TUE-52: Dynamic PBPK for Pharmacology in Intensive Care Medicine

Marco Albrecht [1,*], Stephan Schaller[1]

1 esqLABS GmbH, Saterland, Germany
*corresponding author: marco.albrecht@esqLABS.com

Introduction

Fluid therapy is a standard treatment at intensive care units (ICU). It has implications for the absorption, distribution, metabolism, and excretion (ADME) properties in critically ill patients, leading to inadequate treatment decisions at intensive care units [1]. The simplest validated model for fluid distribution is volume kinetics, which shares similarities with pharmacokinetic modeling on the organism level (**Figure 1**) [2]. However, a transfer to physiology-based pharmacokinetics (PBPK) has not been proposed to our knowledge.
The current physiology-based pharmacokinetics (PBPK) software has a good representation of the steady-state in physiology, useful for most use-cases in drug development and regulatory authorization. However, the dynamic nature of rapidly changing physiology, such as volume shifts, in intensive care patients requires a likewise dynamic PBPK software to assess the pharmacology of drugs in intensive care. Consequently, a modeling and simulation (M&S) framework is developed to predict the effects of fluid resuscitation on molecule levels to inform drug therapy decisions at the ICU.

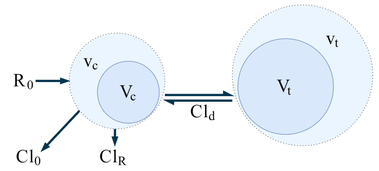


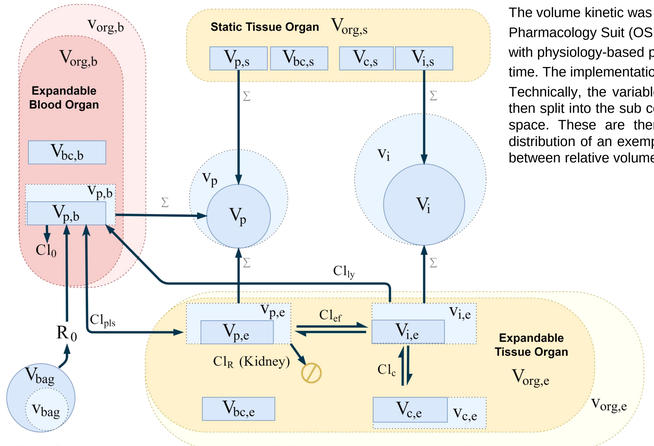
Figure 1: Concept of classical volume kinetics in analogy to classical pharmacokinetics: The constant reference volumes V and the associated variables $v(t)$ are defined for the central $V_c|v_c$ and peripheral $V_p|v_p$ compartment. The spaces expand upon infusion of volume with the rate R_0 and are connected via the distribution constant Cl_d. The central compartment loses constantly volume with the base rate Cl_0 and volume-dependent with the renal clearance rate Cl_R.

Objectives

The aim is a PBPK-model that can accompany drug-dose-decisions during the curse of treatment at the bedside. Thus:

- The impact of infusion on drug distribution will be investigated
- The PBPK will be dynamized to change with the patient
- The compatibility between volume kinetics and PBPK will be explored

Methods



Infusion Bag

Figure 2: OSPS Implementation: Tissues are grouped in expandable blood and tissue organs as well as static tissue organs. The latter group encompasses stiff structures like bone and tissues of neglectable size. An infusion fluid initially expands venous blood with the rate R_0, and the excess volume outbalances with arterial blood via parameter Cl_{ps} (not in Figure). The average volume excess in the blood organs is outbalanced with the relative plasma volume states in expandable tissue organs via parameter Cl_{ps} (Figure bottom left). The volume between plasma and interstitial space is mediated via the endothelial filtration rate constant Cl_{ef} and relies currently on differences in relative volume change. In expandable tissues, the relative volume deflection in the interstitial space and parameter Cl_{ly} determine the adjusted lymph flow to the venous blood compartment. In the kidney, the relative excess of plasma above the urination threshold UT leads to loss of volume, which also depends on the renal water clearance parameter Cl_R and the glomerular filtration rate. The volume exchange with cells is implemented but deactivated.

The volume kinetic was implemented in the Open Systems Pharmacology Suit (OSPS) [4] and consequently combined with physiology-based pharmacokinetics (PBPK) for the first time. The implementation occurs as described in **Figure 2**.
Technically, the variables age, sex, ethnicity, body weight, and height define organ sizes, which are then split into the sub compartments: plasma, red blood cells (RBC), interstitial space, and intracellular space. These are then summed up to numbers representing the whole organism. The volume distribution of an exemplary 60-year-old African-American woman is depicted in **Figure 3**. Differences between relative volume changes $(v(t) - V)/V$ enforce volume shifts between PBPK compartments.

