MINIMUM ENTROPY GENERATION IN THE CARDIOVASCULAR SYSTEM

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

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ABSTRACT

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This study was performed under the motivation to find a scheme that could describe the complex behavior of cardiovascular homeostasis. This is hypothesized to be manifested in a thermodynamic description of the cardiovascular system (CVS). Seen from a thermodynamic framework, the mechanics of blood flow can be gauged in similar terms as metabolic exchange at the capillaries – thereby providing a holistic and novel perspective on overall CVS function.

Entropy generation, a thermodynamic calculation, represents lost work and is hypothesized to reveal something about the "optimal" state of the CVS. In particular, it is hypothesized that the CVS state that generates minimal entropy, given certain constraints, will be physiologically preferred and that cardiovascular control operates to find this state. This will be tested by first proposing a method to calculate entropy generation in the CVS, and secondly characterizing entropy generation across unique CVS states by simulation of a mathematical model.

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INTRODUCTION

It is important to understand the homeostasis or control logic of the cardiovascular system for the treatment of cardiovascular disease. As a result, disease treatment can be planned to follow an optimal trajectory. In addition, the effect of a perturbation (disease or treatment) can be reliably predicted if the inherent control logic is defined. Given the enormity of cardiovascular disease, such understanding is a significant worldwide concern. However, despite decades of important scientific contributions to define this control logic, the complexity of cardiovascular system (CVS) homeostasis has not been successfully reduced into a coherent scheme. However, it is the proposal of this study that an innovative and effectual way to intellectually navigate the inherent complexity of the CVS, particularly CVS homeostasis, is to use classical thermodynamics.

Homeostasis is a cornerstone concept within physiology – it is the ability of a system to maintain balance in the face of changing internal and external factors. The CVS demonstrates homeostasis by adjusting or maintaining blood flow in accordance with metabolic demand. For example, blood flow is relatively low in the resting state and high during exercise. However, even though blood flow can be altered in various ways by the CVS, the manner in which blood flow is changed has revealed patterns that cannot be justified or fully appreciated. Furthermore, these patterns seem to be optimal for the system given its metabolic needs. This pattern has been studied by focusing solely a prominent arm of the cardiovascular circuit (left ventricle and contiguous arterial bed) and is likewise referred to as ventricular-arterial coupling

(VAC) or ventricular-vascular coupling (VVC) studies. VAC theories, much like the work in this thesis, hypothesize that the cardiovascular system changes states in response to need in an optimal manner. The existence of optimum state/states would explain why the cardiovascular system *in vivo* occupies and moves through a limited set of states despite the alternatives available. However, none of the VAC theories have been able to reach full acceptance in the literature. This could be due to the narrow scope within the cardiovascular anatomy and physiology. After all, the ventricle and arterial bed are not the only components that impact blood flow. In addition, these theories largely ignore the capacity of a CVS state to meet metabolic demand which is an important facet of cardiovascular function and efficacy.

The CVS is very challenging to understand, especially in a quantitative sense. Therefore, it is prudent that the simplest possible model is used as a starting point - just as the studies concerning VAC theories have done. This thesis expands upon the current VAC thinking to include more detail concerning the cardiovascular system anatomy (whole circuit CVS and not just the ventricle to artery) and physiology (including metabolism and metabolic demand). Even so, new assumptions and simplifications were also made in this work out of necessity.

The CVS, like all physiological systems that achieve homeostasis, is dynamical, nonlinear, and robust. The robustness is often due to the presence of redundant mechanisms. A common method for understanding a complicated system is to reduce the system into smaller, simpler parts, and is likewise referred to as the reductionist approach. The assumption is that the function of the system is equal to the sum of the

parts. However, redundant mechanisms as well as nonlinear behavior confound the identity of the system using the reductionist approach. Using the reductionist approach to understand the homeostasis of the CVS involves investigating the separate function of the various feedback systems, like the kidneys and the lungs and others, and then considering the integrated function as a whole as the simultaneous function of the parts. This method is unlikely to yield an accurate representation of the integrated whole for at least two reasons: 1) the assumption that the function of the feedback system in isolation is the same as it is within the integrated whole (in vivo) is not necessarily valid, and 2) the inherent complexity of physiological systems (dynamical, nonlinear, and robust).

Alternatively, this thesis employs a more holistic style to understanding the homeostasis of the CVS. This is done using thermodynamics and is hypothesized to be a suitable approach to understand the systems-level operation of the CVS because it avoids the pitfalls associated with the more traditional, reductionist techniques. In any case, the application of cycle thermodynamics to the CVS is a new idea that has not yet been attempted. Specifically, it is hypothesized that entropy generation, a thermodynamic calculation of the CVS, is minimized, given constraints. Processes that contribute to entropy generation represent "work lost" and therefore it is reasonable that the optimum state is defined in terms of minimum entropy generation. Therefore, the focus of this thesis is to characterize entropy generation within the CVS as a means to address the hypothesis that entropy generation is minimized near normal or typical CVS states, given constraints.

BACKGROUND

Hemodynamic Modeling

In 1972, Guyton and colleagues wrote a review on the macroscopic regulation of the CVS using their own vast computational model as an illustration. (13) The very last sentence of this Guyton's review states: "If the general principles of this systems analysis are correct, and we believe they are, then it seems clear that the field of circulatory physiology is on the verge of changing from the realm of a speculative science to that of an engineering science." (13)

It is due to many, especially Guyton, who showed the value of an engineering approach to the study of the CVS. In fact, the past forty years has yielded an explosion of computational analyses and models of the CVS thanks to modern numerical solvers and computational power. Additionally, the fact that there exists many models attests to the complexity of the CVS system – since virtually all models cannot claim to be general-purpose, but rather make simplifications according to a specific context. Yet, Guyton's model is unique given the large scope including not only the CVS but also various feedback mechanisms under the umbrella of integrative physiology. Guyton's model is able to show that the physiology of the CVS, which is difficult to intuit, can be effectively studied by pairing electrical circuit analysis with biology.

Guyton's model is still studied and discussed in recent years. In 2006 there were a series of point/counterpoint-style articles concerning Guyton's approximations of the basic forces that determine blood flow. (1, 3, 4, 21, 22, 25, 29, 30, 32, 33, 43) The introductory remarks in the point/counterpoint debate set the

stage with this comment, "What makes the blood go around? This must be one of the most fundamental questions in cardiovascular physiology." (21) This may be a surprising statement, because it seems obvious that it is the beating heart that drives blood flow. Conversely, ever since investigators began quantitative evaluations of the cardiovascular system, evidence indicates that various other factors are important and can often dominate over the influence of the heart. For instance, the Guyton model assumes a particular aspect of the CVS to be a primary factor that ultimately determines blood flow – this aspect has little to do with the heart directly. The reasoning is the heart is inconsequential to analyzing the hemodynamics in the steady-state because it acts to maintain the major pressure differential across the system and not create it. The heart, in the steady state, ejects exactly the amount of blood returned to the input, also called venous return. Rather, according to Guyton, creation of the major driving pressure difference (right atrial pressure vs. mean systemic filling pressure) is attributed to various downstream parameters having to do with features such as vessel diameter or resistance. Likewise, the title of this debate was "The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct". (1, 3, 4, 21, 22, 25, 29, 30, 32, 33, 43) More recently, in 2011, Beard's critique of the Guyton model and the Guyton point/counterpoint debates indicates that the confusion amounts to identifying the dependent vs. independent variables. (2) In particular, a common misinterpretation of the Guyton model is that right atrial pressure functions to impede venous return, and therefore cardiac output is a function of right atrial pressure. This is not always true for the CVS *in vivo*. However Guyton's model does

produce a change in cardiac output in a proportional sense with a change in right atrial pressure as a consequence of holding a constant total blood volume. Total blood volume is a variable, especially in the clinical setting. Beard insists that the independent variable is actually cardiac output and right atrial pressure is a function of flow. Another point Beard makes is that there is misinterpretation of the term "venous resistance". Guyton had originally referred to a "resistance to venous return" which is dependent on the relative capacitances of the arteries and the veins. This is distinct from the "venous resistance" which is a particular feature of the anatomical veins exclusively. It is evident that modeling of the CVS in mathematical terms is not a straightforward task.

Regardless, Guyton's model was able to impress upon the scientific and especially the medical community that the cardiovascular system is essentially a mechanically coupled system of the heart-pump and the dynamic vasculature gwhere the influence of the vasculature and its various control mechanisms were emphasized.

Then, in a 1975 critique of Guyton's model, Sagawa makes a number of interesting observations. (36) Notably, he remarks that the Guyton model cannot actually make the claim to be a general-purpose model since there are a few important elements left out, like metabolic processes and the effect of blood volume distribution within lumped compartments of the vasculature. Furthermore, the endeavor to make a model more perfect by making it larger and more complex does not appear to be a worthwhile pursuit given this other comment by Sagawa about the ability of the model to make deductive predictions: "The probability of obtaining valid

(useful) conclusions becomes increasingly smaller as the number of incorporated assumptions increases." (36) Given this feedback from Sagawa, it seems that the reductionist way of studying the overall regulation of the CVS is the gain of small steps at the expense of tremendous, maybe infinite, effort.

Since the main focus of this thesis is thermodynamic analysis of the CVS, an initial idea was to use a published CVS model, like Guyton's model, to provide a basis for the thermodynamics. However after scanning the literature, it was found that published CVS models would not be suitable for this application. For example, the assumptions and simplifications made by Guyton and colleagues toward creation of their model were done in the context of describing the etiology of long-term blood pressure regulation disease. Therefore, given that the timescale for processes relevant to the development of hypertension (>> 24 hrs) are much slower than the duration of a single heartbeat (~1 sec), the Guyton model was conceptualized as a non-pulsatile or steady-state approximation of CVS behavior. Non-pulsatile dynamics alone are not sufficient for this study as it results in a loss of information that may significantly impact thermodynamic analysis and entropy generation calculation. Even so, Guyton's model is very influential to this work for at least two reasons: 1) for proving the merit of the idea of circulatory physiology as an engineering science, and 2) for seeking to answer the large-scale, "systems" properties of the CVS.

However, Guyton is certainly not the first credited for attempting a quantitative study of CVS physiology. Many reviews usually give this credit to William Harvey and his 1628 book *Exercitatio Anatomica de Motu Cordis et Sanguinis in*

Animalibus (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings). Before Harvey's work it was thought that the heart merely warmed the blood while the liver produced venous blood. Harvey used mathematics to prove that it was impossible for the liver to produce the amount of blood necessary. Instead, Harvey showed that the blood circulated. Harvey used tourniquets on arteries and veins to demonstrate this circulation as well as the existence of one-way valves. Reviews on the evolving understanding of circulation since Harvey include works by Noordergraaf (28), Coleman (8), Melchior (23) and Shaw (38). Most hemodynamic models are very similar. In fact, most are variants of *Windkessel* models of the arteries. *Windkessel* models are actually conceptual circuit models used to describe blood flow. The analogy of circuit analysis to CVS physiology is described next.

The dimension or structure of the blood vessels has significant bearing on the pressure-flow relationship in the CVS. Common practice is to approximate a resistive component of blood vessels by modeling them as static, cylindrical tubes. It has been shown in cylindrical tubes that experimentally, under steady pressure-flow conditions, tube dimension has a direct relationship with pressure and flow. This relationship is shown in Equation 1 and is referred to as Poiseuille's equation.

Alternatively, changes in flow are generally thought of in terms of properties that hinder it, commonly referred to as resistance or impedance. Rearranging Poiseuille's equation to cater to this perspective results in Equation 2.

Equation 1 - Poiseuille's Equation

$$Q = \frac{n \pi r^4 \Delta P}{8 \eta L}$$

Q = flow
n = number of tubes in parallel
r = radius
P = pressure
η = fluid viscosity
L = tube length

Equation 2 - Poiseuille's Equation Modified to Calculate Resistance

$$R = \frac{\Delta P}{Q} = \frac{8 \eta L}{n \pi r^4}$$

The most physiologically significant variable of resistance is radius. Slight changes in radius will yield magnified changes in resistance and therefore induce pressure and flow responses. Furthermore, by framing the analysis in this way is strikingly similar to circuit analysis, specifically Ohm's law, shown in Equation 3, where pressure is like voltage (V), flow like current (I), and resistance has the same term in both cases.

Yet static flow conditions do not justly characterize cardiovascular pressure-flow relationships. The arteries are supple and radius will change in submission to pressure surges, such as systolic pressure escalation during ejection. This pulsatile

component of impedance is termed compliance and defines the change in volume due to a change in pressure, shown below in Equation 4.

Equation 3 - Ohm's Law

$$V = I \cdot R$$

V = voltage
I = current
R = resistance

Equation 4 - Physiological Compliance

$$C = {}^{\Delta V}/_{\Delta P}$$

C = compliance
V = volume
P = pressure

The circuit analogy for compliance is the capacitor which is defined in electrical terms in Equation 5 In this case, capacitance (C) is like compliance, charge (Q) is like volume, and voltage (V) is akin to pressure.

Equation 5 - Electrical Capacitance

$$C = {}^{Q}/_{V}$$

C = capacitance
Q = charge
V = voltage

Both compliance and capacitance reflect a storage capacity: storage of blood in the vessels and storage of charge in the capacitor. The inverse of compliance, elastance, is also typically used to describe the vasculature. Elastance is defined mathematically in Equation 6.

Equation 6 - Elastance (E) - Compliance (C) Relationship

$$E = {}^{1}/_{C}$$

The low compliance (high elastance) property of arteries allows them to transfer pressure as flow, versus highly compliant vessels, like veins, that simply attenuate pressure by yielding to it and effectively storing volume. Elastance, and also resistance, can also be altered by neural control of the smooth muscle tone that lines the arteries. Neural control is only one example of the many control systems involved with the CVS.

In addition to resistance and compliance, there exists a third property of vascular impedance caused by fluid inertance which is like the electrical inductor.

Because of this analogous relationship to blood flow, the well-studied properties of electric current flow and impedance can be used to understand properties of the arterial system as they relate to blood flow.

The interpretation of arterial properties into a "lumped" resistor-inductor-capacitor (RLC) model was introduced by Otto Frank in 1899. Frank referred to this model as a *Windkessel.* This concept has been modified through decades of study, yet most hemodynamic models of the vasculature are basically modified *Windkessels*. It is

important to point out that this analogy fails in at least one important regard: the electric RLC model is linear, time-invariant while physiological RLC are not.

Modeling the action of the heart is a more challenging task, and unlike the arteries, there is no generally-accepted model. In fact, unlike the arteries which are best described in the time domain, the performance of the heart is best described in the pressure-volume (PV) domain. The left side of Figure 1 illustrates one complete cardiac cycle or heartbeat, in the PV domain, which transitions about four distinct phases: ejection, relaxation, filling and contraction. The right side of Figure 1 demonstrates that a complete cardiac cycle is actuated by changes in cardiac elastance with the maximum elastance occurring at the transition from the ejection phase to the relaxation phase.

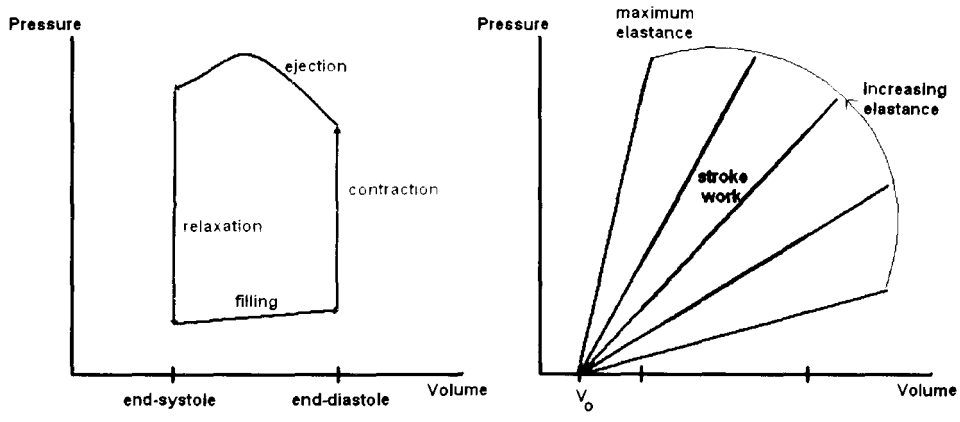


Figure 1 - Performance of the Heart in the Pressure-Volume Domain

Furthermore these changes in elastance of the heart muscle are dependent on many factors, specifically volume in the ventricles. This dependence of pressure generation on volume is well-known in cardiac physiology and is referred to as the

Frank-Starling law of the heart. If multiple beats are considered, the PV loops seem to be constrained by a two main envelopes shown next in Figure 2.

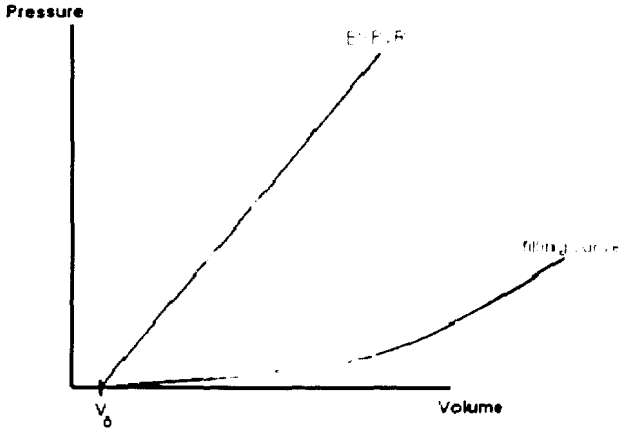


Figure 2 - Constraints on the Operation of the Heart

This scenario shown in Figure 2 illustrates an idealized heart (constant inotropic state) in response to a decreasing input volume. The gray lines which form loops are the pressure-volume within the ventricle. The minimum volume needed to keep the wall from collapsing is known as the dead volume (Vo). For volume in excess of the dead volume, pressure increases nonlinearly with increasing volume. This relationship defines the filling phase during diastole. In addition to filling phase, a relationship for the maximum elastance or end-systolic elastance (Ees) is realized from multiple beats. For corresponding increments of filling volumes, a linear trend in Ees is observed. This line is known as the end-systolic pressure volume relation (ESPVR) and is attributed to contractility or inotropic state of the heart. The nervous system has influence over the heart by altering its inotropic state (thereby changing the slope of the ESPVR) as well as heart rate.

Overall, the main parameters of ventricular function as a pump include: ESPVR, Ees, filling curve, and dead volume. Models of the CVS that include consideration of the heart as a pump most likely incorporate these parameters. One such model proposed by Ewert and colleagues is a circuit equivalent model of the heart that frames the heart as an ideal pressure source paired with volume-sensitive source impedance which can account for the dynamic nature of the myocardial viscoelasticity. (11) A circuit model of the heart pairs well with the Windkessel model of the arteries because it allows for cohesive study of the closed-loop CVS.

To model the entire closed-loop circulation including heart-pump and vasculature will also necessitate the valves for an accurate representation of pulsatile behavior. However only a few have attempted CVS models with valves in the past, but it is considered a necessary feature to explore now in this thesis because the valve energetics may play a significant role in overall CVS entropy generation. The reason valves are difficult to implement is that numerical representation of nonlinear behavior, like that of the valves, is especially cumbersome. Hann et. al. have proposed a method for reducing computational complexity by introducing the use of Heaviside functions. (15) These functions are designed so that the valve is in the "open" state when the pressure differential is large enough, and conversely, "closed" when the flow is low. An event solver is used to detect these instances and trigger the change in phase - contraction phase to ejection phase, for example. Smith has developed a minimal model that includes both valves and inertia. (39) According to Smith, "Of the numerous models in the literature, few mentioned valve function, and the author could not find a realistic valve law for models that use inertia. The solution developed

allows the system state to change dynamically while solving." Therefore, Smith's model switches between different systems of equations depending on an event solver as a surrogate to valve operation.

A concern with using a "switching" model is numerical stability and accuracy. This is an even bigger issue when various simulations of the same model are to be compared.

In summary, due to the unique context of this model and the numerically complicated but obligatory task of implementing the operation of the valves, a new model was created for this study.

Optimal Control Logic

Even though consideration of a valid hemodynamic model alone is a complex endeavor, it is not enough to make meaningful, clinical impact. This is because a hemodynamic model reveals all possible CVS states as equivalent. For example, there are infinite possible CVS states that can all result in the same cardiac output. The bigger question naturally follows: if there are infinitely many combinations of parameters that give rise to the same cardiac output, which one(s) is (are) optimal and why? There are a number of theories, such as VAC or VVC theories that have attempted to answer this question.

Definition of control logic basically amounts to a function or a criterion that is hypothesized to be optimized. There are at least three criterion functions that have been previously proposed as a control logic or optimal state. They are as follows:

1. Maximal mechanical power

2. Maximal mechanical efficiency

3. Minimal relative oscillatory power.

Maximal mechanical power refers to the maximum external work delivered from the ventricle to the arterial load, and is thought to occur when the stiffness of the heart matches the stiffness of the arteries. This is analogous to the concept of impedance matching in circuit analysis. Impedance matching, for a simple circuit consisting of a source, source impedance and load impedance, results in maximum power transfer if the load impedance is equivalent to the source impedance. However, the literature is not particularly precise about what is considered to be a physiological impedance match. (16, 27, 41)

Maximal mechanical efficiency is defined as the maximum ratio of external work generated by the ventricle relative to the myocardial oxygen consumption (MVO2), which can be roughly approximated as the fuel used by the heart. (27, 41)

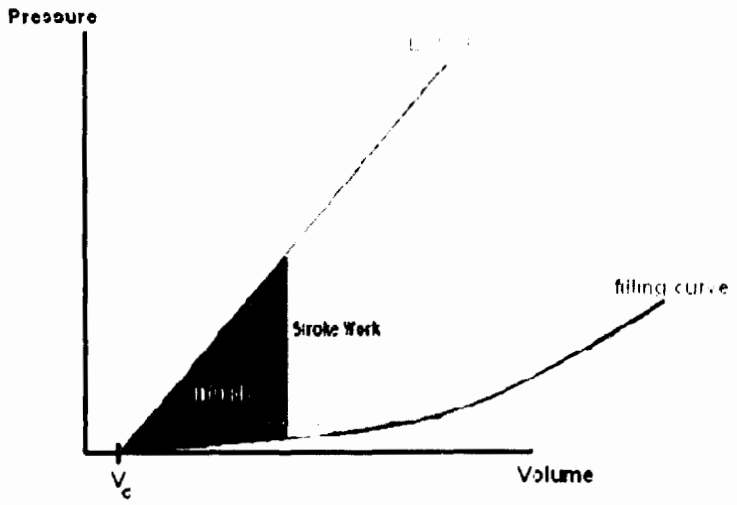
Minimum relative oscillatory power weighs the loss of energy required for the pulsatile pump action of the heart that generates the net flow of blood. (27)

The three aforementioned criterions have been observed in some way to define the optimal coupling of the ventricle to the arteries. However, the scope of all is limited to only a portion of the CVS – the ventricle and the arteries. More importantly, the three theories are not robust in that many states exist that result in either maximal mechanical power, maximum efficiency, or minimum relative oscillatory power, but are not truly "optimal" – they do not necessarily meet metabolic demand, for example.

Considering the achievements of the initial theories of VAC and acknowledging their shortcomings have motivated the notion of a new optimal criterion which embraces the entire CVS. This new optimal criterion is proposed to be contained in the language of energy transformations: thermodynamics.

Thermodynamics & Entropy Generation

Thermodynamic analysis of the CVS circulation is a novel approach; however, thermodynamics has been successfully applied to living systems and even isolated parts of the CVS. For example, Denslow and colleagues showed that thermodynamics can provide additional support for the PVA-MVO2 relationship by approximating the cardiac cycle as an ideal thermodynamic cycle. (9) The PVA-MVO2 relationship relates MVO2 with a feature of the PV loop of the left ventricle. This feature is the area enclosed by the dead volume, ESPVR, filling curve, and the PV loop. This area is specifically referred to as the pressure-volume area (PVA) and is shown in Figure 3 as



;ure 3 – Illustration of the PVA

the sum of the areas labeled "triangle" and "stroke work". As a result, the MVO2 can easily be approximated using only left ventricle pressure and volume data.

In fact, thermodynamics seems like a natural tool to study optimization of the CVS given that thermodynamics has been successfully used to optimize engines for decades. Furthermore, thermodynamics and entropy are extremely fundamental: "Scientists discovered that heat was produced by the collision of millions of particles in a perfect gas, generating irreversible entropy, a lower level of energy. However, Poincare showed that it is practically impossible to study the motion of more than three bodies and thus understand the process. Boltzmann (1872) bridged this gap by introducing statistical methods to describe kinetic phenomena and equate their average kinetic energy with entropy." (37) In light of this, the beauty of thermodynamics is that useful information about a system can be found without the need to reduce that system into a set of deterministic mechanisms. This is an attractive concept in the realm of systems biology, such as the study of the CVS, in which the emergent behavior seems to transcend the most thorough deterministic models and careful reductionist techniques.

Prigogine's minimum entropy production principle is an application of thermodynamics to understand systems that are stable yet not at equilibrium, which is the case for all biological systems. (31) At a high-level understanding, it is logical that a living system would tend to maintain a functional order and reduce energy loss due to irreversible processes. However, the complexity that lies around the definition of "entropy" – in both the qualitative and the quantitative sense – is a major roadblock

to its successful application as pointed out in a number of reviews on the matter. (17, 19) Therefore, with the cautions of previous misuse of entropy in the life sciences in mind, a cursory, initial attempt is made here to help understand the optimal state of the CVS as an alternative to classical, reductionist attempts.

The application of thermodynamic analysis to the CVS has been considered in an unpublished work by Ewert, Penoncello, and Swope. (10) With the authors' permission, portions of that work have directed this section of the background which will provide the basic thermodynamic foundation which follows.

The novel application of thermodynamic analyses to the CVS will mimic methods typically employed when analyzing engineering-based cycles. The first step in this process will be to represent the CVS hemodynamics as a thermodynamic cycle. To represent as a thermodynamic cycle, the CVS must be studied as a series of so-called control volumes each delineated by a system boundary. The control volumes will exchange mass at a certain rate defined by Equation 7.

Equation 7 - Definition of Mass Flow Rate

$$\dot{m} = \rho * A * v$$

ρ = density of fluid
v = velocity of substance
A = area of flow, $\dot{m}$

Furthermore, if this control volume does not change (in terms of net volume) over time, it is in a steady-state, steady-flow (SSSF) condition, which is shown in Equation 8.

