USER MANUAL

FOR THE OPEN SOURCE PATIENT SIMULATOR

V.01 - September 2024

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This user manual is designed to help you download and use our advanced patient simulator. The guide will walk you through the steps required to access, install, and effectively use the simulator for your needs.

For more information, please contact: erhan.yumuk@ugent.be

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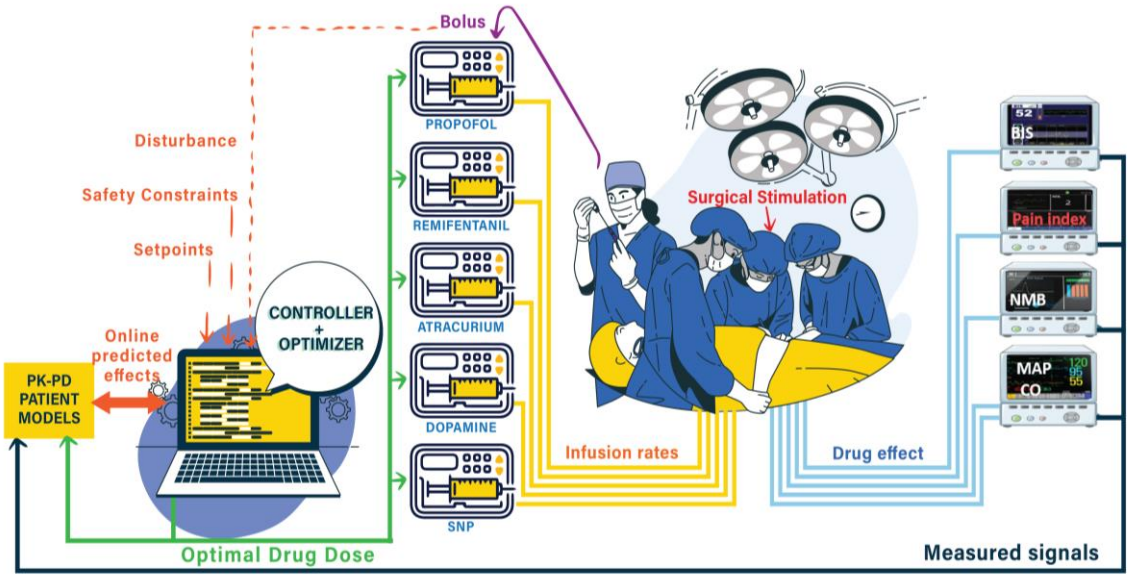
1 About the Patient Simulator



The simulator offers modeling of the interactions between general anesthesia and hemodynamic stabilization, incorporating states which are hypnosis (unconsciousness), analgesia (absence of nociception), neuromuscular blockade (no movement), cardiac output (CO), and mean arterial pressure (MAP). Those states are achieved using the following drugs: Propofol, Remifentanil, Atracurium, Dopamine, and Sodium Nitroprusside (SNP). Please, see **Appendix A** for more information.

The system simulates real-world conditions. The simulator includes two patient databases (young and elderly), enabling detailed analysis of both intra- and inter-patient variability.

Key features of this updated version of simulator include:

- Three different response surface models characterize the interaction
- The effect of CO on BIS signal.
- between Propofol and Remifentanil.
- Limits for inputs/outputs.

2 How to Download Our Simulator

To download our simulator, follow these steps:

i. Visit our website: https://amicas.ugent.be/.

ii. Navigate to the **"Software"** section in the main menu.

iii. Click on **"Matlab/Simulink"** to download the “zip file”.

Figure 1

iv. After downloading the zip file, you will have the following files:

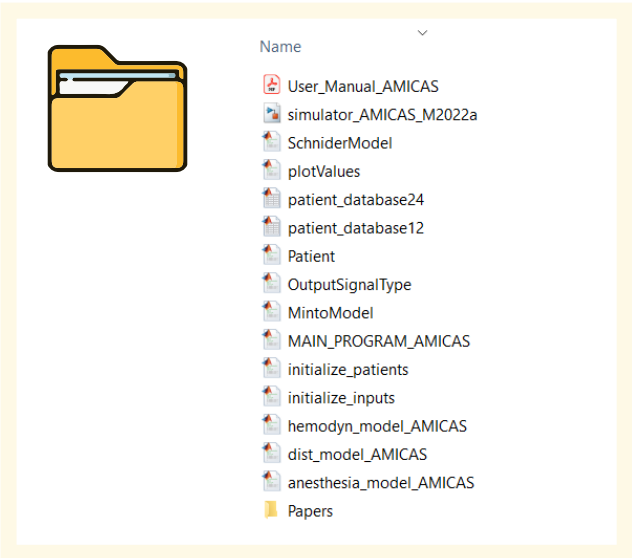


Figure 2

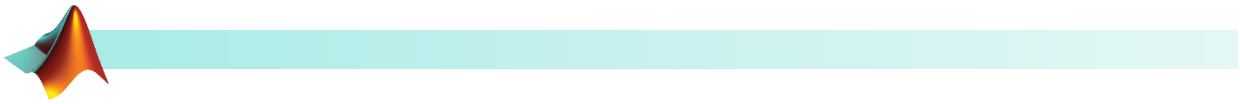
3 GUIDELINES

This section provides essential instructions to help you understand and effectively use this manual.
This manual presents an open-loop system designed to simulate patients undergoing general anesthesia. The simulator has been developed using **MATLAB R2022a (version 9.12)**.

In the manual, we introduce a main program ***'MAIN_PROGRAM_AMICAS.m'*** that integrates several subprograms. Key components are visually highlighted for clarity:

- **Main program code**: Highlighted in yellow and in:

- **Subprograms**: Highlighted in blue.



Key features of the manual include:

- **Modifiable sections**: Areas of the program where users can make adjustments are clearly marked with this specific symbol. 

- **Detailed code reference**: Each code line relevant to specific details is highlighted immediately after the corresponding section subtitle, making it easy to locate or modify the necessary components.

The main program includes default parameters, which are sufficient for running simulations and generating results directly in MATLAB. If you wish to modify any of these parameters, you can do so within the main program code. The main changes are summarized on **pages 7** and **8**.

Note: There is no need to make changes in the Simulink model, as all modifications can be handled directly in the main program.

The following sections will guide you through the steps necessary to adjust these parameters, you should choose to customize the simulation. After making any adjustments, you can simply rerun the MATLAB script to obtain updated results based on your modifications.

4 Simulator Usage Summary

This section gives you **a summary** to obtain an open-loop system simulation results using the simulator. The simulator presents flexibilities about patient databases, surface response models etc. All these flexibilities are located in the main program file ***'MAIN_PROGRAM_AMICAS.m'.*** The changes that you can make in the file are summarized as follows:

- **Step 1: Choose your database**

In the simulator, there exist two different patient databases, i.e. 12 patient database, 24 patient database. 12 patient database is selected as default.

To choose a database, go to Line 18 in Main Program and set:

- `database_type=1` for 12 patient database
- `database_type=2` for 24 patient database

- **Step 2: Specify the simulation time**

You can also specify the simulation time. The default simulation time is selected as 300 min in our simulator (Tsim = 300).

If you want to change the simulation time, please go to Line 23 in Main Program.

- **Step 3: Choose your inputs**

You can specify the amount of drugs, Propofol, Remifentanil, Atracurium, Dopamine, and SNP using the following ranges.

Propofol infusion rate	`(0, 2.50) [mg/kg/min]`
Remifentanil infusion rate	`(0, 4.00) [ug/kg/min]`
Atracurium infusion rate	`(0, 29.50) [ug/kg/min]`
Dopamine infusion rate	`(0, 20 ) [ug/kg/min]`
SNP infusion rate	`(0, 10 ) [ug/kg/min]`

For this aim, please change the values in Line 26-30. The default value of propofol are selected as 0.2 mg/kg/min, the others are set to 0.

- **Step 4: Choose your response surface model**

The simulator consists of three types of response surface models (Greco, Minto and Reduced Greco). The default type is Greco surface model.
Please, go to Line 35 to change the type of surface model. Please assign:

- `RSM_type = 1` for Greco
- `RSM_type = 2` for Minto
- `RSM_type = 3` for Reduce Greco model.

- **Step 5: Choose anesthesiologist in the loop**

Simulator has anesthesiologist in the loop option. The default case is no anesthesiologist in the loop (Line 41), set:

- `Anest_loop = 1` for no anesthesiologist in the loop
- `Anest_loop = 2` for the anesthesiologist in the loop

(Note: It is for the closed-loop control)

- **Step 6: Choose patient(s)**

The program includes for loop (starting from Line 45). When you run the main program, you will see the simulation result for the first patient in the selected database (for index = 1:1).
If you want to see the results of all patients in the selected database, you need to set *`for index = 1:noOfPatients`*. *(*Line 45 in Main Program*)*. Moreover, you may see the result of the specific patient, e.g. set *`for index = 3:3`* for the third patient.

5 How to Use it

Content

- This user manual (PDF)
- 1 Simulink Model
- 11 Matlab Codes
- 2 Patient databases
- 1 folder that contains 3 of our works

5.1. Simulink File

The Simulink file *'Simulator AMICAS_M2022a.slx'* is compatible with MATLAB 2022a and later versions. If you are using an earlier version of MATLAB, you will need to convert the file to a compatible format.

When you **open** the Simulink file *'Simulator AMICAS_M2022a.slx'*, you will see:

- 5 inputs (Propofol, Remifentanil, Dopamine, Sodium Nitroprusside, Atracurium).
- 5 outputs (BIS, RASS, CO, MAP, NMB).

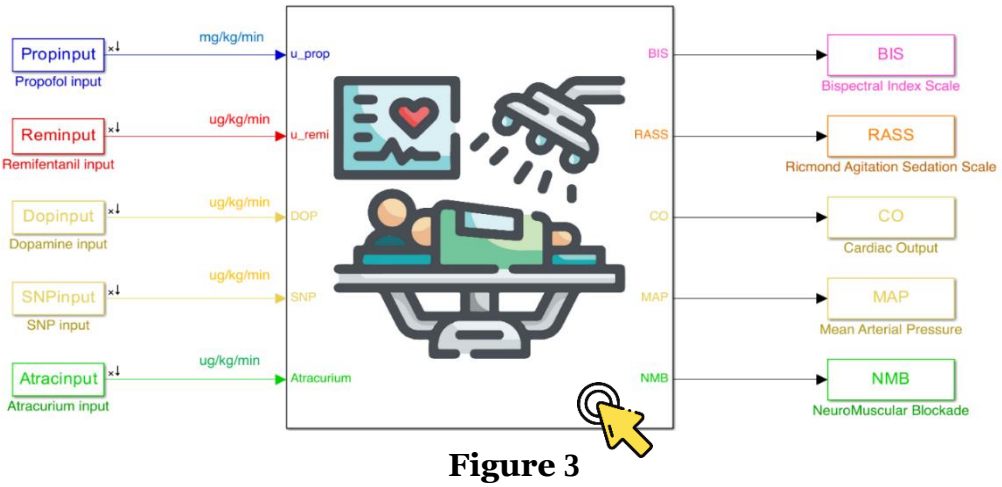


Figure 3

When you **double-click** on the mask in Figure 3, you will see 5 modules in Figure 4:

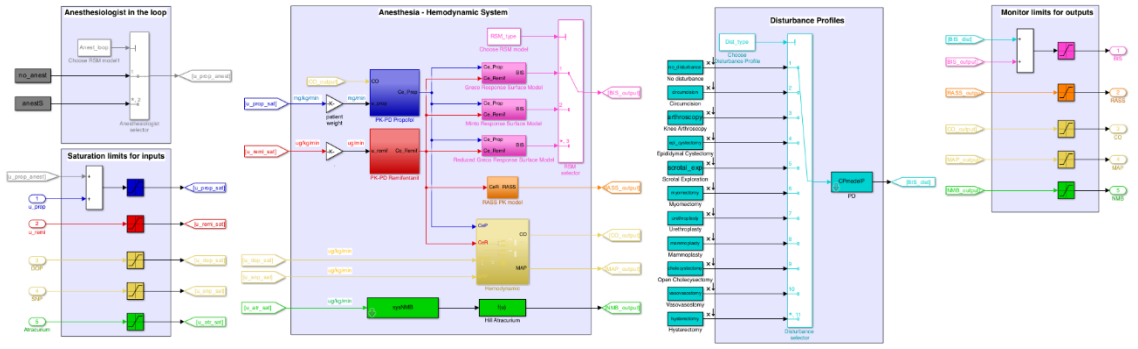


Figure 4

Each block scheme will be detailed alongside the main program which is introduced in the next section.

