

CVSys: A Coordination Framework for Dynamic and Fully Distributed Cardiovascular Modeling and Simulation

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ABSTRACT

This paper presents a new framework, CVSys, for dynamic and fully distributed cardiovascular simulation with natural behavior flow and dynamic simulation control. This coordination framework uniquely incorporates attributes of open-endedness in terms of dynamic interactive entry of changing states during runtime, flexibility of event handling and system extensibility. The coordination framework relies on the autonomous object paradigm underlying a new distributed computing environment, MESSENGERS¹.

CVSys exploits extensive parallelism found in physiological processes. Natural behavior flow is the guiding principle of design and development, closely coupling model and compute processes to actual physical entity flow patterns, resulting in a more indigenous and a more integrated system representation. Dynamic simulation control serves to interject new events or state changes into the simulation in a random and dynamic method during runtime without halting execution and under fully distributed control. We distinguish two types of dynamic simulation control, Reflex arc network activated internally at receptor sites from detected state changes, and Simulation steering activated in response to externally introduced events. The CVSys Coordination Framework including natural behavior flow and dynamic simulation control features enable a more expressive cardiovascular modeling system. Also noteworthy is the representation of regional circulatory beds with related short term response adaptations, handled in a fully distributed and dynamic approach. Advancement of the current state of cardiovascular simulation is found in CVSys, realized through the introduction of new distributed and parallel computing methods.

Keywords: Cardiovascular modeling, Distributed interactive simulation, Autonomous objects, Intelligent monitoring

1. INTRODUCTION

Given the complexity of human physiology, simulation is a critical instrument for research, patient assessment, intelligent monitoring, and training. Currently lacking is a fully distributed framework to support large scale interactive biomedical modeling and simulation. This coordination framework facilitates *live simulation*, that is the interaction of patient state changes during execution of this dynamic system. CVSys utilizes new computing approaches that uniquely provides close alignment of computing processes to physiological behaviors. More expressive modeling and simulation result from the exploitation of inherent concurrence, from extensible system integration, and from the injection of dynamic, open-ended interactive state changes. These features make CVSys particularly suitable for interactive, intelligent monitoring.

Cardiovascular disease is by far the greatest cause of death each year, claiming as many lives as the next eight leading causes of death combined². Through the use of new distributed computing schemes in this new coordination framework, we hope to introduce an additional means of providing insights to indirectly benefit cardiovascular health care. The complex cardiovascular system presents an ideal testbed application comprised of a high degree of innate parallelism, interactive response systems and multiple integrated subsystem components. CVSys models fluid and mechanical dynamics of the full body, pulsatile cardiovascular system. Inherent parallelism of the cardiovascular physiology as found in the peripheral perfusion of organ beds and their associated resistance/conductance control mechanisms is modeled and processed concurrently in an autonomous-object based, coordinated environment.

The goal of CVSys is to advance current methods providing quantitative analysis of cardiovascular physiological functions with reactive interaction of both internal and external sources; through utilization of new parallel and distributed computing

approaches³. This research demonstrates the value of dynamic distribution, of interactive state changes, of autonomous computational distribution, and of system extensibility. The Coordination Framework is facilitated through features of MESSENGERS, an open-ended, flexible, autonomous objects computing environment, enabling distributed control. This Framework includes newly introduced Natural Behavior Flow and Dynamic Simulation control. Natural Behavior Flow closely couples natural physiological processes to parallel and distributed computing processes. We distinguish two types of Dynamic Simulation Control 1.) Reflex Arc is activated internally and triggers dynamic computational functions that perform adaptive adjustments without interrupting execution of the circulatory closed loop system. 2.) Simulation steering supports the ability of the executing system to interact with data and/or events introduced externally (i.e. changing patient states).

MESSENGERS is used as a control language to coordinate the operation and interaction of compiled node resident functions, which carry out the actual computations of the model. The basic approach is to map separate entities such as organs and individual regions of vasculature onto separate processing nodes running interpreters. These nodes contain the necessary sets of computational functions with equations, constants, and local variables describing the local organ or regional vasculature behavior. The flow of blood is implemented as waves of Messengers, which cycle through the organism along the predefined serial and parallel paths, thus closely mimicking the actual flow through the full body over time and events. As they pass through the entities, they trigger the execution of the appropriate functions to compute the new values for that organ or vascular region at the current simulated time or event increment. Additional Messengers are invoked and cycled to appropriate sites to trigger reactionary short-term regulatory functions.

This paper will present CVSys, a coordination framework for distributed and dynamic cardiovascular simulation and analysis and how it addresses peripheral region circulation. First, will be discussed the mapping of the physiology into computation. Most notable coordination framework design and implementation features will be discussed, including natural behavior flow, reflex arc network and simulation steering. Described are the methods used to represent regional circulatory responses. Preliminary results of modeled circulatory responses and how this system offers benefits to the concept of intelligent monitoring are shown. Finally, conclusions and future work are discussed.

