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USING A PHYSIOLOGICAL MODEL FOR PREDICTION OF THERAPY EFFECTS IN HEART DISEASE

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Abstract

The multitude of interacting processes in the cardiovascular system make reasoning about the possible effects of therapies very difficult and these difficulties are compounded by the various diseases that change the physiological relationships. As part of a project whose overall goal is to develop a program to assist the physician in reasoning about the diagnosis and management of patients in heart failure, we have developed a methodology, based on signal flow analysis, for predicting hemodynamic changes using a model of physiological relationships. The methodology has the advantage that it provides a justification for the predictions in terms of the physiological pathways from the intervention to the effect, accounting for the feedback paths that affect the pathway. Using this methodology and cardiovascular relationships derived from the physiological literature and clinical expertise, we are developing a model for anticipating and understanding the effects of therapies and other interventions on the patient with cardiovascular disease. This paper presents the methodology and its application to mitral stenosis, aortic stenosis, and aortic regurgitation.

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1 Introduction

As the variety of diagnostic and therapeutic modalities for cardiovascular disorders has expanded, the task of planning and assessing patient management has become increasingly difficult. Much of the reason for this difficulty stems from the many interacting physiological mechanisms that together determine the effect of any intervention in a particular disease context. Anticipating the mechanisms that will have the most important effects is a skill that requires considerable experience. The goal of the Heart Failure Program is to provide a tool that the practitioner can use for assistance in reasoning about the diagnostic and therapeutic questions involved in managing a patient[1]. While the program addresses many facets of the patient management process, this paper focuses on the development of a method to predict the response of a patient in a known disease state to a particular therapy or action.

The Heart Failure Program is organized around a causal physiological model of the cardiovascular system. This model is the knowledge base specifying the relationships among parameters in general as well as being the structure for recording the specific states and relationships in the patient. Around this physiological model are program modules for interpreting patient input, for reasoning about the possible diagnoses, and for reasoning about therapy. The problem of reasoning about therapy includes suggesting possible therapies for the patient state and explaining to the user the possible effects, both good and bad, that the therapies might have. Since the diagnosis is unlikely to completely reveal the state of the patient and our present understanding of physiology still allows considerable interpatient variation in responses, the predictions of therapy effects should include as much of the range of possibilities as is consistent with the known state of the patient. We are not yet at the stage of predicting the range of possible effects, but the thrust of the methodological development is toward reasoning about changes even when states and relationships are not completely determined and toward explaining predictions in terms of the mechanisms with the strongest influence on the results.

2 Methodology

The problem of predicting the consequences of a change applied to a variable in a set of constraints too complex for explicit solution has traditionally been solved by simulating the constraint equations. The prime example of that strategy in the cardiovascular domain is Guyton's cardiovascular simulation[2]. That program consists of a large number of equations relating the physiological parameters. To simulate the effect of some intervention, all parameters are set to a consistent initial state, the values of the intervention variable are set to correspond to the desired change, and the model is run forward in time by determining next values for the parameters from the equations at appropriate time increments. There are three problems with this strategy for our purposes.

1. It does not allow for variation in the equations to reflect the interpatient variation of correlations in parameters.
2. It does not allow for uncertainty in the patient's parameter values to reflect lack of information about the true state of the patient. Both of these problems might be addressed by using ranges of values instead of individual values, or using values and expected deviations. However, such methods tend to diverge so rapidly as to be useless.
3. The process of computing the successive states does not help in abstracting the mechanisms that were important in determining the changes. This problem spells the difference between a black-box providing one possible scenario without a way of assessing its sensitivities and a mechanism to help the user understand the problem.

Work on qualitative reasoning has produced a second kind of simulation strategy partially addressing these problems. The qualitative simulation approach applied to the medical field is exemplified by Kuipers work with Kassirer on qualitative simulation of fluid balance[3]. Using this technique, only the direction (monotonicity) of the relationship between two parameters is used to determine the changes. However, when the models become complicated, the amount of ambiguity in the solution increases. In a model as complicated as the essential relationships in the cardiovascular system, the predictive capability of this methodology is severely limited.