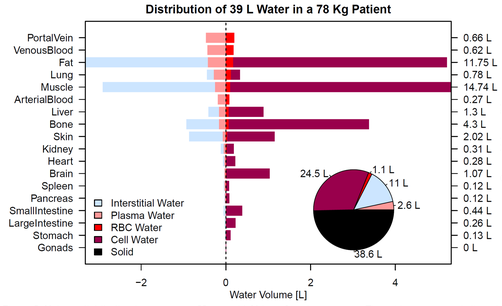


Figure 3: Volume distribution in an average 60-year-old African-American woman: The right axis represents the volume of the organs listed on the left axis. The bar graph shows the water volume of interstitial, plasma, RBC, and cell water. The extracellular water is depicted left from the dashed line and while the right side represents intracellular water. Both bars directly adjacent to the dashed lines sum up to the blood volume. The difference between the water content and the organ volume describes the solid fraction as shown in the right-bottom pie diagram for the whole-body volume distribution.

Results I – Fit to Data

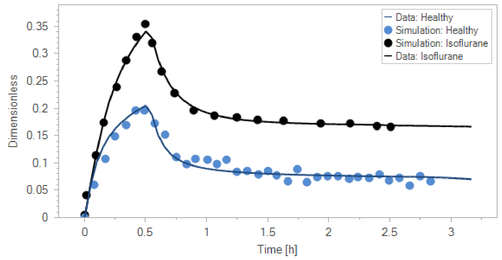


Figure 5: Simulations of the plasma dilution: The data is based on hemoglobin dilution after infusion of 25 mL/min Ringer solution for 30 minutes [6]. **Top:** Thyroid surgery with isoflurane sedation. **Bottom:** Healthy population [7].

Each infusion therapy expands the plasma compartments and dilutes hemoglobin [5, 6]. Thus hemoglobin dilution data directly results in the volume dilution displayed in **Figure 5**. The volume clearance is reduced in sedated individuals undergoing thyroid surgery.

This medical therapy alters the fitting parameters as follows:

- The urine production reduces in sedated patients as the urination threshold (UT) doubles from 0.08 to 0.18 and the dimensionless renal clearance parameter Cl_R falls from 33 to 4.
- Sedated patients seem to have only half of insensible volume loss (sweating and exhaling) as the base volume clearance rate Cl_0 falls from 0.94 to 0.39 mL/min.
- The lymph flow rate seems to double in sedated patients in surgery as the rate Cl_{ly} increased from 37.23 to 82.5 mL/min.
- The tissue plasma compensation seems to be delayed in sedated patients as the rate Cl_{pls} falls from 197 to 134 mL/min
- The endothelial volume seem to reduce as the distribution volume clearance falls from 92.3 to 49 mL/min

In contrast to the original Hahn model, the PBPK model does not allow for free adjustment of distributions volume as this is determined by the physiological data of a chosen individuum.

Results II – Volume Kinetics in Different Organs

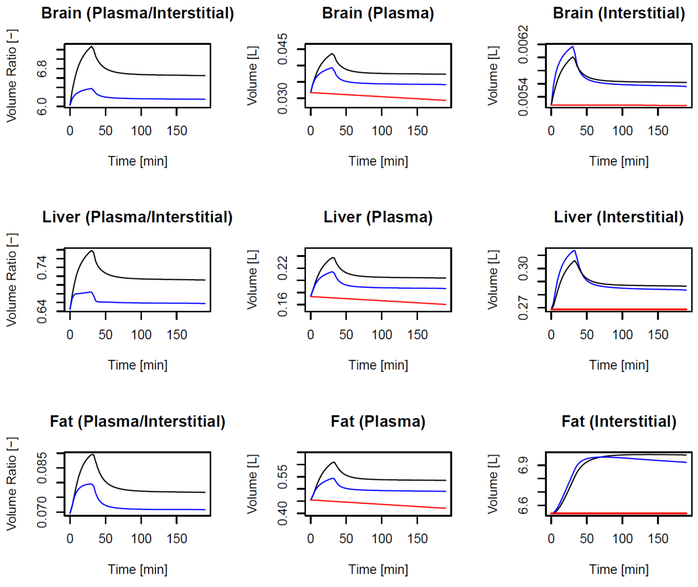


Figure 4: Temporal volume change in brain, liver, and fat: The volume level change is shown for both the tissue plasma space and the interstitial space compartment as well as for the ratio of the two. **Red:** No infusion in healthy individuals. **Blue:** Ringer infusion in healthy individuals. **Black:** Ringer infusion in individuals undergoing thyroid surgery with isoflurane sedation.