2. COMPUTATIONAL MAPPING OF PHYSIOLOGY INTO COORDINATION FRAMEWORK

In CVSys, the cardiovascular representation is based on Rampling's basic premise, *the cardiovascular system consists essentially of a double, reasonably synchronized, pumping system each side of which feeds the other through a peripheral circulation made up of a vast number of series and parallel circuits*⁴. CVSys is a bio-fluid, mechanical model with the heart treated as a pump, with valve opening/closure functionality; and fluid dynamics of the blood circulation computing flow, pressure, volume, resistance, compliance and radius in blood vessel regions and compartments. CVSys represents the whole body circulatory system with segregated peripheral circulatory beds and associated short-term reactive control mechanisms. Activation of distributed regulatory functions and resultant varying resistances and flows to these parallel organ beds are addressed. The present model does not address distribution of blood within a given organ or tissue. Note the close model alignment to the actual physiological system, as Figures 1 and 2 denote the basic closed loop physiology modeled in CVSys.

Fig. 1 denotes the abstraction of vessels partitioned into regional boundaries. The model addresses size and geometry of vessels on a regional basis. Regional properties change with time and pulse wave position. This abstraction provides the means for linearization and discretization. At the start of each vessel region, properties are known from previous region boundary conditions. The general approach is to idealize flow as pulsatile in nature and discretize regional computations into propagated steps over changing heart rate and time.

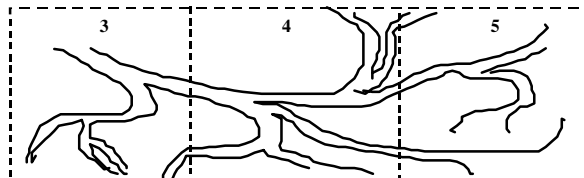


Figure 1. Abstraction of vessels partitioned into linearized, discretized regions.

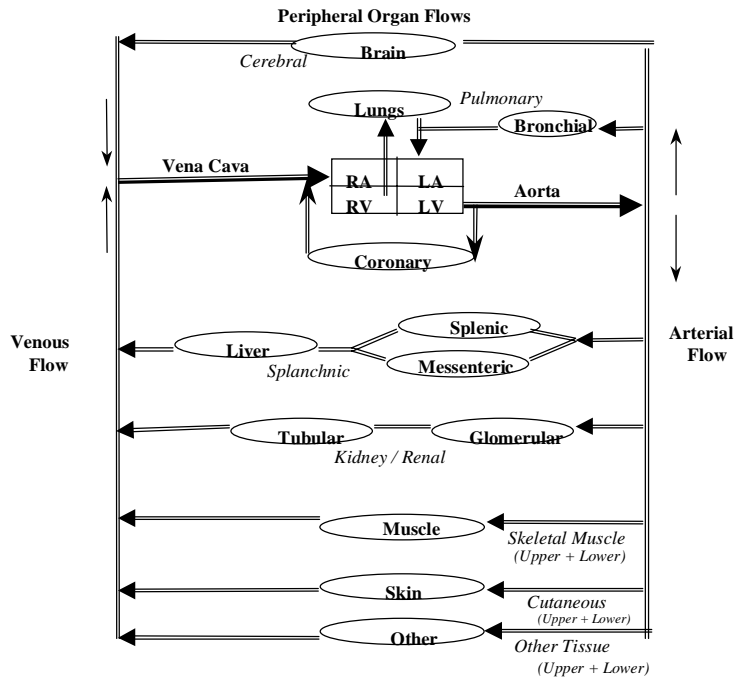


Figure 2. Basic circulatory physiology represented in CVSys with multi-region arterial system, multi-region venous system, distributed regional organ perfusion systems, pulmonary and cardiac components.

Regions are represented as logical nodes which are linked in a logical network and mapped to actual physical processing nodes. For example, a region representing a physiological entity such as aortic arch has a logical node on a physical node where computations occur and property values for the most current heart beat pulsewave are stored for that region. The circulatory physiology is implemented as a series of 4 heart chambers, 21 arterial nodes, 21 venous nodes, 7 peripheral organ beds with 7 associated arteriole regions and 7 associated venule regions. The nodes are connected to neighbor nodes by logical links by which blood Messengers will flow. For example, Figure 2 and in more detail, Figure 5 shows propagated flow through linearized, discretized regions. For example, blood flow Messengers traverse from the Left Ventricle (LV) node to Aorta node, to Artery1 node, and onto remaining arterial nodes. The peripheral perfusion flow from aorta to coronary is an example of branching flows.

Although CVSys models the entire body circulatory system, in this paper we briefly allude to the whole body circulation and focus on the peripheral organ bed perfusion. We describe related resistance computations and peripheral regulatory controls. The body's multiple regulatory systems act to maintain systemic blood pressure by regulating regional flow. The peripheral organ circulation beds and related control mechanisms offer the greatest opportunity for parallelism in the simulation system with concurrent fluctuating levels. CVSys implements eight peripheral perfusion regions of systemic organ bed, designated: cerebral, coronary, pulmonary, splanchnic, renal, skeletal muscle, cutaneous and other tissue. One arteriole region is associated with each of the eight organ beds. As blood flows from the discretized arterial regions through arterioles into the organ beds and through venules to veins, baroreceptor and cardiopulmonary reflex mechanisms affecting the flow are represented in a dynamic and distributed manner. In representing the short-term response mechanisms we concentrate on affected resistance of the arteriole regions and conductances of the venule regions.

