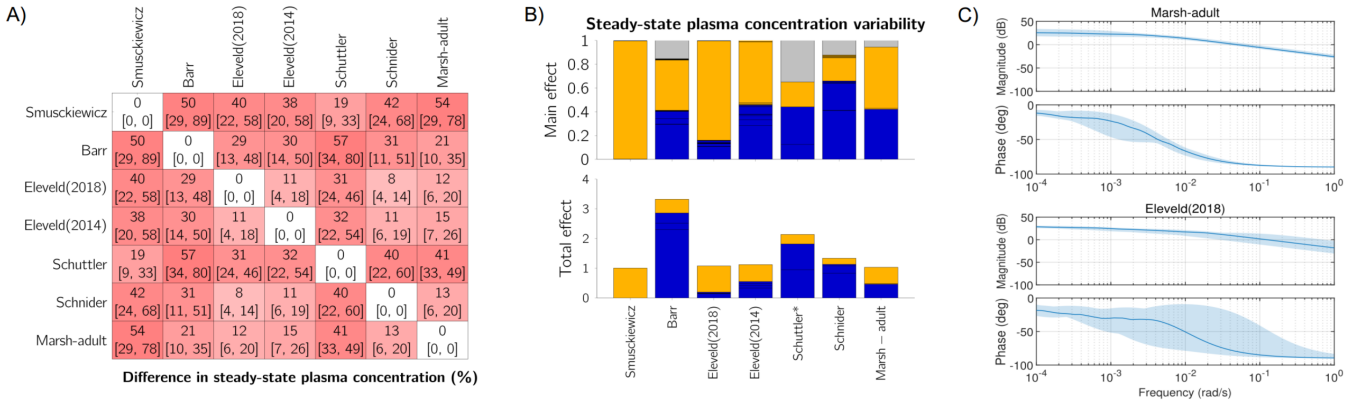

Figure 1. Illustration of analyses performed. A) Pairwise comparison of predicted steady-state plasma concentration for individual simulated patients. B) Sobol' global sensitivity analysis for each PK model. Variability in steady-state plasma concentration contributed by biometric information is in blue and variability in steady-state plasma concentration contributed by additional random inter-individual variability is in orange. C) Frequency response of two of the PK models examined, showing that they are approximately stable first order systems. The solid blue lines are the medians and the shaded regions are the 95% confidence intervals.