Dynamics of vasodilation drug on cardiovascular system

Introduction

In this project, we simulate a PK/PD model of vasodilation drug - cardiovascular system. It reflects how blood pressure dynamically reacts to the vasodilation drug under the regulation of arterial baroreflex system, which is controlled by medullary cardiovascular control center (MCCC) in the brain. For this model, the vasodilatory drug has the pharmacodynamic effect to reduce the mean arterial pressure (MAP) by decreasing the total peripheral resistance (TPR). This change is sensed by baroreceptors and subsequently conveyed to MCCC. MCCC responds to the input by transferring corresponding neural signals to organs in the cardiac parasympathetic system such as heart and blood vessels. These organs take actions to increase heart rate (HR) and ventricular myocardium contractility to up-regulate MAP. When the MAP decreases to the threshold, this negative feedback system works the opposite way so as to maintain the systemic homeostasis of MAP.

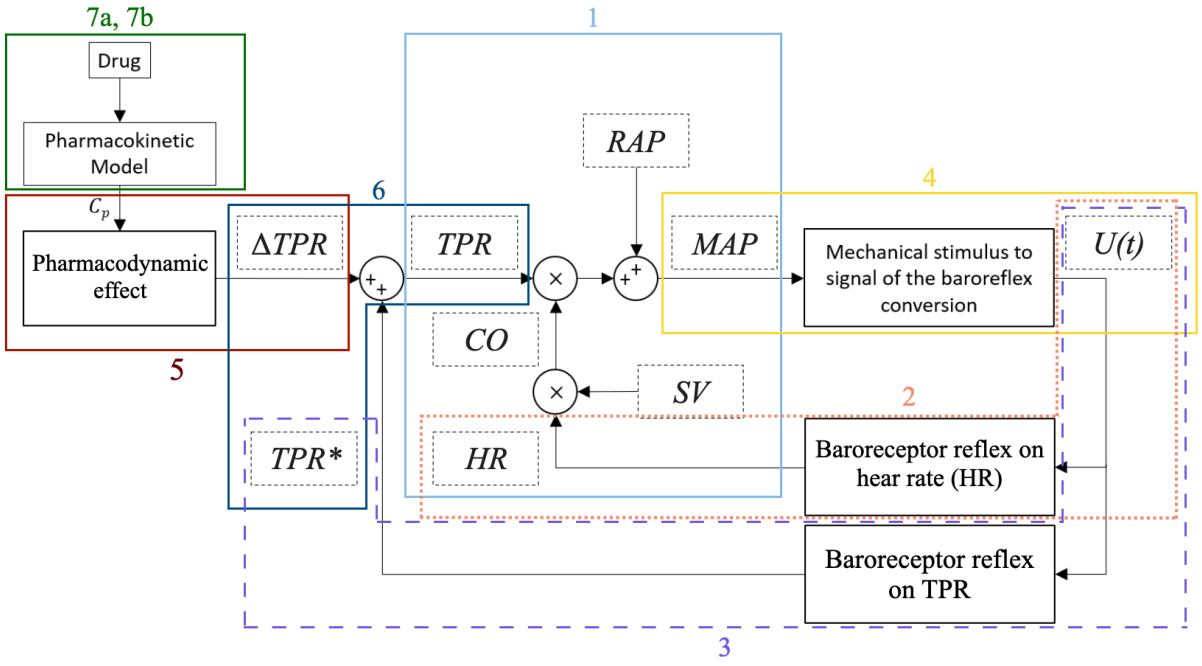

Figure 1. Schematic diagram of the drug effect on MAP

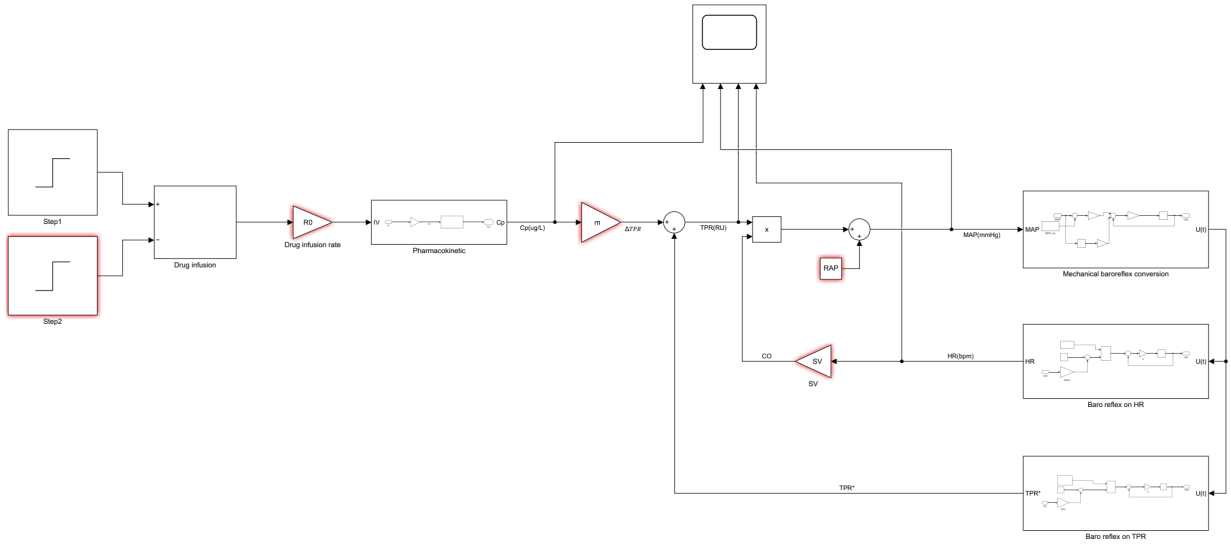