5.2. Main Program

The Main program *MAIN_PROGRAM_AMICAS.m* presents flexibilities about patient databases, surface response models, etc. The changes that you can make will be introduced in this section.

In general, this code is divided into subsections, which will be explained individually. Overall the subsections are:

• Variable Initialization in	`%% variable initialization`	Line 7
• Patient databases in	`%% Choose patient database`	Line 17
• Simulation Time in	`%% Choose simulation time (min)`	Line 22
• Drugs input values in	`%% Choose input values`	Line 25
• Surface models in	`%% Choose surface model type`	Line 34
• Anesthesiologist in the loop in	`%% Choose anesthesiologist in loop`	Line 40
• The simulation loop in	`%% run simulation for every patient`	Line 43
• Plotting the results in	`%% Results`	Line 63

5.2.1. Variable Initialisation

Line 7 in the subsection `%% variable initialization` in the MAIN_PROGRAM_AMICAS

When you first open the code, you will see this window

MAIN_PROGRAM_AMICAS.m

```
1   % MAIN PROGRAM FOR BENCHMARK PATIENT SIMULATOR
2   % Ghent University, MAY 2024
3   % ERC AMICAS 2022-2027
4
5   clearvars; clear memory; close all; clc;
6
7   % variable initialization
8   BIS_all= []; RASS_all = []; CO_all = []; MAP_all = []; NMB_all = [];
9
10  Ts = 5/60; % sampling time 5 seconds (5/60 min)
11  ST = 0.1*Ts; % simulation step size
```

The 5 output variables (BIS, RASS, CO, MAP, and NMB) are defined and initialized in Line 8. The sampling time is set to 5 seconds, which is then converted to minutes (5/60) to match the patient model's parameters (which are defined in minutes).

Line 13 is % initialize patient independent models which include the hemodynamic models. The Matlab code in Line 15 includes the Anesthesiologist in the loop. For this matter, **"Anesthesiologist in the loop"** is explained after the hemodynamic model on the next page.

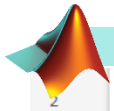
MAIN_PROGRAM_AMICAS.m

```
13  % initialize patient independent models
14  hemodyn_model_AMICAS      % hemodynamic models
15  dist_model_AMICAS         % disturbance models
16
```

5.2.2. Hemodynamic model

Line 14 in `% initialize patient independent models` in MAIN_PROGRAM_AMICAS.
`hemodyn_model_AMICAS.m` in the simulator Folder (Figure 2).
Hemodynamics block in Simulink "simulator_AMICAS_M2022a.slx".

The "`hemodyn_model_AMICAS.m`" is a Matlab code file that can be found in the folder from Figure 2.



hemodyn_model_AMICAS.m

```
1  %% Initialisation of hemodynamic models
2
3  %% Set basis MAP and CO
4  Cobasis = 5; MAPbasis = 80;
5
6  %% Interaction Prop to hemodynamic
7
8  %Interaction from Propofol to CO
9  k1Pco = 0.81; k0Pco = 0.81; E0Pco = 5; EmaxPco = 5; gainPco=10; gammaPco = 4.5; C50Pco = 8;
10
11 %Interaction model from Propofol to MAP
12 k1Pmap = 0.61; k0Pmap = 0.81; E0Pmap = 5; EmaxPmap = 5; gainPmap=15; gammaPmap = 4.5; C50Pmap = 6;
13
14 %% Interaction Remi to hemodynamic
15 %Interaction model from Remi to CO
16 k1Rco = 0.51; k0Rco = 0.51; E0Rco = 15; EmaxRco = 5; gainRco=10; gammaRco = 4.5; C50Rco = 12;
17
18 %Interaction model from Remi to MAP
19 k1Rmap = 0.31; k0Rmap = 0.31; E0Rmap = 70; EmaxRmap = 70; gainRmap=10; gammaRmap = 4.5; C50Rmap = 17;
20
21 %% Hemodynamic model for a nominal patient
22 K11 = 5; tau11 = 300; T11 = 60; K21 = 12; tau21 = 150; T21 = 50; %dopamine
23 K12 = 3; tau12 = 40; T12 = 60; K22 = -15; tau22 = 40; T22 = 50; %snp
24
25 s = tf('s');
26 g11 = ((K11)/(1+tau11*s))*(1)/(1+T11*s+(T11*s)^2/2+(T11*s)^3/6 + (T11*s)^4/24);
27 g12 = ((K12)/(1+tau12*s))*(1)/(1+T12*s+(T12*s)^2/2+(T12*s)^3/6 + (T12*s)^4/24);
28 g21 = ((K21)/(1+tau21*s))*(1)/(1+T21*s+(T21*s)^2/2+(T21*s)^3/6 + (T21*s)^4/24);
29 g22 = ((K22)/(1+tau22*s))*(1)/(1+T22*s+(T22*s)^2/2+(T22*s)^3/6 + (T22*s)^4/24);
```

The effect of the Anesthesia model on the hemodynamic system (Cardiac output and Mean Arterial Pressure) is represented in lines 6 to 12 and lines 14 to 19 for Propofol and Remifentanil respectively. Lines 21 to 29 represent the transfer functions of the hemodynamic MIMO model (Dopamine and SNP as inputs, CO and MAP as output) introduced in [1]

Those can be found in ***"Simulator AMICAS_M2022a.slx"*** in the ***Anesthesia – Hemodynamic*** block (see Figure 4).

To see the implementation of those equations, follow the steps:

- **Double-click** on the patient mask (Figure 5)

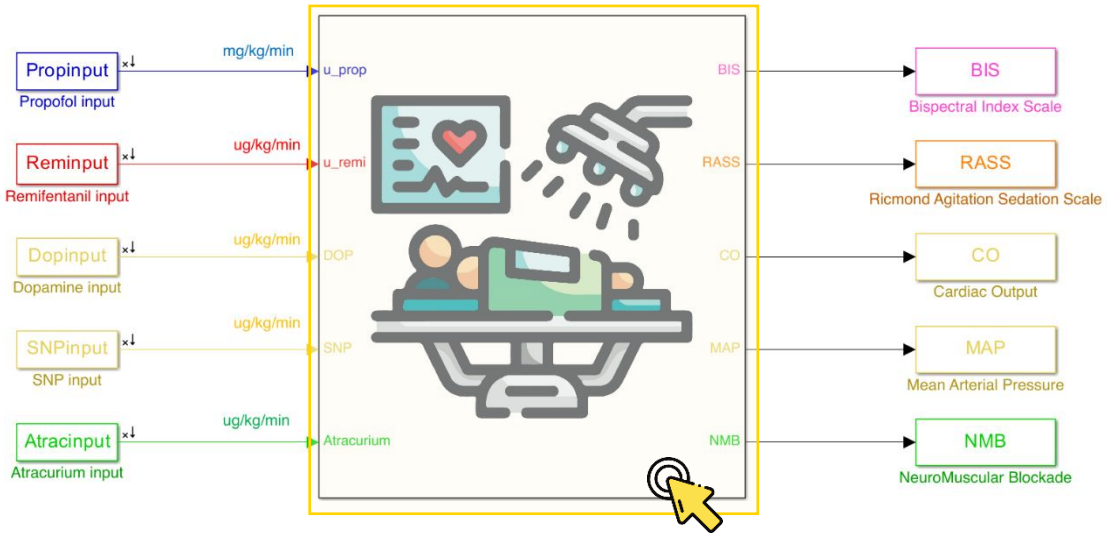


Figure 5

- **Double-click** on the hemodynamic block (Figure 6)

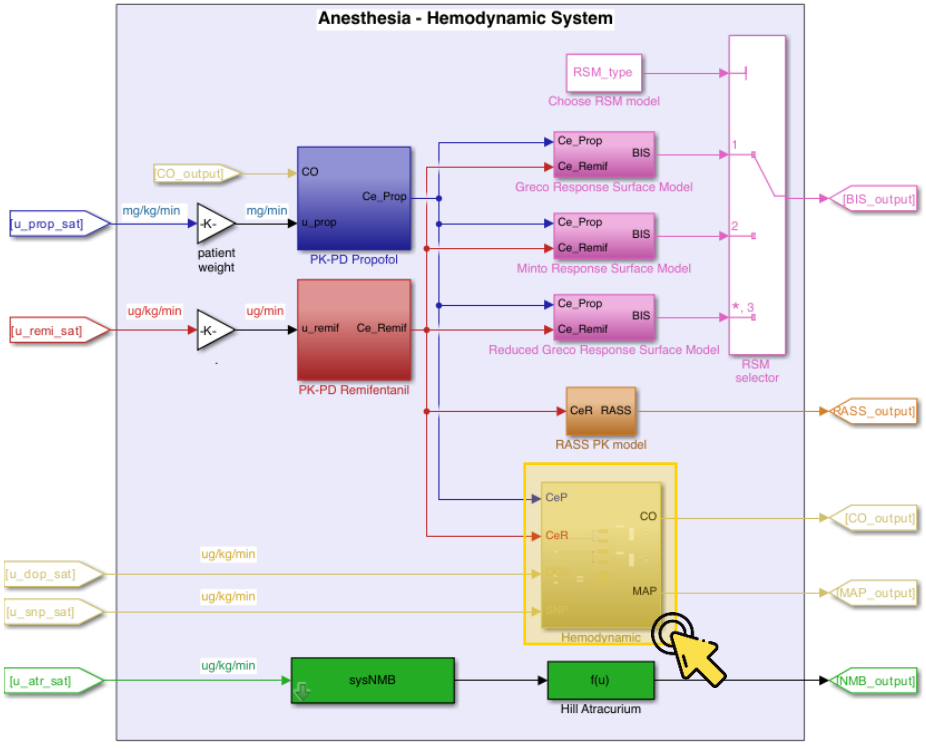


Figure 6

- **Double-click** on DOP - SNP Block (Figure 7)

Note: The values from the lines 6 to 20 are visible in the top part of this block (Figure7)