Equation 8 - Steady-State, Steady-Flow (SSSF) Condition

$$\sum \dot{m}_i = \sum \dot{m}_e$$

$\dot{m}_i$ = mass flow rate into control volume

$\dot{m}_e$ = mass flow rate out of control volume

The SSSF assumption is valid over time scales longer that the period of a heart beat (~1 sec) but shorter than blood volume regulation processes (hours). Therefore, to apply SSSF simplifications is to the analysis, time-averaged CVS control volumes were used to meet this criterion. The motivation for this is to simplify the initial stage of thermodynamic analysis, but it is anticipated that pulsatile dynamics (non-SSSF) behavior could/should be investigated in the future.

Thermodynamic analysis is based upon two general laws. The general laws of thermodynamics will be shown, along with simplifying assumptions to allow for a more convenient mathematical form.

The first law, shown in Equation 9, relates the rate of heat transfer into the volume as the sum of three main quantities: 1) rate of energy stored, 2) rate of net energy entering, and 3) power produced.

For uniform states of mass crossing the control surface, the first law can be simplified to as shown in Equation 10.

Equation 9 - First Law of Thermodynamics for a Control Volume

$$\dot{Q}_{C.V.} = \frac{d}{dt}\int_V (\mathrm{e} * \rho)\, dV + \int_A \left(h + \frac{v^2}{2} + g * Z\right)(\rho * v_{r.n.})dA + \dot{W}_{C.V.}$$

$\dot{Q}_{C.V.}$ = rate of heat transfer into the control volume (C.V.) surface

e = energy contained in volume, dV

ρ = density of fluid

h = enthalpy of substance

v = velocity of substance

g = gravitational constant

Z = elevation of substance

$v_{r.n.}$ = outward-directed normal velocity

dA = area of flow, $\dot{m}$

$\dot{W}_{C.V.}$ = work done by the control volume (C.V.)

Equation 10 - Modified First Law

$$\dot{Q}_{C.V.} + \sum \dot{m}_i \left(h_i + \frac{{v_i}^2}{2} + \mathrm{g} * Z_i\right) = \frac{d}{dt}(E_{C.V.}) + \sum \dot{m}_e \left(h_e + \frac{{v_e}^2}{2} + \mathrm{g} * Z_e\right) + \dot{W}_{C.V.}$$

$\dot{m}_i$ = mass flow rate into control volume

$\dot{m}_e$ = mass flow rate out of control volume

Furthermore, if one assumes steady energy content in the control volume, that the control volume does not move relative to the coordinate frame, and that the mass flux and its state do not change in time, and finally, that $\dot{Q}_{C.V.}$ and $\dot{W}_{C.V.}$ remain

constant, one obtains a steady-state, steady-flow (SSSF) equation as shown in Equation 11.

Equation 11 - Steady-State, Steady-Flow Version of the First Law

$$\dot{Q}_{C.V.} + \sum \dot{m}_i \left(h_i + \frac{v_i^2}{2} + g * Z_i \right) = \sum \dot{m}_e \left(h_e + \frac{v_e^2}{2} + g * Z_e \right) + \dot{W}_{C.V.}$$

The CVS does not operate under SSSF conditions, as mentioned previously the pulsatile or intra-beat dynamics may prove to be important considerations of CVS thermodynamics. However, as an initial step forward, SSSF conditions where used over time-averaged hemodynamics. However, the same hemodynamic model will allow for seamless integration to pulsatile time-domain thermodynamic analysis in the future.

If a chemical reaction takes place or if there is a transformation of material within the control volume, the enthalpies take the form as displayed in Equation 12.

Thus, under SSSF conditions and neglecting kinetic energy and potential energy, a system which undergoes heat transfer, work and chemical transformation can be described by Equation 13.

Equation 12 - Consideration of a Chemical Reaction in Terms of the First Law

$$m_i h_i = H_i = n_1 \overline{h_1} + n_2 \overline{h_2} + \cdots + n_n \overline{h_n}$$

$n_n \overline{h_n}$ = product of moles and molar enthalpy of species n

$$\overline{h_n} = \left[h_f^\circ + \Delta \bar{h} \right]_n$$

h_f° = enthalpy of formation at reference temperature and pressure

$\Delta \bar{h}$ = enthalpy change due to non-reference temperature and pressure

Equation 13 - SSSF First Law with Chemical Reactions

$$\dot{Q}_{C.V.} + \sum \dot{n}_i \bar{h}_i = \sum \dot{n}_e \bar{h}_e + \dot{W}_{C.V.}$$

With the first law in place, the second law of thermodynamics can now be considered as shown in Equation 14.

Equation 14 - Second Law for a Control Volume

$$\frac{d}{dt}\int_V (s * \rho)\, dV + \int_A (s * \rho * v_{r.n.})\, dA = \int_A \left(\frac{\dot{Q}_{C.V.}/A}{T} \right) dA + \int_V \left(\frac{L\dot{W}}{T} \right) dV$$

s = entropy
T = temperature
$L\dot{W}$ = lost work due to irreversibility

Equation 14 is showing that, for a control volume, the sum of the rate change in entropy plus the net entropy leaving is equal to the sum of entropy due to heat transfer plus entropy generation. This relationship can be modified under the simplification of SSSF conditions as shown in Equation 15.

In summary, thermodynamic analysis of the CVS will be based on first law (Equation 11 or Equation 13) and second law (Equation 15) applied to distinct control volumes that constitute the CVS. As seen in Equation 15, calculation of entropy

generation per control volume is possible given a few assumption (i.e. SSSF) and hemodynamic quantities (i.e. pressure and mass flow rates).

Equation 15 - SSSF Version of the Second Law

$$\dot{\sigma} = \sum \dot{m}_e s_e - \sum \dot{m}_i s_i - \int_A \left(\frac{\dot{Q}_{C.V.}/_A}{T} \right) dA$$

$\dot{\sigma}$ = entropy generated

s_e = entropy exiting the control volume

s_i = entropy entering the control volume

METHODS

The following analyses were performed under the motivation to find a way to simply describe the complex behavior of cardiovascular control. This is felt to be manifested in a minimal description of CVS hemodynamics that allow for fundamental thermodynamic investigation. The thermodynamics, in turn, are hypothesized to reveal something about the "optimal" state of the CVS. In particular, it is hypothesized that the CVS state that results is minimum entropy generation will be physiologically preferred and that cardiovascular control operates to find this state. To test this hypothesis, entropy generation was calculated over many unique hemodynamic states via simulation of a mathematical model. The method of analysis, which lastly results in the calculation of entropy generation, is explored in this chapter in three stages: 1) hemodynamics, 2) thermodynamics and 3) simulation method. The Matlab code created to implement the following models is attached in Appendix A.

Hemodynamics

The hemodynamic model is based upon an analogous circuit model (*Windkessel*) which serves as a framework to derive the mathematical equations that describe the cardiovascular hemodynamic state over time. The mathematical equations include a system of state space equations plus additional auxiliary equations. Lastly, the parameter values and initial conditions necessary to solve the aforementioned equations are included. The following section explores the derivation of the equations, while the actual implementation of this model into code is included in Appendix A.

The dynamics of blood flow are modeled in this work as a series of elastic compartments in a closed-loop configuration and displayed in Figure 4. This closed-loop circuit, for this minimal description, includes four main elastic compartments:

1. Heart (Left and Right)
2. Arteries
3. Veins
4. Pulmonary Vasculature

and two types of additional components:

1. Valves
2. Coronary Vasculature

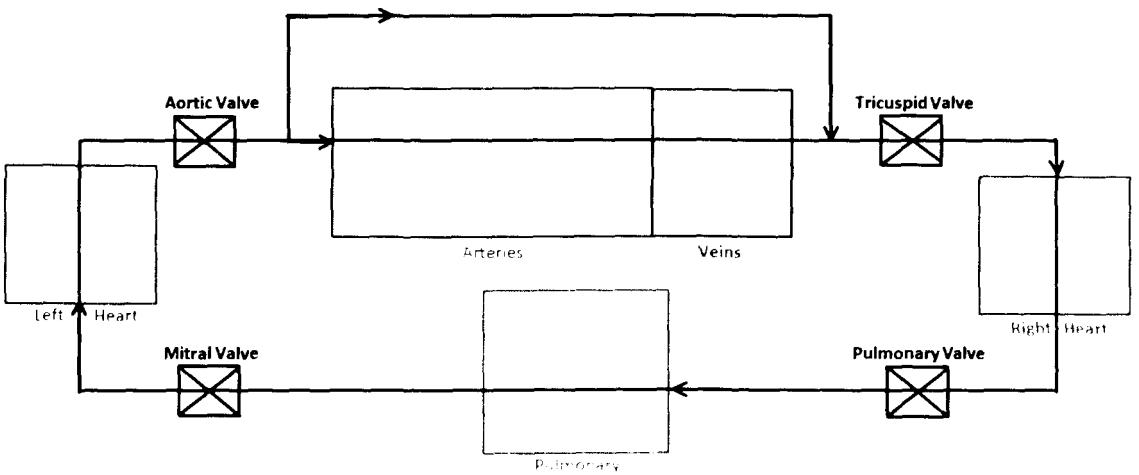


Figure 4 - Elastic Compartments of the Cardiovascular Closed-loop Model

Utilizing classical *Windkessel* theory, each elastic compartment of this model is generally defined by both an elastic and a resistive component as shown in Figure 55.

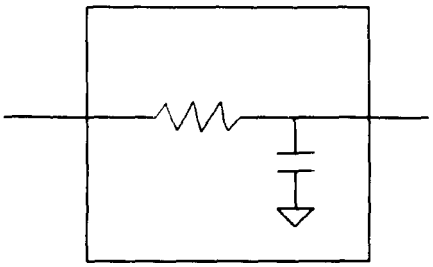


Figure 5 - *Windkessel* Model of Elastic Compartment

The *Windkessel* model is useful for this study as it is a simple approximation of vasculature hemodynamics. Even so, the most important benefit of this type of model is that the components and their parameter values have physiological significance.

The resistive component represents the restriction of axial flow of blood due to, mostly, the caliber of the blood vessel. The elastance component (capacitor) represents the storage capacity of a vessel as well as its ability to recoil in response to pressure transients. The elastance component assumes a certain amount of volume, called the dead volume (V_0), which is the minimum initial volume required to keep the vessel from collapsing. Any amount of volume in the vessel beyond the dead volume is known as the stressed volume or effective volume. Therefore, the value of the capacitor as well as the dead volume will need to be defined as specific parameter values necessary to solve the model equations. The total volume, that is dead volume plus the effective volume, represent the total capacity of the compartment.

In this manner the *Windkessel* is a minimal description for the dynamics of blood flow through an elastic compartment - and a complete mathematical description requires specified parameter values/initial conditions (resistance, capacitance, dead volume, and initial stressed volume). Table 4 and Table 5 lists the values chosen for this model.

The translation of the elastic compartment model of the CVS shown in Figure 4 to a circuit model is shown in Figure 6. As shown, the veins and pulmonary circulation are felt to be adequately captured by the simple *Windkessel* model. However, the arteries experience higher pressures and flows than the other compartments. Therefore, the arteries are modified into a hybrid lumped-distributed model that includes inertance.

Unlike the elastances of the vasculature, the elastance in the ventricles is continuously pulsing to function as a pump. Therefore the elastance of the ventricles is represented as a time-varying capacitor (the symbol of an arrow crossing the capacitor signifies a time-varying behavior). In addition, there exists a resistance in the heart compartment, representing the viscoelastic impedance of the heart muscle cells and surrounding material. Inclusion of the viscoelastic component of cardiac function was hypothesized to be an important consideration with the following thermodynamic analysis in mind. For example, as the heart is using energy to perform work (generate time-varying elastance) some of this energy is turning into heat due to compression of the myocardium (losses dissipated by the viscoelastic resistance). The amount of energy lost in left-ventricular pressure generation may be an important

consideration of entropy generation of the overall cardiovascular system. Representation of cardiac function in this way is analogous to a model proposed by Sunagawa in 1980. (42) In Sunagawa's model of the heart, there is an ideal time-varying pressure source which is referred to as the hydromotive pressure (HMP). Likewise, in this model, the pressure before viscoelastic losses is named HMPl and HMPr for the left and right ventricles, respectively.

The valves, unlike the other compartments, were modeled as a small resistance, an inertance, and a flow-dependent diode in series as illustrated in Figure 7. The inertance will account for the effects of inertia during blood flow. The diode component represents the action of the valves to "opens" for large, positive blood flow, and "closes" for an arbitrarily small or negative flow effectively restricting flow to one direction. Therefore this diode will be represented by a nonlinear function, similar to a step or switch function.

Lastly, the coronary circulation was also modeled as a distinct compartment as shown in Figure 6. While inconsequential to gross hemodynamics, coronary blood flow plays a key role in the energetics of the cardiovascular system. The flow in the coronaries provides metabolic fuel to the myocardium (heart muscle). However, unlike the *Windkessel* dynamics of other elastic compartments, the coronary bed fills only during diastole. This results because pressure, generated by the myocardium during systole, occludes the coronary vasculature. Therefore the coronary resistance is directly related to left ventricular pressure, permitting coronary blood flow only during low left ventricular pressure. To capture this behavior, the coronary

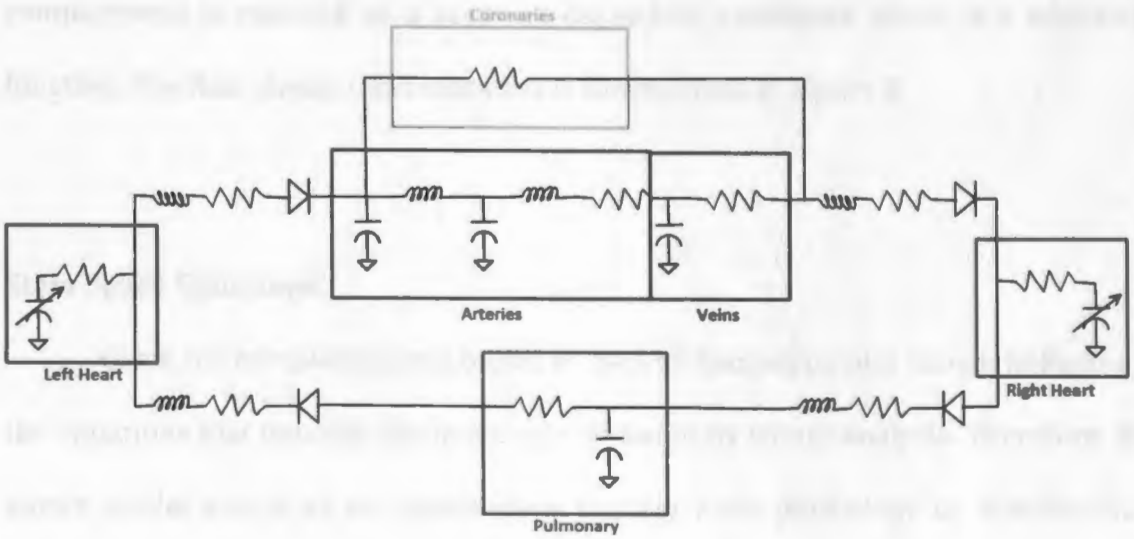


Figure 6 - Cardiovascular Circuit Model (Main Compartments)

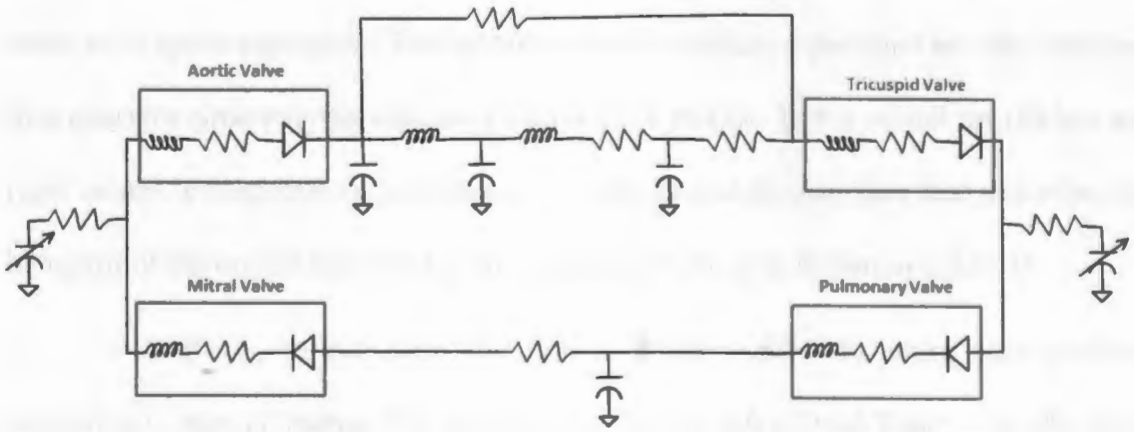


Figure 7 - Cardiovascular Circuit Model (Valves)

compartment is modeled as a pressure-dependent resistance which is a nonlinear function. The final circuit representation is summarized in Figure 9.

State Space Equations

Given the complete circuit model of the CVS hemodynamics shown in Figure 8, the equations that describe the model can be found by circuit analysis. Therefore, the circuit model serves as an intermediate concept from physiology to mathematical equations. So that standard numerical ODE solvers can be used to simulate the model, the math resulting from the circuit analysis was transformed into a system of first-order differential equations. Using this circuit model, there are 14 first-order differential equations that form the backbone of the hemodynamic model. These equations are listed in Table 1.

There are various auxiliary equations that merely simplify expression of the main state space equations. Two notable sets of auxiliary equations are the functions that describe time-varying elastance (named C_{LV} and C_{RV} in the model for the left and right ventricle respectively and shown in Table 2) and the function that describes the behavior of the on/off state of the valve (named D_1-D_4 and shown in Table 3).

In addition, to complete the model, initial conditions were also assumed according to normal human CVS parameters. (5, 14) Table 4 and Table 5 list the major parameters in terms of their corresponding variable name and initial value used for simulation.

Figure Legend

State Variables

Pressure (**Red**)

Flow (**Blue**)

Other Variables (Yellow)

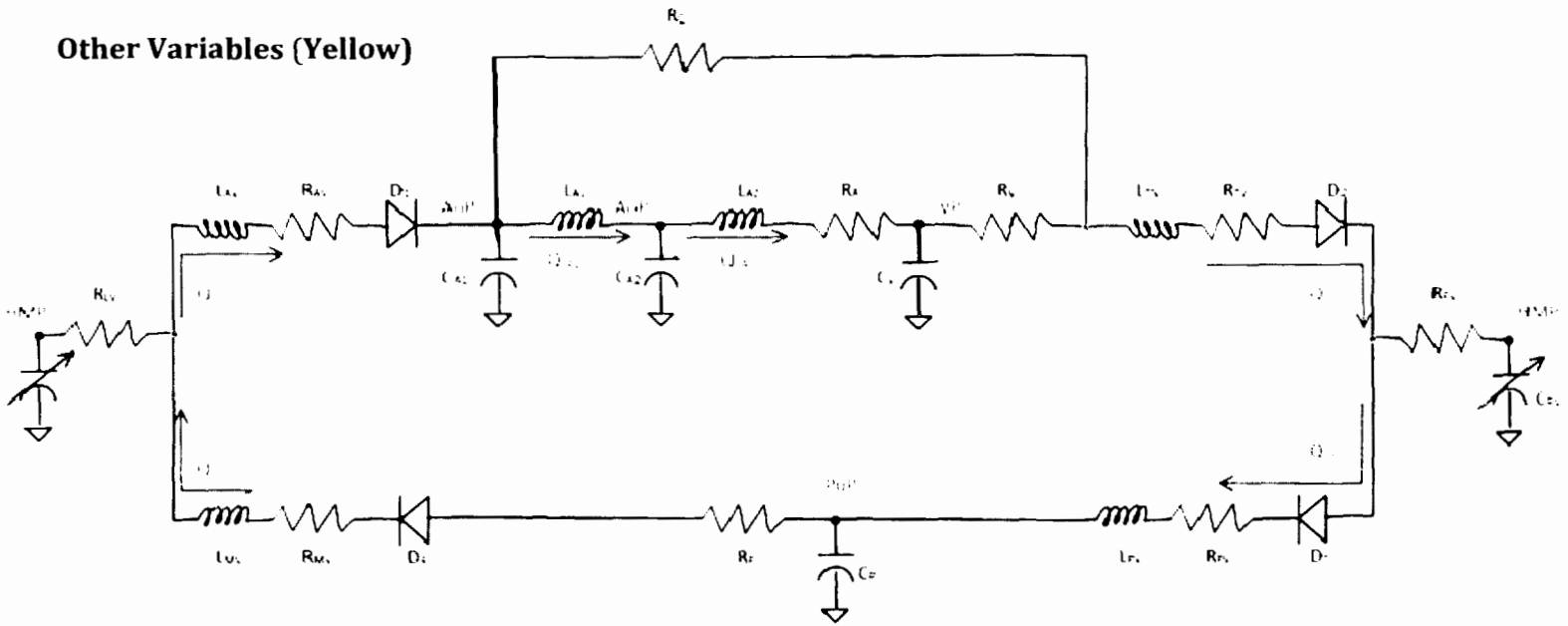


Table 1 - Cardiovascular State Space Equations

#	Equation
1	$\frac{d(LVV_{eff})}{dt} = Q_{iL} - Q_{oL}$
2	$\frac{d(HMP_L)}{dt} = \frac{1}{C_{LV}} \cdot \left(Q_{iL} - Q_{oL} - HMP_L \cdot \frac{d(C_{LV})}{dt} \right)$
3	$\frac{d(Q_{oL})}{dt} = \frac{1}{L_{AV}} \cdot (HMP_L - AoP_1 + R_{LV} \cdot Q_{iL} - (R_{LV} + R_{AV} + D_1) \cdot Q_{oL})$
4	$\frac{d(AoP_1)}{dt} = \frac{1}{C_{A1}} \cdot \left(Q_{oL} - Q_{LA1} - \frac{1}{R_c} \cdot AoP_1 + \frac{1}{R_c} \cdot CVP \right)$
5	$\frac{d(Q_{LA1})}{dt} = \frac{1}{L_{A1}} \cdot (AoP_1 - AoP_2)$
6	$\frac{d(AoP_2)}{dt} = \frac{1}{C_{A2}} \cdot (Q_{LA1} - Q_{LA2})$
7	$\frac{d(Q_{LA2})}{dt} = \frac{1}{L_{A2}} \cdot (AoP_2 - CVP - R_A \cdot Q_{LA2})$
8	$\frac{d(CVP)}{dt} = \frac{1}{C_V} \cdot \left(Q_{LA2} - Q_{iR} + \frac{1}{R_c} \cdot AoP_1 - \frac{1}{R_c} \cdot CVP \right)$
9	$\frac{d(Q_{iR})}{dt} = \frac{1}{L_{TV}} \cdot (CVP - HMP_R + R_{RV} \cdot Q_{oR} - (R_{RV} + R_V + R_{TV} + D_2) \cdot Q_{iR})$
10	$\frac{d(RVV_{eff})}{dt} = Q_{iR} - Q_{oR}$
11	$\frac{d(HMP_R)}{dt} = \frac{1}{C_{RV}} \cdot \left(Q_{iR} - Q_{oR} - HMP_R \cdot \frac{d(C_{RV})}{dt} \right)$
12	$\frac{d(Q_{oR})}{dt} = \frac{1}{L_{PV}} \cdot (HMP_R - PuP + R_{RV} \cdot Q_{iR} - (R_{RV} + R_{PV} + D_3) \cdot Q_{oR})$
13	$\frac{d(PuP)}{dt} = \frac{1}{C_P} \cdot (Q_{oR} - Q_{iL})$
14	$\frac{d(Q_{iL})}{dt} = \frac{1}{L_{MV}} \cdot (PuP - HMP_L + R_V \cdot Q_{oL} - (R_{LV} + R_P + R_{MV} + D_4) \cdot Q_{iL})$

Auxiliary Equations

Cardiac Pump Function

The beating heart is the result of autonomous electrical events as well as cardiac muscle (myocardium) dynamics. Both of these aspects of cardiac function will be empirically modeled as shown below.

The timing of the heart beat is the result of autonomous, oscillating excitation of the myocardium. This excitation triggers rhythmic contraction (increase in elastance) of the myocardium. Therefore, the first aspect of cardiac pump function will be to form a driving function to provide the timing cue for the onset of contraction. This driving function is modeled here as a simple harmonic oscillator function as shown in Equation 16 and plotted in Figure 9.

Equation 16 - Harmonic Oscillator

$$\ddot{E}(t) + \omega^2 \cdot E(t) = 0$$

This mathematical function maintains constant amplitude despite changes in frequency (ω). Therefore, Equation 16 provides a timing cue for time-varying elastance and can tolerate simulated changes in heart rate.

This oscillating function, a sinusoid, is then half-wave rectified, as shown in Figure 10, to simulate the typical pattern of a heart beat: contracting phase (systole) followed by a resting phase (diastole).

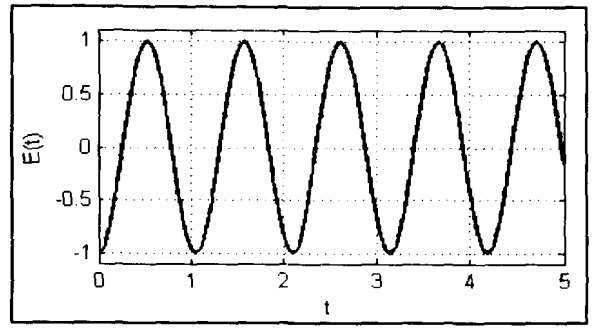


Figure 9 - Elastance Driving Function

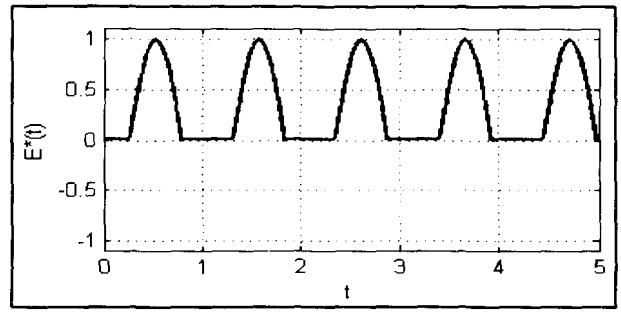


Figure 10 - Rectified Elastance Driving Function

This function is merely a frame to simulate rhythm of the heart – the ultimate pressure generated during a heartbeat is also a function of the mechanical properties of the heart muscle or myocardium. To account for the impact of the myocardium, the driving function is then scaled by a function derived from known pressure-volume relationships of the ventricle. This scaling function is designed from idealized end-systolic pressure-volume relationships (ESPVR). The model ESPVRs and filling envelopes were made from polynomials that were manipulated to resemble pressure-volume relationships seen experimentally. After finding appropriate polynomial functions, the first derivative of both functions (ESPVR and filling curve) were used as

maximum and minimum amplitude of the time-varying elastance. The driving function is ultimately scaled by these volume-sensitive extremes to yield ventricular pressures that succumb to the designed pressure-volume envelopes.

