Drug infusion is a technique used in healthcare to administer medication directly into a patient's bloodstream over a period of time.

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Introduction

A typical research/design project on any topic involves several key steps. First, it is necessary to familiarize yourself with the literature that has been published recently about the topic you wish to investigate. The literature review will give you some idea about recent developments.

The next step is to carry out the study, including laboratory and simulation experiments. There is no standard list of procedures for a case study; that will depend on the subject matter. In the case study presented in the following report, we first gathered data about the effects two drugs had on a "patient." We then used that data to develop mathematical models of the patient's response over time, using those equations to develop controller functions. The controller functions were then incorporated into the patient simulation, and their effects were tested in a simulated heart attack.

The final step in all studies is to draw conclusions. This is, after all, the whole point of performing a study. The conclusion should say something about what you learned in doing the study, and should include whatever recommendations you have for improvements.

The following report is an example of the style of report expected for most research design projects.

Abstract

Blood pressure (MAP) and cardiac output (CO) from an intensive care "patient" were simulated using Simulink. These patient outputs were measured in response to certain drugs (Nitroprusside,

and Dopamine), and mathematical models were calculated to represent the responses.

Using these models, a controller was designed to read the patient outputs and adjust them according to a pre-determined steady-state setpoint using the two drugs, Nitroprusside and Dopamine. With the controller in place on the "patient," a heart attack was simulated as a test of the controller's ability to keep the patient outputs at the steady-state levels.

It was found that the controller worked well using the two drugs, but only in the case of the patient outputs being depressed. A third drug, at least, as well as another controller function will be needed to control step changes in the positive direction.

Motivation

The problem for this study is to model the response of a "patient" to several different infused drugs. The objective is to use this modeled information to design a control device to read several patient outputs, and to adjust the dosage of several drugs accordingly.

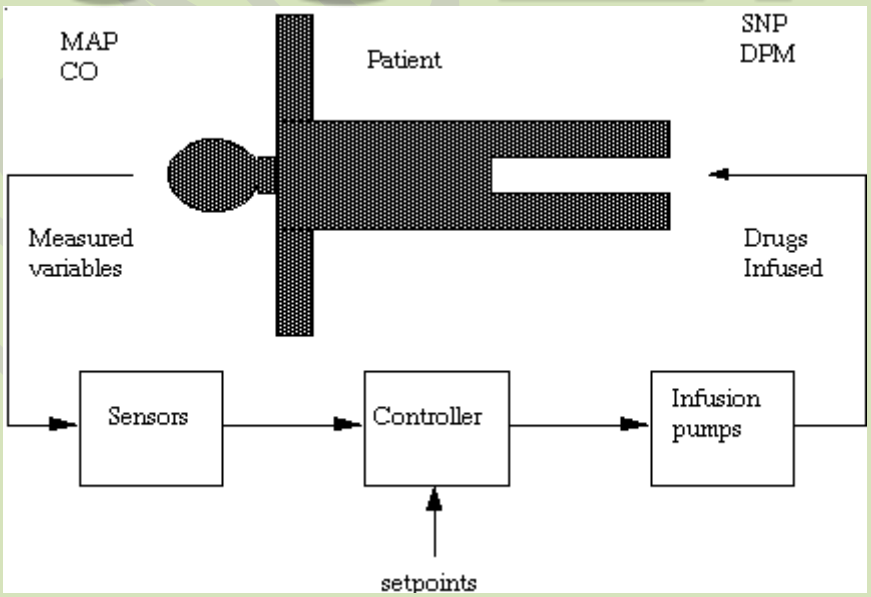

Figure 1: Closed Loop Representation of Critical Care Patient

Literature Review

A background check of the current drug infusion literature is very helpful in seeing the benefits automated control can offer. A few recent articles taken from *IEEE Transactions on Biomedical Engineering* presented a few interesting applications.

