Estimation of The Main Effect and Total Effect of a PBPK Model Based on The Uncertainty of Individual Parameter for Treatment Planning in PSMA Therapy

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Abstract. The purpose of this study was to identify the most important physiologically-based pharmacokinetic (PBPK) model parameters determining the absorbed dose (AD) in prostate-specific membrane antigen (PSMA) therapy. The extended-Sobol’ global sensitivity analysis method was used to analyze the sensitivity of the PBPK model parameters obtained from 3 patients. The investigated PBPK model parameters were the blood flow to the organs, PSMA binding rate, biological release rates, and density of organs receptor. The outputs of extended Sobol method were the main effect Si and the total effect Si, of the parameter of interests for each ADs. The sampling strategy of extended Sobol has been implemented based on the mean and covariance matrix of the parameters. From the simulations, the most important parameters which determine the ADs to the kidney was the kidney receptor density (Si =0.4, S71 = 0.8). For tumors, it was shown that tumor receptor density was the most essential parameter (Si =0.7, S71 = 0.8). In conclusion, measurement of the blood flow and organ receptor densities might be of interest to improve individualized treatment of PSMA therapy.

1. Introduction
Prostate-specific membrane antigen (PSMA) has been shown as a promising target for radionuclide therapy in the most prostate cancer cases [1–4]. It has been shown that individualized treatment planning approach in PSMA therapy has a better accuracy compare to the cohort based treatment planning in predicting the absorbed doses (ADs) [5–7]. However, the uncertainty of the biokinetic parameters in individualized treatment planning might affect the accuracy of the predicted ADs [8–10]. In order to predict the AD of the radiopharmaceutical in the organs during PSMA therapy, a physiologically based pharmacokinetics (PBPK) model has been shown to be a powerful method [11,12]. In brief, the PBPK model includes distribution, metabolism and excretion of radiopharmaceutical in the organs by taking into account the physiological and anatomical information of the subject [7,11].

Recently, it has been shown that identification of the important PBPK parameters determining inter-individual variability in a population using a GSA is beneficial for the calculation of the ADs[13]. However, important PBPK model parameters determining the uncertainty of individual biokinetic data using a GSA in PSMA therapy has never been reported in the literature. Therefore, in this study, we identify for the first time the important PBPK model parameters determining the uncertainty of individual biokinetic data using a Sobol GSA method in PSMA therapy for an accurate determination of the ADs.
2. Materials and Method

2.1. Data and Tools

A software MATLAB r2018b was used to determine the sensitivity analysis. The data (Table 1) in this study was based on secondary data [14]. The standard deviation of these parameters were acquired from Kletting’s publication and some parameters were followed Hardiansyah’s research (CV=10%) [7,15].

2.2. PBPK model for PSMA therapy

The main structure of PBPK model in PSMA therapy consists of blood flow in organs, PSMA binding rate, biological release rates, and density of organs receptor [14,16,17]. In this simulation, there were two models, radiolabeled PSMA and unlabeled PSMA. These models were competed to one another to capture receptors in organs [7,11]. Parameters of the PBPK model in this study contained many fixed parameters which were approximated. For the input parameter of the GSA, the data was collected from each patient’s biokinetic. The list of parameters is shown in Table 1.

| Parameter       | Definition                          | Unit            | CV % (Source) |
|-----------------|-------------------------------------|-----------------|---------------|
| [R_{K,0}]       | Receptor density in kidney           | P1 13  | P2 17  | P3 23  |
| [V_{REST,0}]    | Tumor rest volume                    |                | 10.02 (15)   |
| [R_{TU1,0}]     | Receptor density in tumor1           | P1 87  | P2 73  | P3 7.2 |
| [R_{TU2,0}]     | Receptor density in tumor2           | P1 94  | P2 52  | P3 4   |
| λ_{K, release}  | Release rate in normal tissue         |                | 15.94 (15)   |
| λ_{TU, release} | Release rate in tumor                |                | 11.66 (15)   |
| f_{TU1}         | Serum flow rate towards tumor1       |                | 10 (7)       |
| f_{TU2}         | Serum flow rate towards tumor2       |                | 10 (7)       |
| f_{K.C}         | Kidney blood flow                    |                | 10 (7)       |

2.3. Extended Sobol Method

The extended Sobol is a novel approach for estimating global sensitivity analysis which was introduced by Kucherenko et al [18]. There were 9 biokinetic parameters which had been obtained from reference (Table 1). These parameters were the mean input value, equation 2.1, which were contained receptor density in kidney and tumors, blood flow rate towards tumors, release rate, and kidney blood flow. Covariances matrix, equation 2.2, were the data that was generated from two-dimension data of every
biokinetics parameter, symbolized as $\Sigma_y$, $\Sigma_z$ for the data generated from the same parameters and $\Sigma_{yz}$, $\Sigma_{zy}$ for two different parameters. In this study, the correlation between those data was not included.

\[
Mean \ value \quad X_{value} = \frac{X_1}{X_n} \quad 2.1
\]

Covariance matrix
\[
\Sigma = \begin{bmatrix}
\Sigma_y & \cdots & \Sigma_{yz} \\
\vdots & \ddots & \vdots \\
\Sigma_{zy} & \cdots & \Sigma_z
\end{bmatrix} \quad 2.2
\]

The range value of outputs of Sobol methods (Main Effect and Total Effect) are zero to one (0 – 1) whereas the maximum value is one. If the output value was nearly to reach one, it assumed that value was closer to the true value.