The left heart scaling function is shown below in Equation 17, followed by the plot (Figure 11) of the designed operating envelopes from which the function in Equation 17 was derived.

Equation 17 - Left Heart Pressure-Volume Equation

$$E_{LV} = \left[(-.0083 \cdot LVV_{rel}(t) + 3.1) - (.0003 \cdot LVV_{rel}(t))\right] \cdot E^{*}(t) + .0003 \cdot LVV_{rel}(t)$$

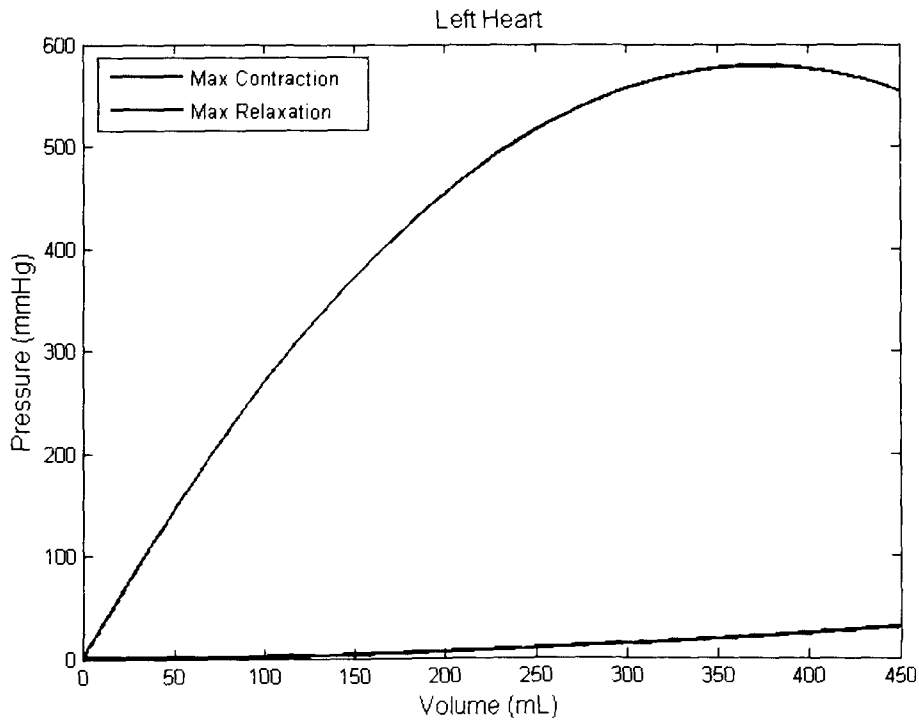


Figure 11- Designed Left Heart Pressure-Volume Envelopes

Since the left heart generates more pressure than the right, there are two separate scaling functions for the left and right heart. Both use the same driving function and are therefore in sync. The right heart elastance is only a diminished version of the left heart elastance function. The right heart scaling function is shown below in Equation 18 and the designed P-V relationships plotted in Figure 12.

Equation 18 - Right Heart Pressure-Volume Equation

$$E_{RV} = \left[(-.0016 \cdot RVV_{eff}(t) + .624) - (.00025 \cdot RVV_{eff}(t))\right] \cdot E^*(t) + .00025 \cdot RVV_{eff}(t)$$

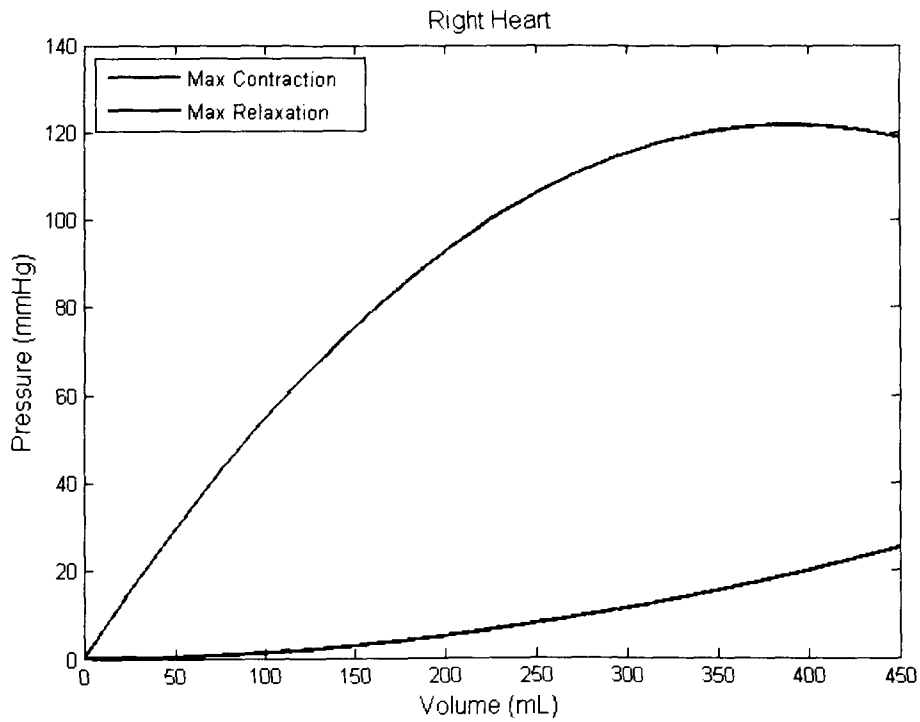


Figure 12 - Designed Right Heart Pressure-Volume Envelopes

Incorporating both pressure-volume envelopes into the elastance function is effectively incorporating feedback dependent on the current volume in the heart. This dependence of pressure generation on volume is referred to as the Frank-Starling law of the heart.

The compliance, which is simply the inverse of elastance, can be solved for and used in the state space system to solve the overall hemodynamics. Table 2, shown below, summarizes the time-varying elastance function (named C_{LV} and C_{RV} in the state-space equations) proposed for this model.

Table 2 - Left and Right Heart Time-Varying Compliance Function Derivation

Description	Equation
Oscillating Driving Function	$\ddot{E}(t) + \omega^2 \cdot E(t) = 0$
Half-wave Rectify	$E^*(t) = E(t) \;\; if \;\; E(t) \geq 0$
Pressure-Volume Envelope Scaling Function (Frank-Starling Law)	$E_{LV} = \left[(-.0083 \cdot LVV_{eff}(t) + 3.1) - (.0003 \cdot LVV_{eff}(t))\right] \cdot E^*(t) + .0003 \cdot LVV_{eff}(t)$ $E_{RV} = \left[(-.0016 \cdot RVV_{eff}(t) + .624) - (.00025 \cdot RVV_{eff}(t))\right] \cdot E^*(t) + .00025 \cdot RVV_{eff}(t)$
Elastance to Compliance	$C_{LV} = \frac{1}{E_{LV}}$ $C_{RV} = \frac{1}{E_{RV}}$

Valves (Diodes)

The valves were modeled as a function which dynamically changes value depending on the input. In this case the function changes resistance, and the input is blood flow. As shown in Figure 13 , this idealized function presents low resistance to high flows and increases resistance, in a smooth, continuous manner to low or negative flows. This function is similar in concept to a "switch" typically modeled as a step or Heaviside function; however, this function is differentiable, and as a result will comply with the numerical ODE simulation of the model.

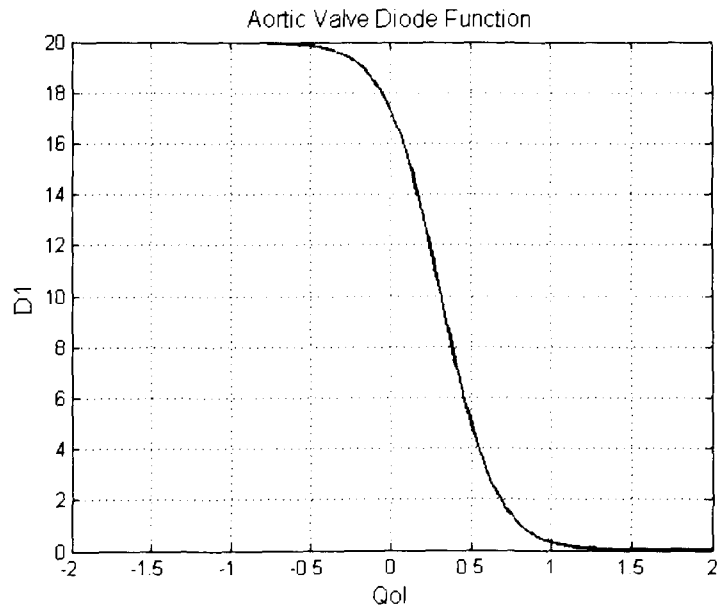


Figure 13- Diode Function Output (D1) versus Input (Qol)

All of the valves use the same form of equation, yet scaled accordingly depending on the magnitude of flow that each valve typically experiences. This was done as a precaution to ensure that the system remains numerically stable. For instance the mitral valve usually experiences low flows while the aortic experiences

high flows. The functions, listed next in Table 3, reflect this distinction. The particular function shown in Figure 13 above is the model for the aortic valve, which is not significantly different from the other three valve functions all shown in Table 3.

Table 3- Valve Diode Functions

Description	Equation
Aortic Valve	$D_1(t) = 20 * \left[-\left(\frac{.15}{.15 + e^{\quad}} \right) + 1 \right]$
Tricuspid Valve	$D_2(t) = 20 * \left[-\left(\frac{1}{1 + e^{\quad}} \right) + 1 \right]$
Pulmonary Valve	$D_3(t) = 20 * \left[-\left(\frac{.15}{.15 + e^{\quad}} \right) + 1 \right]$
Mitral Valve	$D_4(t) = 20 * \left[-\left(\frac{1}{1 + e^{\quad}} \right) + 1 \right]$

Other Equations

Nonlinear resistors were used to simulate the complicated hemodynamics in the coronaries in addition to the viscoelastic resistance of the myocardium. Both of these resistances were made to change depending on the pressure generated in the ventricle.

The viscoelastic resistance in the right and left ventricle (R_{LV} and R_{RV}) are described in Equation 19 and Equation 20 respectively. (11)

Equation 19 - Left Heart Viscoelastic Resistance

$$R_{LV}(t) = k * LVP(t)$$

Equation 20 - Right Heart Viscoelastic Resistance

$$R_{RV}(t) = k_{} * RVP(t)$$

Both functions for viscoelastic impedance depend on ventricular pressure. Ventricular pressure can be solved from the circuit model as shown in Equation 21 and Equation 22.

Equation 21 – Left Ventricular Pressure (LVP)

$$LVP(t) = HMP_{L}(t) - R_{LV} \cdot Q_{oL}(t) + R_{LV} \cdot Q_{iL}(t)$$

Equation 22 – Right Ventricular Pressure (RVP)

$$RVP(t) = HMP_{R}(t) - R_{RV} \cdot Q_{oR}(t) + R_{RV} \cdot Q_{iR}(t)$$

Additionally, the coronary vessel resistance behaves in a similar manner to the viscoelastic impedance function and is likewise modeled by similar functions. During the high pressure phase of contraction in the myocardium, the coronary vessels are occluded. This results in restricting coronary blood flow to the low pressure phases of the cardiac cycle. The function for coronary resistance, shown in Equation 23, is defined to depend on left ventricular pressure (defined in Equation 21) for simplicity.

Equation 23 - Coronary Resistance

$$R_{c}(t) = k_{c} * LVP(t)$$

Hemodynamic Parameter Descriptions and Initial Conditions

For completeness and reference, Tables 4 and 5 list the major parameters in terms of their corresponding variable name and initial value used for simulation.

Table 4 - Parameter Names & Initial Conditions

Name	Value	Description (Units)
Ra	1	Arterial Resistance (mmHg/mL/sec or PRU)
Ca1	1.5	Proximal Arterial Compliance (mL/mmHg)
Ca2	1.5	Distal Arterial Compliance (mL/mmHg)
Cv	60	Venous Compliance (mL/mmHg)
Cp	15	Pulmonary Compliance (mL/mmHg)
w	6	Heart Rate (rad/sec)
La1	0.0001	Proximal Arterial Inertance (mmHg/mL/sec^2)
La2	0.0001	Distal Arterial Inertance (mmHg/mL/sec^2)
Lav	0.0001	Arterial Valve Inertance (mmHg/mL/sec^2)
Lmv	0.0001	Mitral Valve Inertance (mmHg/mL/sec^2)
Lpv	0.0001	Pulmonary Valve Inertance (mmHg/mL/sec^2)
Ltv	0.0001	Tricuspid Valve Inertance (mmHg/mL/sec^2)
Rav	0.01	Arterial Valve Resistance (PRU)
Rmv	0.01	Mitral Valve Resistance (PRU)
Rpv	0.01	Pulmonary Valve Resistance (PRU)
Rtv	0.01	Tricuspid Valve Resistance (PRU)
Rp	0.08	Pulmonary Resistance (PRU)
Rv	0.05	Venous Resistance (PRU)
kc	0.5	Coronary Resistance Factor, Rc=kc*LVP
k	0.0001	Left Ventricle Resistance Factor, Rlv=k*LVP
kr	0.0001	Right Ventricle Resistance Factor, Rrv=kr*RVP
Voa1	250	Proximal Arterial Dead Volume (mL)
Voa2	250	Distal Arterial Dead Volume (mL)
Vov	2700	Venous Dead Volume (mL)
Volv	20	Left Ventricular Dead Volume (mL)
Vorv	20	Right Ventricular Dead Volume (mL)
Vop	200	Pulmonary Vasculature Dead Volume (mL)

Table 5 – System Initial Conditions

Name	Value	Description (Units)
Veff_a1(t=0)	150	Proximal Effective Arterial Volume (mL)
Veff_a2(t=0)	150	Distal Effective Arterial Volume (mL)
Veff_v(t=0)	800	Effective Venous Volume (mL)
Veff_p(t=0)	250	Effective Pulmonary Volume (mL)
LVV(t=0)	150	Total Left Ventricle Volume (mL)
RVV(t=0)	150	Total Right Ventricle Volume (mL)
AoP_1(t=0)	Veff_a1(t=0)/Ca1	Proximal Arterial Pressure (mmHg)
AoP_2(t=0)	Veff_a2(t=0)/Ca2	Distal Arterial Pressure (mmHg)
CVP(t=0)	Veff_v(t=0)/Cv	Central Venous Pressure (mmHg)
PuP(t=0)	Veff_p(t=0)/Cp	Pulmonary Vasculature Pressure (mmHg)
Q_{oR}(t=0)	0	Right Heart Flow-out (mL/sec)
Q_{iR}(t=0)	0	Right Heart Flow-in (mL/sec)
Q_{oL}(t=0)	0	Left Heart Flow-out (mL/sec)
Q_{iL}(t=0)	0	Left Heart Flow-in (mL/sec)
Q_{La1}(t=0)	0	Proximal Arterial Flow (mL/sec)
Q_{La2}(t=0)	0	Distal Arterial Flow (mL/sec)
HMP_L(t=0)	[LVV(t=0)-Volv]*Elv(t=0)	Left Ventricle Hydromotive Pressure (mmHg)
HMP_R(t=0)	[RVV(t=0)-Vorv]*Erv(t=0)	Right Ventricle Hydromotive Pressure (mmHg)

Thermodynamics

The thermodynamic viewpoint of the CVS requires an alternative but complementary model. The analysis will separate the CVS into a series of closed-loop compartments in which energy transfers and/or transformations are the main focus. This will involve organizing the original compartments, as shown in Figure 14, in a manner more suitable for thermodynamic analysis, as shown in Figure 15. The arteries and veins will be lumped into a single compartment. Also the left and right heart will be lumped together to allow for a simpler view of energy exchange at the myocardium. Overall, each compartment will then be treated as a control volume under which first and second-law analyses will ultimately result in a value of entropy generation ($\dot{\sigma}$).

To more easily demonstrate the thermodynamic analysis, the process will first be demonstrated on a simple, generic control volume. The analysis of the simple control volume can be extrapolated to the special cases of each of the CVS compartments.

The first and second law analysis of the CVS components will be shown after the analysis of the simple control volume. Following thermodynamic analysis of each CVS component will be a consideration of the metabolic demand and its impact on thermodynamics within the CVS. Finally, the thermodynamic equations will be recapitulated in the overall context of the CVS thermodynamic cycle which results in a certain value of entropy generation. For completeness, the values of the parameters including initial conditions are listed at the end of this section.

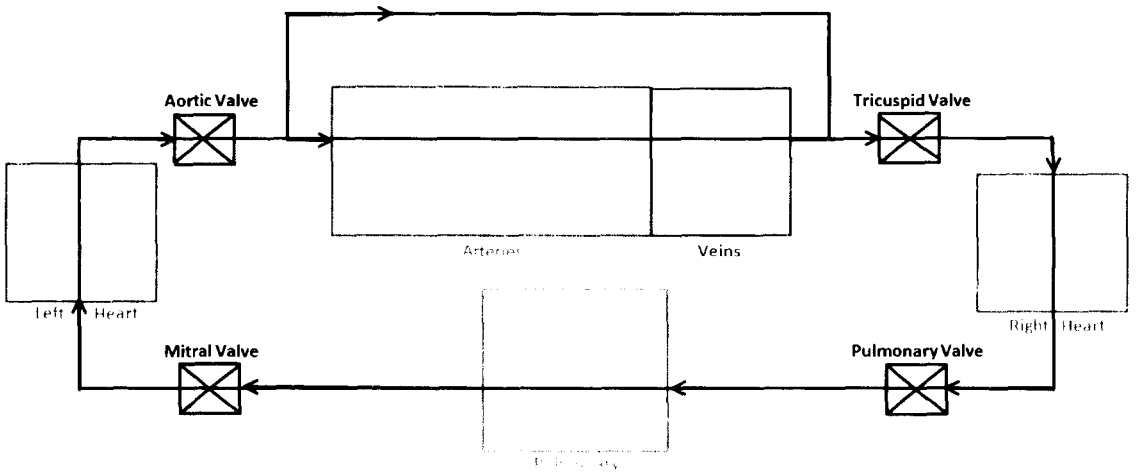


Figure 14 - Hemodynamic Compartmental CVS Model

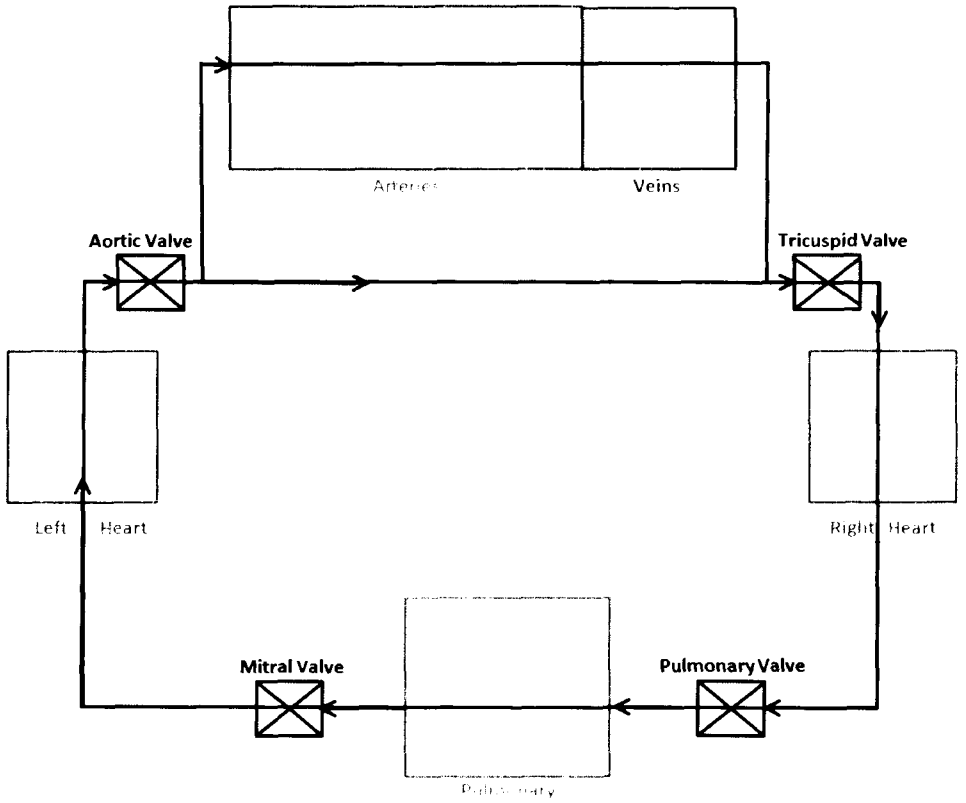


Figure 15 - Thermodynamic Compartmental CVS Model

Introduction to Thermodynamic Analysis

The analysis of a generic control volume, though well established, is shown here for reference as well as for a building block for which the rest of the thermodynamic analysis of the CVS will follow.

The first law of thermodynamics accounts for the conservation of energy. For a closed system (no mass crossing the system boundary) in the absence of kinetic and potential energy changes, the first law is written as shown in Equation 24.

Equation 24 - First Law

$$dU = dQ - dW$$

U = Internal Energy
Q = Heat added to the system
W = Work done by the system

Therefore, the first law assures that a change in internal energy can be accounted for by tracking the heat transfer and/or work performed. When applied to a control volume in which mass is flowing steadily from inlet to exit, the first law can be written in the form (Equation 25) below assuming kinetic and potential energy are negligible.

Equation 25 - First Law Applied to a Control Volume

$$\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$$

$\dot{m}_e$ = Mass Flow exiting
$\dot{m}_i$ = Mass Flow incoming

The sum is used to account for all inlets and exits in the case of multiple flows.

The second law of thermodynamics states that, for a system that interacts with its surroundings, the total entropy change is either zero or positive. A total entropy change of zero represents what is known as a reversible process, whereas a positive total entropy change represents a process that possesses irreversibilities. Any real-world energy conversion process, such as the conversion of metabolic fuel to contracting myocardium, contains inherent irreversibilities that contribute to an overall increase of entropy.

The first law of thermodynamics is a statement of energy conservation. Similarly, the second law of thermodynamics treats entropy as a conserved quantity. For a steady flow process, the second law can be written as shown in Equation 26.

Equation 26 - Second Law Applied to a Control Volume

$$\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$$

$\dot{\sigma}$ = Entropy Generation
s = Entropy

Entropy generation is zero in the case of an ideal reversible process, or positive in the case of a real-world, irreversible process. The magnitude of the entropy generation rate gives an indication of the level of irreversibility within the control volume. From this equation, it can be seen that the entropy generation rate (and thus

the irreversibility) is made up of two components: 1) the entropy change of the flows in and out of the control volume, and 2) the heat transfer to/from the control volume.

In any control volume analysis where the goal is to determine the entropy generation rate due to irreversibilities within the control volume, both the first and second laws of thermodynamics must be used together. The first law allows for the calculation of the heat transfer rate and the second law determines the entropy generation rate.

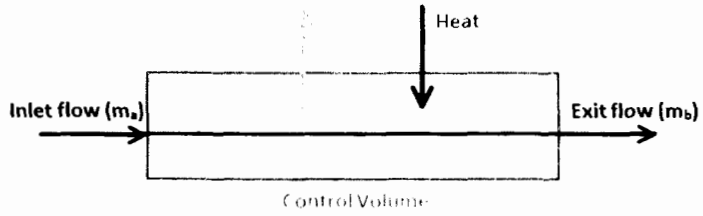
As illustrated next in Panel 1, the entropy generated ($\dot{\sigma}$) within the control volume can be completely determined as long as mass flows ($\dot{m}$), pressures (P), temperatures (T), heat (Q) and work (W) are known. When analyzing the control volumes of the CVS model, the mass flows and pressures will be simulated directly in the hemodynamic model. Temperature and heat transfers will be determined by a combination of assumptions with first law and second law analysis.

Eventually, with the aforementioned analysis, there will be enough information to calculate entropy generation. The same method will be applied to the CVS by applying the analysis of a generic control volume to each control volume or compartment of the CVS with modifications or assumptions where necessary.

First and Second Law Application to the CVS

Following the method shown for a generic control volume, the entire CVS system can be analyzed using the first and second laws of thermodynamics. To start,.