Valcke and Chizek (1997) detail a system of closed loop drug delivery (CLDD) which is developed for use with coronary artery disease. The CLDD is designed to be safe and efficient. A feedback control algorithm is used to dose the patient. The patient's response is then monitored and the drug infusion is adjusted for the large physiological variety in people. Then, the drug infusion system simplifies the physician's job. The system also adds safety, by constantly monitoring the response, and when the patient's response is not withing the "safety limits" or becomes hazardous, the system can notify the operator, or stop the drug delivery altogether. The system is also more uniform and more flexible than injection infusions. Preliminarily, a PD model was constructed. There existed a time delay which was due in part to physiological factors. "From a control design perspective, the important issues from the PD model are the large variability in the observed responses, typical of biological systems, and the significant delay between the HR response and the infusion administration."

Since animal experiments are a lengthy and expensive process, it is often preferable to use simulation. Woodruff *et al.* (1997) have developed a simulator to relate the infusion of certain drugs to changes in physiological parameters. The closed-loop cardiovascular drug delivery simulator models multiple factors. It has 1) a nonlinear, pulsatile-flow cardiovascular model, 2) a physiological regulatory model of the baroreceptors, 3) a pharmacokinetics model, and 4) pharmacodynamic models of the drugs. This is much better than a black box model. Pharmacokinetics data was determined through experimentation. Pharmacodynamics depend on the drug, based on results previously attained, they all include a time delay. The simulator was then validated, first piece by piece, then the complete system. It was validated through published data and physician perceptions. Then five animals were tested, and realistic simulation were

obtained. Without the simulator, many more animal studies would have been needed.

Yu *et al.* (1992) describe a controller to be used to monitor the cardiac output of a congestive heart failure patient, and administer vasodilation and inotropic agents (Nitroprusside and Dopamine) accordingly. This controller uses 6 "most probable" patient models to calculate the control algorithms, and simplify the computations.

In the clinical setting, it is usually better to control multiple variables by administering more than 1 drug to a patient. Until the advent of a controller such as the one described in this article, multiple controllers had been used to infuse drugs such as Sodium Nitroprusside and Dopamine separately. This new controller would greatly simplify the tuning of the overall process by lumping more than 1 process together.

Called the multiple-model adaptive controller because of its use of 6 out of 36 possible patient models, this control unit takes its input from the cardiac output of the patient, compares it to the model predictions, and calculates the amount of each drug to administer to the patient.

In the future, this controller will utilize a "smart" sensor to filter out the noise and help to put these useful medical tools into hospitals where they can help to facilitate the administering of drugs to many cardiac patients.

Introduction - Patient Simulation

This study was conducted to chart the effects of certain drugs on a hypothetical critical care patient in a hospital. The simulated data was analyzed and used to design a controller to administer these drugs in the appropriate amounts to keep the patient "stable."

The patient is modeled using the Simulink package in Matlab. The simulink model is programmed to have 6 possible patient conditions, and therefore 6 possible controller functions. The student chooses a random number between 1 and 6, and the

simulink model is altered accordingly. This study is based on one of these models.

