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Original Research Article

Inter-individual variability in propofol pharmacokinetic/pharmacodynamic (PK/PD) model – A sensitivity analysis

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Abstract: Inter-individual variability is a major challenge to guarantee adequate anaesthesia in patients across the population. This variability can occur as a result of patient physiology (e.g. age and weight), variations in the pharmacokinetic (PK) process and differences in the pharmacodynamic (PD) function. For a safe and effective drug administration, it is important to recognise *which* and *when* these factors of variability cause a higher uncertainty on depth of anaesthesia. This study aimed to quantify the influence of these input factors on the uncertainty in Bispectral Index (BIS). In this study, Sobol' variance-based sensitivity analysis was performed on Schnider PK/PD model. Nine factors were evaluated: age, body weight, height, V_1, V_3, Cl_1, Cl_3, C_{e50}, and γ. The importance of these factors were ranked according to their total sensitivity indices. It was found that C_{e50} has the most determining role on BIS prediction. γ is a significant factor during the induction phase. The PD model alone was found to responsible for 70% to 90% of BIS uncertainty during the maintenance phase. The variability of height has negligible influence on BIS prediction and can be omitted from the PK/PD model.
Keywords: Depth of anaesthesia, pharmacokinetic-pharmacodynamic model, inter-patient variability, and variance based sensitivity analysis

INTRODUCTION:

Due to the presence of inter-individual variability, an accurate prediction of the dose-effect relationship is difficult. As a result, achieving adequate anaesthesia in patients across the population is a demanding task.

The inter-individual variability can be caused by patient physiology (e.g., age, weight and gender), variations in the pharmacokinetic (PK) process and/or differences in the pharmacodynamic (PD) function [1]. To improve the dose-effect prediction, these factors have been taken into account during the construction of population PK/PD models. For example, significant covariates were integrated into the model while PK/PD parameters with the highest likelihood were proposed based on model fitting [2, 3]. Nonetheless, these covariates and parameters were subjected to variation and were responsible to varying degree of uncertainty to the resulting depth of anaesthesia.

For a safe and effective drug administration, it is important to recognise *which* of these factors is more likely to cause a higher uncertainty on the depth of anaesthesia. Previous studies have all suggested that PD variability is considerably higher than PK variability [4-6]. However, to what extend is its influence is higher? This leads to the second question of *by how much* its contribution to uncertainty is higher. Thirdly, since PK/PD is a dynamic model, the mode of administration and duration of the patient being anaesthetised will also influence the importance of each factor. Hence, we are also desired to understand *when* each of these factors contributes higher uncertainty to the anaesthetic end point. Then, with the help of this knowledge, uncertainty can be reduced by focusing on the appropriate variability factors thereby driving a more informed-decision making.

To answer the questions above, sensitivity analysis is a useful tool. Sensitivity analysis is a systematic method that assesses how the uncertainty in

the output of a model can be apportioned to different sources of uncertainty in the model input [7]. The importance of each input factor is ranked by its sensitivity index; input factors with high sensitivity index are more likely to affect the model output.

Previously, Silva *et al.;* [5] have performed a local differential sensitivity analysis on neuromuscular blockade and propofol-remifentanil models. However, the partial derivative method that they have employed is only applicable for relative small changes on the input factors [8]. Furthermore, for nonlinear model, global approach is a more appropriate choice compared to local approach [7]. Recently, Krieger *et al.;* [6] have conducted a global sensitivity analysis on an isoflurane-based inhalation model. Among the PK/PD parameters, it was found that the effect site concentration that produces 50% of the maximum effect (C_{e50}) has the highest sensitivity. This finding has later motivated them to design a model predictive controller that estimates C_{e50} online [9], which is a measure to reduce the uncertainty causes by C_{e50}. Note that both of these studies do not include covariates as the input factor, presumably because the patient's age, weight, and gender are known in advance before the anaesthetisation take place. However, the inclusion of these factors can provide us a better insight of the PK/PD model. For example, body weight has always been a key indicator for anaesthetist to estimate the required propofol dosage. But how much uncertainty can be reduced by knowing the patient's weight? Also, how many weightage does each parameter or covariates carry in a given model? These quantitative understanding of the PK/PD model can in turn help us to point out important assumptions of the model and perform comparison between different models.

