

Closed-loop control for propofol administration during anesthesia based on real-time concentration measurement: a simulation study



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Introduction & Objectives

- ♦ Open-loop Target Controlled Infusion (TCI) devices are widely used to control propofol intravenous administration during anesthesia.
- ♦ The classic TCI algorithm adjusts drug infusion rates to rapidly achieve and maintain stable target brain concentration according to model-based pharmacokinetic (PK) predictions¹.

Models:

- ♦ Schnider *et al.*²:
 - developed on 24 volunteers;
 - low between-subject variability (BSV);
- ♦ Eleveld *et al.*³:
 - developed on 660 volunteers and patients;
 - important BSV.

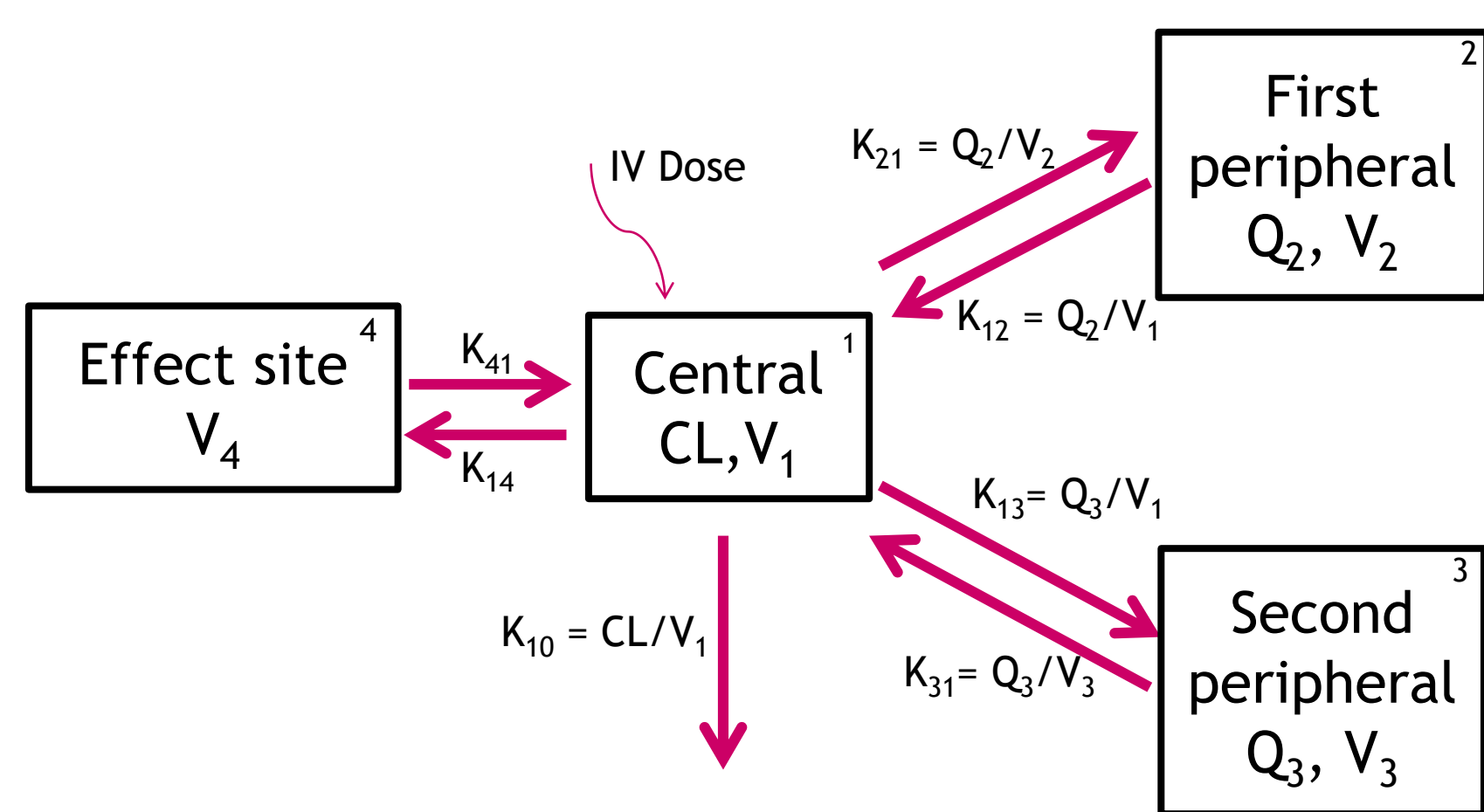


Figure 1: Propofol structural PK model. CL, clearance; V_1 , V_2 , V_3 , and V_4 , volume of distribution of central, first and second peripheral and effect site compartments; Q_2 and Q_3 , intercompartmental clearances of peripheral compartments; K_{ij} , first-order transfer rate from compartment i to j ; IV, intravenous.