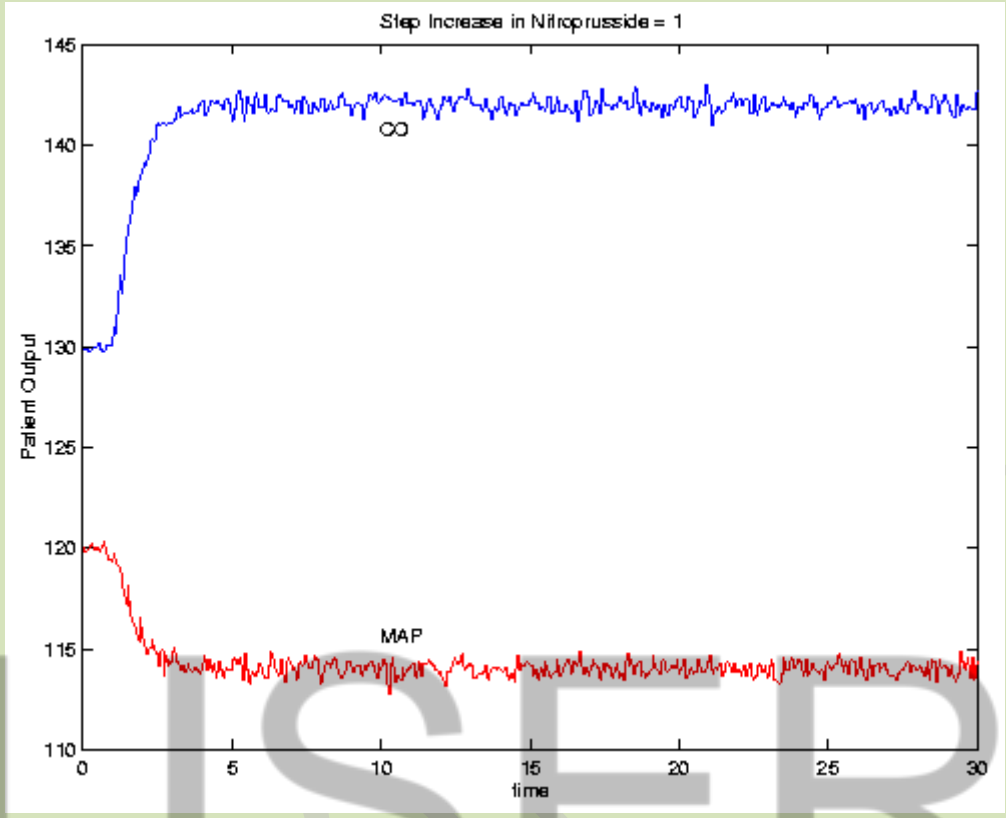

Figure 2: Open Loop Step Response to Sodium Nitroprusside

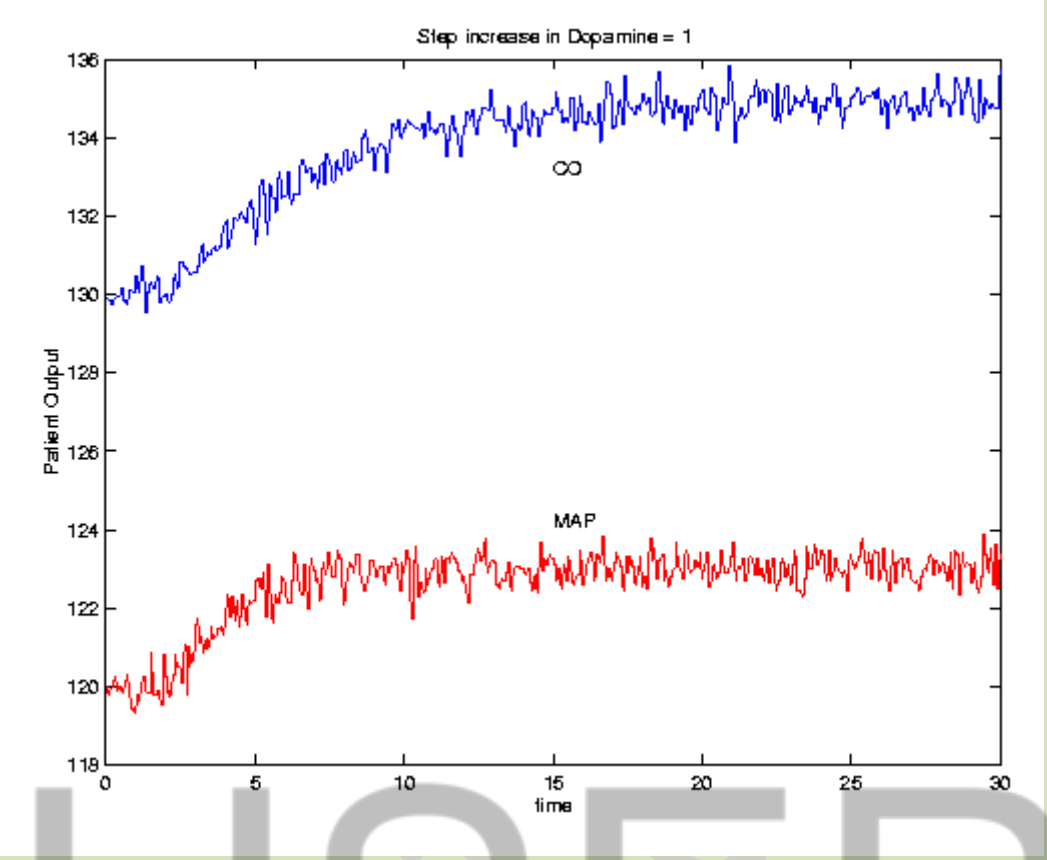

Figure 3: Open Loop Step Response to Dopamine

Model Development for Controller Design

The first task in analyzing the data is to determine transfer functions to model the data. The Simulink feature in the Matlab program is very useful in this regard. From the data presented in figure 2, we can see very clearly that the process gains are approximately +12 and -6 for CO and MAP, respectively, and in figure 3, the process gains are approximately +5 and +3. Observation also tells us that the time delay (theta) is approximately 1 minute for Nitroprusside, and 2 minutes for Dopamine. The time constant for the processes are about 1 minute for both CO and MAP in the response to a step increase in Nitroprusside, and 5 minutes for CO, and 3 minutes for MAP in the step response for Dopamine.

$$\frac{K_P e^{\theta s}}{\tau_P s + 1}$$

K_P = Process Gain

$e^{\theta s}$ = Time Delay Term

τ_P = Process Time Constant

Figure 4: First order transfer function template

In approximating the values for the transfer function, the model is plotted against the actual data to observe the "fit." Using this type of trial and error analysis, a very good correlation between the actual data and the model is attained. The plots of both the data and the model can be plotted on the same graph to check the results.