This study aimed to quantify the influence of variability of input factors on propofol-induced anaesthesia through a global variance-based sensitivity analysis. Here, the Schnider propofol PK/PD model and Bispectral Index (BIS) were chosen as the model and the model output, respectively. PK/PD parameters and the relevant covariates (age, weight and height) were treated as the input factors.

This paper is organised as follows. Section 2 explains briefly the concept of Sobol' variance-based sensitivity analysis. Section 3 defines the variability bound of each input factors. The result and discussion were discussed in Section 4. Finally, Section 5 concludes the study.

Sobol' variance-based sensitivity analysis

Variance-based sensitivity analysis is a global approach that uses variance to "measure" uncertainty [10]. Consider a model

$$y = f(X) \tag{2.1}$$

Where y is the model output, f is the model functions and $X = (x_1, x_2 \ldots x_n)$ denotes the n uncertain input factors, each associated with a probability density function. The overall uncertainty can be represented by the unconditional variance $V(y)$ where all the parameters are varied over their entire variability range.

The importance of a single factor x_i can be quantified by calculating the expected variance reduction when it is fixed or known, or $V(y) - E[V(y \mid x_i)]$. According to the law of total variance, this is equals to the variance of conditional expectation $V[E(y \mid x_i)]$, or V_i in short [11].

Normalising V_i with unconditional variance gives

$$S_i = \frac{V_i}{V(y)} \tag{2.2}$$

Where S_i is called the "first order sensitivity index". Each S_i is ranges between 0 and 1. The higher the S_i value, the more significant is the factor.

However, the first order sensitivity index does not consider the influence contributed by interaction between factors. To include all the interactions between factors, the "total effect sensitivity index" is a useful measure. It can be computed by

$$S_{Ti} = \frac{V_{Ti}}{V(y)} = \frac{V(y) - V[E(y \mid x_{\sim i})]}{V(y)} \tag{2.3}$$

Where $x_{\sim i}$ denotes all factors but x_i.

Finally, the Sobol' method decomposes the variance and partial variances in equations (2.2) – (2.3) into terms of increasing dimensionality and compute them using the Monte Carlo techniques [12].

Input factors and its distribution

Variance based sensitivity analysis takes into account the shape of the input factor. Hence, each input factor has to be assigned with a probability distribution that reflects its possible variation. In this section, the input factors and its distribution for this study were defined.

Various multi-compartment PK models for propofol have been published in the literature. These include the Marsh [13], Schnider [2], Schüttler [14] and Eleveld [15] models. Among these models, the Marsh and Schnider models are the two most commonly used models in the commercial target-controlled infusion pumps (TCI) to guide the delivery of propofol. Due to its important role in the current clinical practice and a better reported predictive ability [16], the Schnider PK model was selected for the analysis.

The Schnider PK model has six parameters, namely the central volume (V_1), rapid peripheral volume (V_2), slow peripheral volume (V_3), clearance (Cl_1), rapid inter-compartmental clearance (Cl_2) and

slow peripheral clearance (Cl_3) [2]. All parameters were assumed to exhibit lognormal distribution, i.e.,

$$P_i = \theta_{TV} e^{\eta i} \quad (3.1)$$

Where P_i is the value of parameter in the i individual, θ_{TV} is the typical value of the parameter in the population, and η_i is a random variable with mean zero and standard deviation (σ). η_i is assumed to be independent normally distributed [17].

The original variation of each PK parameter was employed in this study. The σ was calculated from the reported coefficient of variance (CV) from the following relationship

$$CV = \sqrt{\exp(\sigma^2) - 1}. \quad (3.2)$$

However, the CV value of V_2 and Cl_2 was very small (less than 1%). Hence, these two factors were omitted from the analysis.

For integrated PK/PD model, Schnider et al. has recommended 0.456 min^{-1} as the rate constant between plasma and effect site, k_{e0} [18]. To preserve the model consistency, the PD model from Martín-Mateos *et al.;* [19] was selected; it used the Schnider's PK model parameters and k_{e0} = 0.456 min^{-1} to identify the PD parameters.

The Martín-Mateos PD model was based on the following sigmoid equation:

$$BIS = BIS_0 - (BIS_0 - BIS_{\min}) \frac{C_e^{\gamma}}{C_{e50}^{\gamma} + C_e^{\gamma}} \quad (3.3)$$

Where the BIS_0 is the baseline BIS in the absence of drug, BIS_{min} is the minimum value of BIS, C_{e50} is the effect concentration at 50% reduction of BIS, and γ is the steepness of concentration versus response. In their study, BIS_0 was assumed as 95.6 while BIS_{min} was considered as 8.9. Only two PD parameters were identified: C_{e50} and γ. However, they have suggested different models for induction and maintenance phase.