2.1 Natural Behavior Flow

The cardiovascular system has inherently concurrent physiological components. *The entire cardiovascular system is such that blood flows in a continuous loop with many parallel branches*⁵. Our Natural Behavior Flow approach enacts distinctive themes around which all the CVSys development revolves:

1. To exploit the inherent parallelism of the cardiovascular system application
2. To couple natural physiological processes with dynamic and distributed computing processes.

Natural behavior flow is the guiding principle and critical feature of both design and development. The modeling and processing are guided by the behavior of actual physiological processes. Natural behavior flow approach results in models representative of the physiological system and in computing processes resembling natural behaviors. In Figures 1, 2, and 3, many concurrent flows are evident, all proceeding in a natural manner. In CVSys normal flow patterns proceed analogous to blood flow such as the arterial and peripheral closed-loop flows while dynamic regulation mechanisms are propagated autonomously and concurrently through the system. Rather than systems with close synchronization controls that would normally halt flows to incorporate fixed level regulatory changes, CVSys initiates detection from the receptor sites (depicting neural impulses to various levels of the central nervous system), calculates and perceives adaptive changes at the local effector site entity node variables via Messengers (depicting the regulating chemicals in the blood stream). As the pulsatile blood flow makes its next cycle through these sites the regulatory changes are carried on to subsequent locations with the normal blood flow, much as in the natural physiological processes. The system is fully distributed in the sense that properties of nodes are communicated only to neighbor nodes and carried by Messenger flow along links. This approach promotes open-ended, fully distributed control with entity interactions coordinated, corresponding to natural behavior flow patterns.

3. ARCHITECTURE OF COORDINATION FRAMEWORK

This section discusses design and system architecture concepts for the coordination framework of CVSys.

3.1 MESSENGERS Autonomous Object Computing Environment

CVSys is implemented in the MESSENGERS^{1,6} autonomous objects computing environment. MESSENGERS is based on the concept of intelligent objects carrying their own behavior and propagating autonomously through the underlying computational network. MESSENGERS provides navigation, computation and control of a truly distributed and parallel network of computer nodes. Combined navigational autonomy, coordination and dynamic composition capabilities realized in MESSENGERS differentiate MESSENGERS from conventional message-based paradigms and enable the distinctive open-ended, dynamic framework of CVSys:

Navigational autonomy provides the ability for each object to navigate through the network according to its own behavioral script. Navigational statements allow individual Messengers to navigate to specified nodes or to follow links emanating from current node it resides on, or by cloning itself to pursue independent paths. Logical networks are dynamically constructed using navigational statements⁶. Objects, representing blood, *flow* from one region to another along emanating paths and along branching paths, analogous to natural blood flow. Navigational autonomy also supports the passage of reflex regulatory responses along their natural paths of invocation and adjustment.

Intra-object coordination allows Messengers to orchestrate the execution of precompiled components dynamically by having that Messenger invoke and control the execution of functions residing on various nodes throughout the network⁶. Temporal coordination is achieved by special functions providing global virtual time (GVT) mechanisms¹. Through coordination, as the blood flows, regional values are computed and updated through local execution of precompiled functions. Heart rate controls and pulse wave propagation is enforced through GVT constructs. Important features of MESSENGERS offer the flexibility of a dynamically changeable environment supporting regulatory and control mechanisms reacting to changing systemic conditions and/or externally introduced events, supportive of a *live simulation* theme.

3.2 Basic Circulatory Model and Peripheral Circulation

CVSys logical nodes are organized into multiple logical network layers. The current prototype includes four layers: Circulatory Model Layer, Reflex Arc Network Layer, Simulation Steering Layer, and Systems Analysis Layer. These logical layers may be envisioned as layered over one another and over the underlying physical network. In addition to concurrent flows in a single layer, layers are processed concurrently as with the case of adjustments during the circulatory flow.

Figure 3 portrays the Circulatory Logical Network Layer. This layer supports the modeling and simulation of the closed loop blood flow throughout the body, including peripheral perfusion of the organ beds. Messengers propagate or flow along logical links to logical nodes, branching to concurrent logical links as appropriate; much like blood pulsating through regions and flowing through branches of the circulatory system.