Panel 1 - Analysis of a Generic Control Volume



First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$\dot{m}_b \cdot h_b - \dot{m}_a \cdot h_a = \dot{Q} - \dot{W}$

Assuming Steady-State Steady-Flow (SSSF) Conditions: $\dot{m}_a = \dot{m}_b$

$\dot{m}_a \cdot (h_b - h_a) = \dot{Q} - \dot{W}$

$\dot{m}_a \cdot (\Delta h_{b-a}) = \dot{Q} - \dot{W}$

Since $\Delta h = \Delta u + v \cdot \Delta P$

and $\Delta u = c_v \Delta T$

then $\Delta h = c_v \Delta T + v \cdot \Delta P$

$\dot{m}_a \cdot (c_v \Delta T_{b-a} + v \cdot \Delta P_{b-a}) = \dot{Q} - \dot{W}$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

Assuming steady-state, steady-flow conditions, $\dot{m}_a = \dot{m}_b$

$\dot{\sigma} = \dot{m}_a \cdot (\Delta s_{b-a}) - \dot{Q}/T$

The entropy change of an incompressible substance is $\Delta s = c_v \ln \frac{T_b}{T_a}$. Therefore,

$\dot{\sigma} = \dot{m}_a c_v \ln \frac{T_b}{T_a} - \dot{Q}/T$

each control volume will have uniquely numbered inlet and exit nodes as shown in Figure 16. This will be used to designate mass flows, temperatures, and pressures

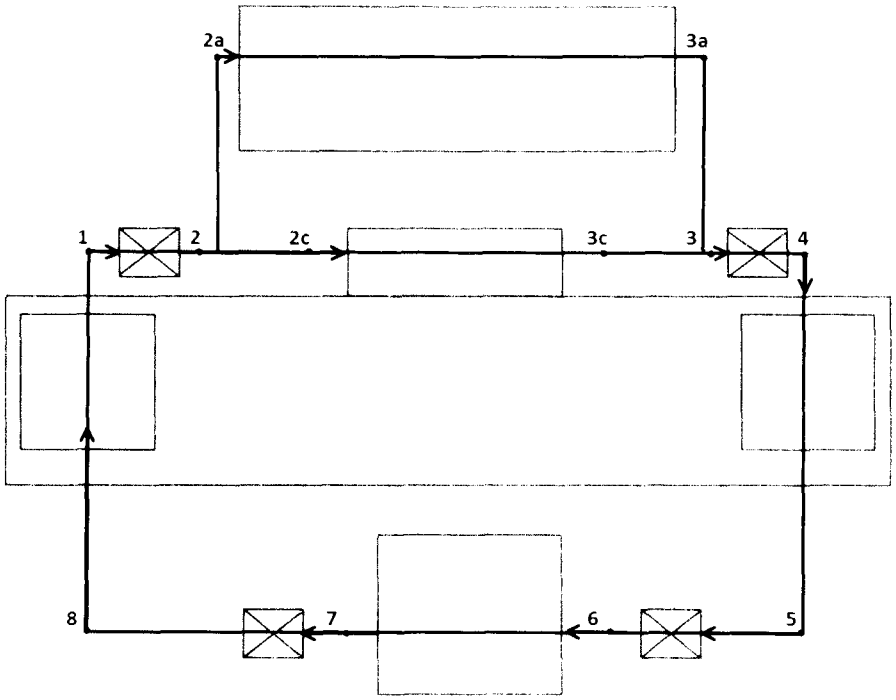


Figure 16- Thermodynamic Compartmental CVS Model with Numbered Nodes

The analysis for the thermodynamic model was done under the assumption of steady-state conditions. Therefore, the hemodynamic data was time-averaged over a single beat. In addition, data was converted to units that are convenient for thermodynamic analysis. There are two main conversions:

1. pressure (mmHg to Pascals)
2. blood flow (volumetric flow in mL/sec to mass flow in g/sec).

The hemodynamic pressure across the left and right heart is conceptualized differently from the steady-state, steady-flow thermodynamic model. For example, the pressure at node 8, P_8, is the average left ventricular pressure during systole and P_1 is the average left ventricular pressure during diastole – therefore representing the extremes of pump function. However, in the previous hemodynamic model, the equivalent node represented anatomic inlet and outlets which could vary over time.

To start, the important energy transfers need to be identified, such as work and heat, to orient the following thermodynamic discussion – the model proposed for this study is shown in Figure 17.

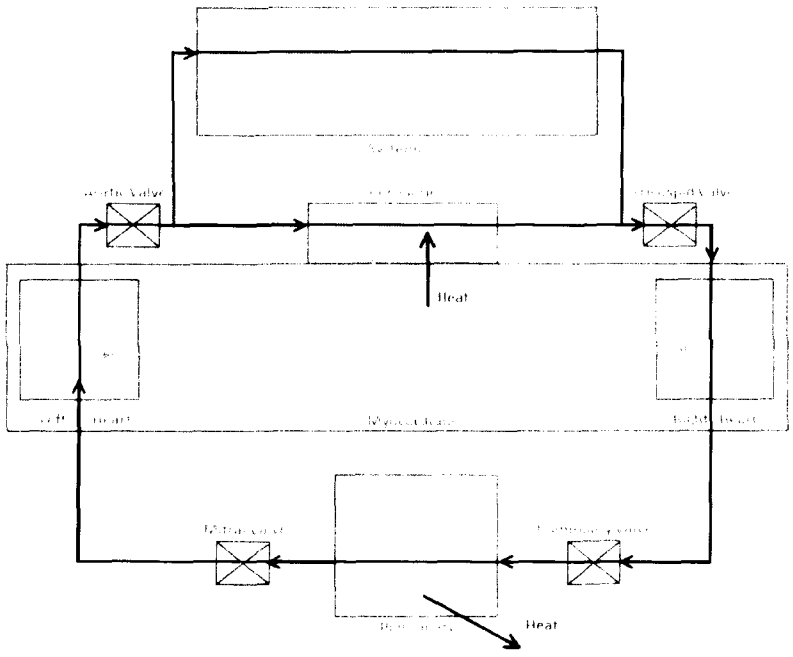


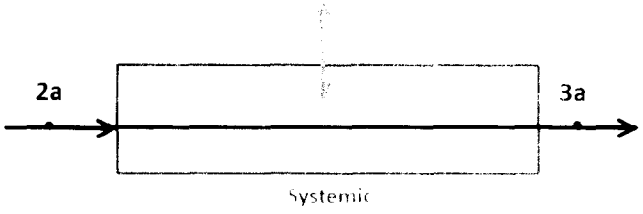
Figure 17 - Thermodynamic Compartmental CVS Model with Energy Transfers

First of all, the metabolic exchange at the systemic vasculature is assumed to be balanced. That is, the metabolic energy consumed by the body is exactly replenished by metabolic fuel intake. Next, it is assumed that a core body temperature is maintained via a single point of heat transfer at the pulmonary compartment. Lastly, the various energy transformations occurring within the heart are revealed by the hemodynamics – that is the pressure and volume of blood in the ventricle reflect the work done by the myocardium. The heat generated to do this work is assumed to transfer entirely to the coronaries. Although some heat may also transfer into the ventricle, it is assumed to be negligible.

Given the thermodynamic model of the CVS, the first and second law analysis of each compartment or control volume is shown in the following series of paneled images (Panels 2-7). Panel 2 demonstrates the analysis of the systemic compartment. Panel 3 shows the pulmonary compartment. The mitral valve is shown in Panel 4. The next three panels illustrate analysis of the heart by its three main compartments: the coronary vasculature, the myocardium, and the ventricles. Panels 5, 6, and 7 represent the coronaries, myocardium and ventricles respectively.

Analysis of the mitral valve is shown in Panel 4. The other three valves (aortic valve, tricuspid valve, and pulmonary valve) can be analyzed in exactly the same way as the mitral valve since the same mathematical formulation and assumptions apply. Therefore the analysis outlined in Panel 4 for the mitral valve is used for rest of the valves by using the specific flow inlet and exit identities were used as shown in Table 6.

Panel 2 - Analysis of the Systemic Vasculature



Assumptions

1. SSSF: $\dot{m}_{3a} = \dot{m}_{2a}$; $\dot{m}_{met} << \dot{m}_{2a}$

2. Sufficient metabolic fuel to meet demand:
$\dot{m}_{met\_out} \cdot h_{met\_out} = \dot{m}_{met\_in} \cdot h_{met\_in}$

3. No heat or work cross the boundary:
$\dot{Q} = 0 \;\&\; \dot{W} = 0$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$$\dot{m}_{3a} \cdot h_{3a} - \dot{m}_{2a} \cdot h_{2a} + \dot{m}_{met\_out} \cdot h_{met\_out} - \dot{m}_{met\_in} \cdot h_{met\_in} = 0$$

$$\dot{m}_{2a} \cdot (\Delta h_{3a-2a}) = 0$$

$$\dot{m}_{2a} \cdot (c_v \Delta T_{3a-2a} + v \cdot \Delta P_{3a-2a}) = 0$$

$$c_v \Delta T_{3a-2a} = -v \cdot \Delta P_{3a-2a}$$

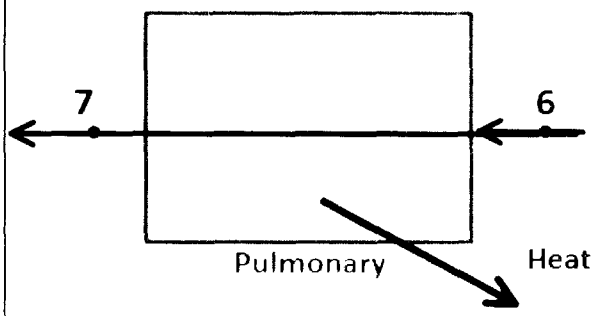
$$T_{2a} = \frac{v \cdot \Delta P_{3a-2a}}{c_v} + T_{3a}$$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

$$\dot{\sigma}_s = \dot{m}_{2a} \cdot (\Delta s_{3a-2a}) + \dot{m}_{met\_in} (\Delta s_{met\_out-met\_in})$$

$$\dot{\sigma}_s = \dot{m}_{2a} \cdot \left(c_v \cdot \ln \frac{T_{3a}}{T_{2a}} \right) + \dot{m}_{met\_in} (\Delta s_{met\_out-met\_in})$$

Panel 3 - Analysis of the Pulmonary Compartment



Assumptions

SSSF: $\dot{m}_6 = \dot{m}_7$

$\dot{Q} = \dot{Q}_p$

$\dot{W} = 0$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$\dot{m}_7 \cdot h_7 - \dot{m}_6 \cdot h_6 = \dot{Q}_p$

$\dot{m}_6 \cdot (\Delta h_{7-6}) = \dot{Q}_p$

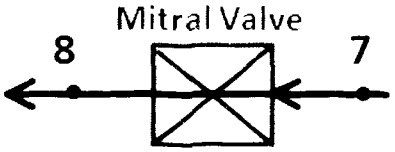
$\dot{m}_6 \cdot (c_v \Delta T_{7-6} + v \cdot \Delta P_{7-6}) = \dot{Q}_p$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

$\dot{\sigma}_p = \dot{m}_6 \cdot (\Delta s_{7-6}) - \dot{Q}_p/T$

$\dot{\sigma}_p = \dot{m}_6 \cdot \left(c_v \cdot \ln \frac{T_7}{T_6} \right) - \dot{Q}_p/T$

Panel 4 - Analysis of the Valves



Assumptions

SSSF: $\dot{m}_7 = \dot{m}_8$

$\dot{Q} = 0$

$\dot{W} = 0$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$\dot{m}_8 \cdot h_8 - \dot{m}_7 \cdot h_7 = 0$

$\dot{m}_7 \cdot (\Delta h_{8-7}) = 0$

$\dot{m}_7 \cdot (c_v \Delta T_{8-7} + v \cdot \Delta P_{8-7}) = 0$

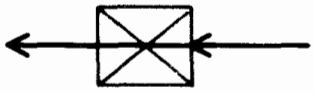
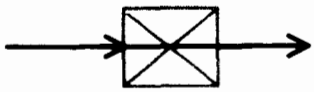
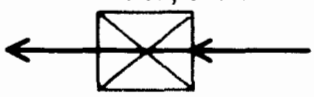
$$T_7 = \frac{v \cdot \Delta P_{8-7}}{c_v} + T_8$$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

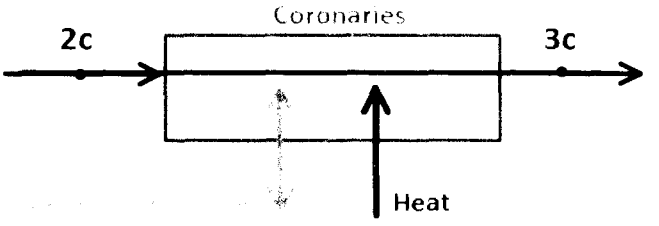
$\dot{\sigma}_{mv} = \dot{m}_7 \cdot (\Delta s_{8-7})$

$$\dot{\sigma}_{mv} = \dot{m}_7 \cdot \left(c_v \cdot \ln \frac{T_8}{T_7} \right)$$

Table 6 - Analysis of the Valves Applied to Each Specific Valve

<table>
<tr>
<td>Mitral Valve
 
<u>First Law Analysis:</u>
$T_7 = \frac{v \cdot \Delta P_{7-8}}{c_v} + T_8$
<u>Second Law Analysis:</u>
$\dot{\sigma}_{mv} = \dot{m}_7 \cdot \left(c_v \cdot \ln \frac{T_8}{T_7} \right)$</td>
<td>Aortic Valve
 
<u>First Law Analysis:</u>
$T_1 = \frac{v \cdot \Delta P_{1-2}}{c_v} + T_2$
<u>Second Law Analysis:</u>
$\dot{\sigma}_{av} = \dot{m}_1 \cdot \left(c_v \cdot \ln \frac{T_2}{T_1} \right)$</td>
</tr>
<tr>
<td>Tricuspid Valve
 
<u>First Law Analysis:</u>
$T_4 = \frac{v \cdot \Delta P_{3-4}}{c_v} + T_3$
<u>Second Law Analysis:</u>
$\dot{\sigma}_{tv} = \dot{m}_3 \cdot \left(c_v \cdot \ln \frac{T_4}{T_3} \right)$</td>
<td>Pulmonary Valve
 
<u>First Law Analysis:</u>
$T_6 = \frac{v \cdot \Delta P_{5-6}}{c_v} + T_5$
<u>Second Law Analysis:</u>
$\dot{\sigma}_{pv} = \dot{m}_5 \cdot \left(c_v \cdot \ln \frac{T_6}{T_5} \right)$</td>
</tr>
</table>

Panel 5 - Analysis of the Heart (Coronaries)



Assumptions

$\dot{m}_{met\_react} \approx \dot{m}_{met\_products} = \dot{m}_{met}$

SSSF: $\dot{m}_{3c} = \dot{m}_{2c}$

$\dot{m}_{met} << \dot{m}_{c}$

$\dot{Q} = \dot{Q}_{c}$

$\dot{W} = 0$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$$\dot{m}_{3c} \cdot h_{3c} - \dot{m}_{2c} \cdot h_{2c} + \dot{m}_{met\_react} \cdot h_{met\_react} - \dot{m}_{met\_products} \cdot h_{met\_products} = \dot{Q}_{c}$$

$$\dot{m}_{2c} \cdot \left(\Delta h_{3c-2c}\right) + \dot{m}_{met} \cdot \left(\Delta h_{met\_react-met\_products}\right) = \dot{Q}_{c}$$

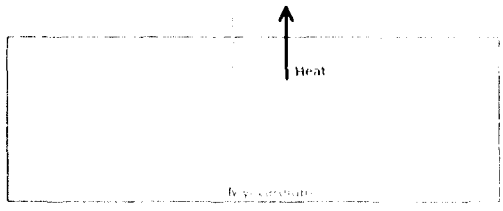
$$\dot{m}_{2c} \cdot \left(c_v \Delta T_{3c-2c} + v \cdot \Delta P_{3c-2c}\right) + \dot{m}_{met} \cdot \left(\Delta h_{met\_react-met\_products}\right) = \dot{Q}_{c}$$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

$$\dot{\sigma}_{c} = \dot{m}_{2c} \cdot \left(\Delta s_{3c-2c}\right) + \dot{m}_{met}\left(\Delta s_{met\_react-met\_products}\right) - \dot{Q}_{c}/T$$

$$\dot{\sigma}_{c} = \dot{m}_{2c} \cdot \left(c_v \cdot \ln \frac{T_{3c}}{T_{2c}}\right) + \dot{m}_{met}\left(\Delta s_{met\_react-met\_products}\right) - \dot{Q}_{c}/T$$

Panel 6 - Analysis of the Heart (Myocardium)



Assumptions

$$\dot{m}_{met\_react} \approx \dot{m}_{met\_products} = \dot{m}_{met}$$

$$\dot{Q} = \dot{Q}_m$$

$$\dot{W} = \dot{W}_{m\_left} + \dot{W}_{m\_right} = \dot{W}_m$$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

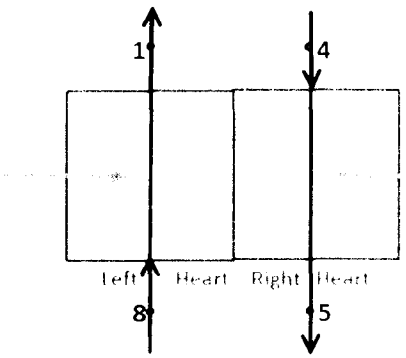
$$\dot{m}_{met\_products} \cdot h_{met\_products} - \dot{m}_{met\_react} \cdot h_{met\_react} = -\dot{Q}_m - \dot{W}_m$$

$$\dot{m}_{met} \cdot \left(\Delta h_{met\_products-met\_react}\right) = -\dot{Q}_m - \dot{W}_m$$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

$$\dot{\sigma}_m = \dot{m}_{met}(\Delta s_{met\_products-met\_react}) + \dot{Q}_m/T$$

Panel 7 - Analysis of the Heart (Ventricles)



Assumptions

SSSF: $\dot{m}_1 = \dot{m}_4 = \dot{m}_5 = \dot{m}_8$

$\dot{Q} = 0$

$\dot{W} = \dot{W}_{m\_left} + \dot{W}_{m\_right} = \dot{W}_m$

First Law Analysis: $\sum \dot{m}_e \cdot h_e - \sum \dot{m}_i \cdot h_i = \dot{Q} - \dot{W}$

$\dot{m}_1 \cdot h_1 + \dot{m}_5 \cdot h_5 - \dot{m}_8 \cdot h_8 - \dot{m}_4 \cdot h_4 = \dot{W}_m$

$\dot{m}_1 \cdot (\Delta h_{1-8} + \Delta h_{5-4}) = \dot{W}_m$

$\dot{m}_1 \cdot (c_v \cdot (\Delta T_{1-8} + \Delta T_{5-4}) + v \cdot (\Delta P_{1-8} + \Delta P_{5-4})) = \dot{W}_m$

Second Law Analysis: $\dot{\sigma} = \sum \dot{m}_e \cdot s_e - \sum \dot{m}_i \cdot s_i - \dot{Q}/T \geq 0$

$\dot{\sigma}_v = \dot{m}_1 \cdot (\Delta s_{1-8} + \Delta s_{5-4})$

$\dot{\sigma}_v = \dot{m}_1 \cdot c_v \cdot (\ln \frac{T_1}{T_8} + \ln \frac{T_5}{T_4})$

$\dot{\sigma}_v = \dot{m}_1 \cdot c_v \cdot \ln \frac{T_1 \cdot T_5}{T_8 \cdot T_4}$

Metabolic Demand

The consideration of the metabolic demand is necessary to ensure the CVS state is physiological viable. Also, metabolism will impact the first and second law calculations.

For practical purposes, it is assumed that all of the body's energetic needs are derived aerobically. The flow of fuel and energy proceeds in the body as shown in Figure 18.

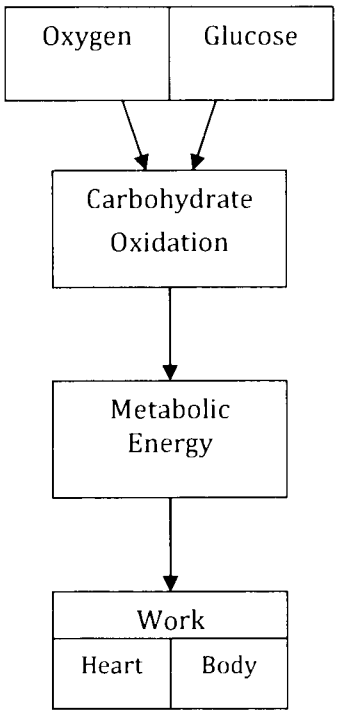


Figure 18 - Metabolism

However, calculation in this study will be retrograde. Therefore the simulation will result in a calculation of total work, and the necessary calculations will backtrack through the stages of metabolism to find the required rate of oxygen needed to

sustain this demand. This oxygen demand must be within normal physiological limits to be a possible CVS state.

For simplicity, the blood was assumed to be initially 100% saturated with oxygen. Normal blood that is 100% saturated carries 20mL oxygen per 100mL blood. Therefore, if a CVS state requires an unattainable oxygen demand – that is more than 20mL of oxygen per 100mL of blood – then the state is considered "unphysiological".

There are two points of metabolic demand in this model: 1) systemic and 2) coronary. Both points of metabolic demands will be analyzed separately.

Systemic

The systemic metabolic demand is an external influence that was set as a constant rate. The value of this was set at a modest level of 100W which his equivalent to the metabolic needs of a 70kg male at rest. (5) Therefore, the oxygen content needed to sustain this demand can be calculated as using the relationship shown below in Equation 27 which is rearranged for convenience in Equation 28.

Equation 27 - Metabolic Energy Demand as a Function of Blood Flow

$$ME = k \cdot \dot{V} \cdot \Delta O_2$$

ME = Metabolic Energy
k = Energy Equivalent of Oxygen
$\dot{V}$ = Cardiac Output
ΔO_2 = A-V Oxygen Difference

Equation 28 - Oxygen Content of Blood Necessary to Meet Metabolic Demand

$$\Delta O_2 = \frac{ME}{k \cdot \dot{V}}$$

This relationship shows that metabolic demand will be sustained by both the rate of blood flow (cardiac output) and the oxygen content of blood. Since ME is declared to be 100W, and k is known to be 20.2 J/(ml O_2), and cardiac output is known from simulation of the hemodynamic model, the oxygen difference, ΔO_2, can be simply calculated. (40)

Using the calculation of ΔO_2, the heat transferred due to conversion of energy can also be deduced. The relationship between oxygen consumed and heat produced by metabolism is dependent on the type of metabolic fuel consumed. This could be a mix of lipids and carbohydrates depending on the diet, but for simplicity, only carbohydrate oxidation will be considered as the metabolic fuel source. This assumption defines the exact stoichiometry for the consumption of fuel (glucose), as shown in Equation 29.

Equation 29 - Glucose Metabolism

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

Based on known properties of this reaction, the heat liberated per mole of glucose consumed is known to be 77.7 kJ/mol. (7) To convert this rate of heat production, which is per mole of glucose, the molar rate of glucose is needed. However since this relationship follows a stoichiometry (see Equation 29) such that for every mole of glucose consumed in carbohydrate oxidation, there are 6 mol oxygen needed. Therefore a sixth of the molar rate of oxygen can be substituted for the molar rate of

glucose. Since oxygen content of blood in the systemic compartment has already been calculated based on the assumed metabolic demand, the molar rate of oxygen can be deduced as demonstrated in Equation 30.

Equation 30 - Molar Rate of Systemic Oxygen Demand

$$\dot{n}_{O_2} = \frac{\dot{V} \cdot \Delta O_2}{\text{con3}}$$

$\dot{n}_{O_2}$ = Molar rate of oxygen (moles O_2/sec)

$\dot{V}$ = Cardiac Output (mL or cc blood per sec)

ΔO_2 = A-V Oxygen Difference (mL oxygen per mL blood)

con3 = Conversion Factor #3 (22400 mL/mole)

After molar rate of oxygen is calculated, and also since glucose consumption is 1/6 that of oxygen, the heat liberated by glucose metabolism to oxygen flow is calculated as follows in Equation 31.

Equation 31 - Heat from Metabolic Oxygen Consumption

$$T\Delta s_{MET} = \dot{n}_{O_2} \cdot \frac{1}{6} \cdot 77{,}700$$

$T\Delta s_{MET}$ = Heat liberated due to glucose consumption (J/sec or Watts)

$\dot{n}_{O_2}$ = Molar rate of oxygen (moles O_2/sec)

In this manner, the rate of oxygen consumption also determines the amount of heat transfer due to metabolism in the systemic compartment (see Panel 2). Therefore the second law formulation for the systemic compartment, shown in Panel 2, can be expanded as shown in Equation 32.

Equation 32 - Entropy Generation in the Systemic Compartment

$$\dot{\sigma}_s = \dot{m}_{2a} \cdot \left(c_v \cdot \ln \frac{T_{3a}}{T_{2a}} \right) + \left[\dot{n}_{O_2} \cdot (1/6) \cdot 77{,}700 \right] / T$$

Coronary

Unlike the systemic metabolic demand, the coronary metabolic demand can be calculated entirely from the hemodynamic data. It has been shown by Suga that a quantity calculated from pressure and volume signals, PVA (pressure-volume area), correlates very closely to the myocardial oxygen demand ($M\dot{V}_{O_2}$) in the relationship shown in Equation 33. (40)

Equation 33 - Myocardial Oxygen Demand as a Function of PVA

$$M\dot{V}_{O_2} = 1.64 \cdot 10^{-5} (PVA) + 0.015$$

$M\dot{V}_{O_2}$ = Myocardial oxygen demand

PVA = Pressure-Volume Area

The calculation of PVA involves analysis of the cardiac cycle in the pressure-volume domain. PVA is a quantity constituted by the total area encircled by both the PV loop (stroke work) plus the triangle between the PV loop and the dead volume (V_0). Therefore, PVA is calculated as the sum of two areas illustrated in Figure 19.

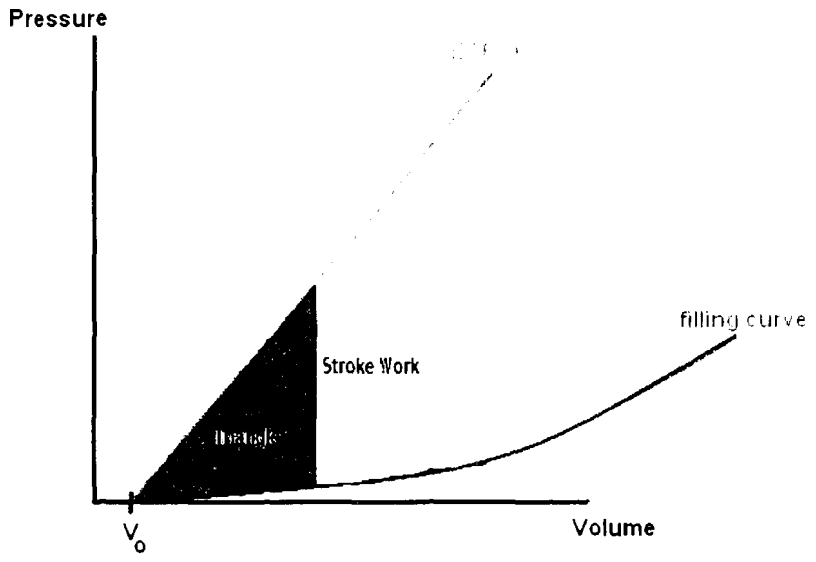


Figure 19 - The Pressure-Volume Area (PVA) = Stroke Work + Triangle

Using this information and the hemodynamic data for left and right ventricular pressure and volume, the myocardial oxygen demand ($M\dot{V}_{O_2}$) can be calculated using Equation 33.

Therefore the work performed reveals the metabolic fuel needed for this demand. Given the simulated value of coronary flow from the hemodynamic model, the coronary oxygen content needed to sustain this metabolic demand can be solved as shown in Equation 34.