The approach we have developed for predicting changes is based on signal flow analysis. Signal flow analysis takes a set of linear equations representing the gains between elements in a circuit and computes the overall gain from input to output if the circuit is stable. To apply this approach in a medical domain, the technique must be extended to consider all parameters as outputs, to do the computation in such a way that the paths of influence are preserved, and to handle quantities that are integrations of other quantities. In addition, it is necessary to make some simplifying assumptions to apply the approach to our domain.

The computational algorithm used in signal flow analysis is Mason's general gain formula[5]. To keep track of the mechanisms of influence and to determine the change in all parameters, we have derived a different version of this algorithm that computes the gain incrementally from parameter to parameter correcting for feedback each time a new feedback path is encountered. In effect the algorithm traces each path from the changed parameter to all other parameters, computing the cumulative gain at each point along the way. The change to a parameter is determined by summing the gains on paths through that parameter. Because the paths are explicitly computed, it is possible to compare the gains across different paths and identify the mechanisms with the most influence on any parameter change.

The problem of integration parameters is made tractable by the assumption of signal flow analysis that the system is in a steady state. For a medical domain, that means that the analysis is answering the question: If the system is in a steady state and a change is applied to the system, what will be the steady state after transients have died down? The assumption that the system goes from steady state to steady state can be relaxed somewhat by taking advantage of the widely differing times required by different mechanisms in the body to change, from seconds for shifts of fluid from pulmonary to systemic circulation, to years for ventricular hypertrophy. By assuming that for the time period of concern, mechanisms that react more rapidly have reached equilibrium and for slower mechanisms no significant change has taken place, it is possible to reason in terms of quasi-steady states. Overall, the assumption of steady states is justified by the stability of the cardiovascular system[4]. The only possible problems would arise if transient states could occur that would change relationships between parameters sufficiently to change the next steady state.

Integrations can be handled because the derivative of the integrated parameter is zero in steady state. For example, the shift of blood in and out of the pulmonary circuit rapidly reaches a state in which both ventricles have the same output. The requirement for a zero derivative yields a set of linear equations in the integrated parameters analogous to the original problem that can be solved for the changes to those parameters by the same algorithm. The changes to the integrated parameters in steady state then become additional inputs to the system of the remaining parameters. Thus, the system can be solved in a two step process. 1) Use the change to determine how the integrated parameters must have changed for their derivatives to be zero. 2) Use these changes to determine the state of the rest of the parameters.

The requirement of linear equations implies that non-linear systems must be approximated by piece-wise linear equations. Many of the relationships between physiologic parameters are non-linear, from the Frank-Starling curve between end diastolic pressure and cardiac output to relationships that are multiplicative. Since the system is dealing with the change from one state to another, the initial gain across a link is the partial derivative with respect to the parameter at the head of the link. For example, the equation determining blood pressure is:

$$BP = CO \times SVR \Rightarrow \triangle BP = \triangle CO \times SVR$$

This approximation is adequate for small changes, but for large changes it is necessary to step through the segments of the change until the complete change is modeled or find values of gain that better approximate the average gain for the change. In effect, this means the change is being applied slowly so that the system is never very far away from a quasi-steady state. In our experience thus far, these approximations seem to be reasonable ones for the domain. Thus, we have a methodology for predicting the effects in a model for any change applied to it.

3 Model of Cardiovascular Physiology

We are developing a cardiovascular model to cover the physiology and pathophysiology as well as the therapies and actions that might be important in managing a patient in heart failure. Several cardiovascular models have been reported in the literature, but none meet the needs of this project. Since the program will ultimately be used in the service of patients, the parameters in the model should be ones that are either measurable in the patient or of demonstrated usefulness for physicians in understanding patient states. Furthermore, only those parameters that are needed to discriminate among the conditions that might respond differently to therapy should be included. Conditions such as valvular lesions, myocardial disease, and renal failure must be included among the parameters because they are important causes of heart failure.