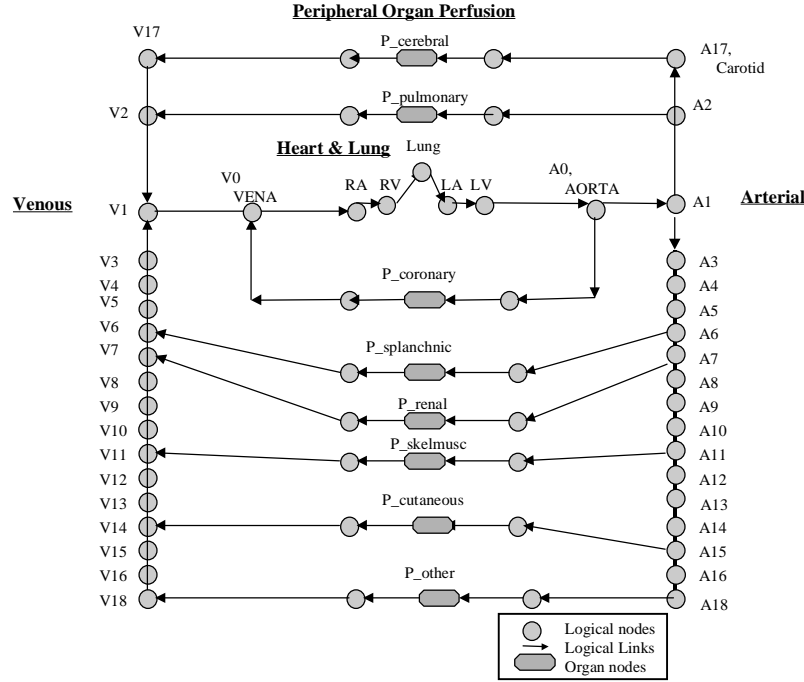


Figure 3. Circulatory Logical Network Layer.

3.2.1 Resistance Affecting Peripheral Circulation

Because resistance is critical to peripheral organ bed perfusion, we address resistance computation and in Section 4, present modeled results of affected peripheral flow. Primarily determined by controlled dimensions of conducting vessels and rheology or properties of the blood, peripheral resistance is also affected by changing conditions. Resistance and directly related vasoconstriction and vasodilation, directly control critical blood flow to the organ beds. First, we show accepted formulas used in deriving resistance values for arterial regions beginning with a laminar flow and factoring in possible turbulence. Then, we show resistance computations for the peripheral arteriole regions and finally, the resistance relation for organs arranged in series and in parallel sequences.

Resistance R, for Arterial Regions Considering Laminar Flow and Turbulence

Resistance R , often termed "impedance" for the pulsatile arterial tree, is calculated each time the pulse wave propagates through each arterial region. Hence resistance is recalculated in each arterial node for each pulse wave generated for each heart beat. Changing resistance levels significantly affect pressure values and flow rates. The most simplistic resistance relation is stated as the pressure gradient over flow.

$$R = \langle \Delta P \rangle / Q$$

In attempting to capture realistic portrayal of the arterial bed resistance, we will first calculate local vascular region radius based on local volume and length. Then steady laminar flow $lamR$ (non-turbulent), is calculated as in a long, rigid, circular tube using rearrangement of traditional Poiseuille flow above, in a pipe with diameter d , viscosity η , constant $128/\pi$, and length l . Poiseuille's law gives very good approximations of flow⁸. The underlying vessel geometry is actually motivated by the change of vessel radius r , enacted by vasoconstriction or vasodilation, causing changes of vessel resistance and consequently vessel conductance, over time. Hence, radius (diameter) is the most consequential variant underlying conductance adjustments, with radius being determined by resistance adjustments made in response to controlling impulses such as arterial baroreceptor responses. This represents the minimum resistance of all possible flows in a tube¹⁰.

$$lamR = \frac{128\eta l}{\pi d^4}$$

After deriving the steady laminar flow, the turbulence of flow will be factored into the resistance equation if the blood flow is determined to be turbulent. Turbulence of flow represented by the traditional Reynolds Number, RN , is defined as the ratio of the inertia force to the viscous force in the flow. To arrive at local RN , the local velocity representing the linear velocity of flow in a tube of cross sectional area⁹, and kinetic viscosity $\langle kv = \eta / (\text{density}) \rangle$ ¹⁰, are derived. RN is then equivalent to $\langle \text{velocity} \cdot d \rangle / (kv)$,¹⁰. The resistance for the arterial region is then derived with RN is factored into the resistance equation. An RN level in excess of 2300 units is considered turbulent if RN is greater than 2300¹⁰.

$$R_{arterial} = lamR \cdot \langle 0.005 \cdot RN^{3/4} \rangle$$

Resistance for Arteriole Regions

Flow resistance determines the amount permitted to flow through vessels or organ region. Arterial resistance, $R_{arterial}$, influences arteriole pressure, P_a , which defines Resistance controlling flow from arterioles to organs. Local flow resistance is calculated in each arteriole node for each pulse wave generated per each heart beat. The resistance $R_{ArterioleToOrgan}$ for each specific organ bed (i.e. splanchnic) is recalculated on each for flow cycle, defined by the local perfusion pressure gradient, P_p , over arteriole to venule in the relationship $(P_a - P_v)$.

$$R_{ArterioleToOrgan} = P_p / Q$$

Peripheral Resistance for Organs Arranged in Series

Total resistance for multiple organ beds that are arranged in a sequential series (i.e. the renal organ circulation of tubular and glomerular), and various resistances as blood flows through that vascular circuit is calculated from a summation relation of those individual resistances as exemplified in the renal circulation of Figure 2 and calculated with R_{series} .