Equation 34 – Myocardial Oxygen Demand as a Function of Coronary Blood Flow

$$M\dot{V}_{O_2} = \dot{\Psi}_c \cdot \Delta O_2$$

$M\dot{V}_{O_2}$ = Myocardial Oxygen Demand (mL oxygen per sec)

$\dot{\Psi}_c$ = Coronary Blood Flow (mL/sec)

ΔO_2= A-V Oxygen Difference (mL oxygen per mL blood)

Equation 34 is rearranged for convenience as Equation 35. Equation 35 shows that the calculation of the necessary oxygen content of coronary blood, or ΔO_2, involves the value for $M\dot{V}_{O_2}$ which in turn is calculated using data from the hemodynamic model and Equation 33 in addition to the value of coronary blood flow also provided by simulation of the hemodynamic model.

Equation 35 - Oxygen Content of Coronary Blood to Meet Myocardial Oxygen Demand

$$\Delta O_2 = \frac{M\dot{V}_{O_2}}{\dot{\Psi}_c}$$

The value for ΔO_2 is bounded by physiological limits of the oxygen carrying capacity of blood. Therefore this value is calculated as a check to ensure that the simulated CVS state is within physiological limits.

Summary

Metabolic demand is sustained by both blood flow and oxygen content of blood. In addition metabolic demand is also proportional to the body's metabolic needs (kept constant in this simulation) and the varying demands of the heart. Interestingly, the heart both consumes energy carried by the blood and also creates the pressure that gives rise to blood flow. Therefore the complicated interplay between both opposing forces will determine whether a CVS state can meet the demand.

Metabolic demand is an important consideration in this study for two reasons:

1. To determine whether simulated CVS state is able to meet metabolic demand
2. To complete the thermodynamic calculations which depend on metabolic energy transfer.

To determine whether a simulated CVS state was able to meet metabolic demand, the required oxygen content of blood was calculated retrospectively for both the systemic and coronary compartments. If a value that exceeded the maximum carrying capacity of blood was found, then the state was excluded from the analysis.

The metabolism-based calculations discussed in this section will contribute further to remaining thermodynamic analysis described next.

CVS as Thermodynamic Cycle

Using the first and second law analysis of the individual CVS components plus the consideration of metabolic demand, there is enough information to solve for entropy generation. This will involve first solving for the temperature changes and heat transfers using the first law equations presented for each compartment presented in Panels 2 through 7. After the temperatures and heat transfer quantities are calculated, entropy generation can finally be calculated.

Temperatures & Heat

Before the temperatures of the CVS can be calculated, quantities associated with metabolism must be addressed beforehand. Note that the metabolic exchange quantity is mutual between the coronaries and the myocardium (see Figure 17). In the coronaries, high-energy metabolic fuel is flowing out, while low-energy waste is flowing in – and vice versa for the myocardium. Therefore the entropy change due to this mutual exchange is equal and opposite. Considering the second law analysis simultaneously over the entire heart, this term cancels out from the calculation. This process is outlined next.

First, as shown in Equation 36, the entropy generation over the entire heart is the sum of entropy generation of each compartment within the heart.

Equation 36 – Entropy Generation for the Entire Heart

$$\dot{\sigma}_{heart} = \dot{\sigma}_c + \dot{\sigma}_m + \dot{\sigma}_v$$

$\dot{\sigma}_{heart}$ = Entropy Generation for the entire heart (J/K/sec)

$\dot{\sigma}_c$ = Entropy Generation for the Coronaries Compartment (J/K/sec)

$\dot{\sigma}_m$ = Entropy Generation for the Myocardium Compartment (J/K/sec)

$\dot{\sigma}_v$ = Entropy Generation for the Myocardium Compartment (J/K/sec)

After substituting the respective equations for entropy generation for the coronaries (see Panel 5), the myocardium (see Panel 6), and the ventricles (see Panel 7) the expanded expression is as shown in Equation 37.

Equation 37 - Entropy Generation for the Entire Heart (Expanded)

$$\dot{\sigma}_{heart} = \left[\dot{m}_{2c} \cdot \left(c_v \cdot \ln \frac{T_{3c}}{T_{2c}} \right) + \dot{m}_{met} (\Delta s_{met\_react-met\_products}) - \dot{Q}_c / T \right]$$

$$+ \left[\dot{m}_{met} (\Delta s_{met\_products-met\_react}) - \dot{Q}_m / T \right] + \left[\dot{m}_1 \cdot c_v \cdot \ln \frac{T_1 \cdot T_5}{T_8 \cdot T_4} \right]$$

The heat transfer terms for the coronaries and the myocardium are in fact one in the same as shown in Equation 38.

Equation 38 – Mutual Heat Transfer from Myocardium to Coronaries

$$\dot{Q}_c = -\dot{Q}_m$$

Using the substitution shown in Equation 38 above and also noting that the entropy change term for the metabolic exchange in the coronaries ($\Delta s_{met\_reactants - met\_products}$) is exactly equal but opposite to the metabolic exchange in the myocardium ($\Delta s_{met\_products - met\_reactants}$), the simplified version of Equation 37 is displayed next in Equation 39.

Equation 39 - Entropy Generation for the Entire Heart (Simplified)

$$\dot{\sigma}_{\text{heart}} = \dot{m}_{2c} \cdot \left(c_v \cdot \ln \frac{T_{3c}}{T_{2c}} \right) + \dot{m}_1 \cdot c_v \cdot \ln \frac{T_1 \cdot T_5}{T_8 \cdot T_4}$$

The only unknown quantity in the expression for entropy generation in the heart, Equation 39, is the ration of T_{3c} to T_{2c}. This ratio can be solved for indirectly by determining the temperature change across the coronaries (ΔT_{3c_2c}) via combination of the first law analysis for all of the compartments of the heart: coronaries, myocardium, and ventricles. The procedure is demonstrated as follows.

First the initial expression for ΔT_{3c-2c} will be used from the first law section of Panel 5. This expression is merely rearranged to form Equation 40 so that the term with ΔT_{3c-2c} is alone.

Equation 40 – Expression for Temperature Change Across the Coronaries Compartment

$$\dot{m}_{2c} \cdot c_v \cdot \Delta T_{3c-2c} = -\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - \dot{m}_{met} \cdot \left(\Delta h_{met\_react\ met\_products}\right) + \dot{Q}_c$$

Next, since it was previously noted in Equation 38 that the heat term $\dot{Q}_c$ is equal and opposite to $\dot{Q}_m$, Equation 40 can be expanded to Equation 42 by first solving for $\dot{Q}_m$ and substituting for negative of $\dot{Q}_c$. To solve for $\dot{Q}_m$, the first law expression from Panel 6 can be rearranged as shown below in Equation 41.

Equation 41 – Heat Transfer from the Myocardium Compartment

$$\dot{Q}_m = \dot{m}_{met} \cdot \left(\Delta h_{met\ products\ met\ react}\right) + \dot{W}_m$$

Equation 42 - Temperature Change Across the Coronaries Compartment (Expanded)

$$\dot{m}_{2c} \cdot c_v \cdot \Delta T_{3c-2c} = -\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - \dot{m}_{met} \cdot \left(\Delta h_{met\_react-met\_products}\right) + \left[-\dot{m}_{met} \cdot \left(\Delta h_{met\ products\ met\ react}\right) - \dot{W}_m\right]$$

The fact that the quantities $\Delta h_{met\_products\_met\_react}$ and $\Delta h_{met\_react\_met\_products}$ are equal and opposite will be used to simplify the final expression for ΔT_{3c_2c} shown in Equation 43.

Equation 43 - Temperature Change Across the Coronaries Compartment (Simplified)

$$\dot{m}_{2c} \cdot c_v \cdot \Delta T_{3c\_2c} = -\dot{m}_{2c} \cdot v \cdot \Delta P_{3c\_2c} - \dot{W}_m$$

Equation 43 can be further modified to Equation 45 by solving for work done by the myocardium ($\dot{W}_m$) which is done by rearranging the expression from the first law analysis of Panel 7 as shown in below in Equation 44.

Equation 44 - Work Done by the Myocardium

$$\dot{W}_m = \left[\dot{m}_1 \cdot \left(c_v \cdot (\Delta T_{1-8} + \Delta T_{5-4}) + v \cdot (\Delta P_{1-8} + \Delta P_{5-4})\right)\right]$$

Equation 45 - Temperature Change Across the Coronaries Compartment (Modified)

$$\Delta T_{3c-2c} = \frac{-\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - \left[\dot{m}_1 \cdot \left(c_v \cdot (\Delta T_{1-8} + \Delta T_{5-4}) + v \cdot (\Delta P_{1-8} + \Delta P_{5-4})\right)\right]}{\dot{m}_{2c} \cdot c_v}$$

The quantities ΔT_{1-8} and ΔT_{5-4} are representative of the temperature change of blood after passage through the ventricles. Although the value of this quantity is also unknown, it is assumed that this particular temperature change is due predominantly

to the dissipation of power in the viscoelastic resistance of the myocardium. Power dissipated can be calculated by multiplying the blood flow ($\dot{V}$) squared multiplied by the resistance (R). Therefore ΔT_{1-8} and ΔT_{5-4} can be solved using the equation for power dissipation through a resistor. The particular equations used in this analysis are shown in Table 7.

Therefore, this alternate calculation of heat in the ventricles can be substituted into the conglomerate first law equation of the heart as shown next in Equation 46.

Equation 46 - Temperature Change Across the Coronaries Compartment (Final)

$$\Delta T_{3c-2c} = \frac{-\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - [heat_{LV} + heat_{RV} + \dot{m}_1 \cdot v \cdot (\Delta P_{1-8} + \Delta P_{5-4})]}{\dot{m}_{2c} \cdot C_v}$$

Finally, given that all of the first law equations define a temperature change, at least one temperature point will have to be defined explicitly before all of the temperature values can be solved. In this model, temperature point T_{3a} was assigned the typical core body temperature value which is 310K (37°C). All of the temperatures are solved by first starting at temperature point T_{3a} and working around the thermodynamic model. This process is outlined in the overall 11-step scheme shown next in Panel 8. The calculation of temperatures of the CVS will allow for calculation of entropy generation in the CVS.

Table 7 - Heat Dissipated by Viscoelastic Impedance of the Myocardium

Name	Value	Description (Units)
τ	Calculated/Declared in the Hemodynamic Model	Period of heart rate (sec)
$\dot{V}_{OL}$		Blood Flow out of left ventricle (cc/sec)
$\dot{V}_{IL}$		Blood Flow into left ventricle (cc/sec)
$\dot{V}_{OR}$		Blood Flow out of right ventricle (cc/sec)
$\dot{V}_{IR}$		Blood Flow into right ventricle (cc/sec)
R_{LV}		Viscoelastic Resistance of left ventricle (PRU)
R_{RV}		Viscoelastic Resistance of right ventricle (PRU)
$heat_{LV}$	$\frac{1}{\tau}\int_0^{\tau}\left(\left(\dot{V}_{OL}+\dot{V}_{IL}\right)^2 \cdot R_{LV}\right)dt$	Left Ventricle power dissipation (Watts)
$heat_{RV}$	$\frac{1}{\tau}\int_0^{\tau}\left(\left(\dot{V}_{OR}+\dot{V}_{IR}\right)^2 \cdot R_{RV}\right)dt$	Right Ventricle power dissipation (Watts)

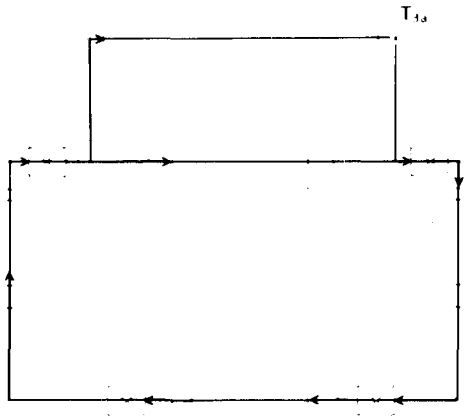
Entropy Generation

Following the calculation of the temperatures and the pulmonary heat transfer, entropy generation can be calculated directly from the second law analysis in each compartment (summarized in Table 8).

Panel 8 - Calculation of CVS Temperatures

Step 1.

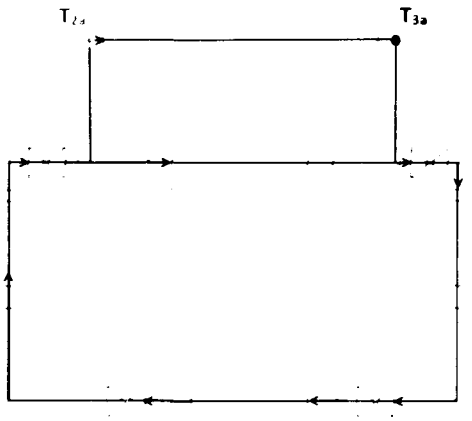
Assign T_{3a} = 310K



Step 2.

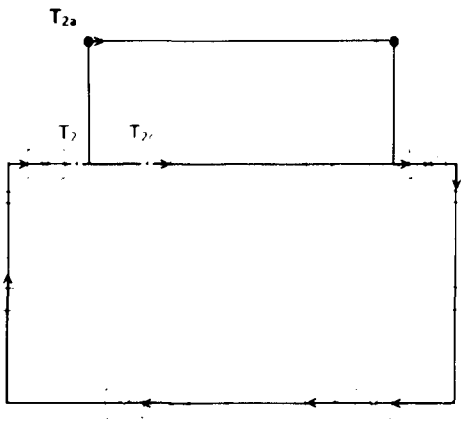
Solve for T_{2a} using first law equation for the systemic vasculature (see Panel 2).

$$T_{2a} = \frac{v \cdot \Delta P_{3a-2a}}{C_v} + T_{3a}$$



Step 3.

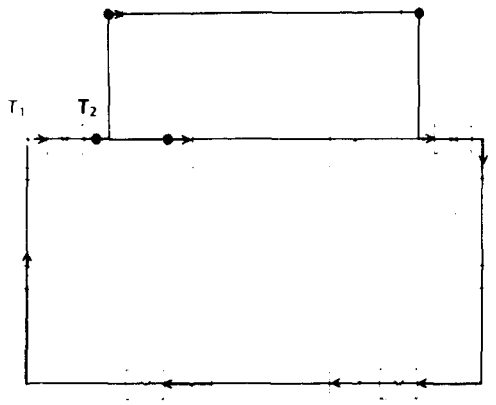
Note that T_2=T_{2c}=T_{2a}



Step 4.

Solve for T_1 using the first law equation for the Aortic Valve.

$$T_1 = \frac{v \cdot \Delta P_{1-2}}{c_v} + T_2$$



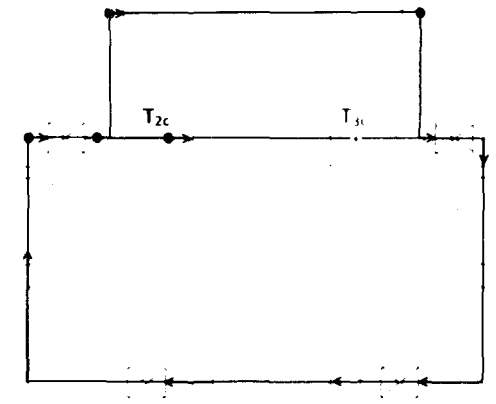
Step 5.

Solve for T_{3c} using the derived equation from the analysis over the entire heart.

$$\Delta T_{3c-2c} = \frac{-\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - [heat + \dot{m}_1 \cdot v \cdot (\Delta P_{1-2} + \Delta P_{3-a})]}{\dot{m}_{2c} \cdot c_v}$$

$$T_{3c} = \frac{-\dot{m}_{2c} \cdot v \cdot \Delta P_{3c-2c} - [heat + \dot{m}_1 \cdot v \cdot (\Delta P_{1-2} + \Delta P_{3-a})]}{\dot{m}_{2c} \cdot c_v} + T_{2c}$$

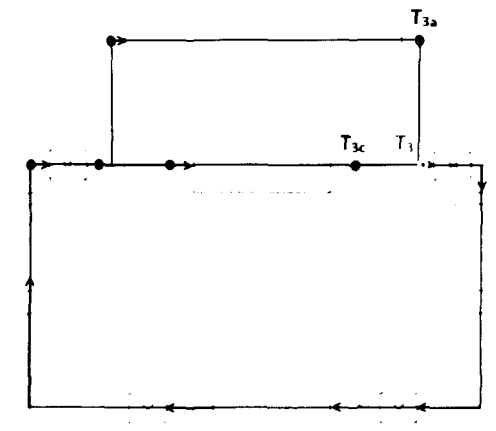
$$heat = heat_{LV} + heat_{RV}$$



Step 6.

Solve for T_3 by using the relationship of mixing between two flows.

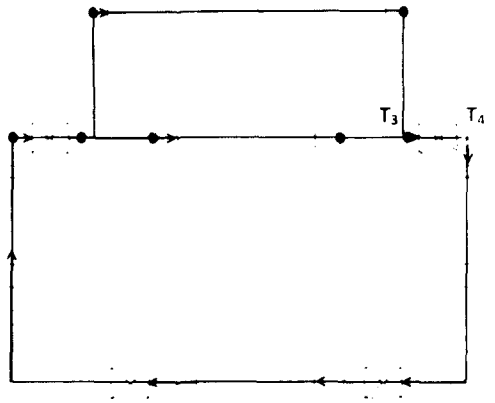
$$T_3 = \frac{\dot{m}_{3a} \cdot T_{3a} + \dot{m}_{3c} \cdot T_{3c}}{\dot{m}_{3a} + \dot{m}_{3c}}$$



Step 7.

Solve for T_4 using the first law equation for the Tricuspid Valve.

$$T_4 = \frac{v \cdot \Delta P_{3-4}}{c_v} + T_3$$



Step 8a. Solve for T_8

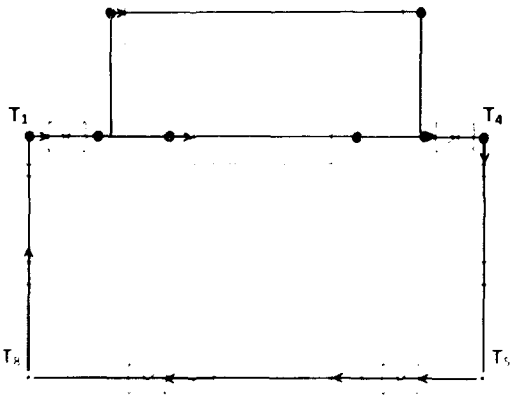
$$\dot{m}_1 \cdot c_v \cdot \Delta T_{1-8} = (Q_{oL} + Q_{iL})^2 \cdot R_{LV}$$

$$T_8 = -\frac{(Q_{oL} + Q_{iL})^2 \cdot R_{LV}}{\dot{m}_1 \cdot c_v} + T_1$$

Step 8b. Solve for T_5

$$\dot{m}_4 \cdot c_v \cdot \Delta T_{5-4} = (Q_{oR} + Q_{iR})^2 \cdot R_{RV}$$

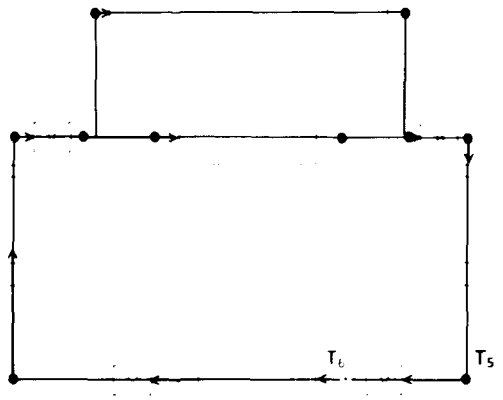
$$T_5 = \frac{(Q_{oR} + Q_{iR})^2 \cdot R_{RV}}{\dot{m}_4 \cdot c_v} + T_4$$



Step 9.

Solve for T6 using the first law equation for the Pulmonary Valve.

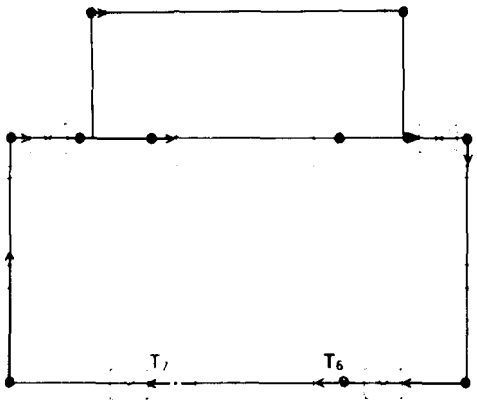
$$T_6 = \frac{v \cdot \Delta P_{5-6}}{c_v} + T_5$$



Step 10.

Solve for T7 using the first law equation for the Mitral Valve.

$$T_7 = \frac{v \cdot \Delta P_{7-8}}{c_v} + T_8$$



Step 11.

Solve for $\dot{Q}_p$ using the first law equation for the pulmonary vasculature.

$$\dot{m}_6 \cdot \left(c_v \Delta T_{7-6} + v \cdot \Delta P_{7-6}\right) = -\dot{Q}_p$$

$$\dot{Q}_p = -\dot{m}_6 \cdot \left(c_v \Delta T_{7-6} + v \cdot \Delta P_{7-6}\right)$$

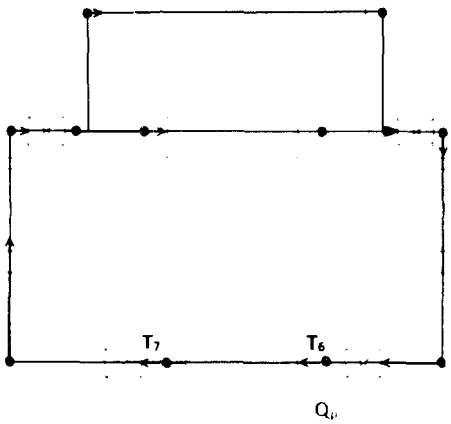


Table 8 - Entropy Generation Equations per Compartment

Location	Equation
Systemic	$\dot{\sigma}_{s} = \dot{m}_{2a} \cdot \left(c_{v} \cdot \ln \frac{T_{3a}}{T_{2a}} \right) + \left[\dot{n}_{O_2} \cdot (1/6) \cdot 77{,}700 \right] / T$
Pulmonary	$\dot{\sigma}_{P} = \dot{m}_{6} \cdot \left(c_{v} \cdot \ln \frac{T_{7}}{T_{6}} \right) + \dot{Q}_{P} / T$
Mitral Valve	$\dot{\sigma}_{mv} = \dot{m}_{7} \cdot \left(c_{v} \cdot \ln \frac{T_{8}}{T_{7}} \right)$
Pulmonary Valve	$\dot{\sigma}_{pv} = \dot{m}_{5} \cdot \left(c_{v} \cdot \ln \frac{T_{6}}{T_{5}} \right)$
Tricuspid Valve	$\dot{\sigma}_{tv} = \dot{m}_{3} \cdot \left(c_{v} \cdot \ln \frac{T_{4}}{T_{3}} \right)$
Aortic Valve	$\dot{\sigma}_{av} = \dot{m}_{1} \cdot \left(c_{v} \cdot \ln \frac{T_{2}}{T_{1}} \right)$
Heart	$\dot{\sigma}_{heart} = \dot{m}_{2c} \cdot \left(c_{v} \cdot \ln \frac{T_{3c}}{T_{2c}} \right) + \dot{m}_{1} \cdot c_{v} \cdot \ln \frac{T_{1} \cdot T_{5}}{T_{8} \cdot T_{4}}$

Thermodynamic Parameter Descriptions and Initial Conditions

The following tables, Table 9 and Table 10, define the parameters as well as initial values for the thermodynamics.

Table 9 - Thermodynamic Parameter Values

Name	Value	Description (Units)
c_v	4.18	Specific Heat of Water (J/g*K)
v	1.0068	Specific Volume (cc/g)
T	310	Reference Temperature (K)
con1	101325/760	Conversion Factor #1 (Pressure in mmHg to Pa)
con2	1/10^6	Conversion Factor #2 (Volume in cc or mL to m^3)
con3	22400	Conversion Factor #3 (mL/mol)
τ	$1/\omega$	Time length of entire heart beat
τ_{ej}	τ when $Q_{oL} > 0$	Time length of ejection phase of heart beat
τ_{rx}	τ when $Q_{iL} > 0$	Time length of relaxation phase of heart beat
$\dot{m}_h$	$\frac{1}{\tau}\int_0^{\tau}(\frac{1}{v}\cdot Q_{oL})dt$	Mass Flow of Blood, Major Circuit (g/sec)
$\dot{m}_c$	$\frac{1}{\tau}\int_0^{\tau}(\frac{1}{v}\cdot Q_{c})dt$	Mass Flow of Blood, Coronary Circuit (g/sec)
k	20.2	Energy Equivalent of O_2 (J/mol O_2)
ME	100	Metabolic Energy, Systemic (W)
EW_L	(area within LVV vs. LVP over one beat)*con1*con2	External Work, Left Ventricle (J/sec)
EW_R	(area within RVV vs. RVP over one beat)*con1*con2	External Work, Right Ventricle (J/sec)
PVA_L	EW_L + triangle	Pressure-Volume Area, Left Ventricle
PVA_R	EW_R + triangle	Pressure-Volume Area, Right Ventricle
PVA	$PVA_L + PVA_R$	Total Pressure-Volume Area

Table 10 - Thermodynamic Parameters Derived From Hemodynamic Variables

Name	Value	Description (Units)
P_1	$\frac{1}{\tau_{ej}}\int_{ej}(LVP)dt$	Pressure at Node 1
P_2	$\frac{1}{\tau}\int_0^{\tau}(AoP_1)dt$	Pressure at Node 2
P_{2a}	$\frac{1}{\tau}\int_0^{\tau}(AoP_1)dt$	Pressure at Node 2a
P_{2c}	$\frac{1}{\tau}\int_0^{\tau}(AoP_1)dt$	Pressure at Node 2c
P_3	$\frac{1}{\tau}\int_0^{\tau}(CVP_2)dt$	Pressure at Node 3
P_{3a}	$\frac{1}{\tau}\int_0^{\tau}(CVP_2)dt$	Pressure at Node 3a
P_{3c}	$\frac{1}{\tau}\int_0^{\tau}(CVP_2)dt$	Pressure at Node 3c
P_4	$\frac{1}{\tau_{rx}}\int_{rx}(RVP)dt$	Pressure at Node 4
P_5	$\frac{1}{\tau_{ej}}\int_{ej}(RVP)dt$	Pressure at Node 5
P_6	$\frac{1}{\tau}\int_0^{\tau}(PuP)dt$	Pressure at Node 6
P_7	$\frac{1}{\tau}\int_0^{\tau}(PuP-Q_{il}\cdot R_p)dt$	Pressure at Node 7
P_8	$\frac{1}{\tau_{rx}}\int_{rx}(LVP)dt$	Pressure at Node 8

Software & Numerical Solver

The entire model was simulated using the computational software package MATLAB® Student Version, version 7.0.1.15 (R14) Service Pack 1 dated Sept 13, 2004 (from the MathWorks, Natick, MA, USA).

