

Instructions for using a Mathematical Model of Heart Rate Response to Fluid Perturbation (with Software Code)

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1. General Information

This software code provides a model of heart rate (HR) response to fluid perturbation. The model is built in MATLAB Simulink environment and the goal is to generate the model's prediction envelope for a test subject. The prediction envelope can be used to evaluate predictive capability performance of the model and show its ability to generate valid virtual HR physiological responses to fluid perturbation for the future non-clinical simulated testing setups to assess physiological closed-loop controlled (PCLC) medical devices. The model, its calibration, and validation analysis are described in [1]. The model is designed to reflect both short-term as well as long-term responses to fluid perturbation. The transient response is the instantaneous change in the HR due to hemorrhage and fluid infusion, while the long-term response refers to the change in the steady-state value of the HR response due to hemorrhage. The model calibration is defined based on the maximum likelihood estimation of its parameters. Also, a compartment-based virtual cohort generation tool defined in [1] is used to simulate virtual subjects and generate a prediction envelope used for model predictive capability performance. The model inputs include hemorrhage, fluid infusion, and urine, and the model outputs HR response.

2. System Requirements

The software code was written in a MATLAB® 2019a environment and consists of a Simulink file "HR_Model.mdl", scripts for model calibration and a script for prediction envelope generation. The model calibration includes a core code "HR_Model_Main.m" and a supplementary optimizer function "HR_Optimizer.m". The prediction envelope generator includes a core code "Cohort_Generation.m". The data from a representative test subject as well as model parameters calibrated against 21 animal subjects have been provided in mat files, entitled "Example_Data.mat" and "Calibrated_Parameters.mat", respectively. Software has been tested in MATLAB® 2019a environment, and it requires the Simulink and Optimization Toolboxes.

3. Data Preparation

HR data from an individual subject are used for i) model calibration, and ii) comparing with generated prediction envelope in a test subject. The data should be recorded under hemorrhage followed by fluid resuscitation. In this work, a 3-point median filter is applied to the collected HR data. An individual sample dataset is included in the software for demonstration purposes. The dataset includes time instants for 3-hour measured HR and median-filtered HR values, fluid infusion, hemorrhage, and urine.

4. Software Package Content

The software package includes 3 hours of HR data, hemorrhage, fluid infusion, and urine from an individual subject used for model calibration and prediction envelope comparison. The package also includes calibrated parameters from 21 individual animal subjects used for virtual cohort generation. The model is presented in Simulink “HR_Model.mdl”. The model calibration includes a core code “HR_Model_Main.m” and a supplementary function “HR_Optimizer.m” and is used to fit the model to the test subject. Virtual cohort generation also includes a main code “Cohort_Generation.m” that generates a prediction envelope using the compartment method presented in [1]. The codes are presented in the appendix.

5. Input and Output of the Software Code

The input and output of the software code is presented in two sections:

A. HR Model Calibration

Code: Main code “HR_Model_Main.m”, supplementary function “HR_Optimizer.m”

Inputs: i) time instants for measured HR “Hemo_Time”, ii) median-filtered measured HR data “Hemo_HR”, iii) fluid infusion “Infusion_inp”, iv) hemorrhage “Hemorrhage_inp”, and v) urine “Urine_inp” all provided in “Example_Data.mat”. The “Example_Data.mat” is a 1x3 cell, the first cell includes time and HR data, the second cell includes infusion, hemorrhage and urine, and the third cell includes the simulation sampling time.

Outputs: i) optimized model parameters for the individual subject “x_opt”, ii) estimated HR response “HR_sol”

B. HR Prediction Envelope

Code: “Cohort_Generation.m”

Inputs: i) time instants for measured HR “Hemo_Time”, ii) median-filtered measured HR data “Hemo_HR”, iii) fluid infusion “Infusion_inp”, iv) hemorrhage “Hemorrhage_inp”, and v) urine “Urine_inp” all provided for the test subject in “Example_Data.mat”, and vi) calibrated parameters from animal subjects used for generating prediction envelope against the test subject provided by “Calibrated_Parameters.mat”.

“Calibrated_Parameters.mat” is a 21x7 matrix, where each row includes calibrated model parameters for each animal subject.

Outputs: 95th percentile prediction envelope “P_envelope”.