The model is based on constraint relations among the parameters. These relations come from both the physiology literature and clinical judgment guided by the medical literature, including some relations derived from those in Coleman's HUMAN model[6]. Since the model is also the primary vehicle for explaining the predictions, it is important that the model be arranged in such a way that the relations are intuitive. The most natural way to think of relations seems to be causally in terms of blood flow. Therefore, that was the primary determinant in selecting the form of each constraint.

The model includes both left and right sides as well as sympathetic response and heart rate. Such factors as renal function, the determinants of ischemia and oxygen supply are also included in the model but are not of concern for this paper. The following is a qualitative view of the model:

1. Left atrial pressure (LAP) is a function of the volume in the pulmonary circuit approximated from the physiological limits and normal values of the parameters. Variations in compliance are not included.

2. Left ventricular output (LVO) is a function of ventricular filling, determined by the Frank-Starling curve, ventricular compliance, and ventricular emptying.

3. Blood pressure (BP) is the product of systemic vascular resistance (SVR) and cardiac output (CO).

4. SVR is modified by sympathetic stimulation as well as exercise and a number of therapies.

5. Left ventricular emptying is a function of left heart strength, sympathetic stimulation, and the load of left ventricular systolic pressure (LVSP).

6. Right atrial pressure (RAP) is the difference between a function of the venous volume and venous return gradient computed from CO and resistance to venous return.

7. Right ventricular output (RVO) is analogous to LVO, as is right ventricular emptying.

8. Pulmonary artery pressure (PAP) is RVO times pulmonary vascular resistance (PVR) plus left atrial pressure (LAP).

9. PVR is modified by the RVO (the flow through the pulmonary vessels).

10. Blood volume, a constant for short time periods, is divided into pulmonary volume, venous volume, and a factor representing unstressed volume that is a function of venous constriction, sympathetic stimulation, and exercise.

11. Pulmonary volume is determined by the integration of the difference between the output of the two ventricles. Therefore in stable states the two ventricles must have equal outputs.

12. Sympathetic stimulation and vagal stimulation are both functions of the change in BP from its normal state and exercise.

13. Heart rate (HR) is a function of normal heart rate, sympathetic stimulation, and vagal stimulation.

14. Time in systole per minute (and therefore diastole) is determined by heart rate.

4 Representation of Disease States and Therapies

The three disease states included in the model and discussed in this paper are mitral stenosis (MS), aortic stenosis (AS), and aortic regurgitation (AR). The representation of these disorders was determined by the physiologic effect of the disorder on the relationships between the cardiovascular parameters. To test and refine the predictive capability of these representations we have compared the results to published data on patients with these disorders.

MS causes a pressure gradient in diastole between the left atrium and left ventricle. For most situations, it is reasonable to assume that the area of the mitral valve orifice is constant. With that assumption, the flow across the valve obeys the properties of turbulent flow, expressed for valve oriface area as Gorlin's formulas. Thus, the pressure gradient is the square of the flow across the valve during diastole:

$$LAP - LVEDP = (CO/DiastolicTime)^2 k/Area$$

To preserve the intuition of causality in direction of flow, this formula is used to determine the LVEDP from the LAP in the model, which in turn is used as the filling pressure for computing LVO. Thus, LVEDP is determined by the LAP and the pressure drop across the valve.

AS is analogous to MS, except that the pressure gradient occurs between the left ventricle and the aorta and the flow happens in systole. Thus, the relationship drawn from the Gorlin formula is:

$$LVSP - BP = (CO/SystolicTime)^2 k/Area$$

The left ventricular systolic pressure is the pressure the ventricle is pumping against, determining the emptying. There is an assumption here that $LVSP - BP$ is an appropriate approximation for the pressure gradient. From the data we have so far, there is evidence that the relationships are more complex, but not enough evidence to suggest a better set of formulas.