The numerical solver parameters are summarized in Table 11. Specifically, the hemodynamic model was solved using a "stiff" ode solver: ode23s (stiff/Mod Rosenbrock). Nonstiff solvers were attempted first, but were not able to handle the abrupt changes that occur in the hemodynamics during phase transitions, like the instantaneous change to ejection during the cardiac cycle.

A stop time of 20 seconds was used to ensure each state would reach a steady-state. The last full beat in the 20 second simulation of the hemodynamics was used for the thermodynamics.

Table 11 - Numerical Solver Parameters

Start Time	0
Stop Time	20
Solver	ode23s (stiff/Mod. Rosenbrock)
Relative Tolerance	1e-3
Initial Conditions	See Table 4 and Table 5

Simulation Scheme

The goal of this thesis is to first propose a method to calculate entropy generation in the CVS, but then also to characterize how entropy generation compares across different CVS states. A CVS state is uniquely defined by the value of the parameters. Therefore the parameters form a "physiological hyperspace". Since there are infinite possible combinations of parameters to choose – and therefore infinite number of possible CVS states in the physiological hyperspace, a few representative points were selected for this study. Five parameters were chosen to be varied because of the key role they play in the hemodynamics and hemodynamic control. Therefore there are five dimensions to this hyperspace.

The values chosen were thought to represent a generous sweep across the "normal" value for each parameter. Arbitrarily, a sweep of five values was chosen for all five variables. For parameters with very small values, a log scale sweep was used. For parameters with large values, a linear sweep was used. The exact values used to form this particular hyperspace are shown in the table. Each combination of parameters was simulated, resulting in a grand total of 5^5 or 3125 simulations.

In summary, each of the values shown in Table 12 represents a coordinate of the CVS hyperspace. And likewise each point in the hyperspace represents a CVS state. Each CVS state will be simulated in a hemodynamic model which will yield the time-series of pressures and flows with the CVS.

Table 12 - CVS Model Hyperspace

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	3	$\frac{\text{mmHg}}{\text{mL/sec}}$
C_{a1}, C_{a2}	0.5	1	1.5	2	3	$\frac{\text{mL}}{\text{mmHg}}$
C_V	40	50	60	70	80	$\frac{\text{mL}}{\text{mmHg}}$
C_P	15	17.5	20	22.5	25	$\frac{\text{mL}}{\text{mmHg}}$
ω	2	4	6	10.5	16	$\frac{\text{rad}}{\text{sec}}$

Simulation will involve solving the system of 14 first order differential equations given the initial conditions. Besides the parameters shown in the table, the other parameters that constitute the CVS model will be kept the same. The initial volumes, for each compartment, were defined so that the total volume was the same across all simulations.

Ultimately, the results of simulation will be used to calculate temperature changes and finally entropy generation for each unique CVS state.

VALIDATION & RESULTS

To calculate entropy generation in the CVS, the CVS was translated as a thermodynamic cycle as shown in the previous chapter. To characterize this value, entropy generation, a range of CVS states were simulated by varying five major hemodynamic parameters: heart rate, arterial resistance, arterial compliance, venous compliance, and pulmonary compliance. Therefore, in this study, the specific values of each of these parameters define a CVS state, and the collection of all CVS states simulated defines the hemodynamic range, referred to here as the simulation hyperspace. Using each unique CVS state within the hyperspace to calculate entropy generation revealed that entropy generation also spans a range of values. Using this range of entropy generation values in context with its respective hemodynamic state, the relationship between entropy generation and hemodynamics are explored next in the results section of this chapter. However, since the quality of the results depend on the validity of the models/assumptions, model validation in established first.

Simulation

As described previously in the Methods chapter, total entropy generation was calculated over a range of CVS states. Each CVS state is uniquely defined by the value of the parameters listed in Table 13.

Table 13- Simulation Parameters that Define the CVS State

Parameter Name	Description
Ra	Arterial Resistance
Ca1	Arterial Compliance
Cv	Venous Compliance
Cp	Pulmonary Compliance
ω	Heart Rate

However, out of the hyperspace chosen for analysis, two states were not stable and therefore excluded from the analysis. Table 14 highlights the two unstable CVS states (marked with either * or # symbol) in the background of all 3125 possible combinations of the parameters values that define the simulation hyperspace.

Table 14 - Unstable CVS States after Simulation

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	3*#	$\frac{\text{mmHg}}{\text{mL/sec}}$
C_{a1}, C_{a2}	0.5*#	1	1.5	2	3	$\frac{\text{mL}}{\text{mmHg}}$
C_V	40*#	50	60	70	80	$\frac{\text{mL}}{\text{mmHg}}$
C_P	15*#	17.5	20	22.5	25	$\frac{\text{mL}}{\text{mmHg}}$
ω	2	4	6	10.5*	16#	$\frac{\text{rad}}{\text{sec}}$

Therefore, out of the 3125 CVS states simulated, only 3123 could be used for thermodynamic analysis. The results of this analysis are shown after the following discussion of model validation.

Validation of Hemodynamic Model

It is important to verify that the hemodynamic model created for this study results in behavior reasonably consistent with physiology. To do this, tests were applied to the model in which a physiologically sound behavior (that was not explicitly programmed for) would be expected. This includes maintenance of a constant total blood volume as well as recognizable profiles of cardiac cycle time-courses. Both of these will be demonstrated on the "normal" state – the state that is expected to generate cardiac profiles that are typical. The parameter values that define the normal CVS state are highlighted below in Table 15 .

Table 15 - The Normal CVS State

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	**1**	2	3	$\frac{\text{mmHg}}{\text{ml./sec}}$
C_{a1}, C_{a2}	0.5	1	**1.5**	2	3	$\frac{\text{mL}}{\text{mmHg}}$
C_V	40	50	**60**	70	80	$\frac{\text{mL}}{\text{mmHg}}$
C_P	15	17.5	**20**	22.5	25	$\frac{\text{mL}}{\text{mmHg}}$
ω	2	4	**6**	10.5	16	$\frac{\text{rad}}{\text{sec}}$

In addition, a vena caval occlusion (VCO) experiment will be simulated to assess the transient behavior of the model in response to a perturbation. The VCO experiment has been demonstrated *in vivo* in various other studies in the literature. (6, 18) For a VCO experiment *in vivo*, the typical implementation involves inserting a

balloon-catheter into the inferior vena cava. By inflating the balloon, the preload to the heart is progressively restricted. As a result of this, the heart fills to a lesser extent with each beat and consequently generates less pressure. In light of this, the VCO effectively demonstrates the Frank-Starling law of the heart. Since the CVS model used in this study implements the Frank-Starling law, it is expected that the model will respond to a decrease in preload in a manner consistent with the defined ESPVR and filling curve.

In summary, the performance of the hemodynamic model will be demonstrated by monitoring the total blood volume and cardiac cycle waveforms for the normal CVS state and also inspecting the response to a perturbation which mimics the well-known VCO experiment.

Hemodynamics of the Normal State

The total blood volume, shown in Figure 20A, remains constant throughout an entire simulation despite redistribution of blood volume between compartments, shown in Figure 20B. This provides support for the model basis (conservation of mass) and implementation (Matlab code) as well as the numerical stability of the ODE solver. Even so, this does not guarantee that the model is a good representation of in vivo hemodynamics. So, to address this, a few select waveforms were shown to illustrate the model's definition of a cardiac cycle for the left and right heart. The cardiac cycle, shown in Figure 21 demonstrates key features that would be expected from a genuine CVS. For example, outflow from the left ventricle, Qol, is active at the

instant left ventricular pressure, LVP, exceeds the aortic pressure, AoP. Also, outflow and inflow (Qol and Qil, respectively, for the left heart) are generally not active at the same time. In fact, there is a brief "isovolumic" phase between these events. While the waveforms capture the essential aspects of a cardiac cycle, there is one aspect that does not: the waveforms for aortic pressure (AoP) exhibit a small degree of high-frequency oscillation or ripple. This is not expected of normal CVS physiology but is typical behavior of an RLC circuit. The oscillations dampen with appropriate tuning of the parameter values (particularly aortic valve inertance and resistances); however, in this model, certain parameter values, like the aortic valve inertance, were kept at the same constant value. Therefore the appearance of the AoP ripple varies depending on CVS state. For this study, this particular artifact was considered negligible.

VCO Experiment

The transient vena caval occlusion (VCO) is a popular method to inspect the pressure-volume properties of the heart. (6, 18) Since the response to a VCO is well-known, it is used here as a validation of the hemodynamic model. To simulate the VCO experiment in the hemodynamic model, the resistance of the pulmonary compartment, Rp, (resistance to left ventricular filling) is defined as a function which increases throughout the timespan of the simulation. The increasing Rp function is shown in Figure 22A. The left ventricular pressure (LVP) response to the increase in Rp in the time domain is shown in Figure 22B. As expected, the LVP decreases as preload (Rp) increases.

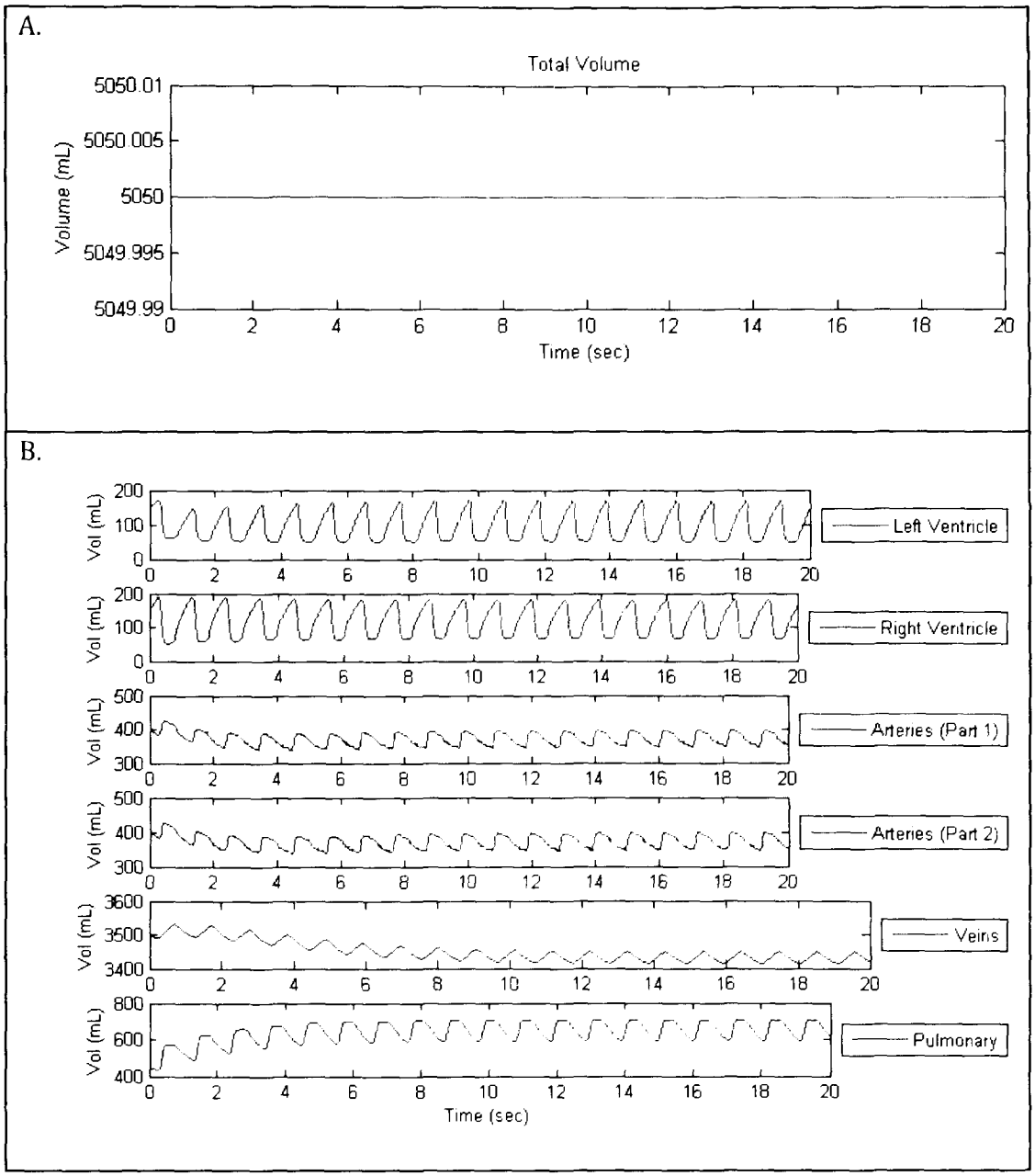


Figure 20 - Demonstration of Constant Total Blood Volume Despite Redistribution

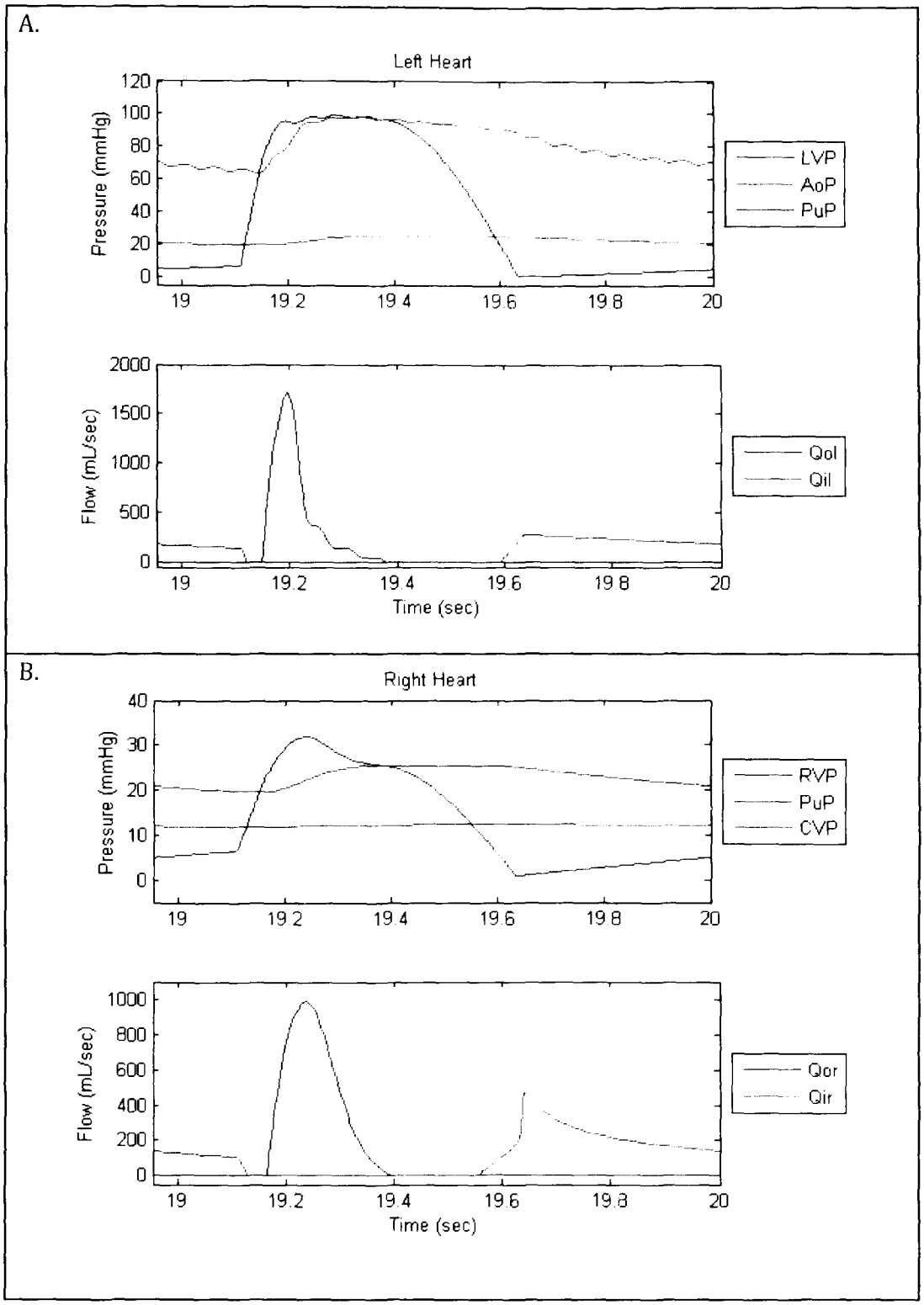


Figure 21 - Cardiac cycle for: A) Left Heart and B) Right Heart

The VCO response is further explored by plotting LVP versus left ventricular volume (LVV). In the PV domain, the response is anticipated to closely follow the predefined elastance envelopes of the left ventricle. This is verified in Figure 22C where the pressure-volume signal is plotted by the black line, the filling curve is in blue and the ESPVR is in red. As expected, the series of PV loops are contained by the ESPVR and the filling curve.

Validation of Thermodynamic Model

Since a thermodynamic analysis of the CVS has never before been attempted, the results cannot be compared with other published studies. There are, however, a few things to expect:

1. the first law analysis of the CVS should result in a balance between the power generated versus the power dissipated, and
2. entropy generation should always be a positive value.

Therefore, these features will be explored next but first the "normal" state will be fully characterized.

Thermodynamics of the Normal State

The thermodynamic calculations are built upon the hemodynamic simulation results as well as assumptions about the metabolic demand. Therefore, the first step in the thermodynamic calculation is to translate results into SI units and average them

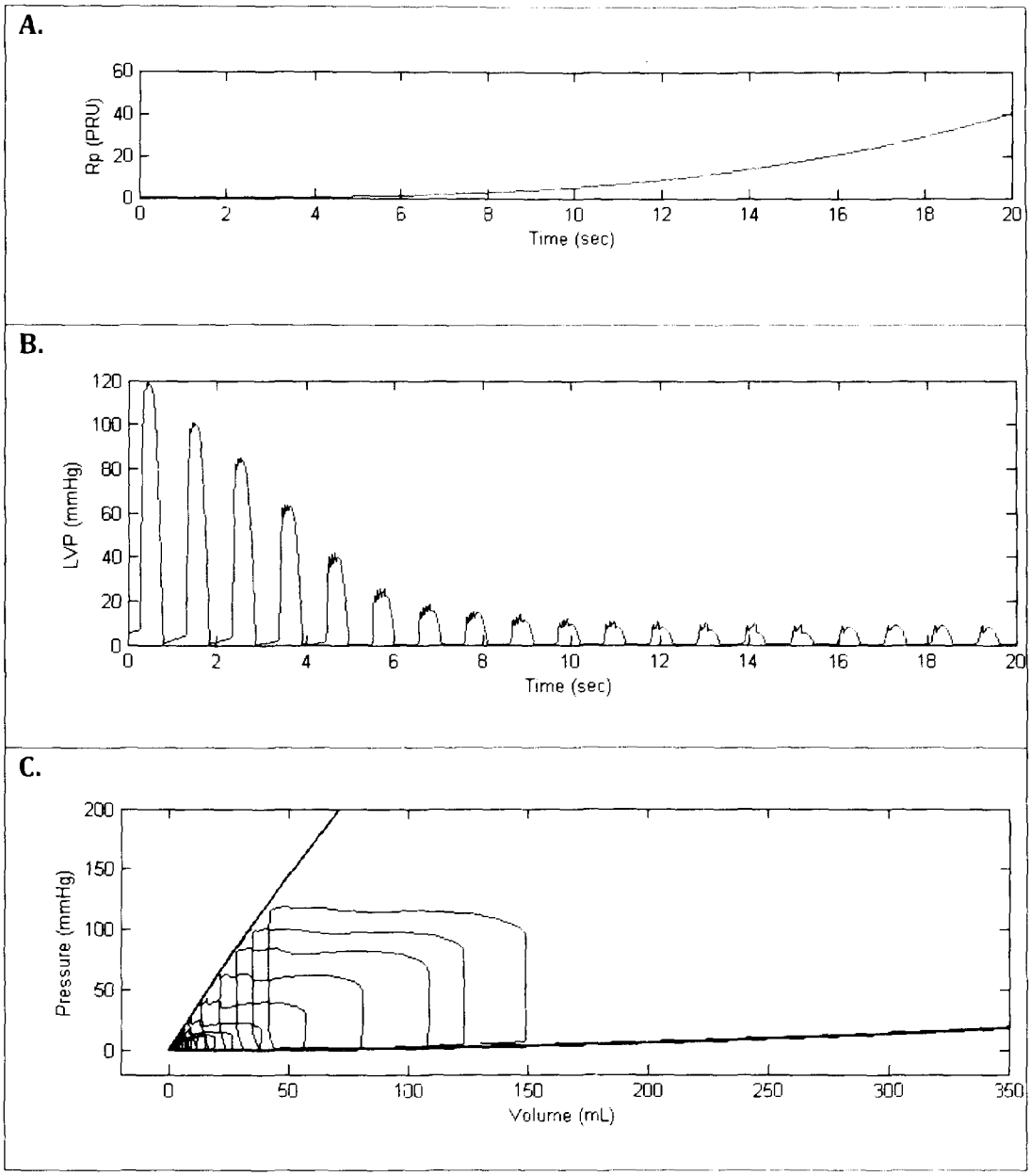


Figure 22 - VCO Experiment Simulation

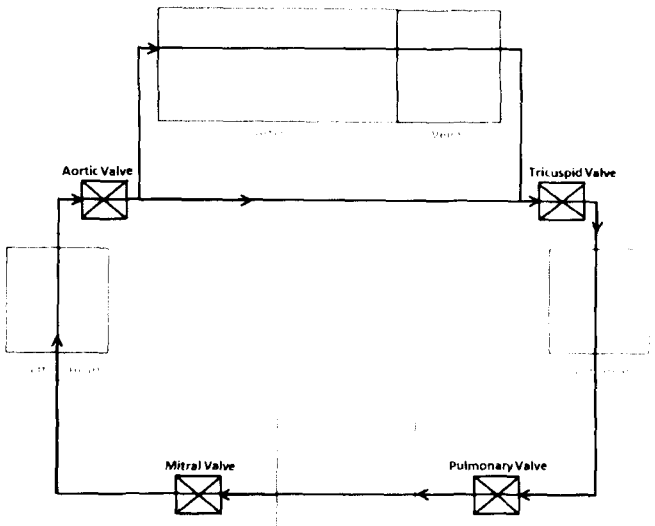
over a single beat to comply with the steady-state form of thermodynamic analysis. Next, using the steady-state form of the hemodynamic data and the assumptions concerning metabolic demand, arterial-venous (A-V) blood oxygen difference, also called ΔO_2, can be calculated. The result of this initial preprocessing is summarized in Table 16 and Figure 23. Further validation of the hemodynamic model is provided by the value calculated for systemic oxygen difference as it agrees with that expected for a normal state. However the coronary oxygen extraction is much lower than expected.

Table 16 - Normal CVS State Results

$\frac{mmHg}{mL/sec}$	$\frac{mL}{mmHg}$			$\frac{rad}{sec}$	$\frac{J/K}{sec}$	$\frac{g}{sec}$		mmHg	$\frac{mL\ O_2}{mL\ blood}$	
1	1 5	60	20	6	0 0188	108 1066	38 7731	82 0815	0 0455	0 0068

Ra = Arterial Resistance
Ca1 = Arterial Capacitance
Cv = Venous Compliance
Cp = Pulmonary Compliance
ω = Heart Rate
σ = Entropy Generation
m_h = Mass Flow of Blood (total)
m_c = Mass Flow of Blood (coronary)
AoP = Aortic Pressure
ΔO_2 = A-V Oxygen Difference

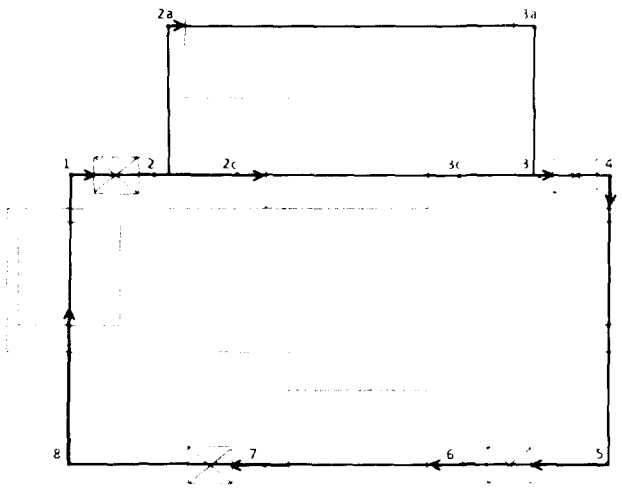
A.



C.

Hemodynamic Pressures (mmHg)	
P1	95.13
P2	82.08
P2	82.08
P c	82.08
P3	8.68
P3a	8.68
P3c	8.68
P4	7.70
P5	27.92
P6	22.99
P7	14.27
P8	12.88

B.



D.

Hemodynamic Flows (g/sec)	
$\dot{m}_h$	108.11
$\dot{m}_c$	38.77
$\dot{m}_a$	69.33

Figure 23 - Summary of the Hemodynamic Data

First Law Balance

The sources that generate power are the left heart and the right heart. On the other hand, the components that will dissipate power are the four valves (Rav, Rmv, Rtv and Rpv) as well as the pulmonary, coronary, and the arterial/venous resistive components (Rp, Rc and Ra). The power generated can be solved using Equation 47 given that the pressure difference is in mmHg and flow is in mL/sec:

Equation 47 - Solving for Power

$$\text{Power} = \Delta P \cdot \dot{m} \cdot \left(\frac{101325 \text{ mmHg}}{760 \text{ Pa}}\right) \cdot \left(\frac{1 \text{ mL}}{10^{-6}\, m^3}\right)$$

Using Equation 47, power generated and power dissipated can be calculated and compared. As shown in Table 17, the calculations are consistent with the first law energy balance – total power dissipated is equal to total power produced.

