PBPK Anesthesia Model

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Introduction

- Physiologically-based pharmacokinetic (PBPK) models are useful to predict clinical scenarios for special populations
  - ie. children or elderly
- Applied during drug development
- Useful for predicting drug-drug interaction magnitudes and drug disposition
- PBK models can describe absorption, distribution, metabolism, and elimination of a drug

Remifentanil

- Administered by intravenous constant infusion following a bolus injection
  - Bolus used to raise the blood concentration immediately
- A drug that is typically used in conjunction with propofol
  - Propofol is a common injectable and intravenous anesthetic that induces and maintains unconsciousness
- Opiod that has fast onset of action within 1 minute
- Typical target concentration ranging from 2-6 ng/ml
  - Higher dose remifentanil infusions can result in opioid tolerance or hyperalgesia

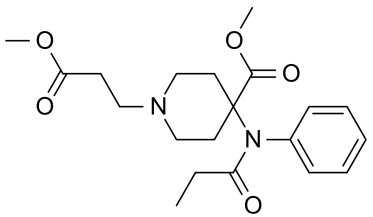
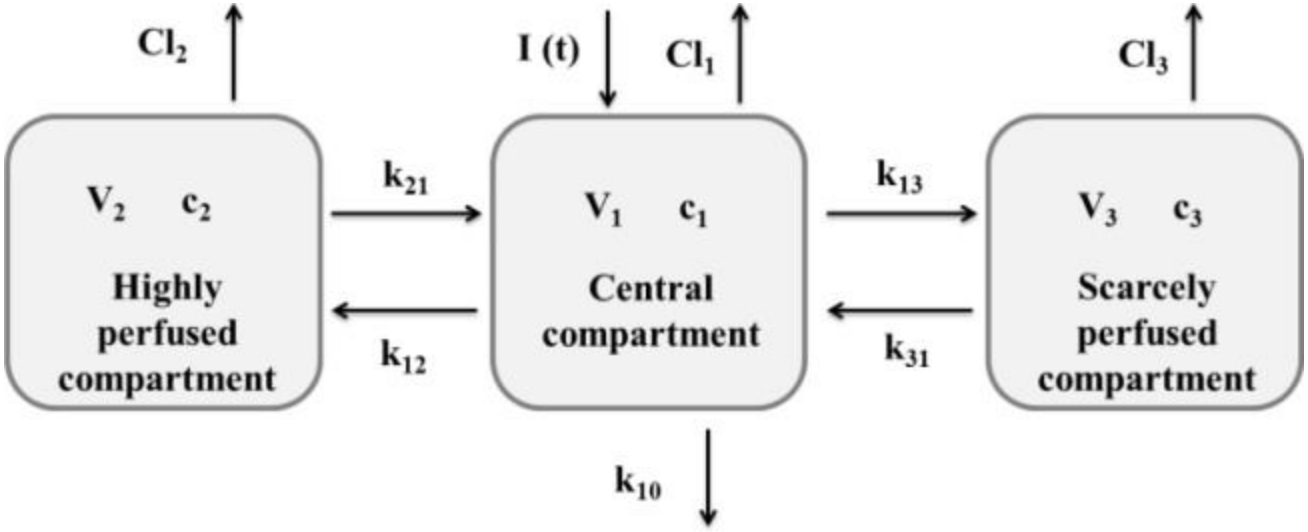


Figure 1. Chemical structure of remifentanil.

Problem Statement

- Current models of remifentanil are not versatile or complete
- Factors such weight and lean body mass are ignored in almost all models
- Adjust model to account for age
  - Adjust the clearance rate by 25% to apply for older patients
  - Adjust the central component volume by 33%

Graphical Model



(

Cascone et al.,2013)

3 Compartments

- Central Compartment
  - Represents Plasma
- Highly Perfused Compartment
  - Organs and tissues highly perfused by blood (ie. heart, kidney)
- Scarcely Perfused Compartment
  - Organs and tissues scarcely perfused by blood (ie. skin)
- These 3 are dependent on each other
  - Need to be solved simultaneously to evaluate drug concentration in each of the compartments