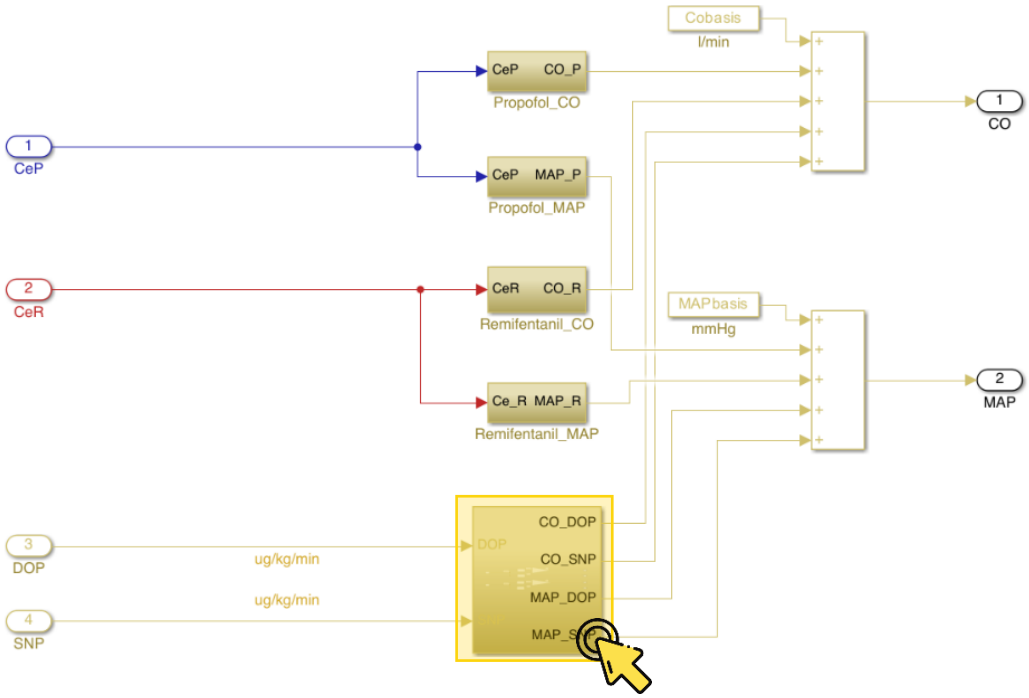


Figure 7

- The transfer function from the lines 27 to 30 is then visible (Figure 8)

Figure 8

The effect of cardiac output (CO) on the BIS signal has recently been added to the simulator as shown in Figure 9.

According to the study referenced as [1], a 20% decrease in cardiac output results in a 12.1% reduction in the clearance rate in the central compartment for adults. The impact of this change in clearance rate on the effect site concentration (Cep) has been calculated and is subsequently modeled using a first-order transfer function as shown in Figure 11.

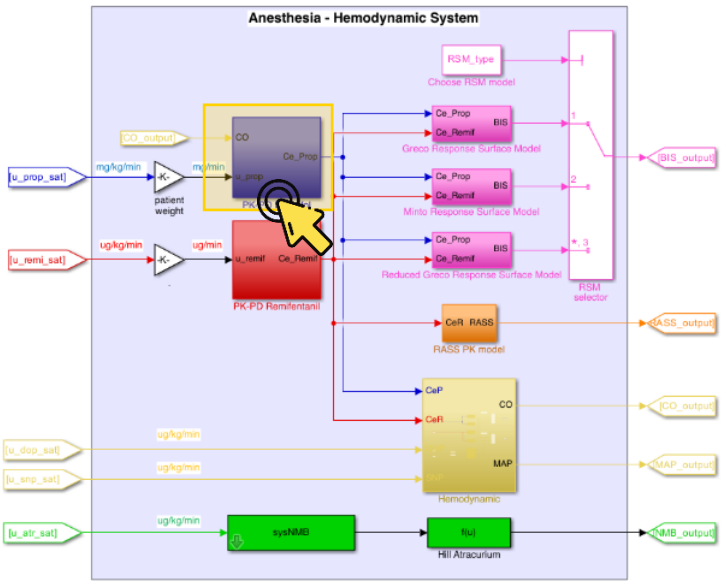


Figure 9

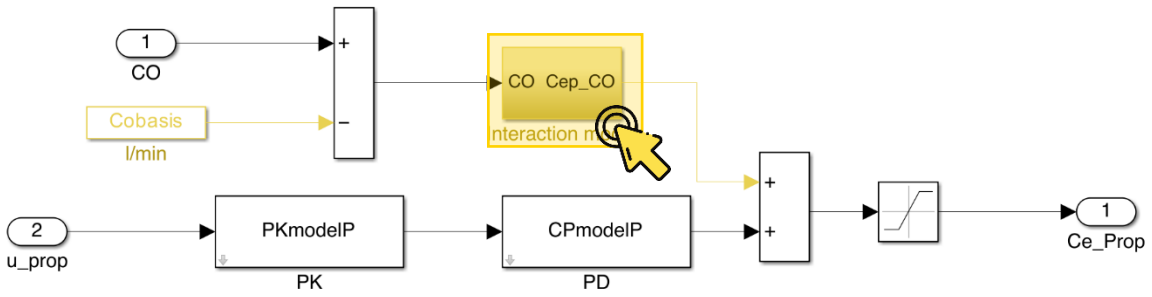


Figure 10

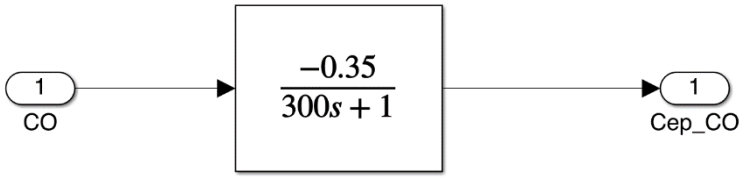


Figure 11

5.2.3. Anesthesiologist in the loop

Line 40 in the subsection `%% Choose anesthesiologist in the loop` in the Main Program
Lines 105 to 111 in the Matlab code `dist_model_AMICAS.m` in the simulator Folder (Figure 2)
Anesthesiologist in the loop Block in Simulink "simulator_AMICAS_M2022a.slx"

Lines 105 to 111 of the **"`dist_model_AMICAS.m`"** code pertain to the "`Anesthesiologist in the loop`". These lines represent a disturbance in the form of "**boluses**" that an anesthesiologist can administer during surgery.

When designing a controller, it is important to remember that while the algorithm operates autonomously, the anesthesiologist retains control and can intervene when necessary. This intervention is crucial, particularly when the anesthesiologist anticipates situations that the algorithm might not handle effectively. This latter might administer an additional **bolus** of the anesthetic drug if they foresee an increase in surgical stress that could disrupt the patient's hypnotic state.

This behavior is implemented in Simulink within the block labeled ***Anesthesiologist in the loop*** as shown in Figure 13. More details can be found in [2]

Note that you don't need to change anything in the "**Anesthesiologist in the loop**" section of the Simulink file. The selector will automatically update when you modify **`Anest_loop`** in the main program.

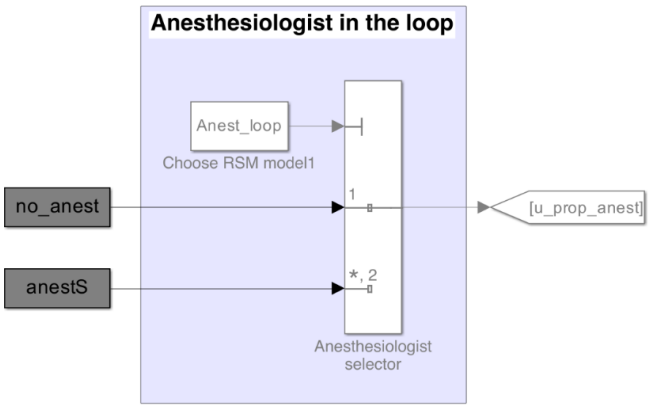


Figure 13

MAIN_PROGRAM_AMICAS.m

```
40
41  %% Choose anesthesiologist in loop or not -> Anest_loop = 1 / Anest_loop = 2
42  Anest_loop = 1;
```

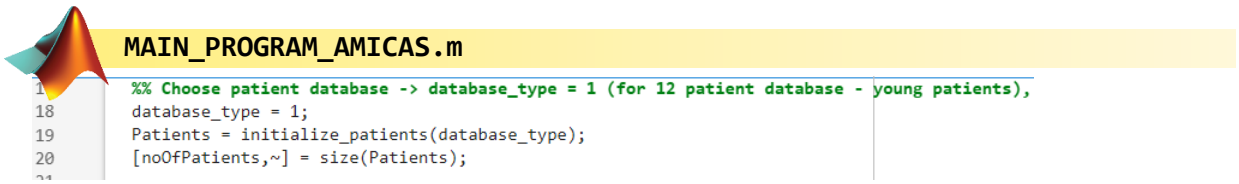
To add this effect to the simulation, go to line 41

- `Anest_loop = 1` The anesthesiologist **does not** affect the system
- `Anest_loop = 2` The anesthesiologist affects the system

5.2.4. Patients databases

Line 17 in the subsection `%% Choose patient database` in the MAIN_PROGRAM_AMICAS Matlab Data "patient_database12"" and "patient_database24" in the simulator Folder (Figure 2) `initialize_patients.m, Patient.m` in the simulator Folder (Figure 2)

Lines 17 to 20 of the code **MAIN_PROGRAM_AMICAS.m** introduces our patient's databases:



In this simulator, there are two different patient databases

- 12 patient database which was published in [3]
- 24-patient database, published in [4]

In Line 18, **"database_type"** helps you select which database you want to use, please select:

- `database_type = 1` for 12 patient database.
- `database_type = 2` for 24 patient database.

The databases are found in the downloaded folder (Figure 2). The lines of the matrix represent the patients, and the columns their respective biometrics:

- Column 1 is the age
- Column 2 is the height
- Column 3 is the weight
- Column 4 is the sex

Those biometrics (Columns) are assigned in **"initialize_patients.m"**, which also can be found in the folder (Figure 2).

In Line 19, **Patients= initialize_patients(database_type)** takes the values of that matrix (the database) and assigns each column to its specific biometric:

initialize_patients.m

```
1  function Patients = initialize_patients(database_type)
2      if database_type == 1
3          load patient_database12.mat % change here for other patient database
4      else
5          load patient_database24.mat
6      end
7
8      Patients = [];
9      for i = 1 : size(patients,1)
10         age = patients(i,1);
11         height = patients(i,2);
12         weight = patients(i,3);
13         sex = patients(i,4);
14
15         Patients = [Patients; Patient(i, age, height, weight, sex)];
16     end
17 end
```

In "`initialize_patients.m`", line 15 takes the biometrics of the patients and then uses the Matlab code "`patient.m`" (also found in the simulator Folder) where it is used to save all the patient metrics into one matrix as shown below:

patient.m

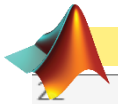
```
1  classdef Patient
2      properties (SetAccess = immutable)
3          id
4          age     % years
5          height  % cm
6          weight  % kg
7          sex     % 1 - male, 2 - female
8          bmi
9          lbm
10     end
11
12     methods
13         function obj = Patient(id, age, height, weight, sex)
14             obj.id = id;
15             obj.age = age;
16             obj.height = height;
17             obj.weight = weight;
18             obj.sex = sex;
19             obj.bmi = weight / ((height/100)^2);
20
21             switch sex
22                 case 1
23                     obj.lbm = 1.1 * weight - 128 * (weight/height)^2; % James Formula for Men
24                 case 2
25                     obj.lbm = 1.07 * weight - 148 * (weight/height)^2; % James Formula for Women
26                 otherwise
27                     disp('Error: undefined gender. You may consider defining new values in Patient.m class')
28             end
29         end
30     end
31 end
```

Line 19 from the above code calculates the BMI (body mass index) and lines 21 to 27 calculate the LBM of each patient. These variables are necessary to calculate the PK model of each patient.
In Line 20 from the main code, **`[noOfPatients,~] = size(Patients)`** extracts the number of patients. This value (**`noOfPatients`**) is then used in a "for loop" to simulate all patients.