To define the variability range of C_{e50} and γ, we have fitted the identified C_{e50} and γ values for the 42 patients in [19] to lognormal distribution using distribution fitting tool in MATLAB. Note that the mean estimated here has a very mild different from the one reported in [19], which may be due to the different setting.

Apart from the model parameters, information on patient's age, weight, height and gender are also needed in Schnider PK/PD model. The possible distribution of age, weight and height was identified through the aggregated dataset of Eleveld et al. [15]. Their dataset contains information on 660 individuals from 21 previously published propofol studies. However, 108 individuals are without height information and 159 individuals are less than 18 years old. Since we are only interested in the adult population, these two groups were excluded from the variability analysis. Then, the distribution of age, weight and height from the 393 individual (273 male and 120 female) were identified through MATLAB. Gender is a discrete factor; it cannot be described by a probability distribution. Hence, the sensitivity analyses for male and female population were conducted separately.

Table 1 shows the summary of the input factors and their distribution in this study. As mentioned earlier, different C_{e50} and γ were suggested for induction and maintenance phase [19]. In this study, the switching from induction model to maintenance model was made at time 2.5 minutes.

To observe the influence of time and mode of administration on input factors, an infusion rate profile (Figure 1) was generated using TIVAtrainer software. The profile was 30 minutes long and includes an initial bolus induction and several random adjustment of target effect concentration.

Finally, the total sensitivity indices of each input factors were computed using equations (2.4). MATLAB and UQlab (http://www.uqlab.com/) were used to compute the sensitivity indices. A sample size of 10,000 was applied in the numerical integration.

RESULT AND DISCUSSION

Nine input factors were evaluated in this study: age, body weight, height, V_1, V_3, Cl_1, Cl_3, C_{e50}, and γ. Their influence on uncertainty was quantified by total sensitivity index S_{Ti}. The higher the index, the more significant is the factor.

Figure 2 shows the total sensitivity indices for male population. From the figure, it can be seen that the variability of C_{e50} was the most determining factor that contributes to the uncertainty of BIS. During the maintenance phase, it contributes up to 78% to 95% of BIS uncertainty. This means that if C_{e50} was known, the uncertainty of BIS output can be greatly reduced.

Table 1: Input parameters for the sensitivity analysis of the propofol pharmacokinetics-pharmacodynamics (PK/PD) model

Input Factors	Unit	Distribution	Male Population		Female Population		Reference
			Mean	Standard Deviation	Mean	Standard Deviation	
Age	*year*	Normal	49	16.07	42	16.37	[15]
Weight	*kg*	Lognormal	75.35	16.43	68.35	15.96	[15]
Height	*cm*	Normal	172.68	9.61	164.78	10.06	[15]
η_{V1}	-	Normal	0	0.0404	0	0.0404	[2]
η_{V3}	-	Normal	0	0.1428	0	0.1428	[2]
η_{Cl1}	-	Normal	0	0.1002	0	0.1002	[2]
η_{Cl3}	-	Normal	0	0.1174	0	0.1174	[2]
$Ce_{50,I}$‡	$mg{\cdot}l^{-1}$	Lognormal	3.51	2.102	3.35	1.201	[19]
$Ce_{50,M}$‡	$mg{\cdot}l^{-1}$	Lognormal	2.25	0.9531	2.22	0.5764	[19]
$\gamma_{,I}$‡	-	Lognormal	1.22	0.6495	1.31	0.5299	[19]
$\gamma_{,M}$‡	-	Lognormal	1.76	0.8627	1.46	0.6038	[19]
V_2	l	Constant					[2]
Cl_2	$l.min^{-1}$	Constant					[2]
k_{e0}	min^{-1}	Constant					[18]
BIS_0	-	Constant					[19]
BIS_{min}	-	Constant					[19]

*Abbreviations of input parameters: V_1; central volume, V_3; slow peripheral volume, Cl_1; clearance, Cl_3; slow peripheral inter-compartmental clearance, Ce_{50}; effect site concentration at 50% reduction of BIS, γ; steepness of concentration versus response. Subscriptions: *I*; induction, *M*; maintenance.