**Main Effect**
\[
S_i = \frac{1}{N} \sum_{j=1}^{N} \left( f(y'_j, z'_j) f(y_j, z_j) - f(y_j, z_j) \right) \quad (3.3)
\]

**Total Effect**
\[
S_{Ti} = \frac{1}{2N} \sum_{j=1}^{N} \left( f(y_j, z_j) - f(y'_j, z'_j) \right)^2 \quad (3.4)
\]

$f(y,z)$ was a model function with finite variance, $y$ was an arbitrary subset of the variables, and $z$ a complementary subset. Notation $z$ dan $z'$ were to differentiate a product vector from the same function and distribution. $D$ was total variance and $N$ was sampling point. Last, quotation mark (‘) were to show a random vector were different from one to another but generated from the same function, such as joint probability density and conditional distribution[18].
As represented in figure 2.1, physiological parameters and standard deviation were the inputs parameter, afterwards the sampling was conducted. By initiated the number of evaluations, the main effect and total effect would have been able to be calculated. If convergency had not reached, which meant a consistency value, a repetition of initiated number of evaluation and calculated would be conducted.

3. Results and Discussion

3.1 Verification of Sample

As the start of research, verifying the distribution of data needed to be conducted to determine an appropriate method for analyzing it. There were 9 parameters of sampling, according to the table 1 list of parameter definition, which had to be checked. The verification was conducted by simulating the sampling step and monitoring the histogram of every parameter one at the time. Avoiding asymmetrical distribution was necessary due to complicated hindrance factors[19]. Figure 3.1 illustrated gaussian distribution for every sampling of receptor density and there were not any differences in distribution, refer to reference[20].

![Figure 2.1. Workflow of Global Sensitivity Analysis in PSMA Therapy.](image-url)
3.2. The Convergenc Graph of Extended Sobol Output

The improvement treatment of administered radiopharmaceutical in radioimmunotherapy was a promising approach of better treatment[5–8]. Unfortunately, the workload and complicated treatment would become hindrances in clinical practice[21]. Thus, by identifying the most essential parameters that cause uncertainty of AD, the challenge is possible to be eradicated.

To discover the most important parameter, quantitative analyses needed to be conducted through GSA extended Sobol method. The outputs of extended Sobol, which were main effect, known as \( S_i \), and total effect (\( S_{Ti} \)), were shown in figure 3.2., 3.3., and 3.4. to illustrate which parameter value in output was closer to one (1). By definition, \( S_i \) was a parameter that reduced variance whenever its parameter was known. \( S_{Ti} \) was a proportion of variance parameters which true value of all parameters, except one parameter, had been discovered[22,23] Known the value \( S_i \) and \( S_{Ti} \) would help to determine the most important that contributed towards the true value of AD organs.

For instance, in figure 3.2., the \([R_{K,0}]\) dominated the upper level of \( S_i \) because at the number of evaluations 1000, \([R_{K,0}]\) had the highest value of \( S_i \), 0.4, compared to the others. This meant the \([R_{K,0}]\) contributed the most on the uncertainty of absorbed dose kidneys. Similar to figure 3.2. (a), figure 3.2. (b) illustrated that the \([R_{K,0}]\) also cause the uncertainty in kidneys (\( S_{Ti} \)=0.8).

**Figure 3.1.** Histogram of Receptor Density in Kidney(a), Tumor 1(b), and Tumor 2(c)

**Figure 3.2.** Absorbed Dose Kidney convergency Graph of \( S_i \) (a) and \( S_{Ti} \) (b)
Referring to the description of $S_i$, Figures 3.3 (a) and (b), also showed that the most essential parameter is $[R_{TU1,0}]$. The simulation results of extended Sobol values were around 0.6 on $S_i$ and 0.8 on $S_{Ti}$. So, it can be indicated that $[R_{TU1,0}]$ was the essential parameter.

The charts, Figure 3.4 (a) and (b), illustrated the similar pattern as the previous graphs of the main and total effects, whereas the receptor density tumor 2 $[R_{TU2,0}]$ had the highest effect among the other parameters. The resulting $S_i$ and $S_{Ti}$ generated from the extended Sobol analysis showed $R_{TU2,0}$ as the most important parameter ($S_i=0.65$ and $S_{Ti}=0.77$). Determined receptor density of every single organ was a significant approach during radionuclide therapy planning because it would help to reduce the workload of workers and faster treatment for patient.

The uncertainty of AD had the tendency to be affected by its own parameter of the organ. This results had a similarity in Hardiansyah’s research which demonstrated kidney blood flow as the most essential parameter AD of kidneys and receptor density in tumor as in tumor organs[21]. Therefore, it was highly recommended to measure these parameters, so that the effectivity of treatment for patient would increase.

4. Conclusion

In conclusion, simulation of 177Lu PSMA therapy has been conducted by applying extended Sobol method on full body PBPK modeling, however deeper insight in validation of this study is still ongoing. By performing this method at least, the most essential of uncertainty parameters in the distribution of radioactive drugs, which will be absorbed by patient’s organs, can be discovered and optimized. This discovery might become a direction during prior treatment which will help to escalate.
the effectivity of absorbed dose in patient’s tumor and the safety of organs at risk. Therefore, the results of this study are adequate to be a basis point of view in support for advance research, such as clinical study in the use of drugs from the resource of natural materials whose waste is environmentally friendly, although further analyzed qualitatively is needed.

5. References

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