Aortic regurgitation is somewhat more complicated because it depends on the reverse gradient between the aorta and ventricle in diastole. From the Gorlin formula the relationship is:

$$ARFlow = AoLvPressGrad \times DiastolicTime \times k/Area$$

The pressure gradient in turn has been approximated as proportional to mean arterial pressure by $BP - 30$ determined from data in a paper in which the heart rate was varied[7]. Given this regurgitant volume, the effective cardiac output (CO) is the difference.

In the papers used for refining the model, the patients were tested for their response to exercise and three therapies: propranolol, nitroglycerin, and hydralazine. Exercise is included in the model as a factor increasing sympathetic stimulation, decreasing vagal stimulation, decreasing vascular resistance, and increasing venous return.

Propranolol decreases the sympathetic stimulation to systolic function and heart rate and to a lessor extent increases the stimulation to systemic vascular resistance and pulmonary vascular resistance by leaving the alpha stimulation unopposed. Hydralazine decreases both the systemic and pulmonary vascular resistances. The effect of hydralazine in increasing cardiac output cannot always be accounted for by these factors alone. Therefore, we tried assuming a small direct positive effect on the inotropic state as well. Nitroglycerin causes venodilitation and a small decrease in the SVR.

With these relations for diseases and therapies included in the model, the model appears as shown in figure 1. The figure also includes some of the parameters for renal function and myocardial ischemia to show how these fit

Figure 1: Cardiovascular Model Showing Mitral Stenosis

into the overall model, but they will not affect the following discussion. The model has been initialized to the rest state in the first paper and is shown predicting the result of exercise on that state. The highlighting shows the primary determinants of the increase in cardiac output. The mechanism for prediction makes it possible to identify the relative contributions of different pathways from the stimulus to any parameter. Thus, the pathways from exercise through sympathetic stimulation both directly and as a result of decreasing the SVR are the strongest influences on cardiac output in this situation.

5 Comparison with Literature

To determine the ability of the model to predict the changes in patient parameters, we selected papers reporting on patients with one of these lesions undergoing a therapy and/or exercise and reporting extensive hemodynamic data. The five papers include two describing mitral stenosis in adults exercised and given propranolol or nitroglycerin, one describing aortic regurgitation in adults exercised and given hydralazine, one describing aortic stenosis in children with exercise and one describing aortic stenosis and heart failure in adults given hydralazine.

The model was adjusted to the patients in each control state by setting constants in the relations between the parameters in the paper to be consistent with the reported values. These adjustments include shifting the Frank-Starling curve up or down to reflect the output at the reported end diastolic pressure and setting the base blood pressure, heart rate, and resistances. To determine the model's prediction for an action, the value of the changed parameter(s) is selected that produces the reported cardiac output, since all of the interventions we considered have a significant effect on cardiac output. The remaining parameters then reflect the ability of the model to predict appropriately.

The two papers on MS used patients with pure MS, no heart failure, and only somewhat elevated pulmonary vascular resistance. The paper by Giuffrida, *et al*[8], measured the patients at rest, after 10 minutes of exercise, after resting for 20 minutes, 10 minutes after administration of propranolol, and after further exercise. We modeled the experiment by fitting the model to the initial rest state and then applying an amount of exercise that increased the CO to the reported level. In addition, the influence of flow on PVR was changed to reflect the trend of increased resistance with increased flow present in both MS papers. That is, it appears that at the levels of LAP present and the chronic pulmonary changes that take place at high pressures, the resistance no longer decreases with increasing flow, but actually increases slightly. With this adjustment to the model, all of the predicted changes (figure 2) closely match the reported changes.

Since the second rest state varies from the first in that the heart rate is still high, the model was readjusted to the second rest state before adding the propranolol. The propranolol change was adjusted to bring the cardiac output down to the reported level. With this change, the parameters changed appropriately. In our experimentation, we initially modeled propranolol as only decreasing sympathetic stimulation to inotropic state and heart rate, but it was clear that to account for the reported changes it was necessary to include small effects increasing SVR and PVR. Expert judgment and the literature indicate that these effects are reasonable.

