A Portable, Tablet-Based PK/PD Simulator for Volatile and Intravenous Anesthetics in Combination

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Pharmacokinetic/pharmacodynamic (PK/PD) simulators have been available as tools for education in anesthesia since the late 1980s, notable examples being GasMan for volatile anesthetic agents and StanPump (and later related works, such as StanGraf) for intravenous agents. However, these tools have two evident weaknesses. Firstly, they are bound to the desktop computing environment rather than being available in a readily portable form. Secondly, these existing tools provide no cross-over between simulation of volatiles and intravenous agents and hence no simulation of their interactions, despite the commonality of inducing and maintaining anesthesia with some combination of a volatile agent and several intravenous agents. In order to address this deficit, a tablet-based, portable, combined volatile and intravenous PK/PD simulator was developed. The project was provisionally titled “Brigham Anesthesia Simulator” with the aim of deploying the project to the iOS platform and making it available for free, worldwide from the Apple iPad App Store for the educational benefit of residents, student nurse anesthetists and medical students.

While most pharmacology simulators only handle one agent at a time, Brigham Anesthesia Simulator can handle any simultaneous combination of any of the medications that it knows. The volatile anesthetic agents available are desflurane, enfurane, ether, halothane, isoflurane, sevoflurane and xenon. The available intravenous agents are alfentanil, atracurium, bupivacaine, cisatracurium, diazepam, d-tubocurarine, etidocaine, fentanyl, fospropofol, hydromorphone, lidocaine, lorazepam, meperidine, mepivacaine, methadone, midazolam, morphine, pancuronium, propofol, remifentanil, rocuronium, ropivacaine, succinylcholine, sufentanil, thiopental and vecuronium. These medications collectively span a range of agents in common and current practice, agents of historical interest, and agents whose activity is expected to be known to residents but whose current availability is limited by manufacturing shortages such that practical experience of their activity is difficult to obtain. For any combination of these intravenous and volatile agents, pharmacodynamics are simulated and forecasted, showing the anesthetic state in terms of a predicted processed-EEG sedation monitor, equipotent analgesia, neuromuscular blockade, local anesthetic serum levels and volatile agent MAC. The administration of a combination of sevoflurane and remifentanil is shown in Figure 1.

Simulations of intravenous agents are performed using an implementation of the standard three-compartment model with effect site. Volatile anesthetics are simulated with the classic three-compartment VRG, muscle and fat compartments, as well as simulation of fresh gas flow
and ventilation into the anesthesia circuit and patient lungs. All simulated medications can be administered either manually with boluses and infusions, or automatically with effect-site targeting. The simulator therefore effectively runs two simulation cores in parallel and in real time; one core handling IV agents, the other handling volatile agents. The combined outputs of these cores are used for pharmacodynamic calculations, based upon equipotency models, and subsequently in the calculation of a response surface model that predicts and projects the output of a bispectral-index-type processed-EEG sedation monitor based on clinical studies by Bouillon (2004)\(^5\) and Schumacher (2009)\(^6\). The correctness of the implementation of the pharmacokinetic models was tested by validating the simulator against results obtained for equivalent medication administration schedules when evaluated on the reference simulator tools of GasMan\(^2\) and StanPump\(^3\). The concentrations of sevoflurane in all compartments was matched to within an accuracy of 0.01%, and concentrations of fentanyl were matched to within an accuracy of 0.01 ng/ml. These tests were found to adequately validate the software for release as an educational tool.

*Brigham Anesthesia Simulator* was released worldwide to the iPad App Store on July 6\(^{th}\) 2018 for download at no cost. It is the most downloaded app released under the Brigham and Women’s marque this year, and also the first such app to be programmed and developed solely by clinicians.

**Image (1 figure of 1 allowed, 300dpi JPEG)**
References