Table 17 - First Law Balance

Power Dissipated (Watts)		**Power Produced (Watts)**	
Rav	0.188	LV	1.185
Rmv	0.020	RV	0.291
Rtv	0.014		
Rpv	0.071		
Rc	0.379		
Ra	0.679		
Rp	0.126		
Total	**1.477**	**Total**	**1.477**

In addition, the magnitude of power (1.477 Watts) is a likely value for the normal state. For example, a standard value for left ventricular pressure change is 100mmHg (or 13.3 kPa) and a typical stroke volume is 90mL (or $0.09*10^{-3}$ m^3). Using these values to approximate stroke work which can be approximated as Δpressure * Δvolume gives 13.3 kPa * $0.09*10^{-3}$ m^3 or 1.2J. Considering a typical heart rate of 60bpm (1 beat per second), the average power can be equated as work multiplied by heart rate in beats per second, which results in 1.2 J/s or 1.2 Watts for the left ventricle. The value for power produced by the left ventricle in Table 17 (1.185 Watts) is very close to this value (1.2 Watts).

Entropy Generation ($\dot{\sigma}$) Inspection

The histogram shown in Figure 24 reveals the total value of entropy generation across all stable simulations of the CVS (n=3123). By inspection, all values are positive, which is expected for second law thermodynamics and supports the derivation.

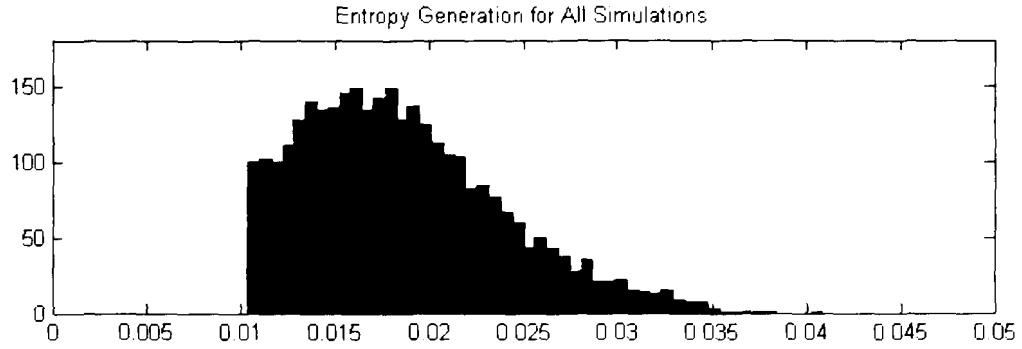


Figure 24- Distribution of Entropy Generation Across All Simulations

Characterization of Total Entropy Generation within the CVS

Searching over all stable CVS states (n=3123), the CVS state that resulted in overall minimum entropy generation ($\dot{\sigma} = 0.010361\ \mathrm{J/K/sec}$) was found to occur at the state highlighted in Table 18.

Table 18 - The Minimum Entropy Generation State

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	3	$\frac{\mathrm{mmHg}}{\mathrm{mL/sec}}$
C_{a1}, C_{a2}	0.5	1	1.5	2	3	$\frac{\mathrm{mL}}{\mathrm{mmHg}}$
C_V	40	50	60	70	80	$\frac{\mathrm{mL}}{\mathrm{mmHg}}$
C_P	15	17.5	20	22.5	25	$\frac{\mathrm{mL}}{\mathrm{mmHg}}$
ω	2	4	6	10.5	16	$\frac{\mathrm{rad}}{\mathrm{sec}}$

Conversely, the state the resulted in maximum entropy generation ($\dot{\sigma} = 0.040859\ \mathrm{J/K/sec}$) is shown below in Table 19.

Table 19 - The Maximum Entropy Generation State

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	**2**	3	$\frac{\text{mmHg}}{\text{mL/sec}}$
C_{a1}, C_{a2}	**0.5**	1	1.5	2	3	$\frac{\text{mL}}{\text{mmHg}}$
C_V	**40**	50	60	70	80	$\frac{\text{mL}}{\text{mmHg}}$
C_P	**15**	17.5	20	22.5	25	$\frac{\text{mL}}{\text{mmHg}}$
ω	2	4	6	10.5	**16**	$\frac{\text{rad}}{\text{sec}}$

To further explore the hemodynamic characteristics that correspond to these entropy generation extremes, entropy generation values will be shown alongside significant hemodynamic variables (see Table 20). In addition to the minimum and maximum entropy generation CVS states, a few of the closest neighbors in terms of entropy generation will be shown in the tables below to give an impression of the correlation between hemodynamics and entropy generation. The first five columns represent simulation parameters, and the sixth column lists the resultant entropy generation. The last five columns show key hemodynamic variables (the variables are defined in the legend of Table 16).

The results of Table 8 show that the states that result in minimum entropy generation do so at extremely low aortic pressures (AoP ~ 20 mmHg). This is not a

Table 20 - Minimum Entropy Generation with Nearest Neighbors

mmHg / mL/sec	mL / mmHg			rad / sec	J/K / sec	g / sec		mmHg	mL O_2 / mL blood	
Ra	**Ca1**	**Cv**	**Cp**	**ω**	**σ**	**m_h**	**mc**	**AoP**	**ΔO_2 systemic**	**ΔO_2 coronaries**
0.2	3	80	17.5	2	**0.0104**	53.16	4.67	22.11	0.093	0.010
0.2	3	80	20	2	**0.0104**	52.84	4.99	21.66	0.093	0.010
0.2	0.5	80	22.5	2	**0.0104**	53.52	2.66	22.94	0.092	0.026
0.2	3	80	22.5	2	**0.0104**	52.32	5.21	21.22	0.094	0.009
0.2	0.5	80	25	2	**0.0104**	52.71	2.75	22.41	0.093	0.025
0.2	2	80	25	2	**0.0104**	52.45	4.72	21.41	0.094	0.010
0.2	3	80	25	2	**0.0104**	51.85	5.45	20.79	0.095	0.008

reasonable human hemodynamic profile. To ensure survival, the CVS must spend an excess of energy to maintain a CVS state that is capable of quickly meeting an increased metabolic demand, particularly a sympathetic or "flight or fight" response. Therefore to explain why the minimum entropy state is not a physiologically preferred state is to acknowledge the existence of these so-called survival reserves. To give a rough impression for the criteria of survival reserve maintenance, it was arbitrarily chosen to limit the search for minimum entropy generation over the CVS states that result in an AoP of 80 mmHg or greater. The results of this search are shown next in Table 21.

The CVS state, shown above, is similar to the minimum entropy state shown earlier in Table 18; however, the main difference is the increased arterial resistance (Ra). This compensation was enforced by requiring a normal blood pressure, although there are a number of ways the CVS could increase blood pressure with the five

Table 21 – The Minimum Entropy Generation State for AoP > 80 mmHg

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	3	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	0.5	1	1.5	2	3	$\frac{mL}{mmHg}$
C_V	40	50	60	70	80	$\frac{mL}{mmHg}$
C_P	15	17.5	20	22.5	25	$\frac{mL}{mmHg}$
ω	2	4	6	10.5	16	$\frac{rad}{sec}$

parameters. For example, a list of similar CVS states (in terms of entropy generation) is provided in Table 22 on the next page. An inspection of the values in the first five columns (the five parameters of the CVS state) shows that Ra and ω are consistent while the compliance values vary. This pattern indicates that entropy generation is most strongly correlated with ω than the other four variables given that compensation via an increase in ω does not make the minimum entropy criteria. However, this set of CVS states extract more oxygen (ΔO_2 systemic) in order to meet the metabolic demand than is expected for normal hemodynamics. A more complete definition of survival reserve may include consideration of the oxygen carrying capacity of blood in addition to blood pressure.

Table 22 - Min Entropy Generation (for AoP > 80 mmHg) with Nearest Neighbors

$\frac{mmHg}{mL/sec}$	$\frac{mL}{mmHg}$			$\frac{rad}{sec}$	$\frac{J/K}{sec}$	$\frac{g}{sec}$		mmHg	$\frac{mL\ O_2}{mL\ blood}$	
Ra	**Ca1**	**Cv**	**Cp**	**ω**	**σ**	**m_h**	**mc**	**AoP**	**ΔO_2 systemic**	**ΔO_2 coronaries**
3	3	70	15	2	**0.0128**	45.90	19.79	82.73	0.1071	0.0049
3	3	60	17.5	2	**0.0130**	47.76	19.93	84.80	0.1029	0.0051
3	2	80	17.5	2	**0.0130**	46.41	19.81	87.42	0.1059	0.0052
3	3	60	20	2	**0.0128**	47.49	20.22	81.86	0.1035	0.0048
3	2	80	20	2	**0.0129**	46.33	20.40	84.23	0.1061	0.0048
3	2	70	22.5	2	**0.0130**	47.23	20.15	85.91	0.1041	0.0051
3	2	80	22.5	2	**0.0127**	46.27	21.00	81.04	0.1063	0.0045
3	3	50	25	2	**0.0129**	48.41	20.33	81.25	0.1016	0.0049
3	2	70	25	2	**0.0128**	46.90	20.73	82.45	0.1048	0.0048
3	1	80	25	2	**0.0129**	46.25	20.04	84.27	0.1063	0.0050

To contrast the aforementioned results, the maximum entropy generation states are shown in Table 23. The blood pressures (AoP ~ 200 mmHg) are exceedingly high in this case and very little oxygen is extracted from the blood to meet metabolic demand.

Table 22 and Table 23 demonstrate the extremes of entropy generation given the constraints of normal cardiovascular function. By comparing the two tables, heart rate (ω) and arterial resistance (Ra) have the greatest influence on total entropy generation (σ) while the compliance values do not show a correlation with entropy generation.

Table 23 - Maximum Entropy Generation with Nearest Neighbors

mmHg / mL/sec	mL / mmHg			rad / sec	J/K / sec	g / sec		mmHg	mL O_2 / mL blood	
Ra	**Ca1**	**Cv**	**Cp**	**ω**	**σ**	**m_h**	**mc**	**AoP**	**ΔO_2 systemic**	**ΔO_2 coronaries**
2	0.5	40	15	10.5	**0.0360**	126.51	27.17	222.31	0.0389	0.0402
2	0.5	40	15	16	**0.0409**	143.31	33.66	235.23	0.0343	0.0426
2	1	40	15	16	**0.0361**	140.67	47.52	201.56	0.0350	0.0227
2	0.5	50	15	16	**0.0374**	138.92	40.65	213.80	0.0354	0.0295
2	0.5	40	17.5	16	**0.0384**	138.93	35.70	222.48	0.0354	0.0368
2	0.5	50	17.5	16	**0.0352**	134.87	41.66	202.03	0.0365	0.0267
2	0.5	40	20	16	**0.0371**	138.51	40.94	212.01	0.0355	0.0290
2	0.5	40	22.5	16	**0.0351**	135.20	43.00	200.64	0.0364	0.0254

The following plot, Figure 25, explores the distribution of entropy generation values over all stable CVS states (n=3123). Specifically, Figure 25A demonstrates that, over the entire CVS hyperspace, there are many states that result in similar values of entropy generation while the states that contribute to maximum entropy are rarer. Limiting the scope to CVS states that maintain an AoP of 80 mmHg or greater, shown in Figure 25B, eliminates some of the low entropy values but not in a uniform manner. In fact, the resulting profile appears to have two peaks. Future work is anticipated to further explore the basis for this uneven distribution as well as the sharp cutoff at low entropy values. Figure 25C shows the residual states (AoP < 80mmHg) which also distribute over two peaks.

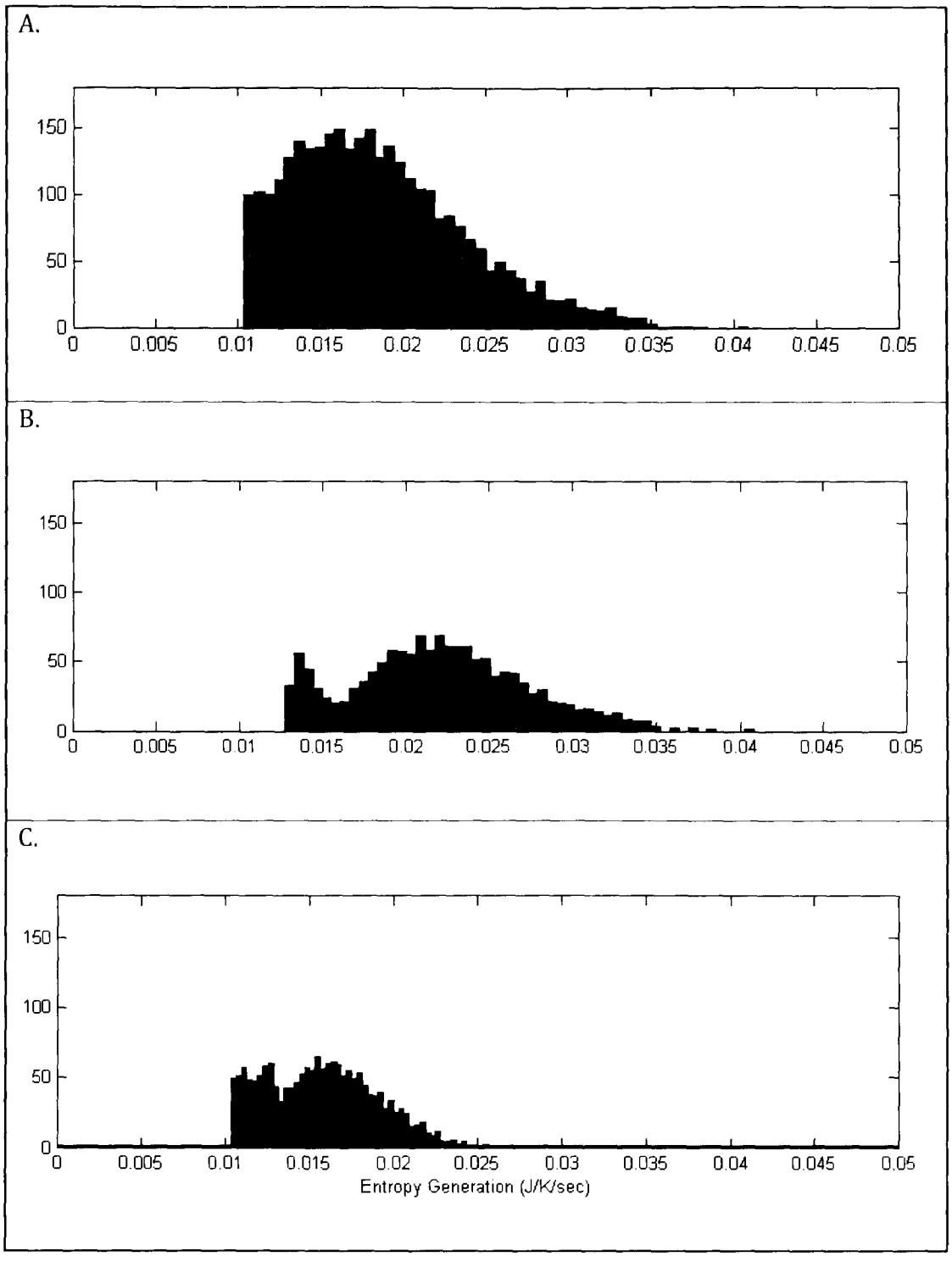


Figure 25 - Entropy Generation (J/K/sec)

Entropy Generation per Compartment

Total entropy generation is a sum of individual entropy generation per compartment within the CVS model. While the previous discussion focused on the identity of total entropy generation in terms of four major states that mark the extremes of entropy generation (normal, min, min with AoP > 80mmHg, and max), the next set of results, Figure 26 on the next page, explores the relative contribution of entropy generation per compartment for these same four CVS states. The results demonstrate that the major contributions to total entropy generation are due almost completely to the heart and the systemic compartments. Furthermore, the distinction between the extreme states is closely associated to changes in entropy generation within the heart specifically.

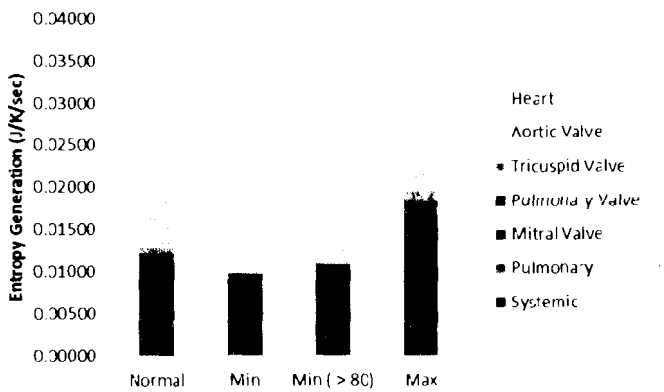
Summary

To summarize the results of calculation of entropy generation in various different CVS states, the extreme states are outlined in Figure 27 on the next page. The unstable states are also shown for reference. The normal state does appear to lie in the middle between the extremes of entropy generation. It was hypothesized that normal CVS physiology would prefer states of minimum entropy generation. However, the states that result in minimum entropy generation do not match the normal CVS state. This may be explained by the conflicting need to minimize entropy generation while also maintaining adequate survival reserves. Therefore this normal state may be characterized by the balance between these two conflicting needs.

A.

	Normal	Min	Min (> 80)	Max
TOTAL	0.01882	0.01036	0.01307	0.03498
Systemic	0.01144	0.00947	0.01039	0.01670
Pulmonary	0.00041	0.00009	0.00012	0.00103
Mitral Valve	0.00006	0.00010	0.00020	0.00008
Pulmonary Valve	0.00023	0.00001	0.00002	0.00049
Tricuspid Valve	0.00005	0.00005	0.00007	0.00011
Aortic Valve	0.00061	0.00005	0.00015	0.00114
Heart	0.00603	0.00059	0.00212	0.01544

B.



C.

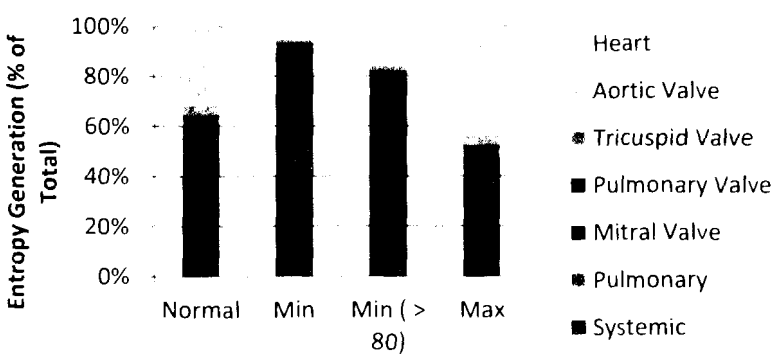


Figure 26 - Entropy Generation per Compartment for Four Extreme States

This was roughly approximated by searching for minimum entropy generation while maintaining a blood pressure of at least 80 mmHg. Blood pressure is used as a surrogate for survival reserve, but could be defined in other ways. This state does slightly move closer to the identity of the normal state. However, it appears that heart rate is strongly associated with entropy generation that a search for min entropy generation, regardless of blood pressure, will automatically assume a low heart rate. Also, when the relative values of entropy generation per compartment were analyzed, it was found that the heart compartment overwhelmingly determines the variability in entropy generation. In conclusion, a definition of the survival reserve is needed to test this new hypothesis: normal CVS tends to minimize entropy generation while maintaining an adequate survival reserve and meeting the metabolic need.

A. The Unstable State (not used in thermodynamic analysis)

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	3**	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	0.5**	1	1.5	2	3	$\frac{mL}{mmHg}$
C_v	40**	50	60	70	80	$\frac{mL}{mmHg}$
C_p	15**	17.5	20	22.5	25	$\frac{mL}{mmHg}$
ω	2	4	6	10.5*	16*	$\frac{rad}{sec}$

B. Normal

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	**1**	2	3	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	0.5	1	**1.5**	2	3	$\frac{mL}{mmHg}$
C_v	40	50	**60**	70	80	$\frac{mL}{mmHg}$
C_p	15	17.5	**20**	22.5	25	$\frac{mL}{mmHg}$
ω	2	4	**6**	10.5	16	$\frac{rad}{sec}$

C. Min Entropy Generation

Parameter	Simulation Hyperspace					Units
R_a	**0.2**	0.5	1	2	3	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	0.5	1	1.5	2	**3**	$\frac{mL}{mmHg}$
C_v	40	50	60	70	**80**	$\frac{mL}{mmHg}$
C_p	15	17.5	20	22.5	**25**	$\frac{mL}{mmHg}$
ω	**2**	4	6	10.5	16	$\frac{rad}{sec}$

C. Max Entropy Generation

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	**2**	3	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	**0.5**	1	1.5	2	3	$\frac{mL}{mmHg}$
C_v	**40**	50	60	70	80	$\frac{mL}{mmHg}$
C_p	**15**	17.5	20	22.5	25	$\frac{mL}{mmHg}$
ω	2	4	6	10.5	**16**	$\frac{rad}{sec}$

D. Min Entropy Gen for AoP > 80mmHg

Parameter	Simulation Hyperspace					Units
R_a	0.2	0.5	1	2	**3**	$\frac{mmHg}{mL/sec}$
C_{a1}, C_{a2}	0.5	1	1.5	**2**	3	$\frac{mL}{mmHg}$
C_v	40	50	60	70	**80**	$\frac{mL}{mmHg}$
C_p	15	17.5	20	**22.5**	25	$\frac{mL}{mmHg}$
ω	2	4	6	10.5	16	$\frac{rad}{sec}$

Figure 27 - Comparison of Four Extreme CVS States

DISCUSSION & CONCLUSION

The models used in this study are not perfect representations of the CVS (no model is). For example, the human CVS is integrated with other control systems of the body and also affected by the environment external to the body. Therefore the CVS is involved with many other aspects of regulation in addition to regulation of blood flow and is sensitive to factors such as temperature, metabolic demand, nutrition, age and sex. Many of these confounding factors impact the CVS in some way, but the physics of blood flow follow the same relationships regardless. Therefore this study uses a minimal, generic model which focuses on the physics of blood flow (hemodynamics) exclusively while simplifying or neglecting these confounding factors. However, it is unknown the extent which these underexplored features, especially temperature and metabolic demand, may contribute to the overall entropy generation within the CVS. Therefore these assumptions are discussed in detail next. Furthermore many of these approximations are intended to be the aim of future work to allow this thesis to focus on essential features of the hemodynamic/thermodynamic model as a means of introductory exploration. An interpretation and concluding thoughts of the results, with the assumptions and approximations in mind, are stated at the end of this chapter.

Approximations & Limitations

Assumed Perfect and Simple Thermoregulation

To anchor the thermodynamic analysis, it was assumed that every CVS state generated by simulation was able to maintain the same fixed core body temperature

which is assigned in this model to be exactly 37 °C. This assumption allowed for assigning a fixed temperature which served as a reference for all other temperature points around the CVS. Core body temperature is indeed regulated *in vivo* to be very near 37°C despite fluctuating temperature gradients between the body and the environment. (26) Therefore declaring a fixed core body temperature is expected to be a reasonable approximation especially for a timespan of a single cardiac cycle and also given the model assumes a resting metabolic rate of 100W which is equivalent to that of a 70kg man at rest.

In this analysis, the point T_{3a} (see Panel 8) was arbitrarily used as the fixed point representing the tightly controlled core body temperature. The calculation of temperatures assumes that the system always maintains this fixed point. The resulting consequence is, according to this model, the pulmonary compartment must transfer the exact amount of heat to maintain a constant fixed point at T_{3a} since the pulmonary is the only compartment defined in this model to experience a heat transfer to the environment. In reality, heat transfer with the environment may occur at other locations, like the cutaneous blood vessels. In fact cutaneous heat loss, being a variable under cardiovascular control, is significantly employed by the body to thermoregulate during scenarios of increased metabolic demand or exercise. (34) However the overall effect of this value of heat loss is uncertain given that it is largely dependent on factors like external environment or clothing. In addition, metabolically active tissues will also tend to transfer heat to the blood vessels that perfuse them. Therefore this net heat transfer (cutaneous heat loss versus bioheat gain from tissue) is unclear and was thought to be reasonably close to zero for resting metabolic rates

in an ideal environment. Therefore these other heat transfers were neglected in this simplified analysis. In general, the simplifying assumption was made for this study that all other heat loss to the environment besides the heat loss from the pulmonary compartment is negligible.

Metabolism & Perfect Respiration

In addition to the forces that circulate blood through the CVS, an equally important focus of this analysis is the transport of metabolites. Metabolic demand is reliant on blood flow to adequately deliver oxygen and fuel but also to remove waste. The only aspect (in terns if transport) of this relationship considered in this analysis is oxygen - the other components, fuel and waste, were assumed to be sufficiently transported or regulated as long as oxygen delivery was sufficient. In general, the system model was assumed to be in a state of perfect regulation of all other integrated variables, such as glucose supply and initial oxygen saturation of blood. In doing so, it was intended that the discussion of entropy generation would be entirely in context of the CVS hemodynamics alone.

Contrary to what was originally expected, the systemic metabolic demand does not appear in the first law analysis of the systemic compartment based on the assumption the systemic compartment includes both the point of fuel input, such as food absorption in the gastrointestinal tract, but also the point of fuel delivery, such as an active skeletal muscle. Therefore, given the earlier assumption that metabolic fuel was constantly perfectly regulated, the enthalpy due to fuel delivery should be equal and opposite to the fuel consumed. In addition, the exchange of metabolites/waste

should be treated separately from the gas exchange (oxygen for carbon dioxide) as they occur at separate anatomical locations - however in this analysis the gas exchange was lumped into the systemic compartment.

Hemodynamic Model Limitations

Another shortcoming discovered with this model is that the coronary blood flow is higher than expected for human coronary blood flow, which in turn resulted in a calculated coronary oxygen difference that is much less than expected. This may be improved by using a more robust model of coronary circulation.

Thermodynamic Calculations

The thermodynamic analysis was conducted assuming steady-state steady-flow conditions for all compartments. Also kinetic and potential energy effects were assumed to be negligible in this analysis.

The data was converted to SI units for the thermodynamic calculations. The conversion between units is straightforward, except for cases in which the thermodynamic properties of blood were unknown. In those cases, blood was approximated as water. This was done for the conversion from volumetric flow to mass flow and also in the calculation of entropy change. Both of these calculations are shown next.

The translation of volumetric flows from the hemodynamic model to mass flows is done via the simple relationship shown below in Equation 48.

Equation 48 - Conversion of Volumetric Flow to Mass Flow

$$\dot{m} = \frac{1}{v} \cdot \dot{\forall}$$

$\dot{m}$ = Mass Flow of blood (g/sec)
v = Specific Volume (mL/g)
$\dot{\forall}$ = Volumetric Flow of blood (cc/sec)

The specific volume of blood was approximated as the specific volume of water evaluated as a saturated liquid at 37°C which is 1.0068 mL/g

Furthermore, fluids, such as blood, can be assumed to be incompressible $(dv \cong 0)$ which simplifies the Gibbs equation from the form shown in Equation 49 to the form shown in Equation 50..