The final state was simulated by adding exercise to the state with propranolol. The model required less exercise to predict the reported cardiac output, which is consistent with the reported decrease in exercise tolerance among the patients. The combination of effects on SVR from the propranolol

state		HR	CO	BP	LAP	EDP	PAP
rest	A	83	5.7	88	23	9	32
exercise	A	130	8.0	113	39	9	55
	P	127	8.0	112	42	9	58
rest	A	95	5.9	93	22	9	32
propranolol	A	82	4.8	91	18	11	29
	P	82	4.8	92	21	12	31
propranolol	A	104	6.4	95	30	10	46
+ exercise	P	108	6.4	98	29	12	45

A= actual values, P= predicted values, HR= heart rate, CO= cardiac output, BP= mean arterial pressure, LAP= left atrial pressure, EDP= left ventricular end diastolic pressure, PAP= mean pulmonary artery pressure

Figure 2: Actual and Predicted Parameters in Mitral Stenosis

state		HR	CO	BP	LAP	EDP
rest	A	79	4.5	94	27	12
exercise	A	116	6.3	111	43	13
	P	121	6.3	109	47	12
rest	A	82	5.2	91	27	11
nitroglycerin	A	87	4.6	85	21	8
	P	93	4.6	85	22	8
nitroglycerin	A	113	5.9	102	37	10
+ exercise	P	122	5.9	99	34	9

Figure 3: Actual and Predicted Parameters in Mitral Stenosis

and exercise resulted in a lower SVR even though simply adding the effects would have resulted in an increase in SVR. This total effect is consistent with parallel resistances only part of which is affected by the exercise.

In the second MS paper by Bornheimer, *et al*[9], the patients went through a similar protocol, except they were given nitroglycerin. These patients also had some heart failure with the majority on digitalis and diuretics. As a result, the SVR was elevated in these patients and decreased more with exercise than in normal patients. When the model was adjusted to account for this behavior, the predictions were as indicated in figure 3. The measured parameters changed as reported except for the LAP which is predicted to be somewhat higher than it actually was. This may be a problem with the assumptions about MS since the difference in mitral valve

state		HR	CO	LVSP	BP	LAP	PAP
rest	A	95	7.6	114	83	9	16
exercise	A	151	13.4	136	88	10	19
	P	154	13.4	139	89	9	18

LVSP= left ventricular systolic pressure

Figure 4: Actual and Predicted Parameters in Aortic Stenosis in Children

state		HR	CO	LVSP	BP	LAP	PAP	RAP
control	A	82	3.8	110	93	27	39	11
hydral-	A	85	5.7	-	88	25	36	11
azine	P	102	5.3	108	83	28	38	11
	I	94	5.7	120	87	26	38	10

I= predictions assuming an inotropic effect for hydralazine, RAP= right atrial pressure

Figure 5: Actual and Predicted Parameters in Aortic Stenosis

areas computed from the two rest states is more than enough to account for the LAP difference.

The changes with nitroglycerin were made from the second rest state. The appropriate level of nitroglycerin to produce the reported cardiac output produced the reported change in all of the parameters. When exercise was added to this state, again at a lower level reflecting the decreased exercise tolerance, the parameters changed as indicated. The predicted HR was higher than actual and the LAP lower. There is a pattern of differences among the parameters indicating that the patients probably had additional impediments to increasing their cardiac output.

The second disease studied was AS. The first paper[10] considered the effects of exercise in children with AS. From the data it was clear that the PVR decreased with increased flow as in normal individuals. Also, exercise seems to produce more decrease in SVR than in the adult chronic cases considered before. Finally, the relationship between heart rate and systolic time is altered in AS. A suitable systolic time relationship was derived from the two papers. With these changes to the model, the predictions were all within the limits in the paper.