Mathematical Model

Central compartment:

$$V_1 \cdot \frac{dC_p}{dt} = -Cl_1 \cdot C_1 + k_{21} \cdot V_2 \cdot C_2 + k_{31} \cdot C_3 \cdot V_3 + \\ - \left[(k_{12} + k_{13} + k_{10}) \cdot C_1 \right] \cdot V_1 + I(t)$$

Highly perfused compartment:

$$V_2 \cdot \frac{dC_2}{dt} = k_{12} \cdot C_1 \cdot V_1 - k_{21} \cdot C_2 \cdot V_2 - Cl_2 \cdot C_2$$

Scarcely perfused compartment:

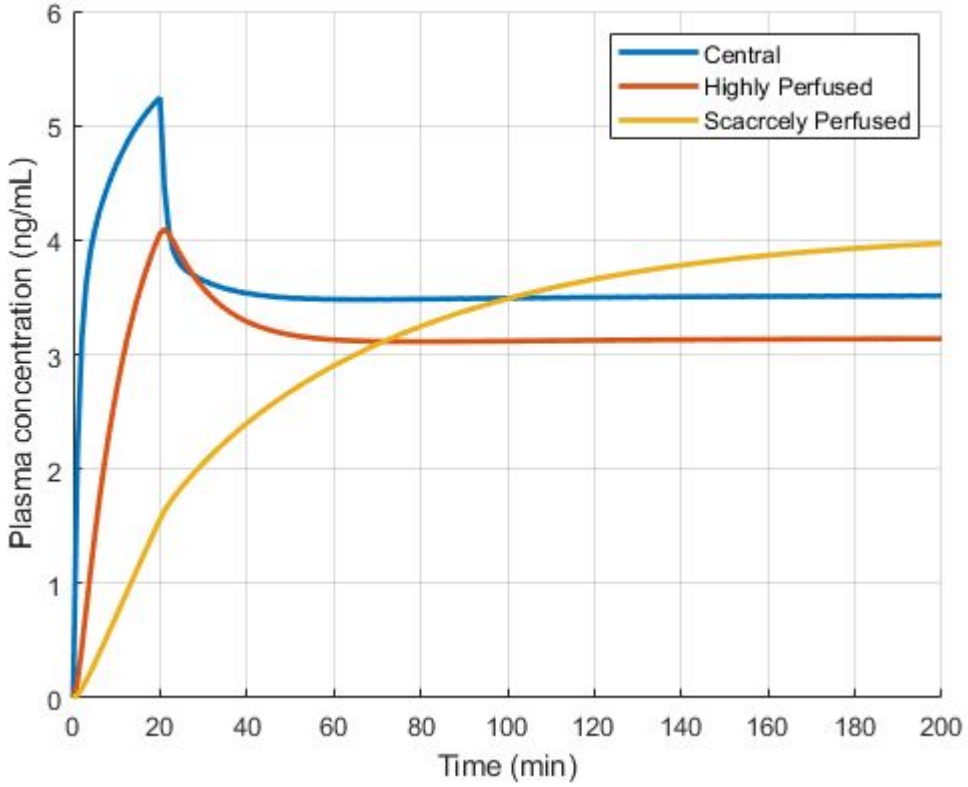
$$V_3 \cdot \frac{dC_3}{dt} = k_{13} \cdot C_1 \cdot V_1 - k_{31} \cdot C_3 \cdot V_3 - Cl_3 \cdot C_3$$