Problem: Actual propofol levels can significantly differ from classic TCI predictions (Schnider model, no BSV), so to deliver inadequate drug dosages with possible clinical consequences⁴.

Solution: Closed-loop system implementing feed-back from circulating concentration measurements might improve the safety and the quality of anesthesia, as well as the convenience for anesthesiologists.

Study aim: To develop a closed-loop algorithm for propofol administration driven by real-time plasma measurements and to evaluate its performances through a simulation study.

Methods

Closed-loop algorithm

- ♦ Bayesian optimization to iteratively estimate individual PK parameters based on real-time plasma measurements.
- ♦ Classic TCI algorithm integrating these PK parameters to predict individual blood/brain exposures and to adjust accordingly the infusion rate¹.

Simulation Study

Virtual population: 1000 female subjects (70 kg, 170 cm, 36 y) with *real* PK parameters obtained from the model of Eleveld *et al.* with BSV³.

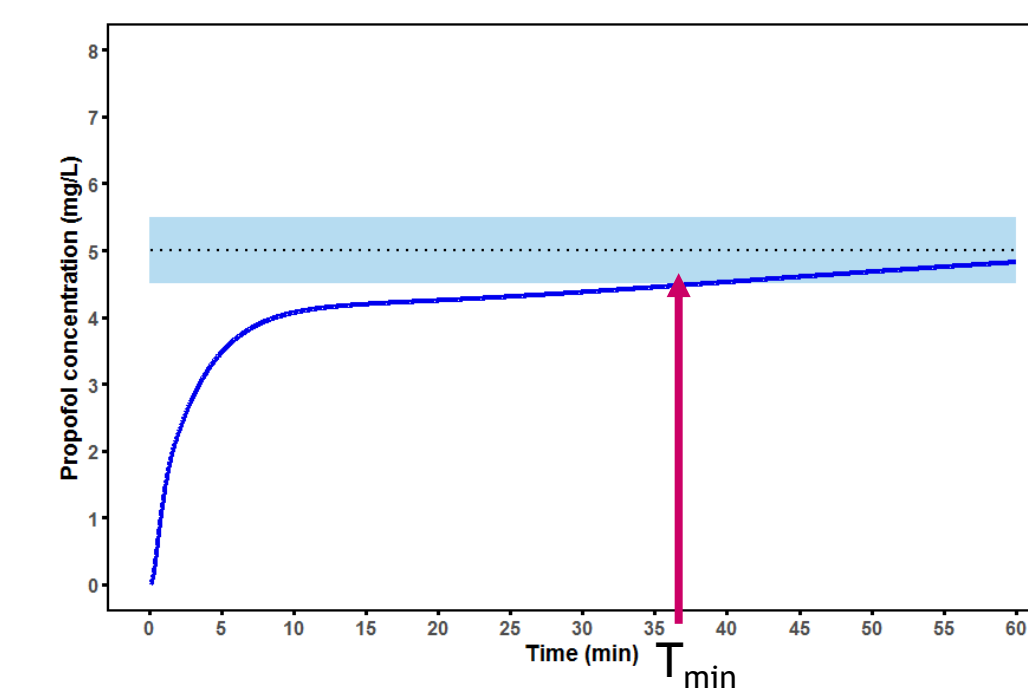
Target brain level: constant 5 mg/L over a 60 min surgery.

