A Mixed Qualitative/Quantitative Acute Cardiovascular Model: Preliminary Report

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1 Motivation and Objectives

In many medical settings precise numerical data for all findings of interest either is unavailable or is too time-consuming to measure. In such situations where a mixture of exact and approximate data is available, a model which can reason with such data and produce output of precision proportional to the the precision of the available findings is desirable. We are developing an acute cardiovascular model which can reason with mixed qualitative and quantitative data, the principles of which can be applied to any mixed-data situation.

Our objective is to construct a computationally efficient, first-principles model of the cardiovascular system's response to blood loss and fluid replacement. Such a model can be used to estimate the volume of blood loss within therapeutically acceptable ranges and predict the future clinically–relevant cardiovascular states of the patient, i.e. to predict initial blood transfusion requirements within ± 1 unit (500cc), and to predict when the patient may go beyond Class II shock (1500cc blood loss or 30% blood loss) either in the absence of remedial procedures or in the presence of fluid replacement or other therapeutic actions. For the model to be usable in Emergency Medicine, however, it must be able to: (1) use the qualitative estimates of patient parameters whose precise values are not available in an Emergency Center (EC); (2) run in real-time; (3) behave qualitatively well.

Our work entails developing both a quantitative and a qualititative model of acute hemorrhage, and then integrating the two to create a mixed qualitative/quantitative (Q/Q) model. The quantitative model assumes all quantitative input, and since it is verified against actual patient data, it is used as a baseline against which the output of the Q/Q model is to be judged. How accurately the model performs will be based on actual patient data obtained from the Medical College of Pennsylvania Emergency Center. The model will be required to provide values to within ten percent of actual values for given hemorrhagic states. The qualitative model assumes all qualititative input, and produces a set of system behaviors which (from a qualitative perspective) contains the behavior(s) of a quantitative model. The Q/Q model reflects: (1) the values of interest to EC personnel— physicians are more interested in the level of shock of a patient rather than precise values for blood loss, cardiac output, etc.; and (2) data availability— data available in the EC consists of a mixture of quantitative and qualitative data; for example, blood pressure and heart rate are known accurately, while systemic resistance (RS) is estimated qualitatively using extremity temperature, and distensible capacity or compliance of the venous systemic system (CVS) using jugular venous distension.

The significance of a model of acute hemorrhage is that the model may be used to project possible results of remedial procedures to stabilize a patient. The results would be based on the patient's current condition and therapeutic hypotheses proposed to rectify that condition. Initialized to reflect the current status of a patient, the model will project in time how the patient's condition will advance if left alone, and also how the condition will change given modifications by an attending physician. Subsequent modifications may also be introduced by the physician, and the model will readjust to the new information.

The model of the circulatory system is not only useful for the problem of exsanguinating trauma, but also for other hemorrhagic conditions such as gastro-intestinal bleeding, ruptured aneurysms, or intra-operative bleeding, and not only for the emergency center setting, but also for the ambulance, the intensive care unit, and the operating room. It may also be extended to include not only the perfusion with blood, but the more general issue of delivery of oxygen. Another long-term objective for the development of the model is its applicability in the classroom for use as a tool to teach emergency and medical personnel about shock and other emergency-related health concerns.

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2 Acute Quantitative Cardiovascular Model

Of the many cardiovascular (CV) models created to date, no published models consider acute hemorrhage in humans; interest has focused on steady-state conditions, or return to steady-state after small perturbations are imposed upon the steady-state, to avoid having to deal with numerous major nonlinear relationships simultaneously.

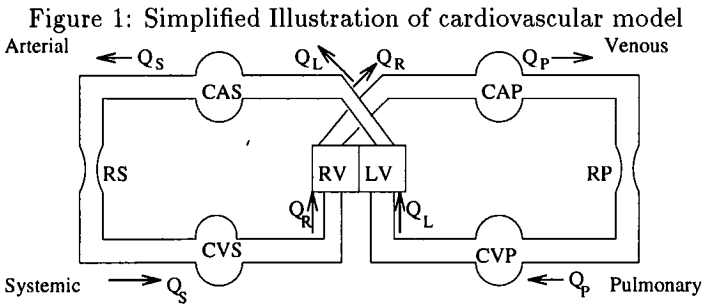
Under the conditions of acute hemorrhage, neither the steady-state condition nor the long-term adaptation of the cardiovascular system is of importance to patient management. Rather, the transient responses of the CV system are important, since they are necessary for answering questions about stabilizing victims after massive blood loss: how soon may the patient go into shock, what fluid replacement is necessary, and so on. Examining physiologic processes during acute hemorrhage demands a short time-scale for the model of minutes to hours.