$$R_{series} = \sum_{i=1}^{series} R_i$$

Peripheral Resistance for Organs Arranged in Parallel

Total Peripheral Vascular Resistance (TPR) of compensating circuits positioned in parallel is equivalent to the summation of conductances g , remembering that g is the reciprocal of R hence, $g = 1/R$, equal to $Q / (P_a - P_v)$ flow over perfusion pressure. Referring back to Figures 2 and 3, there is a parallel relationship with the splenic and messenteric flows; as well as parallel relationship for all of the 8 peripheral organ flows. The summation of reciprocal resistances for regional organ perfusions is propagated as an accumulative Messenger variable. This summation, TPR , provides a compensatory relationship for the multiple organ flows and affects systemic arterial blood pressure. In the peripheral circulation, increases or decreases in a given organ will not have a major impact on pressures, however tremendous differences in flow rates exist between the various organs and therefore there are also large differences in the regional resistances. These regional resistance and flow differences are influenced by various physical exertion states as we are studying with CVSys.

$$TPR = \langle \frac{1}{R_{parallel}} \rangle = \langle \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_n} \rangle = \langle \sum_{i=1}^{parallel} \frac{1}{R_i} \rangle$$

TPR describes the total vascular resistance across all systemic organ beds of the body. That total resistance and cardiac output, CO , ($CO = \text{heart rate} \times \text{stroke volume}$), helps to maintain an average systemic arterial blood pressure, SAP .

$$SAP = CO \times TPR$$

These Resistance algorithms are enacted in the CVSys Circulatory Level at the local nodes. Once derived, the local vascular resistance values are used to determine local organ flow, $Q = P_p / R$, and as reflected in Figure 7. The local Short term adjustment mechanisms causing local recalculation, in the Reflex Arc Network Layer. Particularly emphasized are short-term factors affecting distributed changes in multiple vascular resistance beds, resulting in vasoconstriction or vasodilation of peripheral resistance vessels and affected regional blood flows.

3.3 Reflex Arc Network

The Reflex Arch Network approach provides an indigenous representation of compensatory mechanisms such as baroreflex and cardiopulmonary reflex response mechanisms. Also administered at this level are venous volume displacement, venous return, variation of heart rate, stroke volume and cardiac output levels. As explained by Sagawa⁷, the physiological system actually involves multiple neural signals to various levels of the central nervous system and multiple efferent pathways to multiple effector organs. The physiological response mechanisms in which baroreflex and cardiopulmonary responses are elicited

is accurately defined as a multi-input, multi-output, and multi-level control system. The body's multiple regulatory systems are designed to maintain systemic arterial blood pressure by sacrificing flow to various organ systems and peripheral regions through various internal and external regulatory mechanisms.

Illustrated in Figure 4 is the Reflex Arc Network Layer. This layer enacts the reflex response mechanisms regulating the underlying circulatory layer. Receptor sites detect events and initiate neural signals to layers of the central nervous system represented by the links from the carotid node, aorta node, vena cava node, right atrium and lung nodes to the Ans node. The solid logical links represent multiple efferent pathways to affect resistance of arterioles, flow of venules, venous return to right atrium, heart rate of cvs node and right heart nodes, and cardiac output from left atrium. Signals and adjustments propagated along these various logical links enact prescribed short-term baroreflex and cardiopulmonary responses.

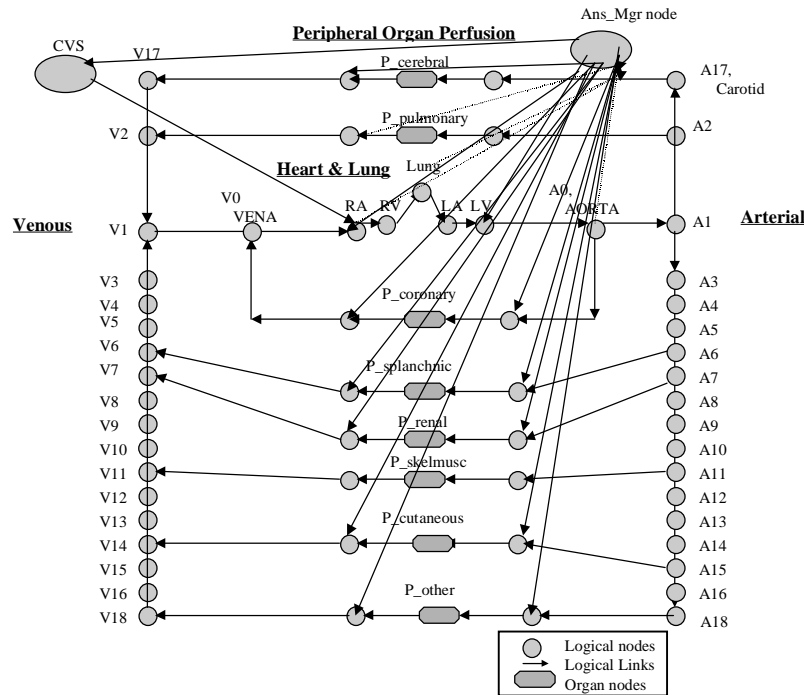


Figure 4. Reflex Arc Network Layer.