Variable Description

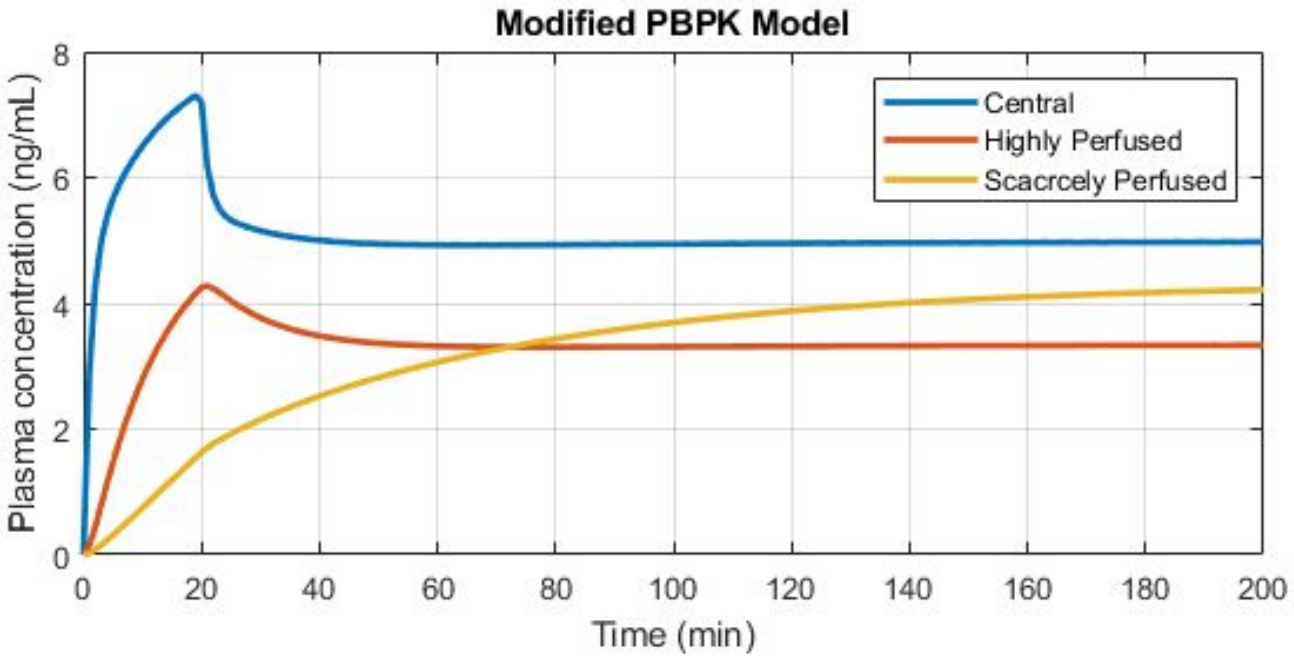
Table 1. Description of variables in the model

Variable	Description
C1	Drug Concentration of central compartment
C2	Drug Concentration of highly perfused compartment
C3	Drug Concentration of scarcely perfused compartment
V1	Volume of central compartment
V2	Volume of highly perfused compartment
V3	Volume of scarcely perfused compartment
Cl1	Clearance of central compartment
Cl2	Clearance of highly perfused compartment
Cl3	Clearance of scarcely perfused compartment
k12/k21	Transport Coefficients between central and highly perfused compartments
k13/k31	Transport Coefficients between central and scarcely perfused compartments
k10	kinetic constant of drug elimination from central compartment