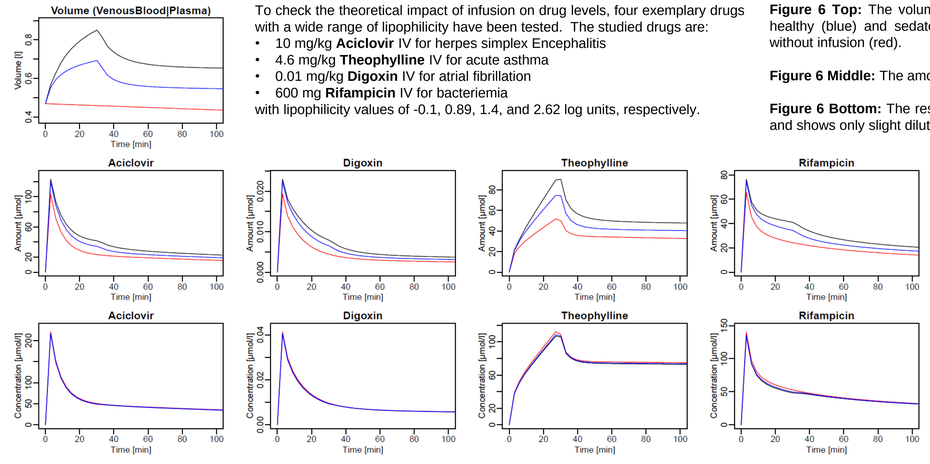
To check whether the model is reasonable, the volume changes are checked for plausibility in various sub compartments and organs (**Figure 4**).

Plasma to interstitial space ratio
Tissues differ in their sub-compartment volume fractions so that the ratio of plasma to interstitial space falls from 6 in the well-perfused brain to 0.07 in fat. As the additional volume occurs first in the plasma and then into the interstitial space, the ratio spikes with the dilution peak.

Base clearance
Without infusion, the baseline volume in plasma declines slowly and is part of the natural dehydration due to insensible water loss. A water retention mechanism in the kidney is not implemented here. This model only describes the renal excretion of excess volume above a certain threshold.

Interstitial volume expansion
The expansion of the interstitial volume is delayed and if the interstitial space is large compared to the plasma volume, the volume deflection is long-lasting as shown for the fat compartment.

Results III – Impact on Drug Concentration Levels



To check the theoretical impact of infusion on drug levels, four exemplary drugs with a wide range of lipophilicity have been tested. The studied drugs are:

- 10 mg/kg **Aciclovir** IV for herpes simplex Encephalitis
- 4.6 mg/kg **Theophylline** IV for acute asthma
- 0.01 mg/kg **Digoxin** IV for atrial fibrillation
- 600 mg **Rifampicin** IV for bacteriemia

with lipophilicity values of -0.1, 0.89, 1.4, and 2.62 log units, respectively.

Figure 6 Top: The volume in venous blood plasma increases in healthy (blue) and sedated (black) patients compared to control without infusion (red).

Figure 6 Middle: The amount of drug increases.

Figure 6 Bottom: The resulting concentration is almost unaffected and shows only slight dilution effects.

Process rates such as glomerular filtration rate as well as the renal and hepatic clearance change over time, but the profiles are identical between cases investigated (not shown).

Figure 6: PK profiles of four drugs in brain plasma: Red: No infusion in healthy individual. **Blue:** Ringer infusion in healthy individuals. **Black:** Ringer infusion in individuals undergoing thyroid surgery with isoflurane sedation.

Conclusion

A **first step** toward a PBPK model with dynamic physiology is done. With the infusion, one of the most frequent and basic therapies can be described with PBPK and volume kinetics.

- The model can be aligned with plasma dilution data based on hemoglobin measurements
- The excess volume in various organs outbalance across all organs
- The shift of volume in different compartments can be initially studied in theory
- The drug molecules follow concentration gradients so that dilution effects in the central compartment are outbalanced. However, the impact of volume overload on kidney function and thus renal clearance may be more critical than the dilution alone.

Various **extensions** need to be established to approach realistic results such as

- Volume regulation and urine flow by the kidney
- Blood loss determination
- Glymphatic system (Specialized lymphatic system of the brain)
- Refinement of the endothelial filtration

References

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