The second AS paper[11] considered patients with AS and congestive heart failure who were given hydralazine. This paper illustrates a problem with the modeling of hydralazine. If hydralazine is assumed to have no

state		HR	LVO	CO	BP	LAP	PAP	RAP
control	A	84	15.1	5.1	89	14	24	6
exercise	A	113	-	9.7	125	21	45	-
	P	119	24.5	9.7	124	21	47	8
hydral	A	94	-	8.6	86	9	19	5
-azine	P	94	17.5	8.6	84	9	21	7
hydral +	A	126	-	12.7	108	12	29	-
exercise	P	125	24.4	12.7	106	9	29	7

LVO= left ventricular output, CO= net forward flow

Figure 6: Actual and Predicted Parameters in Aortic Regurgitation

inotropic effect, it is impossible to duplicate the changes that occurred. Giving enough hydralazine to produce the reported change in SVR yields the first line of predictions in figure 5. The CO is too low and LAP is increasing instead of decreasing. If it is assumed that there is some inotropic effect, the prediction labeled *I* is produced. This second prediction accounts for all of the changes except that the HR is still too high. This inotropic effect for hydralazine may have some other explanation with a more detailed model of the effects of afterload on CO, but inotropy is the simplest hypothesis at this level of modeling.

The final paper[12] reports on patients with chronic aortic regurgitation exercised and given hydralazine. These patients were all chronic cases with mild to severe heart failure. Digitalis and diuretics were continued without change. Again, the SVR was higher than normal and responded more to exercise than in patients without heart failure. There was also a reported increase in the LAP that was not consistent with the model predictions. It was hypothesized that since these patients had a large blood volume, the exercise effects on the venous volume may be accentuated. With these modifications the predicted values after exercise are all within the stated limits. It may be that the explanation is a flatter Frank-Starling curve, but there is not enough data to distinguish between these possibilities. It is also true that without some quantitative measure of exercise, increasing venous volume response and SVR response is equivalent to decreasing the sympathetic response, which is also likely in these patients.

The patients were then given hydralazine and brought to maximum beneficial level over 24 hours. This time delay complicates the analysis again, since it is possible that the blood volume has changed. Hydralazine was modeled as in the previous case, but at the appropriate SVR, the pressures and output are all too low. If blood volume were to increase 400ml the results in figure 6 are obtained. This is consistent with the tendency of hydralazine to cause water retention, but there may be other explanations. With exercise and hydralazine at the increased blood volume, the predicted changes were consistent with the reported changes except that LAP was lower than reported.

6 Conclusions

Adding these three diseases to the cardiovascular model and comparing the model predictions to the cases reported in the literature has helped to clarify the potential of this methodology for predicting the effects of therapies and maneuvers. In the process, a number of effects were discovered and then verified. Initially, propranolol was modeled as decreasing the effect of sympathetic stimulation on heart rate and inotropy. It became clear that the predicted SVR was too low, making it necessary to add the indirect effect of propranolol on SVR by leaving alpha constriction unopposed. Similarly, the propranolol effect on PVR was added, and there is some evidence for this, at least in acute interventions. Hydralazine was originally modeled as decreasing the SVR, but comparison of predictions to reported values indicated that there must also be an effect on PVR, which was confirmed by the literature. The apparent inotropic effect of hydralazine has also been alluded to in the literature. Thus, the model seems to be very sensitive to the effects of the therapies and able to account for the pathophysiological states with considerable accuracy.

This effort has also pointed out some of the weaknesses of the model. One of the main problems was the presence of heart failure in three of the cases, a pathological state not yet adequately covered by the model. There are places in the model for adjusting the basic systolic function, but the sympathetic response also changes in heart failure. Sympathetic response in general is a more complicated and subtle issue than is captured in the model, particularly in how vascular resistance changes. The dependence of systolic time on heart rate and valvular lesions is only partially captured. Still, the majority of the model seems to be robust and adequate for making predictions, at least in cases with the appropriate patient data. Therefore, it should be possible to extend this model to the other important disease entities in the domain as well as correct the weaknesses.

The computational methodology also shows promise in that it allows rapid computation of the steady state patient values and allows the user to investigate the relative contribution of various pathways to a particular effect.

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