‡During the simulation, the switching from $Ce_{50,I}$ to $Ce_{50,M}$ and $\gamma_{,I}$ to $\gamma_{,M}$ was made at time = 2.5 minutes.

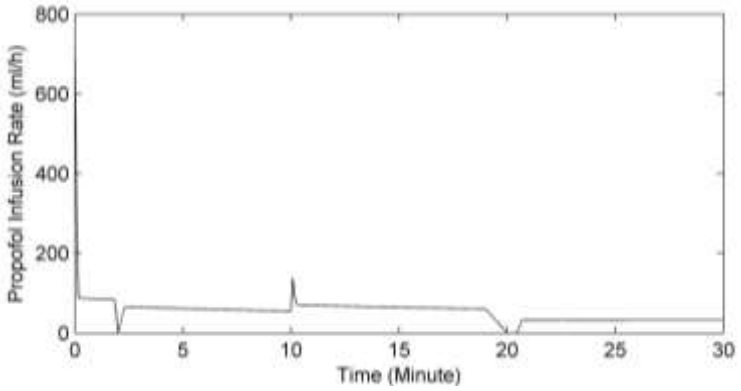

Fig 1: Propofol infusion rate generated for PKPD model simulation.

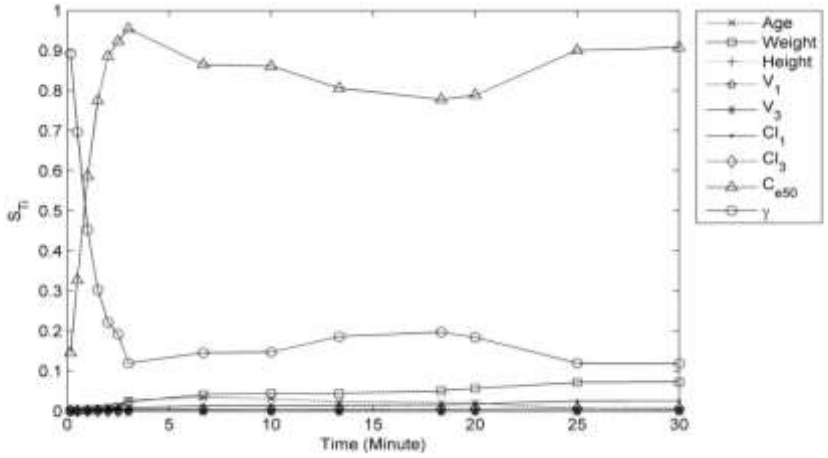

Fig 2: Total sensitivity indices for male population.

Next, γ was found to be the second most significant factor. Its sensitivity index is the highest during the bolus administration but declined gradually as it enters into maintenance phase. However, when there is an increase in the propofol infusion rate, the importance of γ will increase again.

Compared to PD parameters, the effect of variability in PK model was relatively small. Among the PK parameters, Cl_1 has the highest sensitivity index. Its sensitivity started from a very small value and increase gradually to 0.025 S_{Ti} at 30 min. This means that the longer the patient is anaesthetised, the higher influence its variability has on BIS.

The figure shows that the variability of the three other PK parameters, V_1, V_3 and Cl_3 has negligible importance. In other words, it is adequate to treat them as a constant (V_1 = 4.27l, V_3 = 238l and Cl_3 = 0.836l.min^{-1}) without creating uncertainty to the output. However, the extremely low sensitivity index of PK parameters may be due to the small sample size in Schnider study [2]; the parameters were estimated from 24 healthy volunteers. As a result, the variability observed is very small.

In term of covariates, body weight was found to be the most significant covariate. This is of no surprise since body weight has always been a key factor in the estimation of the required propofol dosage. Moreover, its importance was found to increase over time; the longer the patient is anaesthetised, the more important the weight variation is. However, if it is compared with PD parameters, its overall contribution on BIS is very small, which is less than 10%.

Age appears to be influential at the beginning. This can be explained by the fact that the patient's age is a covariate for parameters in the rapid peripheral compartment, i.e., V_2 and Cl_2. Both of these parameters were responsible for the initial reduction of drug concentration in plasma. However, its sensitivity index decreased gradually over time. This is understandable because when the drug concentrations in central compartment and rapid peripheral compartment were close to equilibrium, the changes of V_2 and Cl_2 will have little effect on the reduction of drug concentration in plasma.