In creating a model for acute hemorrhage, we have taken two different approaches to develop the quantitative model of hemorrhagic response (the core model): a continuous flow approach [7] and a pulsatile flow approach [1]. Each method provides advantages in analyzing what is happening to the CV system, and our final quantitative model will be comprised of the most pertinent and effective attributes of each method.

2.1 Continuous Flow Model

The continuous flow model best analyzes the system over longer periods of time, from days to weeks. It determines blood flow in a closed circuit through four compartments (systemic arterial and venous, pulmonary arterial and venous). The left and right heats are considered to close the circulatory loop by uniting the four compartments. Blood flows continuously throughout the system, from the left heart to the systemic arterial, to the systemic venous, to the right heart, to the pulmonary arterial, to the pulmonary venous, and back to the left heart (Figure 1).

Figure 1: Simplified Illustration of cardiovascular model



Baroreceptors in the aortic sinus and aortic arch regulate short-term systemic arterial pressure. As blood pressure changes, the baroreceptors sense the change, and transmit a signal to the brain which responds by sending an efferent signal to the heart to modify its rate. The baroreceptors also affect the resistance, resulting in a negative feedback loop of regulated systemic blood pressure. Under conditions of steady-state, the influence of the baroreflex may be represented by a sigmoidal curve. However, hemorrhage induces a dynamic state in the cardiovasculature, and the sigmoid representation must be modified accordingly. Also, the model must incorporate a time-delay for the afferent and efferent transmission of signals among the baroreceptors, the brain, and the heart.

Heart function is modeled in terms of parameters related to the heart's contractile properties. The pressure in the heart chamber is determined by the heart's volume and developed wall tension, which in turn is determined by the mechanical properties of the muscle fibers. The amount of blood that the ventricles pump into the arterial system per unit time (the blood flow or cardiac output), is equal to the product of the stroke volume (amount of blood per beat) and heart rate.

Figure 1 depicts the closed, regulated cardiovascular system. The left ventricle ejects blood flow Q_L and the right ventricle, blood flow Q_R. The systemic circulation is represented by the arterial compliance CAS, the systemic peripheral resistance RS, and the venous systemic distensible capacity CVS. Similarly, the pulmonary circulation consists of the pulmonary arterial compliance CAP, the pulmonary resistance RP, and the pulmonary venous compliance CVP.

2.2 Pulsatile Flow Model

The pulsatile flow model also determines flow in a closed system. The system is larger, incorporating eight compartments, and is based on circuit theory. Resistors, capacitors, and diodes represent vascular resistance, compliance, and heart valves, respectively. This model operates on a much shorter time-scale, given it analyzes how blood flow varies with each heart beat.

Flow through the system is determined by applying Kirchhoff's law around the circuit. Kirchhoff's law states that the net flow at any point in the circuit is zero, and is upheld by setting the net flow at any point, zero, equal to the sum of all flows entering or exiting that point. The two mathematical definitions of flow employed by the model are (1) pressure difference divided by resistance, and (2) compliance times change of pressure with time. A set of ordinary differential equations, solved simultaneously using an euler numerical solution, indicates how pressure, and thus volume and flow, varies over time in each of the eight compartments.

Critical to the mechanics of this model is the time-

varying compliance of the ventricles. The ventricular compliance varies dramatically over the course of each heart beat, and in modeling this phenomenon, in conjunction with the opening and closing of heart valves, blood flows not continuously (as in the continuous flow model) but rather in a pulsatile manner. Simulation of valve positions is achieved by varying the resistance the valves impose upon the system (0.001 mmHg sec/cc for an open valve, 1000 mmHg sec/cc for a closed valve). As valves do not open and close instantaneously, the resistances of the diodes gradually change over a time-scale appropriate for heart valves.

Currently, with the exception of the ventricular compliances and the diodes, all resistances and compliance values are constant in the model. However, physiologic parameters whose functioning changes dramatically during acute hemorrhage must be identified, and means by which to represent their variations designed into the model. Such parameters include blood viscosity, muscular compliance (for containing hemorrhaged blood which has entered intravascular spaces), time-varying ventricular compliances, and the influence of various catecholamines released during hemorrhage. Physiologic parameters currently defined as constant in the model will be redefined as variable to be able to respond to extreme changes brought on by acute hemorrhage. Algorithms which define how these parameters vary and respond to changes will necessarily be designed and implemented.

3 Acute Qualititative Cardiovascular Model

Qualitative reasoning [12, 11] permits systems to be simulated when not all system parameters are known precisely. For example, in a cardiovascular simulation, systemic peripheral resistance (RS) is typically specified as "low", "normal" or "high" based on extremity temperature. Such qualitative values can be used to simulate the behaviors of the CV system.