6. Model Use Conditions

The model is intended for use with HR data collected under hemorrhage followed by fluid infusion. The HR data subject to only fluid infusion and in absence of hemorrhage could lead to different physiological state, e.g., fluid overload, which should not be used with the developed HR model. For more information, please refer to [1]. Data from sheep subjects were used in this study. Each animal subject underwent hemorrhage and fluid infusion, lasted for 180 min. At the start of each animal study, a 25 ml/kg hemorrhagic shock was induced in the subjects which lasted for 15 min. At 30 min, fluid infusion was started which continued till the end of the experiment. This infusion was performed for resuscitation with a target mean arterial pressure of 90 mmHg. At 50 and 70 min marks, two small 5 ml/kg hemorrhagic shocks were induced, each lasted for 5 min. For more information about the animal study please refer to [2].

7. References

- [1] Varun Kanal, Pras Pathmanathan, Jin-Oh Hahn, George Kramer, Christopher Scully, and Ramin Bighamian, Development and Validation of a Mathematical Model of Heart Rate Response to Fluid Perturbation, Scientific Reports 12, 21463 (2022).
- [2] Abraham Rafie, Paul Rath, Michael Michell, Robert Kirschner, Donald Deyo, Donald Prough, James Grady, George Kramer, Hypotensive Resuscitation of Multiple Hemorrhages using Crystalloid and Colloids, Shock 22, 262-269 (2004).

Appendix

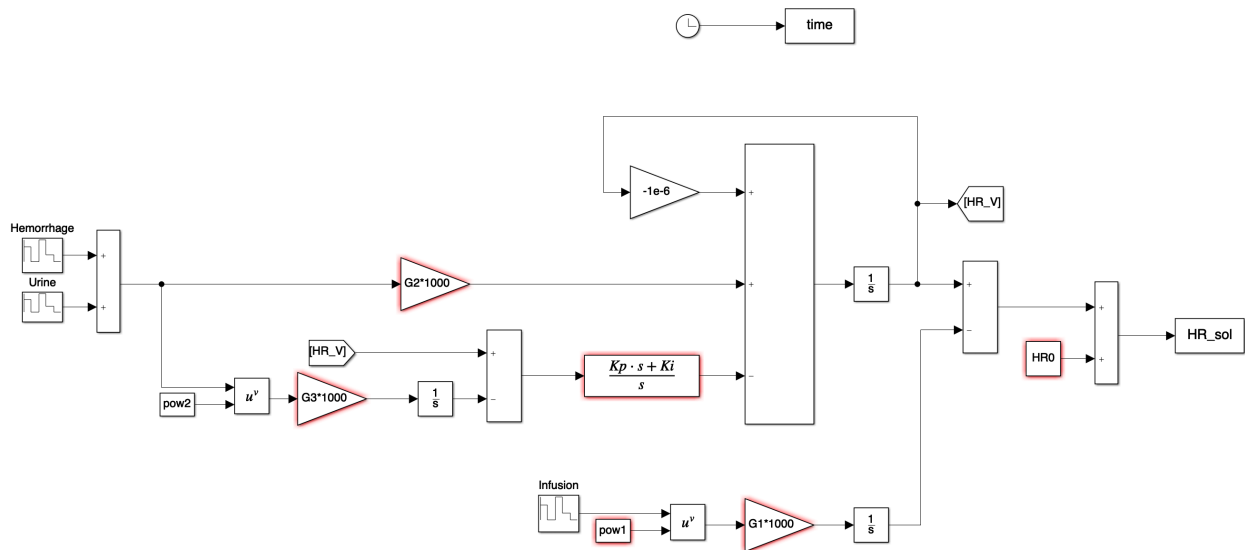
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○ HR Model Simulink:

For model parameters, please refer to [1].