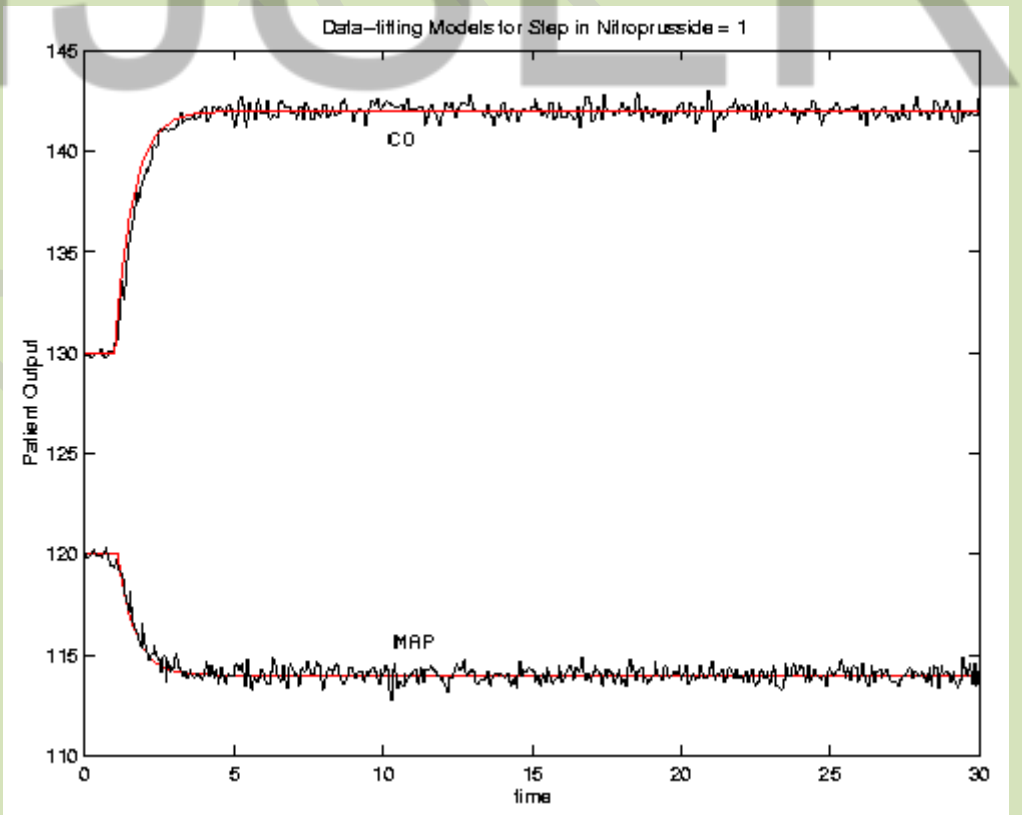

Figure 5: Superimposition of Model on Data for Nitroprusside

Figure 6: Superimposition of Model on Data for Dopamine

This model transfer function can then be used to design a controller to infuse the drugs into the patient. An Internal Model Controller (IMC) basis is used to design a Proportional Integral Derivative (PID) Controller. This is referred to as IMC-based PID Controller design. The mathematics of this method are outlined

With the controller transfer functions arrived at, we can test their effectiveness as Single Input Single Output (SISO) controllers by using them individually to control the patient outputs one at a time. This is shown in the following diagram:

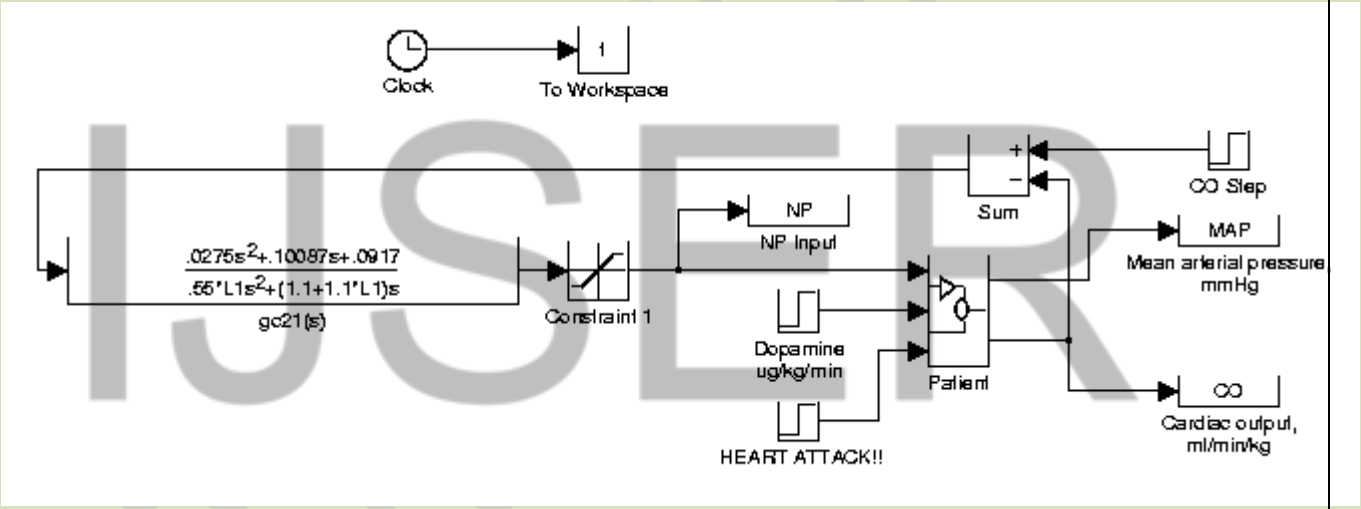

Figure 7: Simulink flowchart of SISO controller for Cardiac Output paired with Nitroprusside

This works well to control BOTH outputs, however, it is desirable for the step increase to only affect the one output while all others remain constant. This means that the controllers must be linked in a Multiple Variable Single Input Single Output (MVSISO) controller setup. This setup would allow all the outputs (in this case, two) to be monitored by controllers which would "cancel out" the effects of a step increase disturbance.

There are many different combinations for output/controller pairings. Some methods result in unstable responses, while others optimize the process responses. A helpful tool to determine the best

pairing is called RGA analysis. It uses a matrix to determine what (if any) the best pairing combination is. The formula is available

RGA analysis, here, is inconclusive; neither of the diagonal values is significantly closer to 1 than the other. We must therefore rely on what we know about the system. We know that the process we want to respond to is a heart attack, where both outputs will decline. The drugs we are infusing control the output in specific ways, and we can use that knowledge to put the drugs in the output/controller loops as beneficially as possible.