Acceptance surfaces:

+/-30% (large criterion, LC), +/-20% (average, AC) and +/-10% (strict, SC).

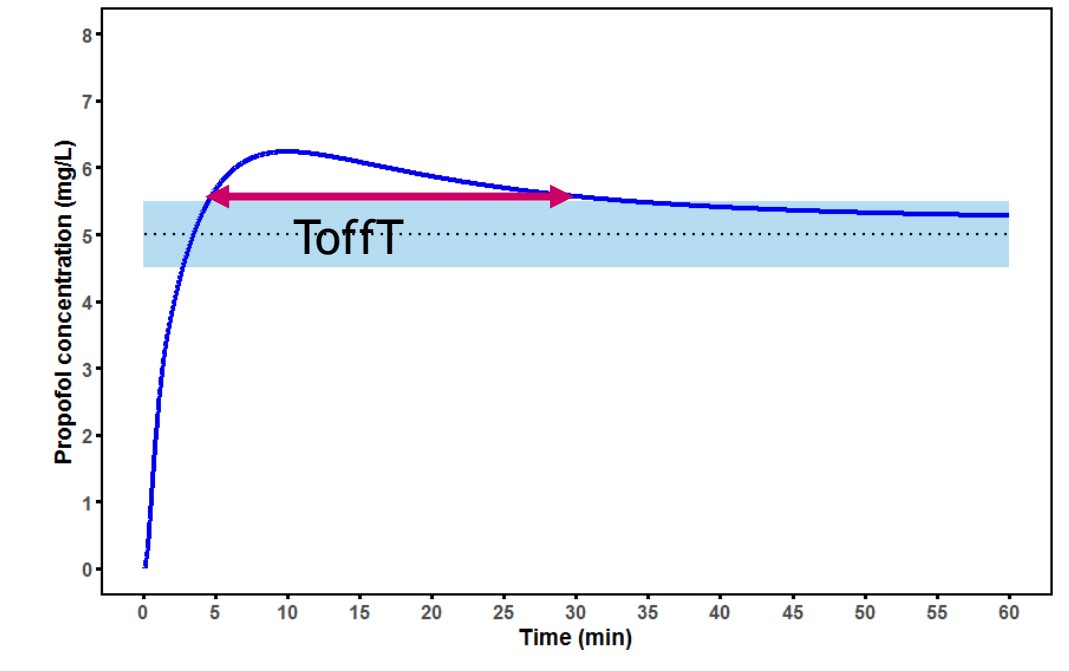
Problematic cases (Pr. cases):

Minimum time to target (T_{min}) > 20 min



Blue line: brain concentration-time profile; dark blue shaded surface: SC acceptance surface; dotted line the target brain level; ToffT: time off target for time > T_{min}

Average concentration outside acceptance surface > 5 min for time > T_{min}



Outcome: Percentages of patients reaching the target (N) and of Pr. cases with:

- ♦ Classic TCI algorithm
- ♦ Our closed-loop algorithm as a function of:
 - measurement steps: 15 or 60 sec
 - measurement delays: 0 or 35 sec
 - proportional error component (*prop*) of the intraindividual variability for step=60 sec: 24% or 47% (refined Eleveld model).