Figure 2. Simulink Model of schematic diagram

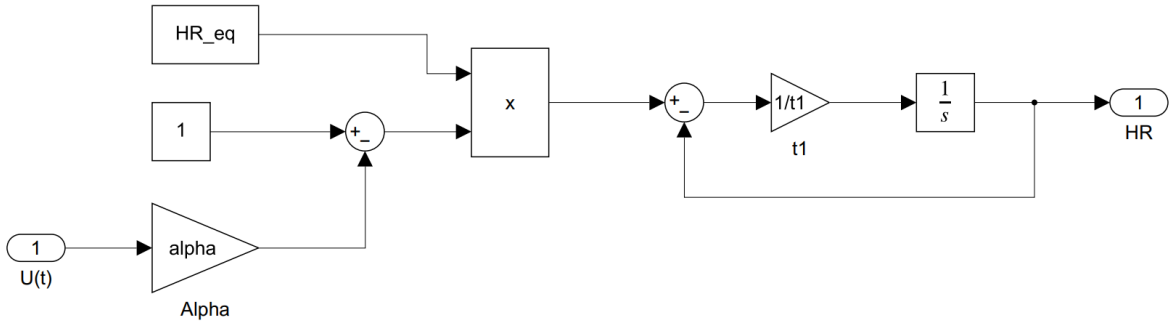

Figure 3. Subsystem of dynamics of HR on baroreceptor feedback

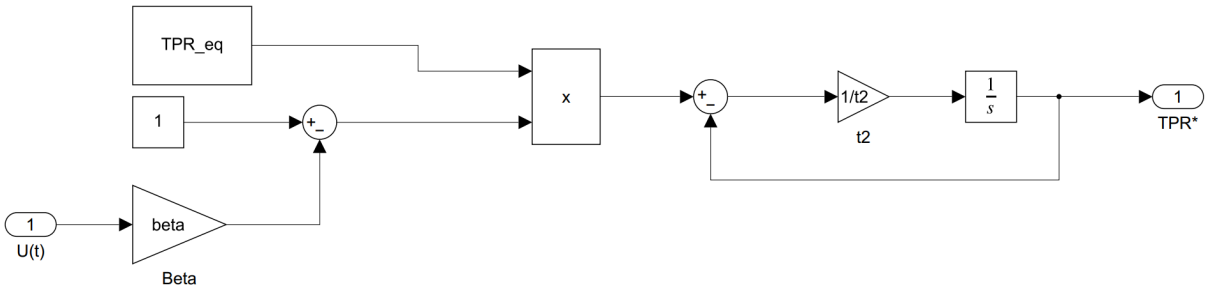

Figure 4. Subsystem of dynamics TPR on baroreceptor feedback

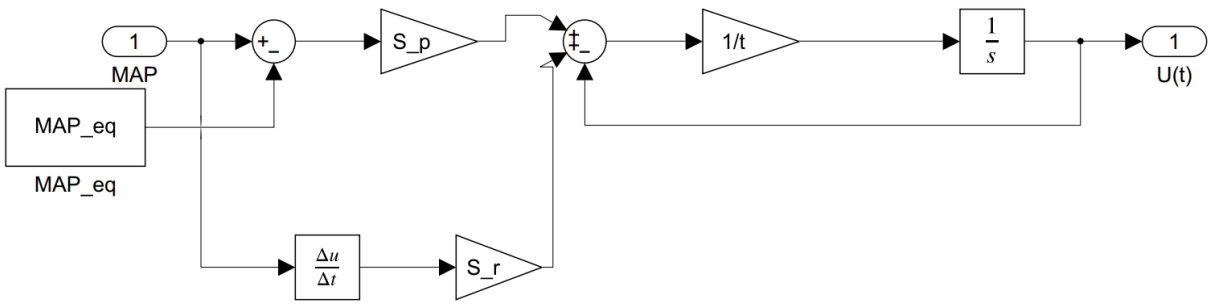

Figure 5. Subsystem of dynamics of baroreceptor transduction

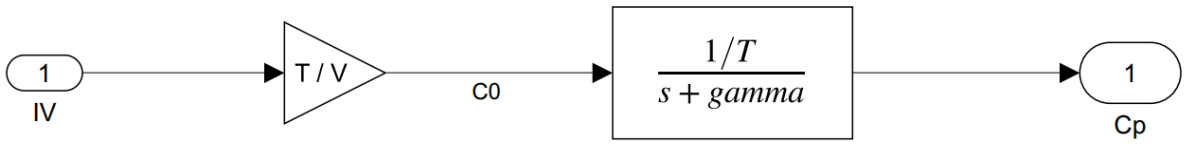

Figure 6. Subsystem of pharmacokinetic model

Simulation results

a) The vasodilation drug effect on cardiovascular responses (MAP, TPR and HR) under the **normal condition**.