The Reflex Arc network is invoked when certain variable results are detected, setting in motion a whole cascade of operations in the form of fired Messenger functions. Arterial blood pressure changes are initiated by changes of the peripheral vascular resistance and/or cardiac output in response to effector mechanisms that react to the receptor firing. Abiding by our guiding theme of coupling computer and natural processes, we implement this activity in a manner resembling the natural processes by injecting Messengers into logical networks representing the neural signal pathways, multiple efferent pathways and blood flows. Analogous to actual physiology, based on gradient changes of certain variable threshold levels where adjustment Messengers are triggered and injected in the case of elevated pressure levels or as in the case of low pressoreceptors with lowered volume levels.

These Messenger objects are dynamically composed, injected into the system, and autonomously propagated during concurrent system execution. From these receptor sites, the triggered adjustment Messengers propagate to an adjustment manager control node. Determined by the type of event, Messengers are replicated to propagate to specified effector sites. At the effector sites, the fractional arguments are used to compute adjustment values. Appropriate local entity node variables are updated over designated time differentials accordingly. Adjusted values are picked up in a natural manner as the blood flows (propagates over the logical network).

Meanwhile, the receptor sites continue to test for conditions and to fire appropriate impulses, so it is not necessary to send acknowledgement communications for successfully adjusted effector sites. For example, if a Messenger is lost and the appro-

appropriate adjustment did not occur, the receptor will continue to sense the condition and continue to initiate Reflex Arc impulses. Hence communication is minimized with the autonomous objects approach. And if such conditions are never encountered then the appropriate Messengers are never composed or injected.

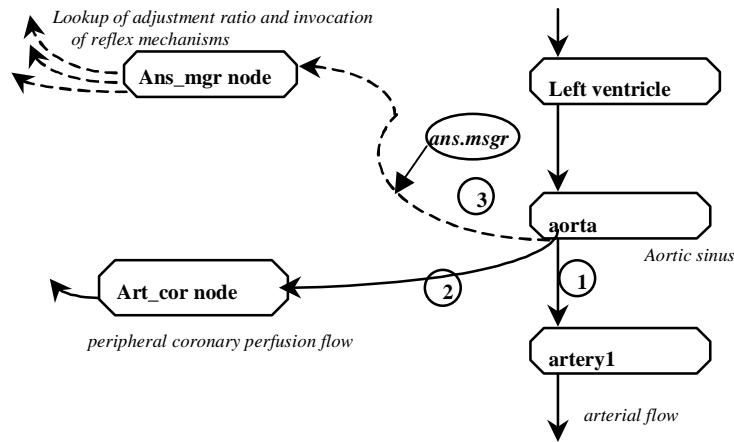


Figure 5. Concurrent Messenger injection from aortic sinus region node (aorta) spawning multiple Messengers in parallel during execution. 1.) Arterial tree Messenger flow 2.) Peripheral organ bed Messenger flow 3.) Potential regulatory adjustment Messenger flow

A level of severity or frequency is associated with a receptor event and natural compensatory mechanisms are set into motion because of measurements detected at receptor points. An example of a Reflex Arc compensatory mechanism is the baroreflex response due to extreme pressure gradients detected from one heartbeat pulsatile wave to the next, in the aortic or carotid sinus regions. Figure 5 shows the aortic sinus region node (aorta) with the spawning of multiple Messengers in parallel during execution. 1.) Normal flow of arterial Messenger traversing from LV (Left Ventricle) to aorta.node to artery1.node and on through the arterial tree. 2.) Peripheral Messenger branches and flows from aorta.node to art_cor.node and will continue through organ bed finally merging into venous flow 3.) If receptor site is activated, automated invocation of ans.msgr Messenger propagates to ans_mgr.node, and thereupon sets into motion regulatory adjustment functions. If the receptor site is not activated, then the ans.msgr is not fired.

3.4 Simulation Steering

Simulation steering is introduced from a user interface, either in the initial setup routines or dynamically from user interfaces during runtime, providing a *live simulation* ability. Using simulation steering during execution affords the opportunity to dynamically change patient conditions or introduce new events, during the execution of the system without restarting for each event or condition. An example of an external event introduced through simulation steering is an accelerated state of physical exertion and/or heat stress, introducing examples of physical exertion for insights of patient assessment or intelligent monitoring. Associated with severity levels of exertion is the relative oxygen uptake VO_{2max} hence, in our profiles we make provision for various levels of VO_{2max} to be used as an exertion level gauge. Indeed, this property of simulation steering affords a very flexible and powerful analytical tool.