5.2.5. Simulation time

Line 23 in the subsection `%% Choose simulation time` in MAIN_PROGRAM_AMICAS

In Line 23, you can select the simulation time (in minutes), according to the duration of the induction and maintenance phases.



MAIN_PROGRAM_AMICAS.m

```
%% Choose simulation time (min) - See user manual
Tsim = 300;
```

The induction phase is the initial stage of anesthesia, during which the patient is transitioned from a conscious state to an unconscious state suitable for surgery. This phase typically lasts between 3 to 5 minutes and serves as a good reference to assess the performance of your designed controller. Ideally, the controller should reach a steady state within this period. You can extend the simulation time (**more than 5 minutes**) to allow the system to stabilize before entering **the maintenance phase**

The maintenance phase is the period during surgery when the anesthetized patient is kept at a consistent level, ensuring they remain unconscious, pain-free, and stable. During this phase, disturbance stimuli begin to take effect. The duration of the simulation will vary depending on the type of surgery chosen. For specific simulation times, refer to the file "**`dist_model_AMICAS.m`**."

In summary, $\mathbf{T_{sim} = T_{induction} + T_{maintenance}}$.

5.2.6. Drug Input

Line 25 in the subsection `%% Choose input values` in the MAIN_PROGRAM_AMICAS

The default value of Propofol is selected as 0.2 mg/kg/min, the others are set to 0.

```
25  %% Choose input values
26  Propofol = 0.2;       % [mg/kg/min]
27  Remifentanil = 0;     % [ug/kg/min]
28  Atracurium = 0;       % [ug/kg/min]
29  Dopamine = 0;         % [ug/kg/min]
30  SNP = 0;              % [ug/kg/min]
31
32  initialize_inputs;
33
```

You can change the amount of drugs: Propofol, Remifentanil, Atracurium, Dopamine, and SNP. However, keep in mind the following ranges (IR= Infusion Rate).

Please see **Appendix B** more information about input ranges.

Propofol IR	(0, 2.50) [mg/kg/min]	Dopamine IR	(0, 20) [ug/kg/min]
Remifentanil IR	(0, 4.00) [ug/kg/min]	SNP IR	(0, 10) [ug/kg/min]
Atracurium IR	(0, 29.50) [ug/kg/min]		

According to this table, you can change the values in Line 26 to 30. These values are then exported to the Simulink as shown in Figure 14:

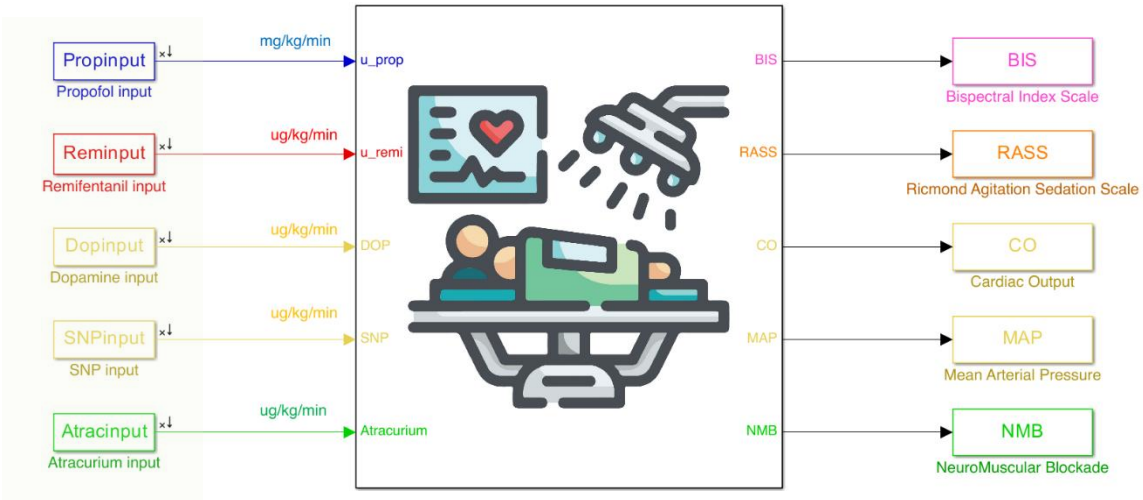


Figure 14

The infusion rate ranges mentioned previously are implemented in the Simulink ***"Simulator AMICAS_M2022a.slx"*** in the ***Saturation limits for inputs*** block as shown in Figure 15.

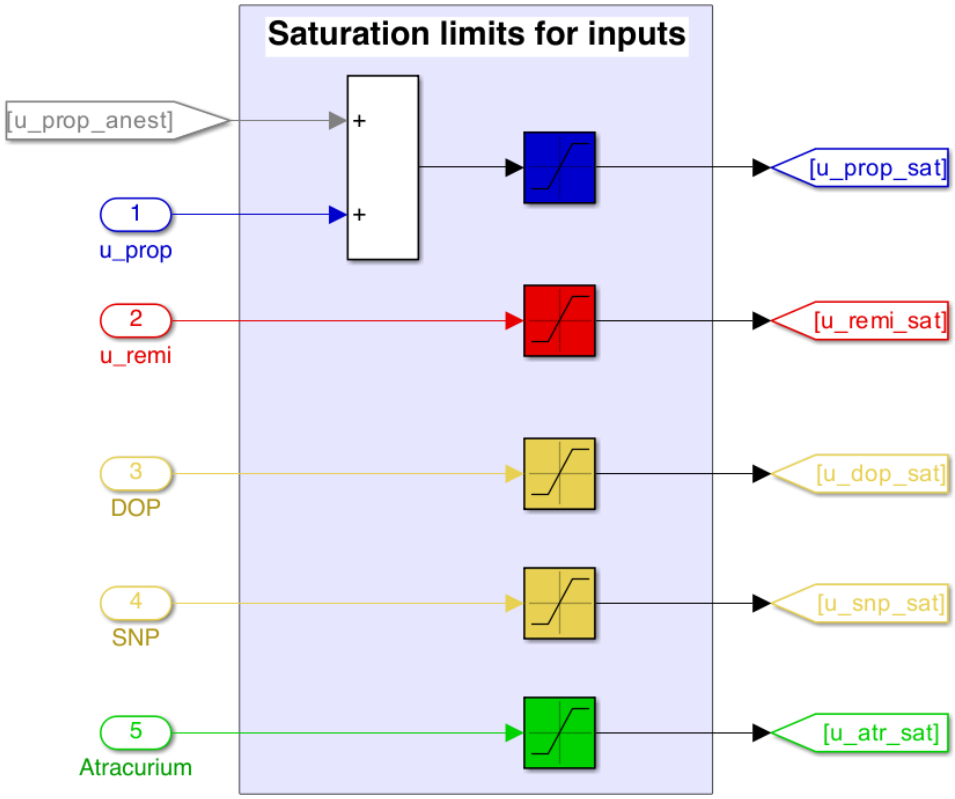


Figure 15

If you want to change the range for a specific drug (or multiple drugs), you can do so by adjusting the values in the corresponding saturation block for that drug.

For example, **double-click** on the blue saturation box to change the range of Propofol input.

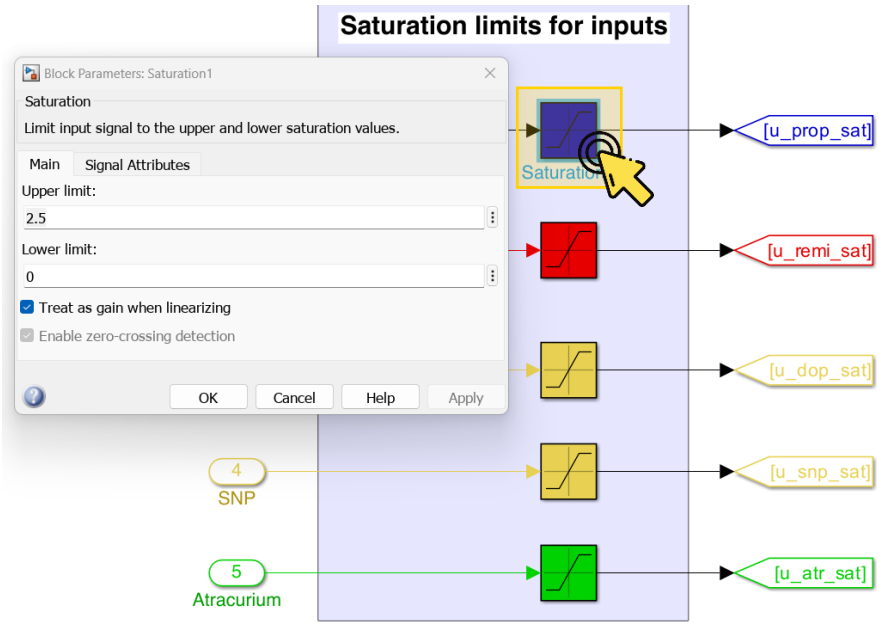


Figure 16

5.2.7. Surface Models

Line 35 in the subsection `%% Choose surface model type` in the Main Program "anesthesia_model_AMICAS.m" Matlab code in the simulator Folder (Figure 2) ***RMS sector*** in the Simulink "simulator_AMICAS_M2022a.slx"

The simulator consists of three types of response surface models: Greco, Minto, and Reduced Greco. The default type is the Greco surface model

In anesthesia, selecting the appropriate response surface model depends on the expected interaction between the drugs being administered.

- **Greco model** is typically used when anesthetic drugs are presumed to have additive effects, where each drug independently contributes to the overall anesthesia depth without significant interaction.
- **Minto model** is preferred in situations where there is potential for complex interactions, such as when combining anesthetics and neuromuscular blockers, where the drugs might interact synergistically or antagonistically, leading to effects that are not simply additive.
- **Reduced Greco model** is used when data are limited or when a simpler, more computationally efficient approach is needed, still assuming additive effects but with fewer parameters, making it useful in settings with limited patient data or when a rapid assessment is necessary.