1. No parameter adjustment.
2. MAP and TPR will decrease, HR will increase.
3. Simulation result:

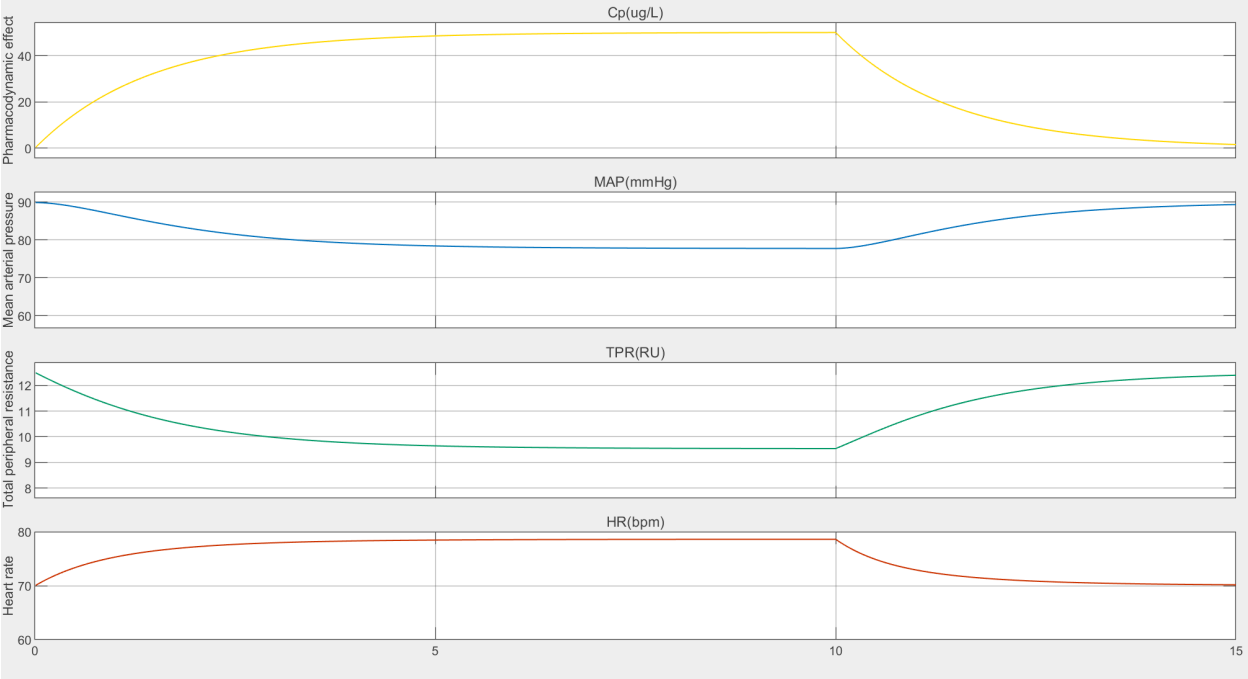

Figure 7. Simulation under the normal case

4. The HR, TPR and MAP responses and the % changes from equilibrium values.

	Equilibrium value	Value at t = 10 hours	% Change from the equilibrium value
MAP	90.000	77.726	-13.638
TPR	12.500	9.539	-23.688
HR	70.000	78.597	12.281

Figure 8. % change in MAP, TPR and HR from the equilibrium values in the normal case.

5. The vasodilatory drug has the pharmacodynamic effect to decrease the total peripheral resistance (TPR), which subsequently reduce the MAP level. The decreasing of MAP is sensed by baroreceptor reflex, which increase the Heart rate.
6. No.

b) The vasodilation drug effect on cardiovascular responses (MAP, TPR and HR) when the physiological feedback effect is **not** considered.

1. Set **α** = 0, and **β** = 0
2. TPR, MAP will constantly decrease (until the stop pf drug input), and heart rate will remain the same.
3. Simulation result:

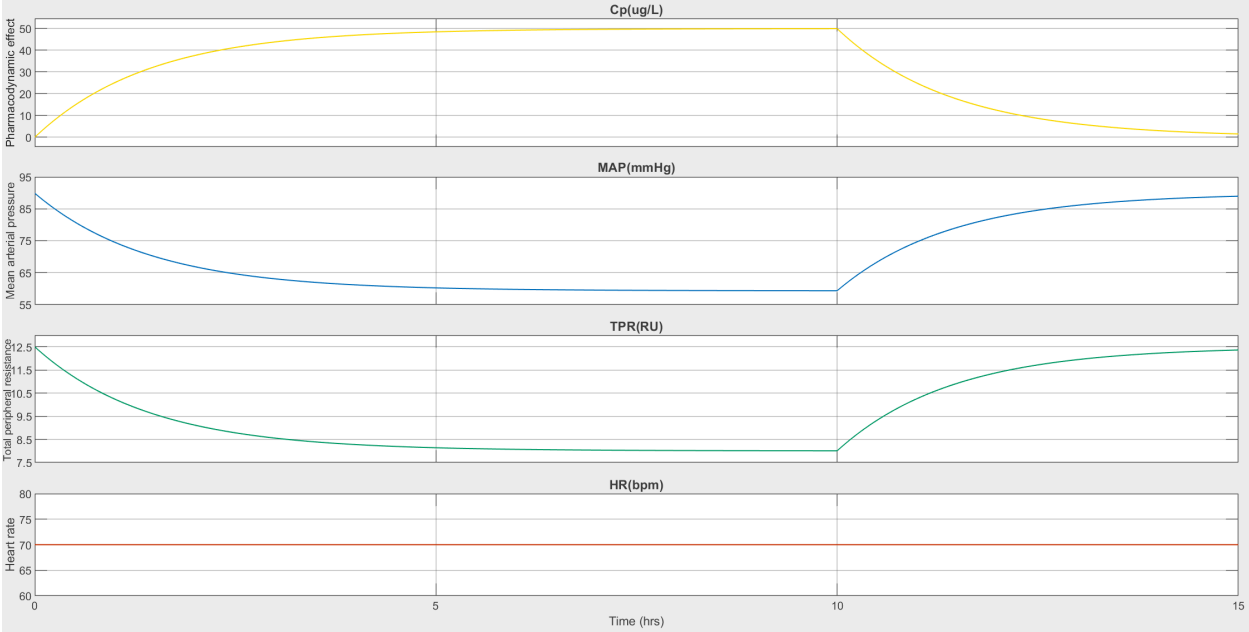

Figure 9. Simulation under the no-feedback case

4. The TPR, MAP will constantly decrease, and HR remains the same.

	Value at t = 10 hours		% Change from the equilibrium value	
	Normal	Scenario b	Normal	Scenario b
MAP	77.726	59.348	-13.638	-34.058
TPR	9.539	8.004	-23.688	-35.968
HR	78.597	70.000	12.281	0.000

Figure 10. % changes in MAP, TPR and HR from equilibrium value in the no-feedback case

5. The drug will reduce the MAP through the pharmacodynamic effect of decreasing TPR. When α and β equal 0, the baroreceptor reflex unable to upregulate the HR and TPR*, thus the TPR, MAP will constantly decrease, and HR remains the same.
6. No.

c) The vasodilation drug effect on cardiovascular responses in a hypertensive patient whose **TPR baroreflex sensitivity is half of a normal person**. The average MAP before drug infusion is 100 mmHg (i.e. higher than a normal person) and the RAP is increased to 15 mmHg.

1. Set MAP_{eq} = 100 mmHg, **β** = 0.5, RAP = 15 mmHg
2. The decrease in TPR will be slightly higher than the normal case, the HR change will be similar to the normal case. The MAP will be higher than the normal case.
3. Simulation result:

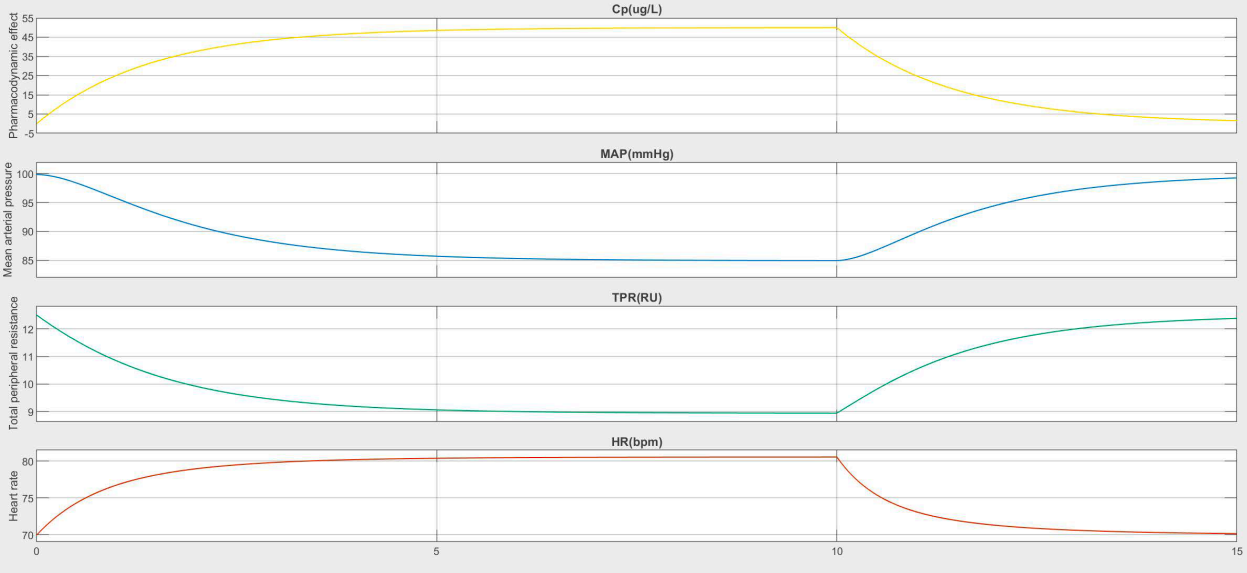

Figure 11. Simulation under the hypertensive case

4. The decrease in TPR is slightly more than the normal case, the HR change is higher than the normal case. The MAP is higher than the normal case.

	Value at t = 10 hours		% Change from the equilibrium value	
	Normal	Scenario c	Normal	Scenario c
MAP	77.726	84.924	-13.638	-15.076
TPR	9.539	8.948	-23.688	-28.416
HR	78.597	80.566	12.281	15.094

Figure 12. % change in MAP, TPR and HR the equilibrium values in the hypertensive case

5. The drug will reduce the MAP through the pharmacodynamic effect of decreasing TPR. Due to the smaller **β**, the upregulation of TPR* by baroreceptor reflex effect of baroreceptor reflex contributes little to restore the MAP, resulting a smaller TPR. Because the patient has higher

MAP_{eq}, the restored MAP is higher than the normal case. The increased HR is caused by higher value of RAP, which contributes to larger upregulation effect from baroreceptor reflex.

6. HR value. Possibly the higher value of RAP contributes to larger upregulation effect from baroreceptor reflex on HR.

d) The cardiovascular responses to a drug that causes **vasoconstriction** (a drug that narrows the blood vessels and thus increases TPR).

1. Set $\boldsymbol{m}$ = 0.09
2. MAP will increase (higher than normal cases), HR will decrease (lower than normal cases), TPR depends on the drug effect.
3. Simulation result:

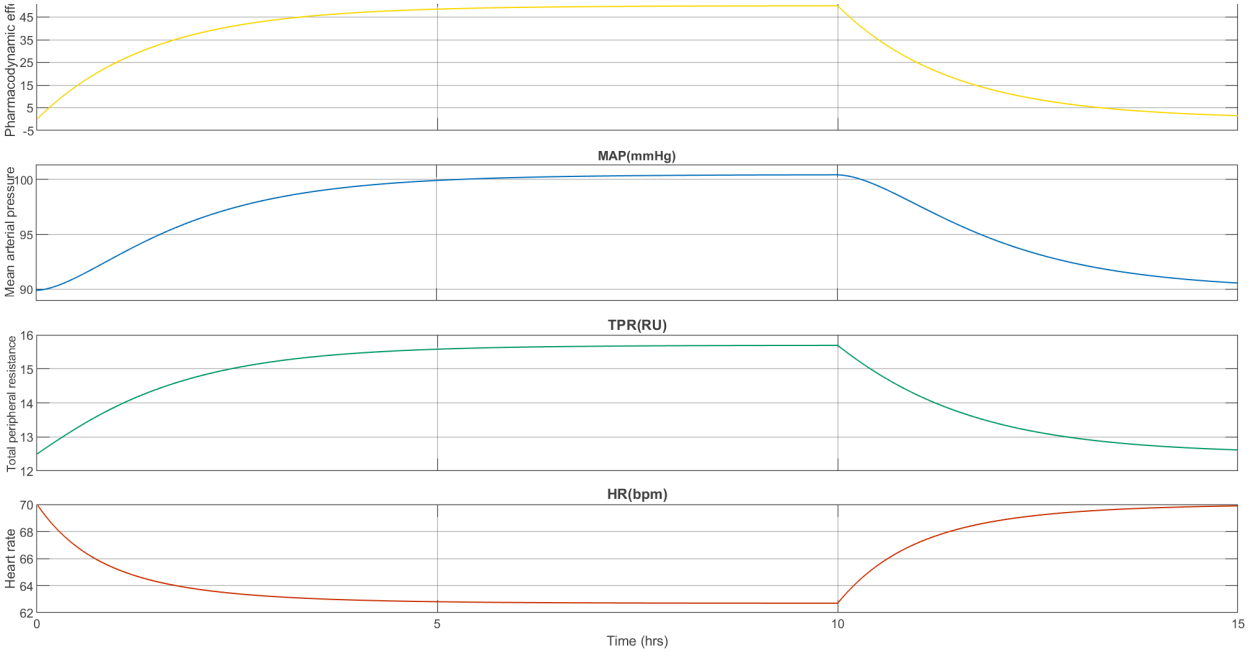

Figure 13. Simulation under the vasoconstriction case

4. MAP increases (higher than normal cases), HR decreases (lower than normal cases). TPR has a higher value relative to normal cases.

	Value at t = 10 hours		% Change from the equilibrium value	
	Normal	Scenario d	Normal	Scenario d
MAP	77.73	100.424	-13.638	11.582
TPR	9.539	15.691	-23.688	25.528
HR	78.60	62.694	12.281	-10.437

Figure 14. % change in MAP, TPR and HR the equilibrium values in the vasoconstriction case

5. The drug will increase MAP through upregulation pharmacodynamic effects on TPR. The baroreceptor reflex senses the increase in MAP and downregulates TPR* and HR. The counteractive effect of TPR* and decreased HR brings down MAP. Therefore, TPR has a higher value relative to normal cases while the HR has a lower value than the normal case.
6. No.

Discussion

The model developed in the project reflect how the vasodilation drug work along with the cardiovascular system to regulate the blood pressure.

The simulation results along with the expectation under the normal condition, no-feedback condition, and opposite condition (the vasoconstriction case). The main discrepancy is the hypertensive case, in which the HR change is higher than the normal case. It is mainly due to the effect of increased RAP value. Overall, this PD/PK model ideally describe how the vasodilator drug cooperate with the auto-regulatory cardiovascular system to balance the blood pressure.

This model also has some limitations. For example, the metabolic of liver will significantly reduce the bioavailability of drug. This model simply hypothesis that *the the pharmacodynamic effect of the drug to be proportional to the plasma concentration,* which is not realizable in some scenarios. Therefore, this model can serve as a general model to predict the action of vasodilatory drugs. It may not be practical under specific conditions.

In clinical practice, I will customize the model parameters according to certain cases. Based on the effect of drug to decide the desirable drug dosage.

Reflection

I learned how to build a PK/PD model including effects of physiological feedback, and how to simulation the model in MATLAB, analyzing and explaining the model results.

Professor Sang Chalacheva is a very very nice teacher, who is very patient and easy-going. I also get a lot of help from teaching assistants from this course, especially Jeongyun (Marie) Kim, who is helpful and kind. Thanks to all the help and 42-782 is really a good course that deserves learning.

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