Finally, the variation of height has negligible influence on BIS prediction. In the Schnider model, height is used to calculate the lean body mass (LBM) of the patient. From this finding, it was showed that the variation in height does not influence the BIS; it is not necessary in the PK/PD model prediction. In fact, the Eleveld model [15] developed recently does not include height in their model.

Figure 3 illustrates the total sensitivity indices for the female population. It can be seen that the trend of each factor is the same as in the male population. The only difference is that the PK parameters and covariates have a higher sensitivity index than in the male population. This is due to the smaller inter-individual variability of PD parameters observed in the Martín-Mateos's study [19]. As a result, the relative importance of PD model is lower.

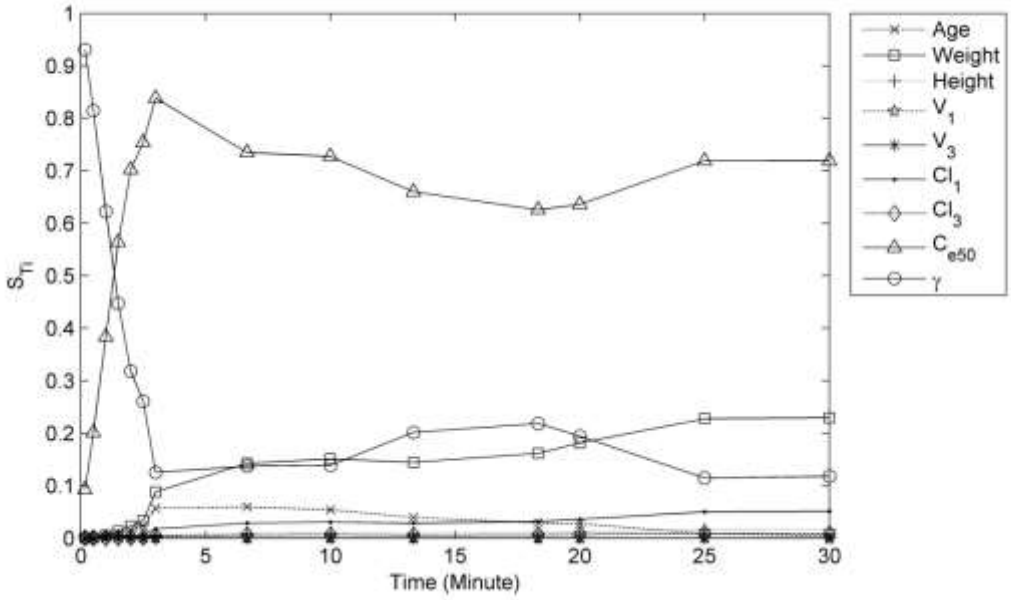

Fig 3: Total sensitivity indices for female population.

This analysis is subjected to a few limitations. First, it was assumed that the Schnider PK/PD model is adequate to predict the anaesthesia end-point. However, it is inevitable that this model is subjected to unmodelled dynamic and prediction flaws. Hence, in the reality, the factors may have influences the anaesthesia end-point in a different way. This limitation can be overcome only by the development of a better PK/PD model.

Secondly, the distribution of each factor will affect its sensitivity indices. It is highly possible that the distribution, mean, and standard deviation of each factor in Table 1 do not represent the exact population. This is especially true for Schnider's study [2] where the study population is very small (i.e., 24 healthy volunteers). This may be the reason for the relatively low sensitivity index of PK parameters in comparison with PD parameters.

Thirdly, the Sobol' sensitivity analysis involves the computation of numerical integration via Monte Carlo technique. The numerical method is susceptible to error. This error can be reduced with a higher sampling size, but with a higher computational cost. For more information on the probable error, readers are referred to [12].

CONCLUSION

In this study, it was found that C_{e50} has the most determining role on BIS prediction. Together with γ, the PD model was found to responsible for 70% to 90% of BIS uncertainty during the maintenance phase. γ and patient's age are of considerable importance when a drastic increase in propofol infusion rate is to be performed, especially during the induction phase. The importance of weight was found to increase with time. This means that the longer the patient is being anaesthetized, the more his/her weight will affect the BIS value. Finally, the variability of height has negligible influence on BIS prediction and can be omitted from the PK/PD model.

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