For more information about those surface models, please refer to [5]

The model parameters of the Greco, Minto, and Reduced Greco models are found in `anesthesia_model_AMICAS.m` in the simulator Folder (Figure 2). (the other lines of this Matlab code will be explained in the Simulation loop section)

anesthesia_model_AMICAS.m

```
%% Hill Functions for Propofol and Remifentanil
% Hill function params from Surface Model paper Erhan

% Minto Model parameters
E0_M = 93.97;
Emax_M = E0_M;
C50P_M = 7.53;
C50R_M = 160.25;
beta_M = 10.74;
gamma_M = 4.13;

% Greco Model parameters
E0_G = 93.97;
Emax_G = E0_G;
C50P_G = 7.66;
C50R_G = 149.62;
gamma_G = 4.07;
alpha_G = 15.03;

% Reduced Greco Model parameters
E0_RG = 93.97;
Emax_RG = E0_RG;
C50P_RG = 8.26;
gamma_RG = 3.59;
alpha_RG = 0.33;
```

To select a specific model, go to Line 35 and put:

- `RSM_type = 1` for Greco surface model (Default model)
- `RSM_type = 2` for Minto surface model
- `RSM_type = 3` for reduced Greco surface model

MAIN_PROGRAM_AMICAS.m

```
%% Choose surface model type ->  RSM_type=1 (for Greco) / RSM_type=2 (for Minto) / RSM_type=3 (for Reduced Greco)
RSM_type = 1;
```

Those surface models are also introduced in Simulink as it is shown in Figure 17

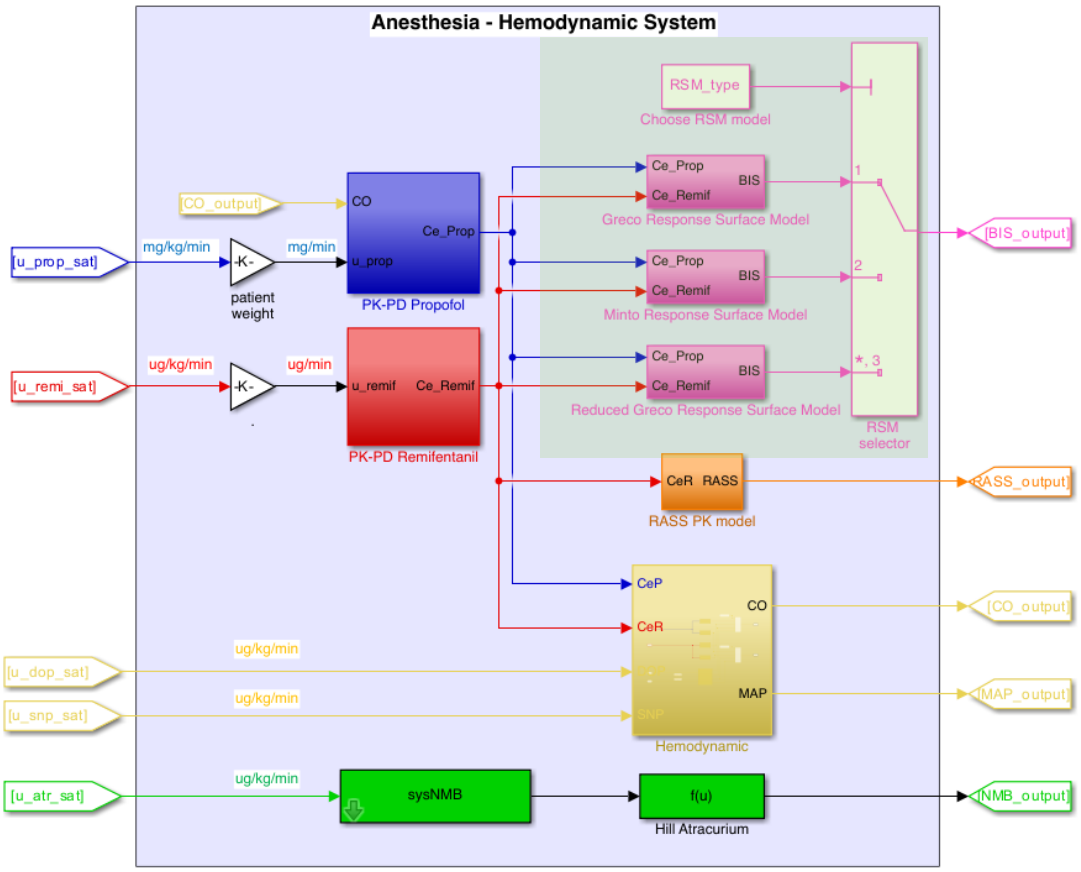


Figure 17

If you reached here and you are looking for an explanation for these 2 subsections, please go back to the first pages. They were explained after the initialization section.

MAIN_PROGRAM_AMICAS.m

```
Dist_type = 1;

%% Choose anesthesiologist in loop or not -> Anest_loop = 1 / Anest_loop = 2
Anest_loop = 1;
```

5.2.8. Open-loop Simulation – Model of the patients

Line 43 in the subsection `%% run simulation for every patient` in the Main Program "`SchniderModel.m`", "`MintoModel.m`", and "`anesthesia_model_AMICAS.m`" in the Folder ***Anesthesia-Hemodynamics*** Block in Simulink "simulator_AMICAS_M2022a.slx"

After finishing everything above, it is now time to start the simulation for our patients. When you run the main program, you will see the simulation result for the first patient in the selected database because the for loop in Line 45 is set to **index = 1:1**. See below the simulation result for the default case:

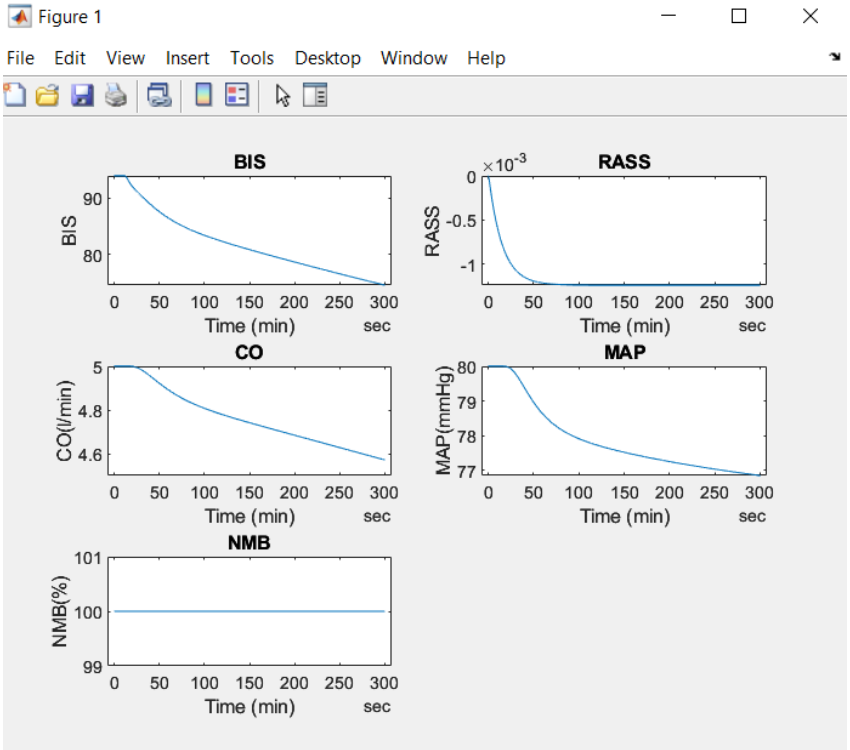


Figure 18

If you want to see the results of all patients in the selected database, change the loop to **index = 1 : noOfPatients**. Naturally, you can simulate and see the results for a specific patient (e.g. set for index = 3:3 for the third patient)

MAIN_PROGRAM_AMICAS.m

```
44
45  for index = 1 : 1 %noOfPatients
46      patient = Patients(index);
47
48      % Initialise patient dependent model
49      anesthesia_model_AMICAS   % anesthetic models
50
51      % run simulation
52      sim('simulator_AMICAS_M2022a.slx');
53
54      % save variables
55      BIS_all = [BIS_all, BIS];
56      RASS_all = [RASS_all, RASS];
57      CO_all = [CO_all, CO];
58      MAP_all = [MAP_all, MAP];
59      NMB_all = [NMB_all, NMB];
60
61  end
62
```

Line 46 extracts the biometrics values of each patient (according to their index) which will be used to calculate the parameter of the anesthesia PK-PD models.

In this simulator, the PK-PD models are the Schnider and Minto for Propofol and Remifentanil respectively, and are defined in Matlab codes "`SchniderModel.m`" and "`MintoModel.m`". The aforementioned Matlab codes are used in "**`anesthesia_model_AMICAS.m`**" which is presented in Line 49.

anesthesia_model_AMICAS.m

```
1  %% Propofol
2  [PKmodelP, CPmodelP] = SchniderModel(patient);
3
4  %% Remifentanil
5  [PKmodelR, CPmodelR] = MintoModel(patient);
6
```

For more information about these models, please refer to [1].

The effect of the drugs is calculated in "**`anesthesia_model_AMICAS.m`**" in lines 7 to 32 for BIS, lines 33 to 39 for RASS, and in lines 40 to 44 for NMB.

All the parameters are then sent into the simulator in Line 52 of the main program. The output variables are saved in lines 55 to 59.

Finally, the results are plotted with the final section in Line 63.

MAIN_PROGRAM_AMICAS.m

```
64  %% Results - use plotValues(signal, type, safetyLimits - bool, showLegend - bool)
65
66  figure;
67  subplot(3,2,1)
68  plotValues(BIS_all, OutputSignalType.BIS, false, false);
69  subplot(3,2,2)
70  plotValues(RASS_all, OutputSignalType.RASS, false, false);
71  subplot(3,2,3)
72  plotValues(CO_all, OutputSignalType.CO, false, false);
73  subplot(3,2,4)
74  plotValues(MAP_all, OutputSignalType.MAP, false, false);
75  subplot(3,2,5)
76  plotValues(NMB_all, OutputSignalType.NMB, false, false);
```

6 Example Study case

The default case given in the previous section:

Step 1: 12 patient database (Line 18 in main program)
Step 2: simulation time of 300 min (Line 23 in main program).
Step 3: Inputs: Propofol are selected as 0.2 mg/kg/min,
the others are set to 0. (Line 26-30 in Main Program).
Step 4: Greco surface model (Line 35 in main program)
Step 5: No anesthesiologist in the loop (Line 41 in Main Program)
Step 6: Patient 1 in the selected database

When you run the main program 

with the previous settings, you will see the following Figure:

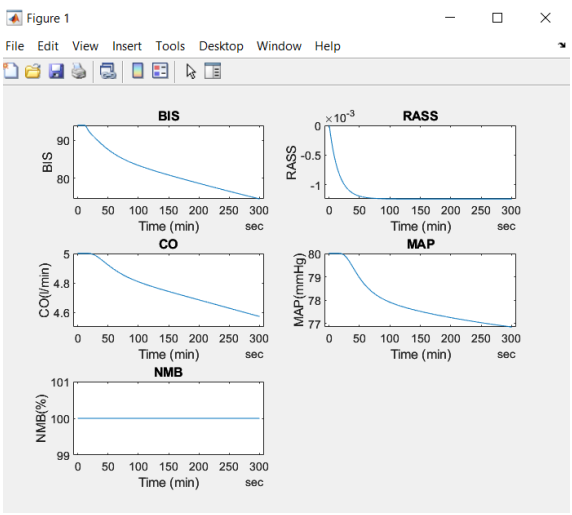


Figure 19

For patient 1

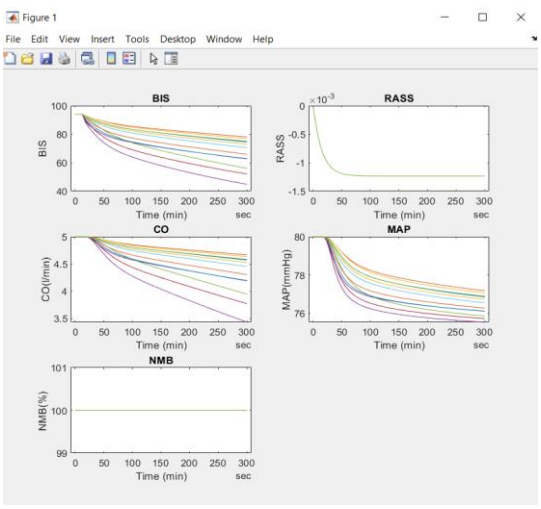


Figure 20

For all patients *for index = 1:NoOfPatient*. Line 45

In these figures, you will only see the effect of Propofol on outputs.
If you want to see the effect of Remifentanil. You need to go **Step 3**, then change Lines 26-30

```
Propofol        = 0  ;      % [mg/kg/min]
Remifentanil    = 0.5;      % [ug/kg/min]
Atracurium      = 0  ;      % [ug/kg/min]
Dopamine        = 0  ;      % [ug/kg/min]
SNP             = 0  ;      % [ug/kg/min]
```

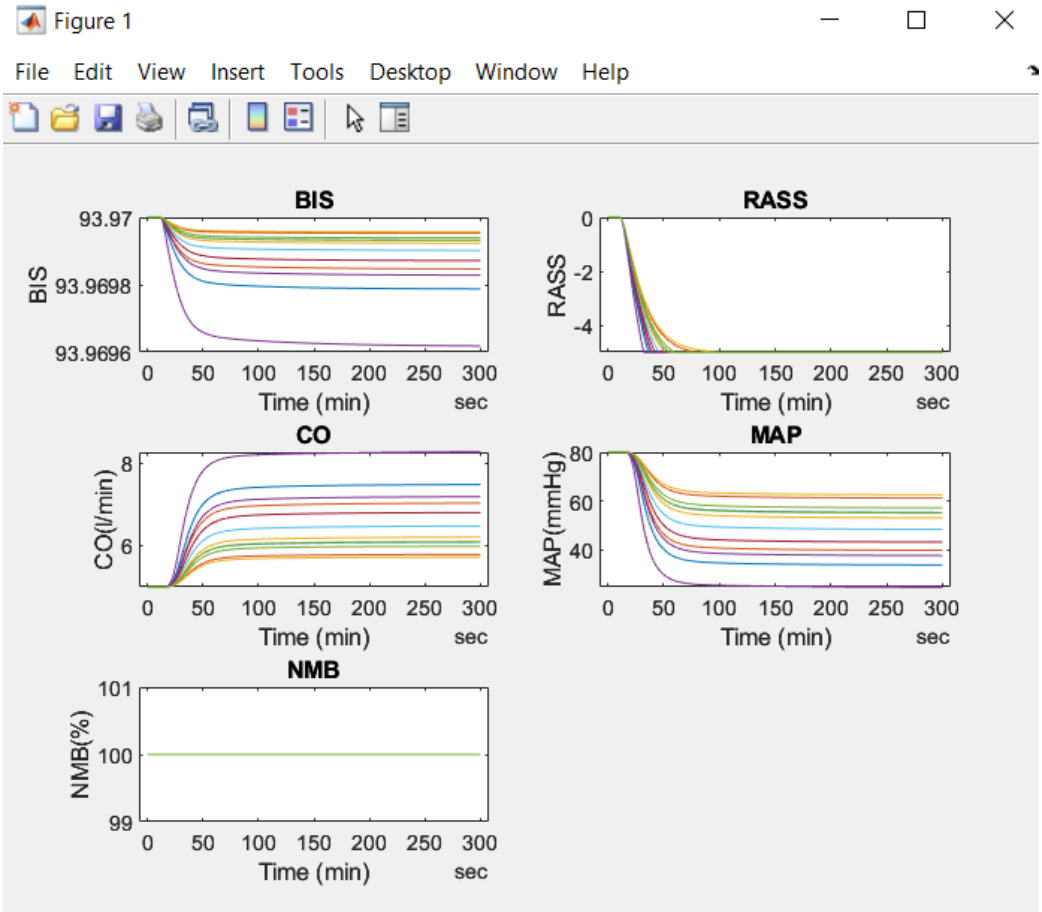


Figure 21

In this next example, the changes are:

- for 24 patients database (**Step 1**: change *database_type=2*. Line 18)
- Reduced Greco surface model (**Step 4**: put RSM_type = 3 Line 35)

The program will produce the following figure.

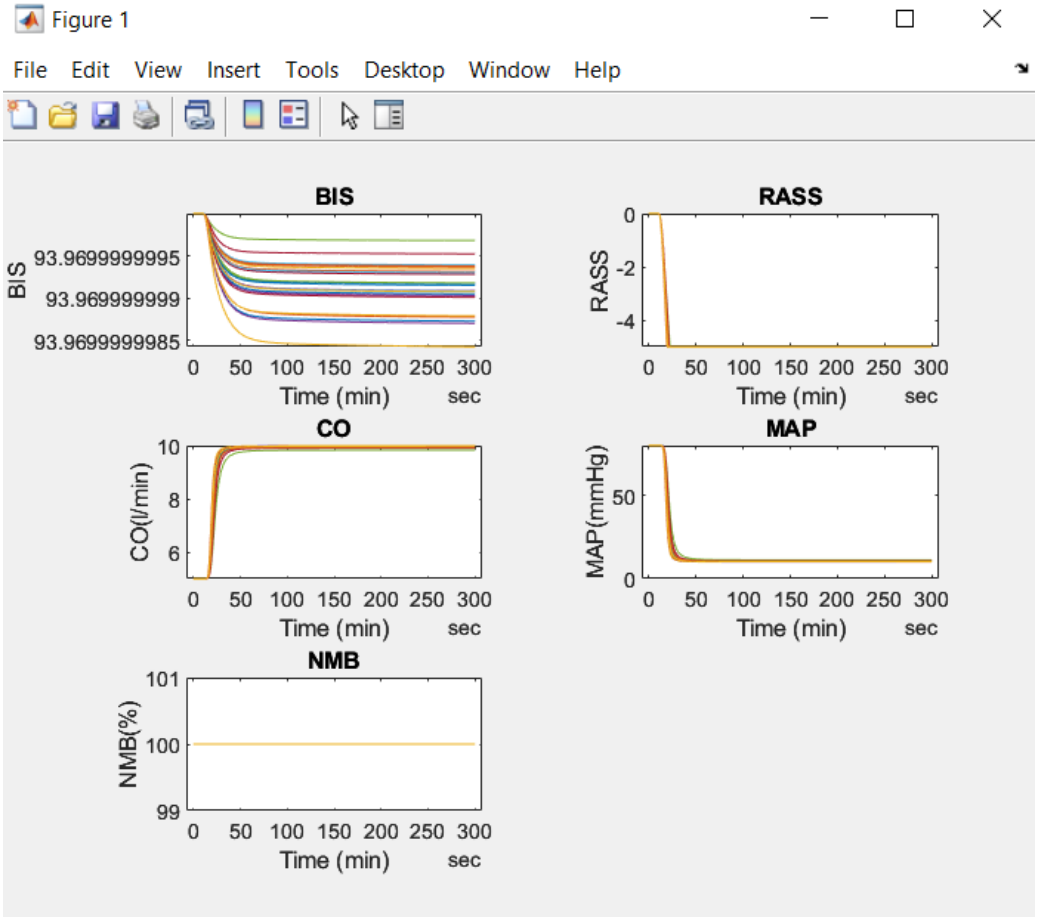


Figure 22

Appendix A.

A1. Understanding General Anesthesia

When a patient undergoes **general anesthesia**, they are placed into a controlled state of unconsciousness where they will not feel pain or have any memory of the procedure. This process is essential for performing surgical procedures without causing discomfort or distress. The anesthesia is typically administered either through inhalation of gases or by intravenous medications, which work together to suppress the central nervous system, including the brain and spinal cord. As a result, the patient will experience a complete loss of awareness, will not feel pain, and will have their muscles relaxed to facilitate the surgery. Throughout the procedure, an anesthesiologist or nurse anesthetist will continuously monitor the patient's vital signs to ensure their safety and adjust the anesthesia as needed to maintain the appropriate depth of unconsciousness [6].

A2. Hemodynamic stabilization

Hemodynamic stabilization is the process of ensuring that a patient's cardiovascular system is functioning optimally, particularly during critical situations such as surgery, trauma, or severe illness. This involves closely monitoring and managing key indicators like heart rate, blood pressure, and cardiac output to ensure that blood is being pumped effectively throughout the body, delivering oxygen and nutrients to vital organs. Achieving hemodynamic stability is crucial to prevent complications such as shock or organ failure. By maintaining stable hemodynamics, we ensure that the patient's organs receive the oxygen and nutrients they need to function properly, which is especially important during and after surgery [6].

A3. Key Components of Anesthesia and Hemodynamic Management

In the context of anesthesia and hemodynamic management during surgical procedures, it is essential to understand several critical components. Each plays a specific role in ensuring the patient remains safe and comfortable throughout the procedure.

A3.1 Hypnosis (Unconsciousness)

Hypnosis, in the medical sense, refers to the state of unconsciousness induced by anesthesia. During hypnosis, the patient is completely unaware of their surroundings and does not respond to any external stimuli. This state is crucial during surgery to ensure that the patient remains unconscious and unaware, preventing any psychological or physical distress. Anesthetics are carefully administered to maintain this state until the procedure is completed.

A3.2. Analgesia (Absence of Nociception)

Analgesia refers to the absence of nociception, which is the body's response to potentially harmful stimuli, commonly perceived as pain. During surgery, analgesia is achieved through the administration of anesthetic agents that block pain signals from reaching the brain. This ensures that the patient does not experience pain during the procedure, contributing to their comfort and overall safety.

A3.3. Neuromuscular Blockade (No Movement)

Neuromuscular blockade involves the use of specific drugs to temporarily paralyze the muscles, preventing any voluntary or involuntary movement during surgery. This is particularly important in procedures where even slight movement could interfere with the surgical process. By blocking the communication between nerves and muscles, the patient remains completely still, allowing the surgical team to perform the procedure with precision.

A3.4. Cardiac Output (CO)

Cardiac output (CO) is a measure of the amount of blood the heart pumps per minute. It is a critical factor in maintaining adequate blood flow and oxygen delivery to the body's tissues. During surgery, it is essential to monitor and maintain an appropriate cardiac output to ensure that all organs, especially vital ones like the brain and kidneys, receive enough oxygen and nutrients. Anesthesia and other medications may affect cardiac output, so careful monitoring and adjustment are necessary to maintain stability.

A3.5. Mean Arterial Pressure (MAP)

Mean arterial pressure (MAP) is the average pressure in a patient's arteries during one cardiac cycle and is a key indicator of overall blood flow and perfusion to the organs. Maintaining an appropriate MAP is crucial during surgery to ensure that all tissues receive sufficient blood supply. Anesthesiologists closely monitor MAP and may adjust medications to keep it within a safe range, preventing complications such as organ ischemia or damage [7,8,9].

