Appendix A:

Pharmacological models are used to describe a body's response to the administration of a drug. They can be split in two parts: the pharmacokinetic behavior of a drug, modeling the relationship between the infusion regimen of the drug and the resulting drug concentration in the blood on one hand, and the pharmacodynamic behavior, quantifying the relationship between the blood concentration and the drug effect on the other hand.

The pharmacokinetic model of a drug can be presented using a set of 1st order linear differential equations, or using the drugs' impulse response equation. The latter is the time-course of the blood concentration after a drug bolus administration. It always has the following layout:

$$c(t) = Ae^{-a.t} + Be^{-b.t} + Ce^{-c.t} \qquad \textbf{Equation 7}$$

It mathematically explains the 'context-sensitive half-life' concept of a drug: the separate exponential coefficients in the equation are the different measured half-life times referred to. Impulse response curves can be extracted from blood samples. For drugs with less complex behavior, one or two coefficients can be zero in **Equation 7**.

The presumed linearity of the infusion-concentration PK model leads to the advantage that the effect of multiple different simultaneous "stimuli" (i.e. bolus or continuous drug infusions) equals the sum of the separate effects of the stimuli. This allows computer-controlled infusion systems to keep track of blood concentrations using **Equation 8**. C(t) is the blood concentration in response to a drug input function over time I(t), using the impulse response c(t):

$$C(t) = \int_0^t I(t)c(t-t')dt' \qquad \textbf{Equation 8}$$

Again because of the linearity, the function c(t) can be inverted in order to calculate the required infusion rate when targeting a certain blood concentration.

The pharmacodynamic drug behavior is equally important when applying closed-loop control. One equation describing the typically non-linear relationship between the drug concentration in the body and the drug effect is the non-linear Hill-curve, described in **Equation 9**.

$$E = E_0 - E_{\max} \frac{C^y}{C^y + C_0^y} \qquad \textbf{Equation 9}$$

The steepness of the curve is determined by *y*, c is the drug concentration, c_{50} is the concentration at 50% of the drug effect.

Observations of drug effect show that a certain time-lag is present between the time of maximum blood concentration and maximum effect of this concentration. This means the concentration c in **Equation 9** cannot be the measured in the blood. To accommodate for this, a mathematical "effect-site" compartment was introduced. A time-constant k_{e0} models the time-lag between blood and effect-site concentration of the drug, using the following equation:

$$c_{effect} = c_{plasma}.(1-e^{-ke0.t}) \qquad \textbf{Equation 10}$$

The effect-site compartment is considered small enough not to influence the distribution of the drug in the other compartments .

The overall pharmacological drug model covariates are usually made up using population kinetics. The obtained values only approximate the ones for the specific patient under treatment.

To improve the accuracy of our controller, we want to tune this general model to the specific patient under control. This is realized in our setup using the infusion versus drug effect relationship measured during induction. Taking into account the limits of the induction phase and the relatively large half-life time of propofol, the induction drug concentration trajectory that can be applied for an average patient under surgery is very limited. This severely restricts the number of pharmacological covariates that can be patient-tuned, so we have to make choices.

In our controller, the internal infusion algorithm of RUGLOOP was used to control the drug pharmacokinetics. These algorithms and population-derived constants are widely accepted, so we used the population-calculated PK covariates without tuning. Moreover, the sigmoïd Emax model equation shows that the absolute value of the blood concentration as calculated by the infusion algorithm is not relevant in case c_{50} is estimated using the same model.

Unfortunately, it can be proven mathematically that it is impossible to measure both k_{e0} and y using an increasing drug concentration for a short time relative to the half-life of the product to be infused:

- Consider a stepwise increase in plasma concentration. The effect-site concentration follows **Equation 10**.

  The Hill-curve then gives the related effect :

$$effect = E_0 - E_{\max} \cdot \frac{c_{effect}^{\ g}}{c_{50}^{\ g} + c_{effect}^{\ g}} \quad \textbf{or}$$

$$effect = E_0 - E_{\max} \cdot \frac{(c_{plasma} \cdot (1 - e^{-ke0.T}))^g}{c_{50}^{\ g} + (c_{plasma} \cdot (1 - e^{-ke0.T}))^g} \qquad \textbf{Equation 11}$$

  Series expansion of $(1\text{-}e^{-ke0.t})$ for small $k_{e0}.t$ yields $k_{e0}.t$ which makes:

$$effect = E_0 - E_{\max} \cdot \frac{c_{plasma}^{\ g} \cdot (k_{e0}.t)^g}{c_{50}^{\ g} + c_{plasma}^{\ g} \cdot (k_{e0}.t)^g} \qquad \textbf{Equation 12}$$

  Which proves k_{e0} cannot be accurately estimated since k_{e0} and c_{50} are linearly dependant for this estimation with small k_{e0} values.

A procedure with both increasing and decreasing effect site concentration levels would be necessary to measure all pharmacodynamic parameters. This forces us to use the population-derived k_{e0} values proposed by RUGLOOP.

So, only the pharmacodynamic covariates c_{50}, y, E_0 and E_{max} will be patient-tuned in our setup. E_0 is the average effect before induction. The other parameters - y, c_{50} and E_m - are estimated using the least squares method on the vertical distance between the acquired samples and the pharmacodynamic curve of the sigmoïd Emax model. This yields a patient-specific curve.