**Standard Operating Procedures For PK/PD Modelling MATLAB Code**

**Summary of Code Purposes:**

**EleveldPKFun**: This code is a function implementation of the three compartment Eleveld PK/PD model, explained here:

Eleveld, D. J., Colin, P., Absalom, A. R., & Struys, M. M. R. F. (2018). Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *British Journal of Anaesthesia*, *120*(5), 942–959. <https://doi.org/10.1016/j.bja.2018.01.018>

It requires a second-by-second propofol infusion rate, participant age, height, weight and sex, and a value for Ke0 to produce a second-by-second effect site concentration.

**Ce\_Curve\_Creator:** This code is used to output an effect site concentration vector as a function of treatment time, making primary use of the EleveldPKFun function.

**Participant\_Doser:** This code is used to:

1. Create a vector describing the second-by-second dosing of a recent propofol treatment

and

2. Generate a dosing recommendation for all treatments of all participants.

**Projection\_Accuracy\_Analysis**: This code is used to analyze the effectiveness of the adapted Eleveld PK/PD model to predict second-by-second burst suppression ratio by optimizing Ke0, Hill and Ce50.

**How to Use**

**Ce\_Curve\_Creator:**

The code will walk you through the steps you need to take for the most part.

In order to generate effect site concentration you need to have first generated a .csv file describing the second-by-second dosing and a .csv file describing the second-by-second BSR. The instructions on how to do this is at the end of this document.

A dosing .CSV is created by using Participant\_Doser as described below.

Once a BSR file and a dosing CSV have been created, this code will combine them to estimate second by second effect site concentration of each treatment of each participant.

**Participant\_Doser:**

If you wish to create a dosing recommendation for the first treatment of a new participant, follow the instructions that the program gives you, including entering age, height, weight and sex and it will generate your dosing using the Eleveld Ke0.

If you wish to save second by second dosing information from a previous treatment, tell the program that this is not the first treatment that the patient has undergone.

If you only want to enter one previous treatment dosing, enter the number 1. If you want to enter more previous treatments’ dosing information, enter the desired number. If you only want to generate a dosing recommendation, enter 0.

To continue entering previous dosing, go the folder in the NAP\_Study corresponding to the most recent treatment of your participant. Select the Timings.pdf associated with the treatment you want to enter.

Follow the instructions to enter the number of boluses and infusions exactly as they were given in the procedure.

The code will then translate this to a second-by-second dosing CSV file saved to your desired directory. It should be saved in the same folder as the BSR CSV that you have created.

After this, the code will prompt you if you want to generate dosing recommendations. If you do want to generate a dosing recommendation, the code will generate a dosing rec for you based upon the participant's PK/PD parameters from their most recent treatment. Or, if it is their first treatment, based on the Eleveld model Ke0, and our participant population medial Hill and Ce50.

**Projection\_Accuracy\_Analysis**:

Run this code and it will analyze your data for you. It outputs the median absolute percent error of treatment height and treatment duration along with 25th and 75th percentiles.

**Creating a BSR .CSV File**

Open the folder NAP\_Study on UBox

Open “All Data and Analysis”

Open the participant folder that you need to create a BSR file for.

Open “BIS Data” folder for that participant

Click on the treatment number you want BSR data for

Open the folder “Raw Data”.

Download the .spa file

Table

Description automatically generated

Open a blank excel worksheet

Click on the “Data” tab at the top

Select “From text/.csv” from the left of the toolbar

Graphical user interface, application, Word

Description automatically generated

In the file importer select the file type as “All Files”

Click on your .spa file to load it.

Click load in the pop up window

Graphical user interface, application, table, Excel

Description automatically generated

Your data is now loaded into your excel workbook.

Select all of column H and copy and paste it into a new tab in the workbook

Graphical user interface, application, table, Excel

Description automatically generated

Delete all leading and trailing zeros in the column vector

Save your document in the folder corresponding to the correct participant as a .CSV (comma delineated) file.

Name your file following the naming convention shown below with the correct corresponding participant and treatment numbers

Graphical user interface, application

Description automatically generated with medium confidence

You have now saved the second-by-second BSR of a treatment as a CSV file.