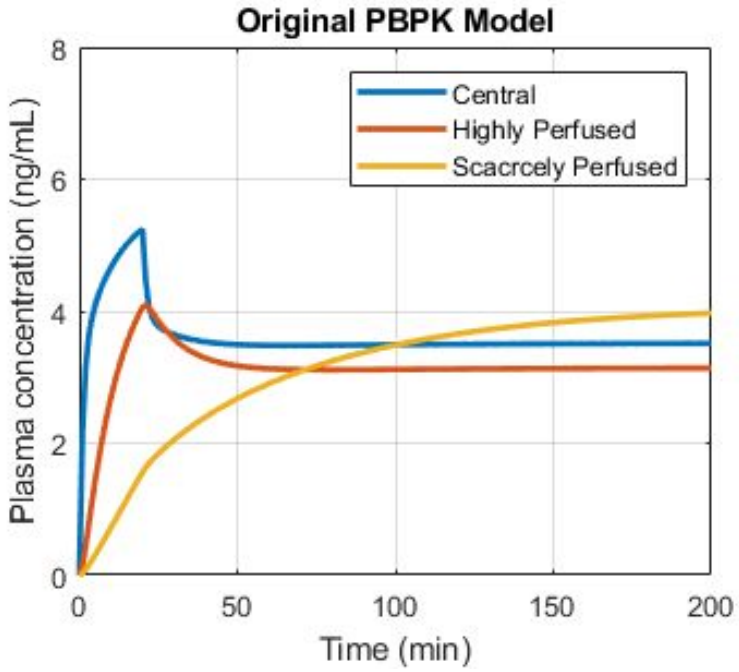
Simulation - Graph

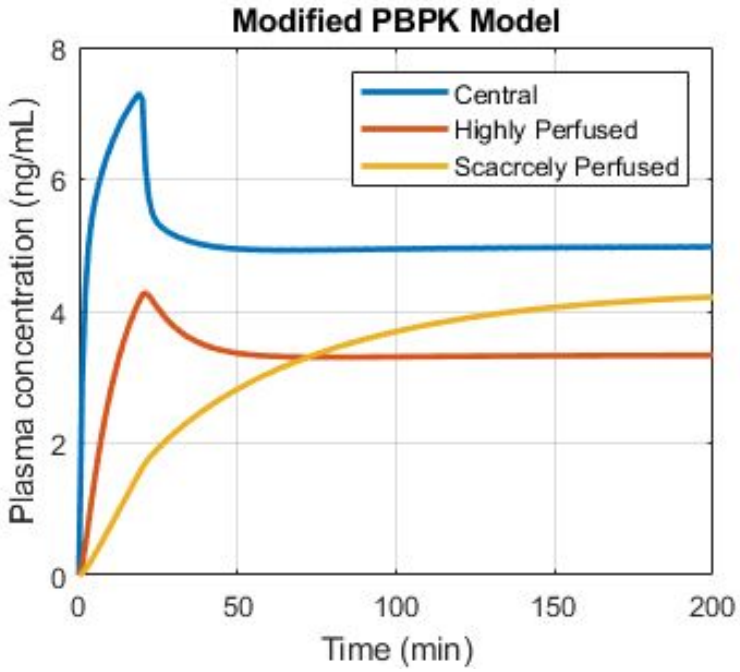


Simulation - Adjusted for Elderly



Side by Side Comparison





Analysis

- Steady of 3.51 ng/mL to 4.97 ng/mL
- Bolus injection in elderly model peaked above 7 ng/mL
  - Typical target concentration ranging from 2-6 ng/ml
  - Higher dose remifentanil infusions can result in opioid tolerance or hyperalgesia
- Approximately 40% increase plasma concentration of the drug in our elderly population model
  - Could lead to side effects if infusion rates are not changed due to age
- Minimal effect on the highly perfused and scarcely perfused compartments

Sensitivity Analysis - Table

Table 2. Values taken from the sensitivity analysis.

Variable	Sensitivity Objective Function (SOF)
V1	**0.503**
V2	**0.130**
V3	0.012
Cl1	**0.477**
Cl2	0.127
Cl3	0.013
k12	**0.175**
k21	0.124
k13	0.024
k31	0.017
k10	**0.316**

Sensitivity Analysis Summary

- Factors most affected:
  1. V1: Volume of the central (plasma) compartment
  2. Cl1: Clearance rate of the central compartment
  3. k10: Kinetic constant of drug elimination from the central compartment
- Other factors significantly affected:
  1. V2: Volume of the highly perfused compartment
  2. Cl2: Clearance rate of the highly perfused compartment
  3. k12: Transport coefficient between the highly perfused and central compartments

Analysis

- Parameters directly related to plasma (compartment 1) were most sensitive
  - V1 being the most sensitive (directly related to concentration)
- The parameters pertaining to the highly perfused compartment were somewhat sensitive
  - Highly perfused meaning more flow
- The parameters pertaining to the scarcely perfused compartment were not sensitive
  - Scarcely perfused = Low flow

Conclusion

- This model demonstrates age is very significant in the pharmacokinetics of remifentanil
- Future work could accompass:
  - Including rates for children and other populations that could be affected
  - Including lean body mass into the model
  - Make use of if statements or switch cases with a UI to incorporate many of these parameters
- Can be used as a more predictive model for find optimal dosing rates

Thank you!

Any questions?

References

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