Physical stresses were chosen as the means to explore the short-term regulation of the human cardiovascular system in CVSys. Particularly emphasized in our system is a scenario commonly termed high frequency / low force or dynamic exercise, aerobic type exertion and closely aligned heat stresses. Physical exertion provides extreme demands on the circulatory system. Extreme metabolic requirements are supplied to skeletal muscle, coronary and pulmonary regions, usually from blood flow redistributed from the venous and splanchnic and renal regions. The body must maintain adequate blood pressure, cardiac filling pressures and stroke volume for the heart to meet increased demands. Exertion often entails combined and interactive effects of upright posture, heat stress and exertion. Regional circulatory functions become crucial. At the onset of physical exertion, very rapid increases occur in blood flow to muscles and cardiac output. The time course and extent of arterial baroreflex effect on arterial blood pressure is still debated, although recent findings have characterized the time course and changes in cardiac output and total peripheral conductance¹⁶.

The logical links of the User Interface(UI)/Simulation Steering Layer in Figure 6 provides the means to introduce external events from the UI. These events include support of dynamic simulation steering. Examples of external events include basic monitored physiological changes such as blood pressure, heart rate, organ function, valve function, etc. Events also include introduced physical conditions such as physical exertion and subsequent $VO_{2\max}$ (oxygen uptake) levels, and heat stress.

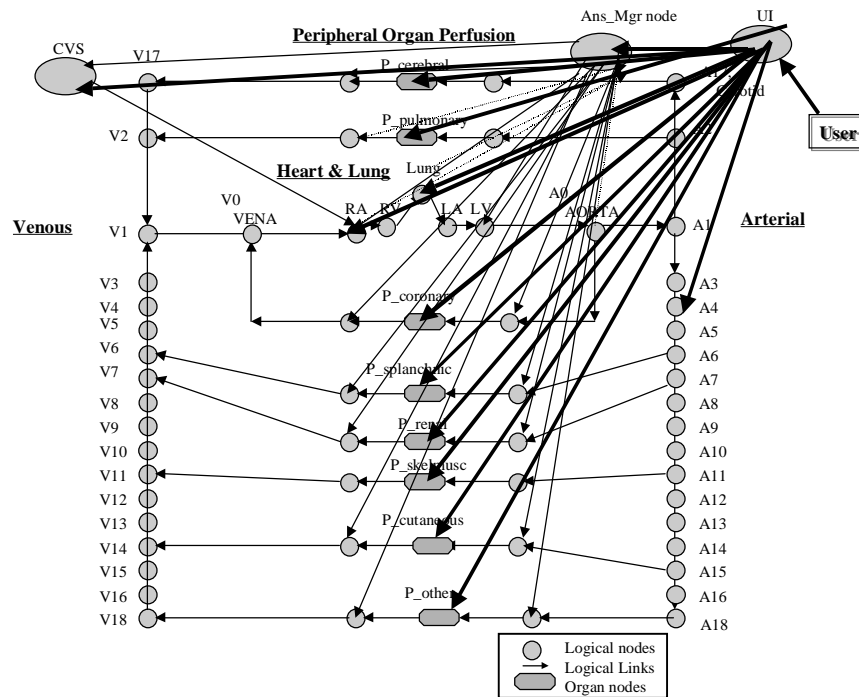


Figure 6. User Interface(UI) / Simulation Steering Layer.

4. RESULTS

The purpose of the following discussion is to illustrate how CVSSys uses the architecture and algorithms above to begin to address peripheral circulatory flow responses to given levels of exertion. The regional resistances calculated in the local arterial branch nodes and in arteriole nodes controlling organ perfusions, result in the regional peripheral flows. Provided are preliminary model results displaying peripheral organ flows given controlled levels of oxygen uptake, $VO_{2\max}$. The levels of $VO_{2\max}$ signify four levels of physical exertion, basal at rest, light, moderate and severe. Graphical analysis of flow resulting from the four levels of exertion are displayed in Figure 7 for specified peripheral regions.

In this stage of System development we are assuming constant total blood volume. These levels are short-term response levels. Obviously with prolonged exertion, distribution of flow must be maintained at levels adequate for continued function of the organs. These preliminary results are consistent with accepted literature^{12,13,14,15}. Although this provides a strong basis at fixed levels of exertion, it is important for us to expand these studies to flow over timesteps. Flow over virtual time intervals is currently being implemented in CVSSys. Other critical factors not reflected here but also under development in CVSSys are the effects of auxiliary pumps and physical conditioning. Especially at the onset of physical exertion, the skeletal muscle pump, the abdominal pump, and the respiratory pump have mechanical effects on circulation, although the mechanical interaction and effectiveness is not yet well understood¹¹. The variables may be abstracted to center around delivery capacity by the pump, resistance and perfusion pressures¹⁶. Physical conditioning affects $VO_{2\max}$ by increasing the capacity of the cardiovascular system to transport oxygen and related increased stroke volume¹¹.