A4. Key Medications Used in Anesthesia & Hemodynamic Management

In the administration of anesthesia and the management of hemodynamics during surgical procedures, several key medications are commonly used. Understanding the purpose and function of each can help ensure effective and safe patient care.

A4.1. Propofol

Propofol is a widely used intravenous anesthetic agent primarily responsible for inducing and maintaining hypnosis (unconsciousness) during surgery. It acts quickly, leading to a smooth and rapid onset of unconsciousness, making it ideal for initiating general anesthesia. Propofol is preferred due to its rapid recovery time, allowing patients to wake up quickly after the procedure is completed. It is important to monitor the patient closely when using Propofol, as it can lower blood pressure and reduce cardiac output.

A4.2. Remifentanil

Remifentanil is a potent, short-acting opioid analgesic used to provide analgesia (pain relief) during surgery. It is particularly effective in preventing the sensation of pain by blocking nociceptive signals. Remifentanil's rapid onset and quick clearance from the body make it ideal for use in procedures where precise control over pain relief is required. It is typically administered as a continuous infusion to maintain a consistent level of analgesia without lingering effects after the surgery.

A4.3. Atracurium

Atracurium is a neuromuscular blocking agent used to induce muscle relaxation, preventing any movement during surgery. It works by blocking the transmission of nerve impulses to the muscles, leading to temporary paralysis. Atracurium is commonly used in procedures that require complete stillness, such as delicate surgeries or those involving the chest or abdomen. Its effects are reversible, meaning that once the surgery is completed, the patient's muscle function can be restored by administering reversal agents.

A4.4. Dopamine

Dopamine is a medication used to support and manage hemodynamics, particularly in situations where blood pressure or cardiac output needs to be increased. It works by stimulating dopamine receptors as well as alpha and beta-adrenergic receptors, which can enhance cardiac output, raise blood pressure, and improve blood flow to vital organs. Dopamine is often used in critically ill patients or during surgery to stabilize cardiovascular function and ensure that organs receive adequate blood supply.

A4.5. Sodium Nitroprusside (SNP)

Sodium Nitroprusside (SNP) is a potent vasodilator used to rapidly lower blood pressure by relaxing the smooth muscles of blood vessels. It is particularly useful in situations where quick control of blood pressure is required, such as in hypertensive crises or during surgery when maintaining a precise blood pressure is critical. While effective, SNP requires careful monitoring, as its potent effects can lead to significant drops in blood pressure, which must be managed to avoid compromising blood flow to essential organs[10].

A5.Monitoring & Managing Clinical Events During General Anesthesia

Clinical events refer to any significant physiological changes or occurrences in a patient during general anesthesia that may require immediate attention or intervention. These events can include changes in heart rate, blood pressure, oxygen levels, or the onset of unexpected reactions such as allergic responses, arrhythmias, or adverse effects from medications.

Importance During General Anesthesia: During general anesthesia, it is crucial to continuously monitor the patient for any clinical events, as they provide critical information about the patient's physiological status. The anesthesiologist and surgical team rely on this information to maintain the patient's safety and to ensure the anesthesia is properly balanced. For example, a sudden drop in blood pressure might indicate that adjustments are needed in the administration of fluids or medications, while changes in oxygen saturation could signal respiratory issues that require immediate correction.

Why This Matters: Managing clinical events promptly and effectively is essential for preventing complications during surgery. By closely monitoring vital signs and responding quickly to any changes, the medical team can maintain hemodynamic stability, ensure adequate oxygen delivery to organs, and keep the patient safe throughout the procedure. The ability to anticipate and manage clinical events is a key aspect of delivering high-quality anesthesia care and optimizing patient outcomes [11].

A6. Understanding Pharmacokinetic and Pharmacodynamic (PK-PD) Variables in Anesthesia

A6.1 Pharmacokinetic (PK) and Pharmacodynamic (PD) variables are critical concepts that describe how drugs move through the body and how they affect the body, respectively. In the context of general anesthesia, these variables are essential for understanding and predicting how anesthetic agents will behave in a patient's system, which directly impacts the effectiveness and safety of anesthesia management.

PK refers to how the body absorbs, distributes, metabolizes, and eliminates a drug. Key PK variables include:

- **Absorption:** How quickly and efficiently the anesthetic enters the bloodstream.
- **Distribution:** How the anesthetic is distributed throughout the body's tissues and organs.
- **Metabolism:** How the body breaks down the anesthetic, usually in the liver.
- **Excretion:** How the anesthetic is removed from the body, typically through the kidneys.

A6.2. Pharmacodynamics (PD)

Pharmacodynamics involves how the drug affects the body, particularly the mechanisms of action and the relationship between drug concentration and its effects, such as sedation, pain relief, or muscle relaxation.

A6.3. Importance During General Anesthesia

Choosing the correct PK-PD model in an anesthesia simulator is crucial because it helps predict how different anesthetic drugs will behave in different patients, allowing for more precise dosing and timing. This is especially important when tailoring anesthesia to individual patients, who may vary in age, weight, organ function, or other physiological factors.

Why This Matters: The accuracy of an anesthesia simulator in mimicking real-life scenarios depends heavily on the selected PK-PD model. A well-chosen model ensures that the simulated drug effects closely match what would occur in a real patient, providing valuable insights into how to adjust dosages and combinations of anesthetic agents during surgery. This can improve the safety and efficacy of anesthesia management, reduce the risk of adverse effects, and enhance patient outcomes.
For example, using an appropriate PK-PD model helps predict how quickly a patient might wake up from anesthesia, how long they will remain pain-free after surgery, or how to avoid overdose or underdose. Therefore, understanding and applying the correct PK-PD models in an anesthesia simulator is a fundamental part of planning and delivering effective anesthesia care[12].

A7. Analyzing Intra- and Inter-Patient Variability in Anesthesia

Intra- and inter-patient variability refer to the differences in how the same patient (intra-patient) or different patients (inter-patient) respond to anesthetic drugs. Understanding and analyzing these variabilities is crucial during general anesthesia because they directly impact the effectiveness and safety of anesthetic management.

Intra-Patient Variability involves differences in how a single patient responds to anesthesia at different times or under different conditions. Factors such as changes in the patient's health status, hydration levels, stress, or concurrent medications can alter how the body processes and responds to anesthetic agents. For example, a patient may require different dosages of anesthesia for similar procedures on different days due to changes in their metabolic rate or organ function.

Inter-Patient Variability refers to the differences between patients in their responses to the same anesthetic drugs. These differences can be influenced by factors such as age, weight, gender, genetic makeup, underlying health conditions, and even lifestyle factors like smoking or alcohol use. For instance, elderly patients may metabolize drugs more slowly, requiring lower dosages, while younger, healthier individuals might metabolize drugs more quickly.

Importance During General Anesthesia

Analyzing intra- and inter-patient variability is vital during general anesthesia because it allows for the customization of anesthetic plans to suit each individual patient. This analysis ensures that the correct drug dosages are administered, minimizing the risk of over- or under-dosing, which can lead to complications such as prolonged recovery time, inadequate pain control, or even adverse drug reactions.

Why This Matters: When using an anesthesia simulator, choosing the correct patient model or database that accounts for intra- and inter-patient variability is essential for accurate simulation. A simulator that incorporates these variabilities can more accurately replicate real-life scenarios, providing insights into how different patients may respond to anesthetics. This helps anesthesiologists prepare for and manage a wide range of patient responses, ultimately leading to better patient outcomes.

For example, a simulator that accurately models variability can help predict how different patients might react to standard anesthetic protocols, allowing the anesthesiologist to adjust dosages or choose alternative drugs based on the simulated responses. This leads to more personalized and effective anesthesia care, reducing the likelihood of complications and improving overall patient safety[13].

A8. Understanding the Greco and Minto Models for Anesthesia Monitoring

Greco Model, **Minto Model**, and **Reduced Greco Model** are important models used to estimate the effects of anesthetic agents on a patient's level of consciousness. These models are integral to the use of the Bispectral Index (BIS) monitoring during general anesthesia. Choosing the appropriate model in an anesthesia simulator is crucial for accurate simulation and effective anesthesia management.

A8.1. Greco Model

The **Greco Model** is a mathematical model used to describe the relationship between the concentration of anesthetic agents in the brain and the level of sedation or unconsciousness. This model provides a detailed simulation of how various anesthetic drugs, such as propofol, affect the patient's state of consciousness. It incorporates complex pharmacokinetic and pharmacodynamic data to predict the impact of anesthesia on the BIS score, which reflects the depth of anesthesia.

A8.2. Minto Model

The **Minto Model** is another sophisticated model used to predict the effects of anesthetic agents on consciousness, particularly for drugs like propofol and remifentanil. This model builds on the Greco Model by incorporating additional factors and data to enhance accuracy, especially in varying patient demographics and conditions. The Minto Model helps in fine-tuning predictions of the BIS score by considering individual patient differences, improving the precision of anesthesia dosing and monitoring.

A8.3. Reduced Greco Model

The **Reduced Greco Model** simplifies the original Greco Model by focusing on key parameters and reducing complexity. It is designed to provide a more straightforward and faster computation for estimating anesthetic effects, making it particularly useful in real-time monitoring and situations where computational resources are limited. While less detailed than the full Greco Model, it still offers valuable insights into the patient's level of consciousness during anesthesia.

A8.4. Importance During General Anesthesia

Choosing the appropriate model for BIS monitoring in an anesthesia simulator is essential because each model offers different levels of detail and accuracy in predicting the effects of anesthesia. Here's why it matters:

- **Accuracy in Monitoring:** The right model helps simulate how anesthetic agents influence consciousness more accurately, allowing for better prediction of the BIS score, which is crucial for maintaining the appropriate depth of anesthesia.
- **Personalization:** Different models account for varying patient characteristics and conditions. By selecting the model that best fits the patient profile, anesthesiologists can tailor anesthesia management to individual needs, enhancing safety and effectiveness.
- **Efficiency:** The Reduced Greco Model offers a balance between detail and computational efficiency, which can be advantageous in real-time scenarios where quick adjustments are necessary.
- **Informed Decision-Making:** Accurate simulations using these models help anesthesiologists make informed decisions about drug dosing and adjustments, leading to improved patient outcomes and reduced risks of complications.

Why This Matters: Choosing the right PK-PD model or BIS monitoring model in an anesthesia simulator ensures that simulations closely reflect real-life scenarios, allowing anesthesiologists to practice and refine their skills in managing anesthesia. It helps in understanding how different drugs will affect consciousness and facilitates better planning and execution of anesthesia protocols [14].

A9. Choosing the Right PK-PD Models for Anesthesia Simulation

When using an anesthesia simulator, selecting the appropriate pharmacokinetic and pharmacodynamic (PK-PD) models for specific anesthetic agents, such as Propofol and Remifentanil, is crucial for accurate simulation and effective patient management. Two widely used models are the **Schnider Model for Propofol** and the **Minto Model for Remifentanil**.

A9.1. Schnider Model for Propofol

The **Schnider Model** is a well-established PK-PD model used to simulate the effects of Propofol, a commonly used intravenous anesthetic agent. This model provides detailed predictions of how Propofol behaves in the body, including its absorption, distribution, metabolism, and elimination. It incorporates data on how Propofol affects the depth of anesthesia and consciousness by modeling its interaction with brain receptors.