○ Model Calibration Core Code:

```
%{  
Authors  
Varun Kanal  
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```

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The HR model is described and published in:

Varun Kanal, Pras Pathmanathan, Jin-Oh Hahn, George Kramer, Christopher Scully, and Ramin Bighamian, Development and Validation of a Mathematical Model of Heart Rate Response to Fluid Perturbation, Scientific Reports 12, 21463 (2022).

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```
%}

clear
clc
close all

global Hemo_Time Infusion_inp Hemorrhage_inp Urine_inp SamplingTime Hemo_HR

load('Example_Data') % load data from one individual
Hemo_Time = Example_Data{1,1}(:,1); % time instants for data
Hemo_HR = Example_Data{1,1}(:,2); % HR data
Infusion_inp = Example_Data{1,2}(:,1); %infusion profile
Hemorrhage_inp = Example_Data{1,2}(:,2); %hemorrhage profile
Urine_inp = Example_Data{1,2}(:,3); %urine profile
SamplingTime = Example_Data{1,3}(:,1); %sampling time
simulation_time = [0:SamplingTime:180]';
%%
lowlimit = [0 0 0 0 0 0 0 40];
uplimit = [5 5 2 2 1 1 0.1 150];
f = [];
for ii = 1:10 % model calibration
    ii
    x0 = lowlimit+(uplimit-lowlimit).*rand(1,length(lowlimit));
    options = optimset('Algorithm','interior-point');
    [x(ii,:),f(ii,1)] = fmincon(@HR_Optimizer,x0,[],[],[],[],lowlimit,uplimit,[],options);
end
f_opt = min(f) % calibration cost function
x_opt = x(find(f==min(f),1),:) % identified parameters
%%
G1=x_opt(1);G2=x_opt(2);pow1=x_opt(3);pow2=x_opt(4);G3=x_opt(5);Kp=x_opt(6);Ki=x_opt(7);HR0=x_opt(8);
sim('HR_Model');

figure(1)
subplot(221)
plot(simulation_time,Infusion_inp*1000,'LineWidth',2)
hold on
plot(simulation_time,-Hemorrhage_inp*1000,'--r','LineWidth',2)
set(gca,'XTick',[0:30:180])
xlim([0 180])
ylim([-100 80])
ylabel('Fluid & Hemorrhage [ml/min]','fontsize',12,'fontweight','b')
set(gca,'XTick',[0:30:180],'FontWeight','bold')
set(gca,'YTick',[-100:20:80],'FontWeight','bold')
legend('Fluid','Hemorrhage','Location','SouthEast')
grid on

subplot(222)
plot(Hemo_Time,Hemo_HR,'ro')
hold on
plot(simulation_time,HR_sol)
xlabel('Time [min]')
ylabel('HR [bpm]')
set(gca,'XTick',[0:30:180],'FontWeight','bold')
set(gca,'YTick',[50:25:250],'FontWeight','bold')
legend('True','Estimated','Location','SouthEast')
ylim([50 250])
grid on
```

○ Model Calibration Supplementary Optimizer Function:

```

function [f] = HR_Optimizer(x)
global Hemo_Time Infusion_inp Hemorrhage_inp Urine_inp SamplingTime Hemo_HR

G1=x(1);G2=x(2);pow1=x(3);pow2=x(4);G3=x(5);Kp=x(6);Ki=x(7);HR0=x(8);

options = simset('SrcWorkspace','current');
sim('HR_Model',[],options)

associated_response = interp1(time,HR_sol,Hemo_Time);
error = [Hemo_HR-associated_response];% HR error
f =normlike([0,std(error)],error)+2*0.5*norm((x(8)-Hemo_HR(1)),2)+2*0.1*norm(x(1:7),2); % cost function

```

○ Cohort Generation Code:

```

%{
Authors
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```

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Varun Kanal, Pras Pathmanathan, Jin-Oh Hahn, George Kramer, Christopher Scully, and Ramin Bighamian, Development and Validation of a Mathematical Model of Heart Rate Response to Fluid Perturbation, Scientific Reports 12, 21463 (2022).

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```

%}
clear
clc
close all

```

```

load('Calibrated_Parameters') % load parameters identified for 21 subjects
Par_aux(15,:) = [];% remove the test subject which is subject # 15 for leave-one-out analysis

```

```

load('Example_Data') % load data for the test subject
Hemo_Time = Example_Data{1,1}(:,1); % time instants for data
Hemo_HR = Example_Data{1,1}(:,2); % HR data
Infusion_inp = Example_Data{1,2}(:,1); %infusion profile
Hemorrhage_inp = Example_Data{1,2}(:,2); %hemorrhage profile
Urine_inp = Example_Data{1,2}(:,3); %urine profile
SamplingTime = Example_Data{1,3}(:,1); %sampling time
simulation_time = (0:SamplingTime:180);
%% Compartment method for virtual cohort generation
[A B C]=ndgrid(1:size(Par_aux,1),1:size(Par_aux,1),1:size(Par_aux,1)); % different combinations of infusion, hemorrhage, and controller compartments
A1=reshape(A,[],1);