Dopamine (DP) boosts both outputs, so, hypothetically, it can be paired with either output. Nitroprusside (NP), however, boosts Cardiac Output (CO), while depressing Mean Arterial Pressure (MAP). The logical pairing would therefore be to control MAP with DP, and CO with NP.

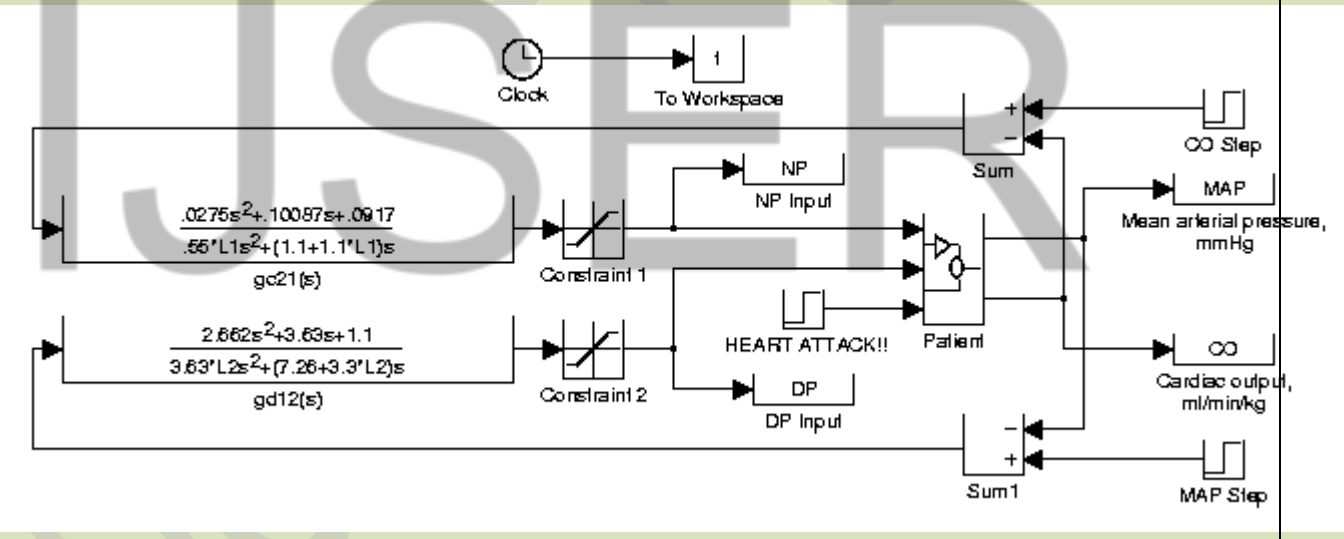

Figure 8: Simulink flowchart of MVSISO controller

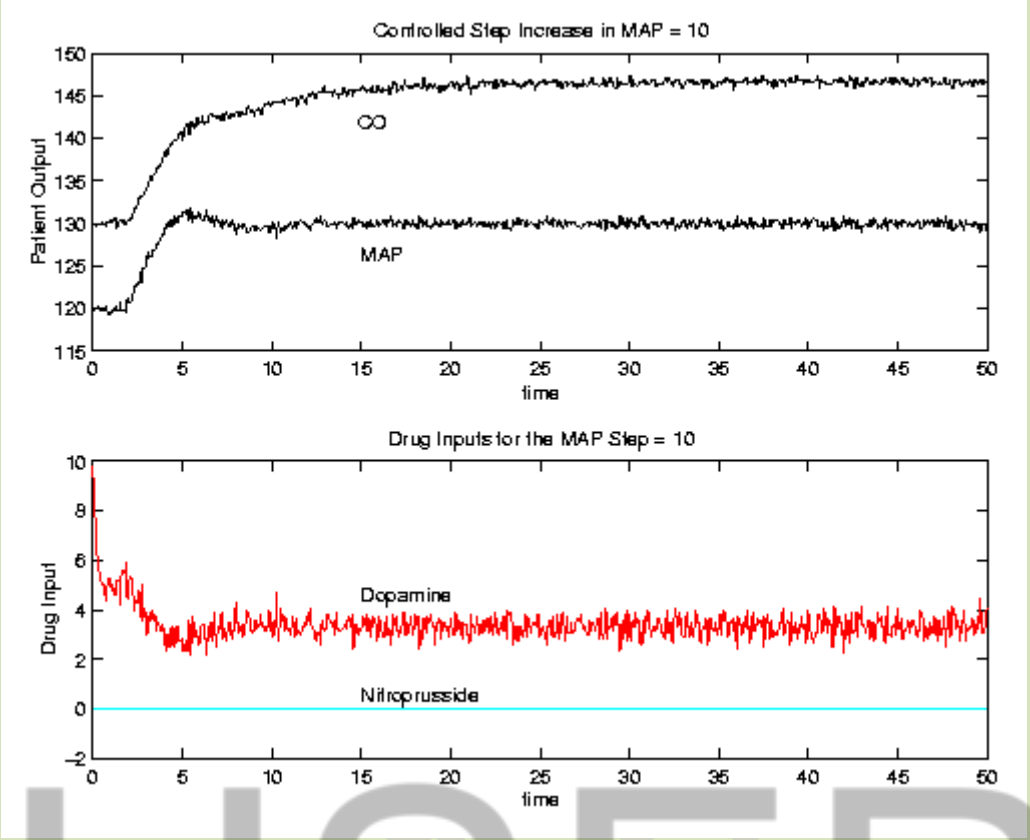

Figure 9: MVSISO control with a step increase in Mean Arterial Pressure