Qualitative simulators bear many resemblances to their quantitative counterparts, but there are some significant differences. First, variables in qualitative simulators may take either qualitative point values, called landmarks (e.g. $RS = low$), or range values between adjacent landmarks ($RS \in low - normal$). Each variable is associated with a *quantity-space*, which defines the domain of possible values for the variable, e.g. (*low, low-normal, normal, normal-high, high*). Second, time in qualitative simulators is represented as a sequence of instants and intervals. Variables may change values only at transitions between time steps; during time intervals values are either assumed to remain constant at a point value or to be contained within a range value. Third, functions can be expressed either precisely as in $CO = HR \times SV$ or using qualitative functions. For example, CO (cardiac output) varying monotonically with HR (heart rate) is represented as $CO = M^+(HR)$. M^+ thus defines a class of functions which relate the independent and dependent variables monotonically. Additional qualitative functional relationships can be specified, such as the M^- inverse monotonic relationship.

We have been developing a general constraint-based simulation tool, *QobiSIM* [9], that is built on a constraint programming language, SCREAMER [8]. SCREAMER accepts both qualitative and quantitative variables and constraints on variables, allowing development of a mixed qualitative/quantitative simulation tool which offers advantages over existing qualitative/quantitative simulation tools, including efficiency, generality and ease of use. Tests on several large qualitative models (e.g. chemical reactors with non-linear proportional integral controllers) have proven the ability of *QobiSIM* to match the results of the well-known simulator QSIM [5], thus verifying the soundness of the implementation.

A first-cut simulation of the continuous flow cardiovascular model has been implemented. The qualitative model is shown in Figure 2.

The time scale for the model is on the order of minutes to hours, in contrast to the seconds to minutes of the pulsatile cardiovascular model of [10], or the days to months of the water balance/CV mechanisms of [4].

Creating this model involved converting the set of ordinary differential equations (ODEs) which define the core model into an equivalent set of qualitative differential equations (QDEs). This set of QDEs is guaranteed not to produce any unsound system behaviors; however, it produces several spurious system behaviors, e.g. behaviors which differ only in unimportant variables, such as 1st and 2rd-order derivatives. Reducing such unwanted behaviors requires defining additional constraints, such as constraints on higher-order derivatives, quantitative constraints, etc. Further work is needed in this area: the purely qualitative model provides output that roughly mirrors the quantitative model, although better constraints are needed to improve its performance and accuracy, and to avoid generating spurious behaviors.[1]

The types of simulations which are being run are:

Steady state: this models the CV state when all state variables are stable;

Step decrease in Blood Volume: this models the effect of blood loss over a short time period;

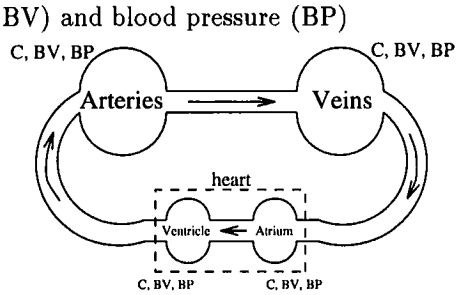
[1] Such problems are inherent in all purely qualitative models.

Leak: this models a person who is losing blood over a period of time;

Infusion: this models the effect of an infusion on a person who may or may not be losing blood.

While the focus of this investigation is to develop our mixed Q/Q model for acute cardiovascular activity, we intend, as an application of this project, to couple the acute qualitative cardiovascular model with models of other physiological systems, such as respiration. Currently, we are also developing a simple, qualitative model for respiration centered on the physical changes that occur during inhalation and exhalation. Our aim in coupling physiological systems is part of our goal to provide a simplified global model that integrates anatomical disruption with physiological change. We are designing our global model to capture the physical properties of anatomical parts, their spatial interactions, and their physiology and pathophysiology.

Figure 2: Simplified Illustration of qualitative cardiovascular model. Each of the three "systems" (heart, arterial and venous) has its own values for compliance (C), blood volume (BV) and blood pressure (BP)



4 Mixed Qualitative-Quantitative Model

Creating the mixed qualitative-quantitative model involves integrating quantitative constraints into the qualitative model. Incorporating quantitative constraints can significantly decrease run-time and spurious behaviors in a purely qualitative model [2, 6]. To the extent possible, we plan to use such numerical constraints from the quantitative core model. The goal is to produce a model which can use either qualitative or quantitative input, as the data is available. We will take advantage of the built–in numerical constraint–solving techniques in SCREAMER (e.g. for real-valued non-linear equations and interval arithmetic) to solve the quantitative constraints. This is similar to the integration of information from *numerical* simulation of differential equations into qualitative models [3]. There are several other techniques developed by quantitative extenstions to QSIM [6] and QPE [2] which can also be used.

We argue that there are many medical domains in which mixed Q/Q models are necessary, and that the principles embodied in QobiSIM will be applicable to all such domains.

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