Importance of the Schnider Model:

- **Precision in Anesthesia Depth:** The Schnider Model helps predict the onset and duration of Propofol's effects on the patient's level of consciousness. This allows for accurate dosing and adjustment to maintain the desired depth of anesthesia.
- **Individual Variability:** By accounting for individual patient characteristics, such as age and weight, the Schnider Model enhances the personalization of anesthesia, leading to more effective and safer sedation.
- **Enhanced Simulation Accuracy:** Using the Schnider Model in an anesthesia simulator provides a realistic representation of Propofol's pharmacokinetics and dynamics, helping practitioners make informed decisions about dosing and monitoring during surgery.

A9.2. Minto Model for Remifentanil

The **Minto Model** is designed for simulating the effects of Remifentanil, a potent and short-acting opioid analgesic. This model offers insights into how Remifentanil affects pain relief and consciousness, taking into account its rapid onset and clearance from the body. The Minto Model provides predictions on how varying concentrations of Remifentanil influence the patient's pain response and overall anesthetic experience.

Importance of the Minto Model:

- **Accurate Pain Management:** The Minto Model helps in predicting the analgesic effects of Remifentanil, allowing for precise titration of the drug to achieve optimal pain control without excessive sedation.
- **Real-Time Adjustments:** Given Remifentanil's quick onset and short duration, the Minto Model enables real-time adjustments to anesthesia, which is crucial for maintaining balanced analgesia throughout the surgical procedure.
- **Simulation of Rapid Pharmacokinetics:** By using the Minto Model in an anesthesia simulator, practitioners can accurately simulate and anticipate the effects of rapid changes in Remifentanil concentrations, improving their ability to manage dynamic anesthesia scenarios effectively.

A9.3. Why Choosing the Right Model Matters

Selecting the appropriate PK-PD model for each anesthetic agent is essential for accurate simulation and effective management of anesthesia. The Schnider Model provides detailed predictions for Propofol's effects on sedation, while the Minto Model offers precise insights into Remifentanil's analgesic impact. Accurate simulation using these models allows for better planning, dosing, and monitoring during anesthesia, leading to improved patient safety and more effective anesthesia management.

Appendix B.

B1. Induction Phase: Output Safety Intervals and Input/ Output Constraints

B1.1. Propofol Dosing (Hypnotic State, Evaluated by BIS)

During the induction phase, Propofol is used to induce hypnosis, and the BIS (Bispectral Index) monitors the depth of anesthesia. Propofol has a rapid onset and a short duration of action, making it ideal for inducing anesthesia [16,17,18].

- **Suggested Input**: A bolus dose of Propofol is typically administered during the induction phase. The user should consider starting with an initial bolus of **1.5-2.5 mg/kg**, depending on the patient's weight, age, and health status. Older patients may require a lower dose due to slower clearance and increased sensitivity.
- **Output Safety Interval**: BIS should aim for a value between **40 and 60**, where **100** indicates full wakefulness and values below **40** indicate deep anesthesia or even a risk of over-sedation. This interval ensures that the patient is sufficiently sedated for surgery while avoiding over-sedation, which can depress cardiovascular function.
- **Input Constraint**: The infusion rate for Propofol during induction typically starts between **3-12 mg/kg/h,** depending on the patient's weight, age, and health condition. However, higher infusion rates should be used cautiously, particularly in elderly or vulnerable patients, to avoid cardiovascular depression and hemodynamic instability.

B1.2. Remifentanil Dosing (Analgesic State, Evaluated by RASS)

Remifentanil is used for analgesia and is often co-administered with Propofol to reduce the overall anesthetic dose [19].

- **Suggested Input Dose:** During the induction phase, the recommended loading dose of Remifentanil is typically in the range of **0.5-1 µg/kg/min**, depending on patient factors, such as age, weight, and clinical conditions. This range is commonly utilized to ensure rapid onset of analgesia without excessive respiratory depression, which is consistent with clinical findings from various studies.

- **Safety Intervals (RASS Monitoring):** It is important to monitor sedation levels using tools like the Richmond Agitation and Sedation Scale (RASS). For optimal conditions during induction, a RASS score between **-2 and -3** is recommended, ensuring the patient is calm but still maintains protective airway reflexes. Going below a RASS of **-4** would indicate a deeper sedation state.
- **Input Constraint:** Care must be taken to adjust dosing, especially in elderly patients. Clinical guidance suggests reducing the Remifentanil dose by **up to 50%** for elderly individuals due to increased drug sensitivity and reduced clearance, which is consistent with the pharmacokinetic data discussed in anesthetic literature. Avoiding bolus doses exceeding **1.5 µg/kg** is critical as higher doses can precipitate significant hemodynamic instability.

B1.3. Atracurium Dosing (Neuromuscular Blockade, Evaluated by NMB)

Neuromuscular blocking agents are used to facilitate intubation and muscle relaxation [19, 20].

- **Suggested Input**: For induction, the recommended dosage for **Atracurium** is **0.5–0.6 mg/kg** . This dose provides satisfactory intubating conditions within about **2-3 minutes** after administration . The onset time for Atracurium is approximately **192 seconds**, and it typically achieves peak effect at 95-100% paralysis, this indicates that almost all muscle activity is suppressed, providing the ideal conditions for surgical interventions.
- **Output Safety Interval**: Atracurium should achieve a **95-100% neuromuscular blockade** to ensure optimal intubating conditions.
- **Input Constraint**: A bolus **should not exceed 0.6 mg/kg** to prevent excessive histamine release, which can lead to hypotension.

B1.4. Hemodynamic Management (Evaluated by MAP and CO)

Induction of anesthesia often leads to hypotension, especially when using Propofol and Remifentanil [19, 21].

B1.4.1. Dopamine Infusion Rate:

- **Suggested Input**: Start with a **5-10 µg/kg/min** infusion for hemodynamic support during induction. This rate provides adequate effects to support cardiac output and maintain blood pressure without excessive vasoconstriction.
- **Output Safety Interval**: The mean arterial pressure (MAP) should be kept above **60 mmHg** to ensure adequate organ perfusion, especially during induction, where hypotension is common.
- **Input Constraint**: Dopamine doses should not exceed **20 µg/kg/min** during induction as higher doses may lead to vasoconstriction, which can reduce tissue perfusion and increase myocardial oxygen demand.

B1.4.2. Sodium Nitroprusside (SNP) Infusion Rate:

- **Suggested Input**: Start with a low infusion rate of **0.3 µg/kg/min**, titrating upward depending on the patient's hypertensive response. SNP is particularly useful for managing blood pressure in patients with intraoperative hypertension [19, 22].
- **Output Safety Interval**: Maintain MAP within **65-75 mmHg** .
- **Input Constraint**: Avoid exceeding **10 µg/kg/min** of SNP, as high doses can lead to cyanide toxicity and excessive hypotension.

B2.Maintenance Phase: Output Safety Intervals and Input/ Output Constraints

B2.1. Propofol Dosing (Hypnotic State, Evaluated by BIS)

During the maintenance phase, Propofol is infused continuously to keep the patient under anesthesia. The dosing must be carefully administrated based on the patient's pharmacodynamic response to avoid complications such as cardiovascular instability or Propofol Infusion Syndrome (PRIS) [19, 23].

- **Suggested Input:** An infusion rate between 3-9 mg/kg/h is recommended during the maintenance phase. The dose should be adjusted based on the patient's condition and response to ensure optimal anesthesia depth, as indicated by the BIS. Higher doses may be necessary for obese patients.
- **Output Safety Interval:** Maintaining a BIS value between 40 and 60 ensures that the patient remains in a stable state of general anesthesia without the risk of intraoperative awareness or excessive sedation, which could lead to hypotension and cardiovascular depression.
- **Input Constraint:** Infusion rates higher than 9-12 mg/kg/h should be used with caution, especially in patients undergoing prolonged surgries. Prolonged high-dose infusions can lead to severe complications such as metabolic acidosis, cardiac failure, and rhabdomyolysis. For maintenance in high-risk patients or longer procedures, an infusion rate of 4 mg/kg/h or less is advised to minimize these risks.

B2.2. Remifentanil Dosing (Analgesic State, Evaluated by RASS)

In the maintenance phase, Remifentanil continues to provide analgesia [18, 19].

- **Suggested Maintenance Dose:** After the initial loading dose, the Remifentanil infusion should be titrated between **0.1-0.4 µg/kg/min** for balanced anesthesia. This range allows for the maintenance of adequate analgesia during surgical procedures while controlling autonomic responses to noxious stimuli. The ability of Remifentanil to suppress autonomic and somatic responses without leading to prolonged respiratory depression makes it ideal for use in procedures requiring rapid recovery.
- **Safety Monitoring:** Even during the maintenance phase, continuous monitoring of sedation depth using tools such as RASS to be adjusted to **-5.**

- **Input Constraint for Elderly and High-Risk Patients:** As with induction, the dose of Remifentanil for maintenance in elderly or high-risk patients should be carefully adjusted. Maintenance infusion rates of **0.05-0.1 µg/kg/min** may be sufficient for achieving the desired effects in this population.

B2.3. Atracurium Dosing (Neuromuscular Blockade, Evaluated by NMB)

Continuous neuromuscular blockade is required for certain surgeries, especially those involving the abdominal or thoracic cavities [19].

- **Suggested Input**: After achieving the initial neuromuscular blockade with a bolus, **Atracurium** can be maintained via a continuous infusion. The typical infusion rate is between **4–20 µg/kg/min**, which ensures adequate neuromuscular blockade during surgery without overshooting paralysis.
- **Safety Interval**: During maintenance, it is recommended to aim for **90-95% blockade**.
- **Input Constraint**: Infusion rates higher than **25 µg/kg/min** should be avoided, as prolonged higher rates can increase the risk of laudosine accumulation, which may lead to CNS stimulation.

B2.4. Hemodynamic Management (Evaluated by MAP and CO)

Hemodynamic stability is crucial during the maintenance phase, particularly in high-risk patients [19, 21].

B2.4.1. Dopamine Infusion Rate:

- **Suggested Input**: During maintenance, dopamine can be maintained between **5-15 µg/kg/min** to continue providing inotropic support, especially in patients who may experience intraoperative hypotension due to anesthesia.
- **Output Safety Interval**: The cardiac output (CO) should be maintained between **4-6 L/min**, and MAP should remain above **65 mmHg** to ensure continued perfusion to vital organs.
- **Input Constraint**: Avoid exceeding the **20 µg/kg/min** threshold, as this may cause excessive vasoconstriction, decreased tissue perfusion, and increased cardiac workload, which is not ideal for prolonged surgical periods.

B2.4.2. Sodium Nitroprusside (SNP) Infusion Rate:

- **Suggested Input**: Continue the SNP infusion between **0.5-8 µg/kg/min**, adjusting as necessary to manage blood pressure spikes that may occur during surgery.
- **Output Safety Interval**: MAP should be tightly regulated between **65-75 mmHg** to avoid both hypertension and hypotension, ensuring stable hemodynamic conditions during the maintenance phase.
- **Input Constraint**: SNP should not exceed **10 µg/kg/min** during the maintenance phase, as cyanide toxicity becomes a concern with prolonged high-dose infusions.

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