Conclusion

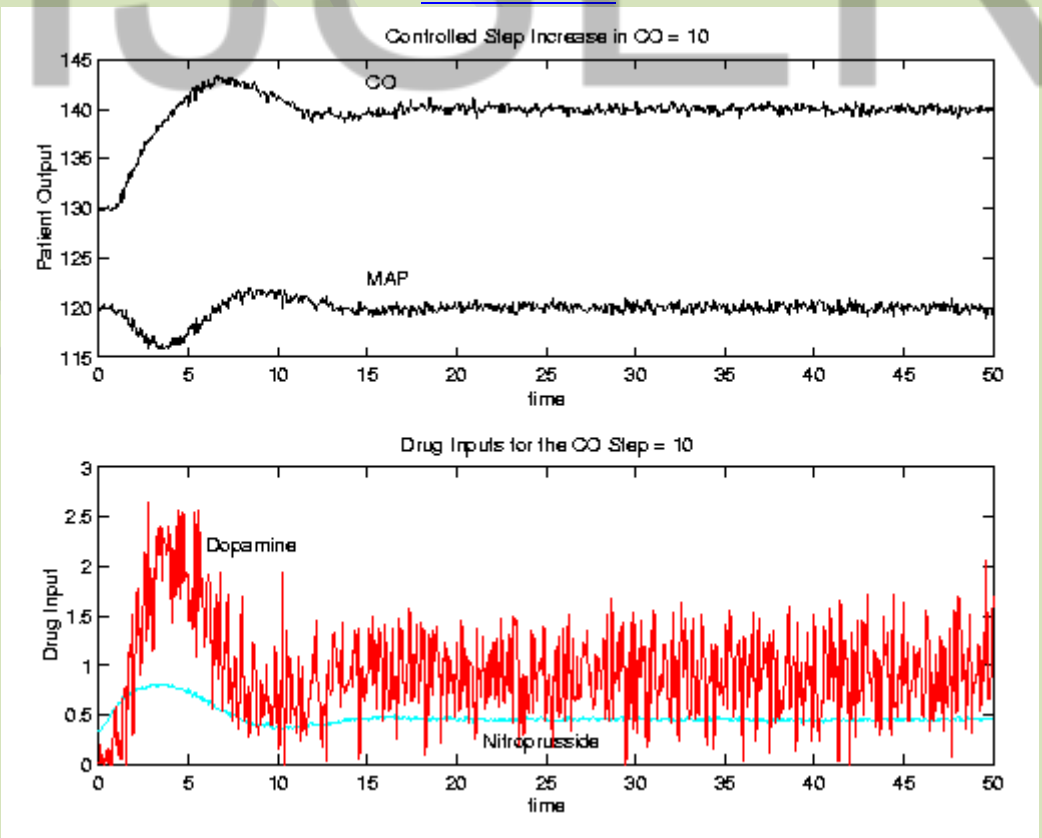

Figure 10: MVSISO control with a step increase in Cardiac Output

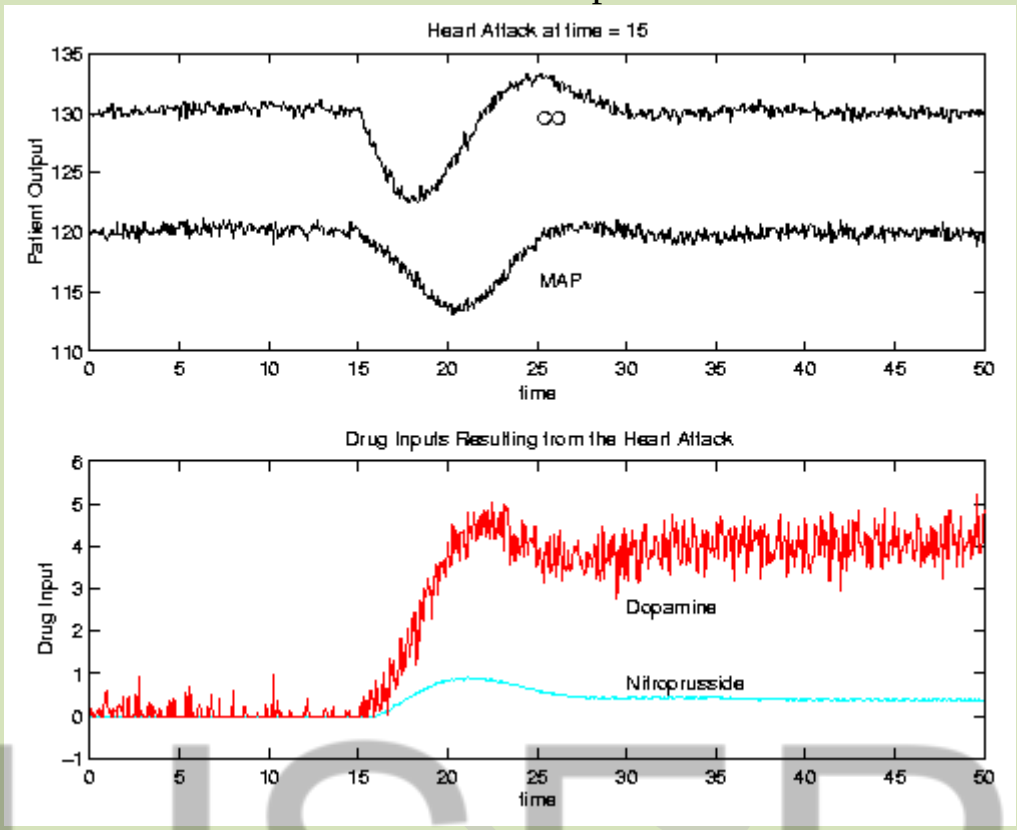

Figure 11: Controller and patinent response to a simulated heart attack

Conclusion

As you'll notice from the above plot that the step increase in MAP, this system is imperfect. When the MAP is increased, the CO also increases, instead of remaining constant. This is because of the limited drugs we use to infuse the patient. There is no drug available to decrease the CO. This configuration does, however, control the heart attack adequately.

The recommendation for improvement to this control system would be to add another drug which can depress CO. This would require another controller and another input, but would allow for better control of the patient's outputs.

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