```

```

B1=reshape(B,[],1);
C1=reshape(C,[],1);
d = [];
d=[A1,B1,C1];
mat_all2 = [];mat_all3 = [];
for ii = 1:length(d)
    mat_all2(ii,:) = [Par_aux(d(ii,1),1) Par_aux(d(ii,2),2) Par_aux(d(ii,1),3) Par_aux(d(ii,2),4:5) Par_aux(d(ii,3),6:7)]; % mixing virtual subject
    combinations
    mat_all3(ii,:) = (Par_aux(d(ii,1),:)+Par_aux(d(ii,2),:)+Par_aux(d(ii,3),:))/3;% average virtual subject combinations
end

mat_all = [mat_all2;mat_all3];% all possible virtual subject parameter combinations
n_size = length(mat_all);% size of all possible virtual subjects to run

%%% Run simulations below
%%%
Physio_subject_count = 0;
HR0 = Hemo_HR(1);% start from the initial heart rate. Uncertainty can be added.
for ii = 1:n_size
    ii
    G1=mat_all(ii,1);G2=mat_all(ii,2);pow1=mat_all(ii,3);pow2=mat_all(ii,4);G3=mat_all(ii,5);Kp=mat_all(ii,6);Ki=mat_all(ii,7);% model
    parameters for each virtual subject
    sim('HR_Model');

    if min(HR_sol)>40 && max(HR_sol)<250 % check the criteria for physiological simulations
        Physio_subject_count = Physio_subject_count+1;% counting the number of physiological simulations
        response_HR_physio(Physio_subject_count,:) = interp1(simulation_time,HR_sol,Hemo_Time);%down sampled HR data for
        physiological subjects
        physio_sample(Physio_subject_count)= ii;
        NRMSE(Physio_subject_count,1) = rms(Hemo_HR-(response_HR_physio(Physio_subject_count,:)))/mean(Hemo_HR);% normalized
        root mean square error
    end
end
%%% Plot the prediction envelope
figure(1)
subplot(221)
plot(simulation_time,Infusion_inp*1000,'LineWidth',2)% plot infusion profile
hold on
plot(simulation_time,-Hemorrhage_inp*1000,'-r','LineWidth',2)% plot hemorrhage profile
set(gca,'XTick',[0:30:180])
xlim([0 180])
ylim([-100 80])
ylabel('Fluid & Hemorrhage [ml/min]','fontsize',12,'fontweight','b')
set(gca,'XTick',[0:30:180],'FontWeight','bold')
set(gca,'YTick',[-100:20:80],'FontWeight','bold')
legend('Fluid','Hemorrhage','Location','SouthEast')
grid on
box on

subplot(222)
hold on
plot(Hemo_Time,Hemo_HR,'vb','LineWidth',1.5,'MarkerSize',7)
grid on
xlim([0 180])
set(gca,'XTick',[0:30:180],'FontWeight','bold')

% Filter out data that meets the NRMSE criteria
Relevant_subjects = find(NRMSE<=0.2);% identify relevant virtual subjects with NRMSE<20%
response_HR_relevant = response_HR_physio(Relevant_subjects,:);% down sampled predction data for relevant subjects

P_envelope = [];
first_percentile = [];
second_percentile = [];
for jj = 1:length(Hemo_HR) % compute 95th percentile envelope

```

```

    first_percentile(jj,1) = prctile(response_HR_relevant(:,jj),2.5);
    second_percentile(jj,1) = prctile(response_HR_relevant(:,jj),97.5);
end
P_envelope = [first_percentile second_percentile]; % 95th percentile envelope

hold on
P_envelope_plot=[P_envelope(:,1)' flipud(P_envelope(:,2))];
fill([Hemo_Time' fliplr(Hemo_Time)], P_envelope_plot, 1,'facecolor','red','edgecolor','none','facealpha',0.4);% plot 95th percentile
prediction envelope
grid on
xlim([0 180])
set(gca,'XTick',[0:30:180],'FontWeight','bold')

```