Results

Classic TCI algorithm

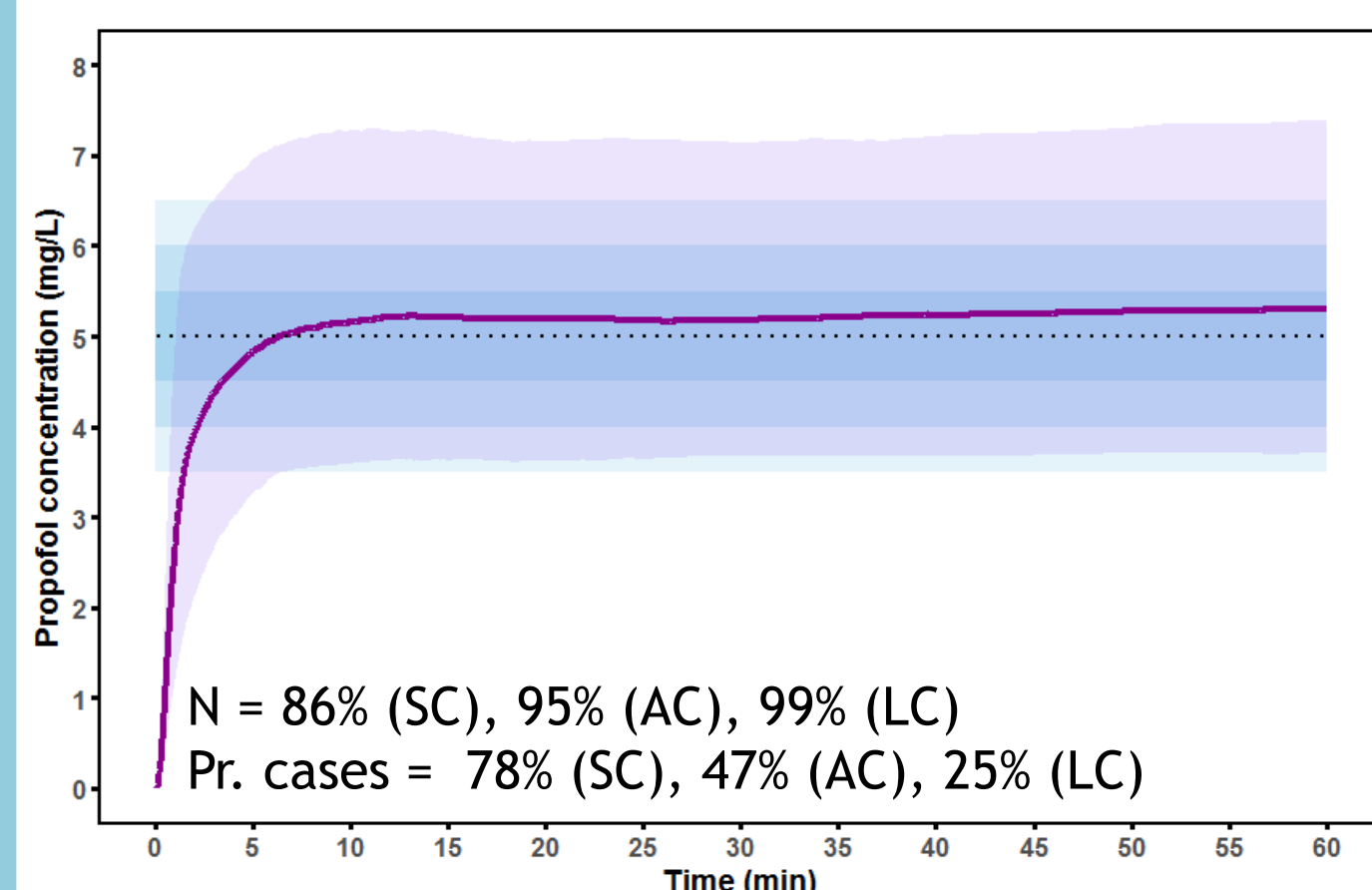
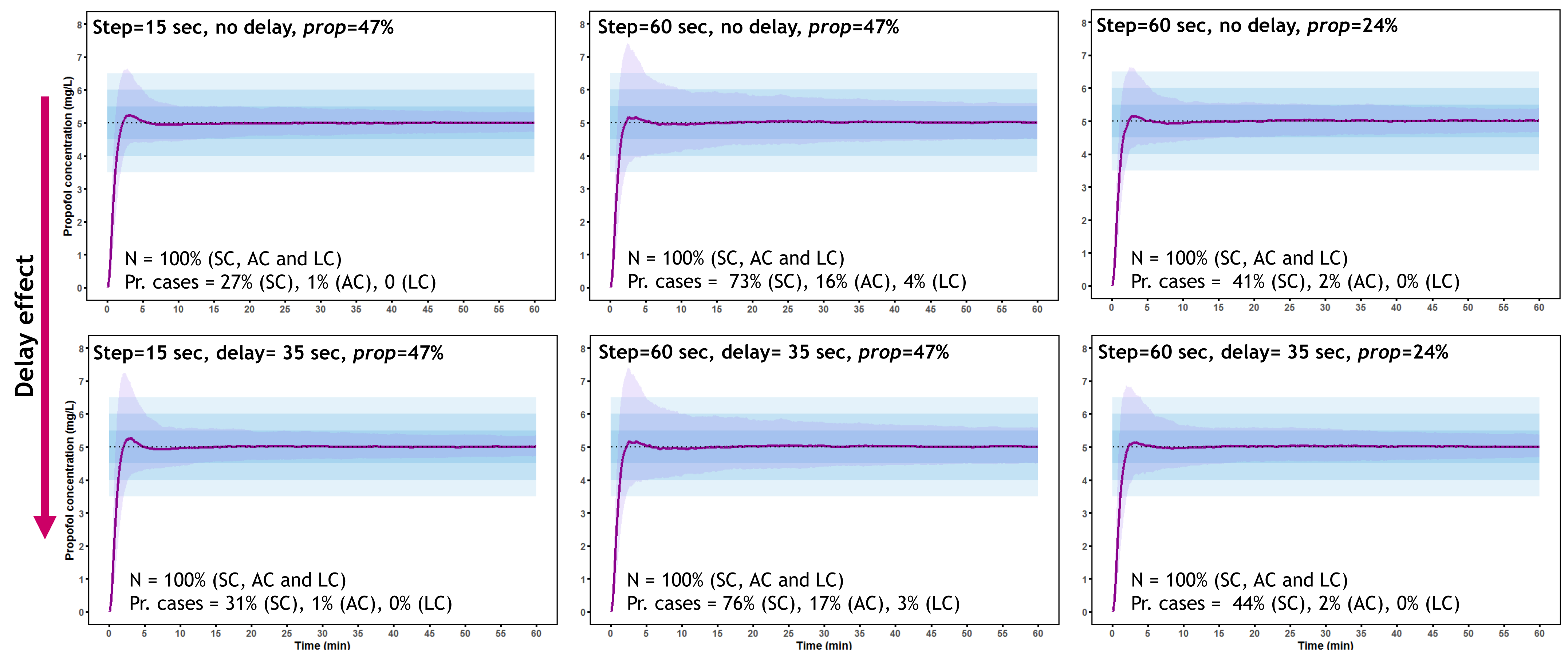


Figure 2: Median (solid line) and 90% prediction interval (PI_{90%}, shaded surface) *real* brain concentration-time profiles of 1000 virtual patients obtained with infusion rates computed by classic (upper panel) and closed-loop (right panels) TCI algorithms. Dark, normal, light shaded blue surfaces represent the strict, average and large acceptance surfaces, dotted line the target brain level.

Closed-loop TCI algorithm



Step effect

prop effect

Conclusions

- ♦ The proposed closed-loop algorithm based on real-time plasma measurement markedly reduces under- or over-exposure during anesthesia compared to classic TCI approach.
- ♦ Intelligent anesthetics infusion control could be significantly improved by implementation of real-time concentration monitoring, as might be achieved with the successful development of a miniaturized sensor⁵.

References

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Acknowledgment: The research work presented in this poster is funded by the CoMofA Project of the Swiss National Science Foundation.