CVSSys has strong potential for application performing patient assessment or intelligent monitoring. The System is able to provide insights into cardiovascular status levels not readily discernible from current non-invasive physiological monitoring methods. Introduction of dynamic patient events, of monitored physiological readings and/or regulatory adjustments through dynamic simulation control result in a type of *live simulation*. This live simulation scenario introduces vast possibilities for

patient assessment and biomedical research testing. The dynamic and fully distributed coordination framework provides a reactively flexible and extensible environment. Hence in the future, CVSys may be employed for non-invasive patient assessment, treatment and/or therapy evaluation, intelligent monitoring, and as an educational or research analysis tool.

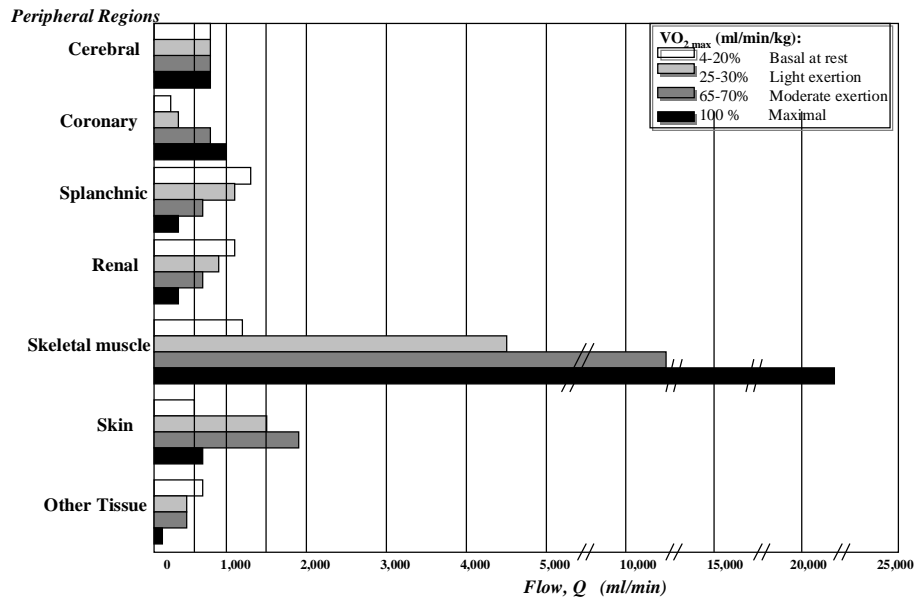


Figure 7. Peripheral region flows over four controlled levels of $VO_2 \text{ max}$ (Oxygen Uptake).

5. CONCLUSIONS

In this paper we have introduced CVSys, the coordination framework for dynamic and fully distributed cardiovascular modeling and simulation. Until recently, computing capabilities have presented obstacles limiting large-scale interactive biomedical simulation. This new coordination framework supports increased runtime flexibility and interactive concurrency. Most notable aspects of the System are: Natural behavior flow, dynamic simulation control including reflex arc network and simulation steering, and parallel processing of short-term regional flow adjustments.

Distinctive of this research is the integration and interaction of complex physiological functions in a truly concurrent and dynamic manner. CVSys development has been guided by the application of computing methods as closely resembling natural processes as possible. More expressive modeling has been experienced through our coupling of natural processes to computing processes through natural behavior flow. The logically layered architecture over a distributed computing network sustains a highly extensible system organization.

Flexibility and dynamics of the coordination framework allow a new forms of steering and regulatory adaptation that we call Dynamic Simulation Control, comprised of Reflex Arc Network and Simulation Steering. Reflex Arc reacts to internally activated regulation, setting into motion reactive adjustments in an independent and dynamic manner. Simulation steering reacts to externally introduced events, also setting into motion a cascade of Messengers and computational functions to enact appropriate circulatory adjustments. Both aspects of Dynamic Simulation Control are built upon overlapping foundations with differences in the invocation mechanisms. Once activated, both Reflex Arc and Simulation Steering set into motion autonomous propagation of appropriate regulatory mechanisms that proceed concurrently during runtime. New Messengers are injected, navigate across their appropriate logical links and coordinate precompiled functions, while a high number of concurrent processes are already in motion during runtime across distributed computing nodes.

Dynamic simulation control provides an extremely flexible patient state change introduced in a dynamic manner during runtime. Also distinctive in CVSys is the fact that steering does not utilize a traditional black box, fixed parameter, forced approach. Rather we've introduced a fractional adjustment to compute local adjustments in accordance with events, time intervals, level of severity, and local regional conditions, thereby resulting in more open functionality of parametric computations. The advanced approaches of CVSys have resulted in a more expressive and a more indigenous biomedical representation than

previously achieved and in a powerful analytical tool. We've discussed how these unique computing characteristics present a new platform for intelligent patient monitoring. Planned near term research includes further model validation and testing, incorporation of pipelining computing methods, and refinement of interactive user interface. Longer term opportunities include increased simultaneous analysis, addition of further logical networks to represent regulating influences such as chemical receptors and particularly the renal-angiotensin system. Furthermore, development of supportive knowledge bases and logic layers in conjunction with the underlying coordination framework would provide a powerful base for intelligent monitoring.

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