Equation 49 - Gibbs Equation

$$T \cdot ds = du + P \cdot dv$$

Equation 50 - Gibbs Equation for an Incompressible Substance

$$T \cdot ds = du$$

Therefore a change in entropy can be calculated as shown in Equation 51.

Equation 51 - Using Gibbs Equation to Solve for Change in Entropy

$$ds = \frac{du}{T} = \frac{c_v \cdot dT}{T}$$

In the equations above, s is entropy, T is the temperature, and c_v is the specific heat. In this analysis the specific heat of blood was approximated to be sufficiently close to that of water, which is 4.18 J/g*K.

Discussion

It is anticipated that characterizing a CVS state in terms of entropy generation is an effectual way to unify major attributes of CVS function so that overall performance can be described quantitatively. The benefit of using a quantitative framework, such as this, is to be able to discern the relative impact of one form of compensation versus another. This knowledge is useful for the design of treatment strategies of cardiovascular disease. Since cardiovascular disease remains prevalent world-wide, cardiovascular therapies are a significant medical concern. The long-term goal of using entropy generation to understand CVS physiology has significant medical potential in this respect. Toward this long-term goal, an initial step of developing a framework for thermodynamic analysis of the CVS was done in a minimal fashion. Now that entropy generation in the CVS has been introduced, the results and newly arisen questions are expected to foster further development.

After inspecting the CVS states that result in minimum entropy generation, it is found that these states are not physiologically viable especially because the blood pressure is extremely low. While this may be a very efficient arrangement, it is not likely to be the state that is ever actually realized in human. However, more accurate control logic of the *in vivo* CVS may be one that seeks minimum entropy generation while maintaining a "survival reserve". This survival reserve could be defined as an

excess of oxygen content in the blood, or a sufficiently high blood pressure, etc... or a combination of things that guarantee a measure of quick fight/flight response. Furthermore the relative importance of survival reserve maintenance can change – there exists "survival states" that are characterized by changing survival needs/reserves. It is expected that future study on entropy generation as an inherent control logic will involve consideration of survival states in addition to the hemodynamics and thermodynamics. The survival states, ranging from hibernation to maximal exercise, are likely to provide a more complete picture of the significance of entropy generation in the context of CVS physiology. Survival states are discussed briefly next as to how it may impact the characterization of entropy generation in the CVS.

Survival States

A normal survival state can be described qualitatively as a state that maintains the capacity to perform work useful for sustaining life – a state far from equilibrium. Furthermore, the manner in which work is performed can vary in terms of quality or efficiency. All processes that keep a system away from equilibrium are irreversible and generate entropy. Therefore a state that is maximally efficient (but not dead) is one that performs the minimum work necessary to sustain life. This state could be approached during sleep or hibernation. Any increase in work beyond this threshold will be increasingly inefficient – that is result in relatively greater entropy generation. Efficiency can be compromised either to maximize work, as in exercise, or to build a

reserve to ensure a capacity to quickly transition to a maximum work state (also referred to here as a survival reserve or fight/flight response).

The normal state is a balance between the opposing forces illustrated in Figure 28. The actual state, or the current state, can navigate this spectrum. A cardiovascular disease, for example, can also compromise efficiency and therefore bring the current state lower on the spectrum.

For humans, high-intensity exercise is a state of maximum work that is also highly inefficient and therefore short in duration. Sleep is a state that seems to be the opposite in that work is low and efficiency is increased. However, certain mammals have the ability to achieve a dormant state, called hibernation, which is much more dramatic and longer in duration than the sleep state in humans. Therefore, hibernation is hypothesized to best exemplify the maximum efficiency state.

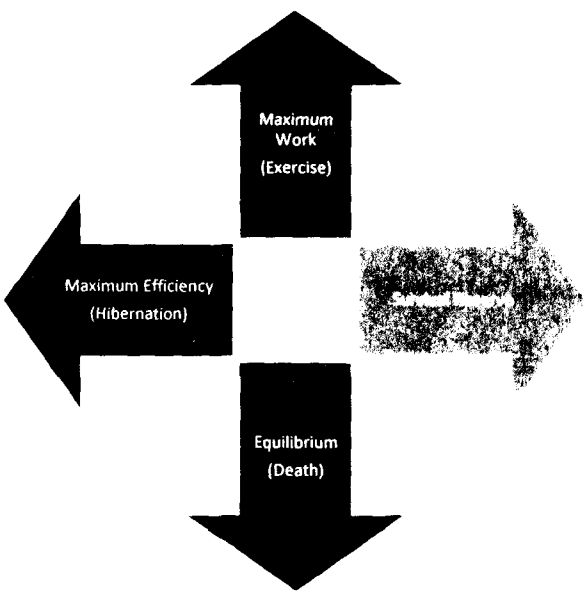


Figure 28 - The Survival State Spectrum

Examples of studied animals that hibernate include ground squirrels (20) and bears (12). Interestingly, the transition to a hibernating state for the bear is different in many aspects from that of the ground squirrel. Particularly the core body temperature of the bear falls only a few degrees Celsius while the ground squirrel radically transitions to a body temperature only slightly above freezing. However, all hibernating mammals experience a significant drop in heart rate. Milsom et. al. report that, in all hibernating mammals, heart rate drops by 50% early in the transition to hibernation – that is before the body temperature changes significantly. This indicates that the diminishing heart rate is part of a concerted maneuver of the body and not a result of the cold environment. (24) On the other hand, the maximum work state is also tightly associated to heart rate. A state of maximum work production is equivalent to a human in a state of maximal exercise. Although humans vary in respect to their functional capacity for maximal exercise, heart rate at maximum exercise approaches 190 bpm for all groups of functional capacities. (35) Therefore, it seems that the extremes of heart rate correlate well with the extremes of survival states. On a similar note, the result of this study has also indicated that heart rate and entropy generation are especially correlated. However, other variables concerning cardiovascular control are more difficult to measure and therefore may simply be underexplored in respect to their role in extreme survival states.

The survival state in the context of a survival spectrum is an alternative but complementary approach to the classical concept of homeostasis in physiology. A quantitative description of homeostasis sets the stage for further analysis, such as sensitivity and stability analysis, which can translate into important clinical

applications. Although this study focuses on the CVS, the above discussion on survival is relevant to the overall integrative physiology. The characterization of entropy generation in the CVS is intended serve as a starting point to quantitatively define efficiency. Efficiency, and likewise entropy generation, is suspected to be a major constituent of the survival state and homeostasis.

Conclusion

In conclusion, entropy generation is proposed here as a novel way to understand cardiovascular physiology. Because entropy generation involves thermodynamics and, therefore, consideration of major energy transformations within the system, this new concept unifies the mechanics of blood flow over the entire system with the aspects of transporting metabolic fuel. Therefore, entropy generation in the CVS is a more holistic form of CVS analysis compared with similar pre-existing theories, such as ventricular-arterial coupling theories.

Since thermodynamics has not been applied to the CVS in this way, the goal of this thesis has been to approximate and characterize entropy generation within the CVS. This has been accomplished by firstly introducing the cardiovascular system as a thermodynamic cycle which generates entropy. In doing so it was found that entropy generation varies in a complex fashion dependent on aspects of the hemodynamic CVS state. This is demonstrated over thousands of distinct cardiovascular simulations which uniquely varied five major parameters (heart rate, arterial resistance, arterial compliance, venous compliance, and pulmonary compliance). Metabolic demand was

defined as an expected normal or resting metabolic rate of 100W. The hemodynamics and metabolic demand were then translated into a thermodynamic cycle and entropy generation was calculated. The results indicate that, in general, heart rate and arterial resistance appear to have the strongest correlation with entropy generation while the compliances do not show a correlation over the simulation hyperspace.

Entropy generation is an aggregate or sum total of many discrete locations within the CVS, therefore it is also of interest to inspect the relative contributions within the CVS. This revealed that entropy generation is due in large to the heart and systemic vasculature, but the other parts of the CVS, like the pulmonary vasculature and the valves, contributed relatively negligible amounts of entropy generation. Total entropy generation variation between CVS states can be solely attributed to the entropy generation within the heart.

In the end, the analysis presented in this thesis introduces entropy generation as a key feature concerning CVS function. The results have generated a new and untested hypothesis for defining the overall control logic of the CVS which involves minimizing entropy generation while maintaining survival reserves.

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APPENDIX A. MATLAB CODE

Model Simulation

CVS_Model_Hyperspace.m

```
% CVS_Model_Hyperspace.m
% Niccole Schaible
% Nov 23, 2011

%%
%Initialize Hemodynamic Model
%Define Hyperspace for Hemodynamic Model Simulation
%Analyze Hemodynamic Model with Numerical Solver over a timespan
%     (repeat for each location within the hyperspace)
%Use results to calculate Thermodynamics
%Organize relevant variables according to CVS State: "cvs()."
%Save all CVS states for entire Hyperspace to file:
%     "simulation_results.mat"
%%

%%
%Calls functions: CVS_ICs
%                 getLastBeat
%                 Calc_Thermo
%                 cvs_hemodynamics
%%


%Initialize Hemodynamic Model
clear all; clc; clf;

global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Ca2 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global P2 del_O2_sys del_O2_cor


%Define Hyperspace for Hemodynamic Model Simulation

Ra_array=[.2 .5 1 2 3];
Ca1_array=[.5 1 1.5 2 3];
Cv_array=[40 50 60 70 80];
Cp_array=[15 17.5 20 22.5 25];
w_array=[2 4 6 10.5 16];
```

```
%Analyze Hemodynamic Model with Numerical Solver over a timespan
%     (repeat for each location within the hyperspace)

for idx_ra=1:5
    Ra=Ra_array(idx_ra);

    for idx_ca=1:5
        Ca1=Ca1_array(idx_ca);
        Ca2=Ca1;

        for idx_cv=1:5
            Cv=Cv_array(idx_cv);

            for idx_cp=1:5
                    Cp=Cp_array(idx_cp);

                    for idx_w=1:5
                    w=w_array(idx_w);


                    %skip states that are unstable: 5,1,1,1,4 % 5
                    if (idx_ra==5 && idx_ca==1 && idx_cv==1...
                        && idx_cp==1 && (idx_w==4 || idx_w==5))
                        disp('51114&5 skipped');
                    else


                    % Display index of current simulation
                    disp(['i = ',num2str(idx_ra)]);
                    disp(['ii = ',num2str(idx_ca)]);
                    disp(['iii = ',num2str(idx_cv)]);
                    disp(['iv = ',num2str(idx_cp)]);
                    disp(['v = ',num2str(idx_w)]);

                    % Declare Initial Conditions
                    CVS_ICs %dependent on adjustable param values

                    % Settings for Numerical Solver
                    options = odeset('RelTol',1e-3);
                    y0 = [y01 y02 y03 y04 y05 y06 y07...
                        y08 y09 y010 y011 y012 y013 y014];

                    % Solve the Hemodynamic Model (from 0 to 20 sec)
                    [t,Y] = ode23s(@cvs_hemodynamics,...
                        [0 20],y0,options);

                    % Find the last beat
                    [t2, Y2] = getLastBeat(w,t,Y);
```

```
%Use results to calculate Thermodynamics

                    % Calculate Entropy Generation
                    [thermo] = Calc_Thermo(t2,Y2);


%Organize relevant variables according to CVS State: "cvs()."
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).del_O2_sys=del_O2_sys;
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).del_O2_cor=del_O2_cor;

cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy=thermo(1);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_sys=thermo(2);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_pulm=thermo(3);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_MV=thermo(4);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_PV=thermo(5);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_TV=thermo(6);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_AV=thermo(7);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_heart=thermo(8);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).P2=thermo(9);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).total_mheat_dis=thermo(10);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).m_dot_h=thermo(11);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).m_dot_c=thermo(12);

                    end
                    end
            end
        end
    end
end


%Save all CVS states for entire Hyperspace to file:
%"simulation_results.mat"
save simulation_results cvs
```

CVS_ICs.m

```
% CVS_ICs.m
% Niccole Schaible
% Nov 23, 2011

global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global Volv Vorv


%---------- Time-Varying Elastance Parameters ----------%

%Left Ventricle
alpha1=3.1;
alpha2=-.0086;
alpha3=.0003;

%Right Ventricle
beta1=0.624;
beta2=-.00185;
beta3=.00025;

%---------- Effective Volumes ----------%

%Ventricles
LVVeff0=130;
RVVeff0=130;

%Systemic
Veffa1=150;
Veffa2=150;
Veffv=800;
Veffp=250;


%---------- Dead Volumes ----------%

%Ventricles
Volv=20;
Vorv=20;

%Systemic
Voa1=250;
Voa2=250;
Vov=2700;
Vop=200;
```

```
%---------- Static Systemic Resistance/Capacitance ----------%

Lav=.0001;
Rav=.01;

La1=.0001;
La2=.0001;

Ca2=Ca1;

Rv=.05;

Ltv=.0001;
Rtv=.01;

Rpv=.01;
Lpv=.0001;

Rp=.08;

Rmv=.01;
Lmv=.0001;

k=.0001; %Rlv=k*LVP
kr=.0001; %Rrv=kr*RVP
kc=.5; %Rc=kc*LVP (coronary resistance)

%---------- State Equation ICs ----------%

y01=LVVeff0;              %LVVeff
y02=RVVeff0;              %RVVeff
y03=alpha3*LVVeff0^2;     %HMPl
y04=0;                    %Qol
y05=Veffa1/Ca1;           %AoP1
y06=0;                    %Qla1
y07=Veffa2/Ca2;           %AoP2
y08=0;                    %Qla2
y09=Veffv/Cv;             %CVP
y010=0;                   %Qir
y011=beta3*RVVeff0^2;     %HMPr
y012=0;                   %Qor
y013=Veffp/Cp;            %PuP
y014=0;                   %Qil
```

cvs_hemodynamics.m

```
function dy = cvs_hemodynamics(t,y)
global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Ca2 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv

%---------- Auxilary Equations ----------%

%% Time-varying elastance (heart beat)

%Sine Wave
e_gen=sin(w*t-pi/2);

%Half-Wave Rectified (+ Derivative)
if e_gen >= 0
    e=e_gen;
    de=w*cos(w*t-pi/2);
else
    e=0;
    de=0;
end

%Left Ventricle
Elv=[alpha1+alpha2*y(1)]*e+alpha3*y(1);
dElv=(alpha2*e+alpha3)*(y(14)-y(4))+[alpha1+alpha2*y(1)]*de;

%Right Ventricle
Erv=[beta1+beta2*y(2)]*e+beta3*y(2);
dErv=(beta2*e+beta3)*(y(10)-y(12))+[beta1+beta2*y(2)]*de;


%% Nonlinear Resistances

Rlv=k*y(3)/(1-k*(y(14)-y(4)));
Rrv=kr*y(11)/(1-kr*(y(10)-y(12)));
Rc=kc*y(3)/(1-k*(y(14)-y(4)));

D1=20*(1-.15/(.15+exp(-6*y(4))));
D2=20*(1-1/(1+exp(-6*y(10))));
D3=20*(1-.15/(.15+exp(-6*y(12))));
D4=20*(1-1/(1+exp(-6*y(14))));
```

```
%---------- State Equations ----------%
z=1/(1+(Rv/Rc));
z2=1/(Rc+Rv);

Qoil = y(14)-y(4);
Qoir = y(10)-y(12);

dy = zeros(14,1);

dy(1) = Qoil;
dy(2) = Qoir;
dy(3) = Qoil*Elv + y(3)*1/Elv*dElv;
dy(4) = (y(3)-y(5)+Rlv*y(14)-(Rlv+Rav+D1)*y(4))*1/Lav;
dy(5) = (y(4)-y(6)-z2*y(5)+z2*y(9)-z2*Rv*y(10))*1/Ca1;
dy(6) = (y(5)-y(7))*1/La1;
dy(7) = (y(6)-y(8))*1/Ca2;
dy(8) = (y(7)-y(9)-Ra*y(8))*1/La2;
dy(9) = (y(8)-z2*y(9)-z*y(10)+z2*y(5))*1/Cv;
dy(10)= (z*y(9)-y(11)+Rrv*y(12)+z*Rv/Rc*y(5)-...
    (z*Rv+Rrv+Rtv+D2)*y(10))*1/Ltv;
dy(11)= Qoir*Erv + y(11)*1/Erv*dErv;
dy(12)= (y(11)-y(13)+Rrv*y(10)-(Rrv+Rpv+D3)*y(12))*1/Lpv;
dy(13)= (y(12)-y(14))*1/Cp;
dy(14)= (y(13)-y(3)+Rlv*y(4)-(Rlv+Rp+Rmv+D4)*y(14))*1/Lmv;
```

getLastBeat.m

```
function [tt, YY] = getLastBeat(w,t,Y)

%Each Simulation runs to 20secs to ensure SS is reached.
%Need only the last beat for thermo analysis.

HMPl=Y(:,3); %Can use any of the state variables
time=t;

T=((2*pi)/w); %period in seconds

start=20-T; %give just enough space to catch last full period

%search for this point and mark the start and end
idx1=find(time >= start,1,'first');
idx2=find(HMPl == HMPl(end));

%output all data for only the last beat
tt=time(idx1:idx2);
YY=Y(idx1:idx2,:);
```

Calc_Thermo.m

```
function [thermo] = Calc_Thermo(t2,Y2)
global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Ca2 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global P2 del_O2_sys del_O2_cor

%% Thermodynamic Parameters (Constants)

cv=4.18;   %water (J/g*K)
vv=1.0068;  %specific volume (cc/g)
con1=101325/760; %%to convert P(mmHg) to P(Pa) {101.325kPa=760mmHg}
con2=1/10^6; %%convert V(cc) to V(m^3) {10^6cc=10^6cm^3=1m^3)
vcon2=vv*con2; %specific volume (m^3/g)
con3=22400; %22400mL/mol

%% Hemodynamic Variables

LVVeff=Y2(:,1);
RVVeff=Y2(:,2);
HMPl=Y2(:,3);
Qol=Y2(:,4);
AoP1=Y2(:,5);
Qla1=Y2(:,6);
AoP2=Y2(:,7);
Qla2=Y2(:,8);
CVP=Y2(:,9);
Qir=Y2(:,10);
HMPr=Y2(:,11);
Qor=Y2(:,12);
PuP=Y2(:,13);
Qil=Y2(:,14);

LVV=LVVeff+20; %Volv=20;
RVV=RVVeff+20; %Vorv=20;

Rlv=k*HMPl./(1-k*(Qil-Qol));
LVP=Rlv/k;
Rrv=kr*HMPr./(1-kr*(Qir-Qor));
RVP=Rrv/kr;

Rc=kc/k*Rlv;

z=1./(1+(Rv./Rc));
CVP2=z.*CVP-z.*Rv.*Qir+z.*Rv./Rc.*AoP1;

Qc=(AoP1-CVP2)./Rc;

D1=20*(1-.15./(.15+exp(-6.*Qol))); %AV
D2=20*(1-1./(1+exp(-6.*Qir))); %TV
D3=20*(1-.15./(.15+exp(-6.*Qor))); %PV
D4=20*(1-1./(1+exp(-6.*Qil))); %MV
```

```
%% Calculate Average Filling/Ejection Pressures

n=length(t2);
ejection_l=find(Qol>0);
filling_l=find(Qil>0);
ejection_r=find(Qor>0);
filling_r=find(Qir>0);

del_t8=t2(filling_l(end))-t2(filling_l(1));
LVP_filling=trapz(t2(filling_l),LVP(filling_l))/del_t8;
del_t1=t2(ejection_l(end))-t2(ejection_l(1));
LVP_ejection=trapz(t2(ejection_l),LVP(ejection_l))/del_t1;
del_t5=t2(ejection_r(end))-t2(ejection_r(1));
RVP_ejection=trapz(t2(ejection_r),RVP(ejection_r))/del_t5;
del_t4=t2(filling_r(end))-t2(filling_r(1));
RVP_filling=trapz(t2(filling_r),RVP(filling_r))/del_t4;


%% Calculate Steady-State Values of the Hemodynamic Variables

T=((2*pi)/w); %period in seconds

Yss=(1/T)*trapz(t2,Y2);

ssLVVeff=Yss(:,1);
ssRVVeff=Yss(:,2);
ssHMPl=Yss(:,3);
ssQol=Yss(:,4);
ssAoP1=Yss(:,5);
ssQla1=Yss(:,6);
ssAoP2=Yss(:,7);
ssQla2=Yss(:,8);
ssCVP=Yss(:,9);
ssQir=Yss(:,10);
ssHMPr=Yss(:,11);
ssQor=Yss(:,12);
ssPuP=Yss(:,13);
ssQil=Yss(:,14);

ssCVP2=(1/T)*trapz(t2,CVP2);
ssQc=(1/T)*trapz(t2,Qc);
ssRlv=(1/T)*trapz(t2,Rlv);
ssRrv=(1/T)*trapz(t2,Rrv);

ssQlv=(1/T)*trapz(t2,Qol+Qil);
ssQrv=(1/T)*trapz(t2,Qor+Qir);

m_dot_lv=(ssQlv)/vv;
m_dot_rv=(ssQrv)/vv;

m_dot_h=ssQol/vv;
m_dot_c=ssQc/vv;
m_dot_a=m_dot_h-m_dot_c;
```

```
P2a=ssAoP1;
P3a=ssCVP2;
P2=P2a;
P2c=P2a;
P3c=P3a;
P5=RVP_ejection;
P4=RVP_filling;
P3=P3a;
P6=ssPuP;
P7=(1/T)*trapz(t2,PuP-Qil*Rp);
P8=LVP_filling;
P1=LVP_ejection;


%------------------%%% POWER BALANCE INSPECTION %%%------------------%

%% Heat Dissipated (using m_dot) %%

% Output Power Produced by Ventricular Pumps
powlv=(P1-P8).*(m_dot_h)*con1*con2;
powrv=(P5-P4).*(m_dot_h)*con1*con2;

total_pow=powlv+powrv;

% Valves
mheatav=(P1-P2)*(m_dot_h)*con1*con2;
mheatmv=(P7-P8)*(m_dot_h)*con1*con2;
mheatpv=(P5-P6)*(m_dot_h)*con1*con2;
mheattv=(P3-P4)*(m_dot_h)*con1*con2;

% Compartments
mheatc=(P2c-P3c)*(m_dot_c)*con1*con2; %Coronaries
mheata=(P2-P3)*(m_dot_a)*con1*con2; %Arterial + Venous
mheatp=(P6-P7)*(m_dot_h)*con1*con2; %Pulmonary


total_mheat_dis=mheatav + ...
                mheatmv + ...
                mheattv + ...
                mheatpv + ...
                mheatc + ...
                mheata + ...
                mheatp;
```

```
% First Law Balance Inspection

disp(['Power Dissipated                Power Produced']);
disp(['Rav=',num2str(mheatav),'        LV=',num2str(powlv)]);
disp(['Rmv=',num2str(mheatmv),'        RV=',num2str(powrv)]);
disp(['Rtv=',num2str(mheattv),'        ----------']);
disp(['Rpv=',num2str(mheatpv),'        Total=',num2str(total_pow)]);
disp(['Rc=',num2str(mheatc),'                      ----------']);
disp(['Ra=',num2str(mheata)]);
disp(['Rp=',num2str(mheatp)]);
disp(['----------']);
disp(['Total=',num2str(total_mheat_dis)]);
disp(['----------']);
disp([' ']);

%-------------------------------------------------------------------------%

del_P_3a_2a=con1*(P3a-P2a);
del_P_2_1=con1*(P2-P1);
del_P_3c_2c=con1*(P3c-P2c);
del_P_5_4=con1*(P5-P4);
del_P_3_4=con1*(P3-P4);
del_P_5_6=con1*(P5-P6);
del_P_8_7=con1*(P8-P7);
del_P_7_6=con1*(P7-P6);
del_P_1_8=con1*(P1-P8);

heatlv=m_dot_lv^2*ssRlv*con1*con2;
heatrv=m_dot_rv^2*ssRrv*con1*con2;

heatc=(Qc).^2.*Rc*con1*con2;
heatca=(1/T)*trapz(t2,heatc);

del_T_1_8=heatlv/(m_dot_h*cv);
del_T_5_4=heatrv/(m_dot_h*cv);



%%%---------- THERMODYNAMIC CALCULATION ----------%%%

%% First Law

%Step1
T3a=310;

%Step2
T2a=(vcon2*del_P_3a_2a)/cv+T3a;

%Step3
T2=T2a;
T2c=T2a;
```

```
%Step4
T1=(vcon2*del_P_2_1)/cv+T2;

%Step5
x1=m_dot_c*vcon2*del_P_3c_2c;
x2=m_dot_h*vcon2*(del_P_1_8+del_P_5_4);
T3c=(-x1-heatlv-heatrv+x2)/(m_dot_c*cv)+T2c;

%Step6
T3=(m_dot_a*T3a+m_dot_c*T3c)/(m_dot_a+m_dot_c);

%Step7
T4=vcon2*del_P_3_4/cv+T3;

%Step8a
T8=-del_T_1_8+T1;

%Step8b
T5=del_T_5_4+T4;

%Step9
T6=vcon2*del_P_5_6/cv+T5;

%Step10
T7=vcon2*del_P_8_7/cv+T8;

%Step11
del_T_7_6=(T7-T6);
Qp=-m_dot_h*(cv*del_T_7_6+vcon2*del_P_7_6);


%% Metabolic Demand

%Systemic (External = Declared as a constant rate)

ME_dot=100; %Metabolic Demand (100W = 100J/s = 70kg male at rest)
kO2=20.2;   %Energy Equivalent of O2 (20.2kJ/LO2=20.2J/mLO2)

del_O2_sys=ME_dot/(kO2*ssQol); %Metabolic demand (systemic) converted to
                               %O2 demand

n_dot_O2_sys=(del_O2_sys*ssQol)/con3; % Molar rate of O2 demand


%Coronary (Depends on Hemodynamics = Work generated by the heart)

%Step1

%Left Heart
EW=polyarea(LVV,LVP); %mL, mmHg
Volv=20; pva2=polyarea([Volv min(LVV) min(LVV)], [0 max(LVP) 0]);
PVA=EW+pva2;
```

```
%Right Heart
EWr=polyarea(RVV,RVP);
Vorv=20; pva2r=polyarea([Vorv min(RVV) min(RVV)], [0 max(RVP) 0]);
PVAr=EWr+pva2r;

%Left-Right Combined
PVA_total=PVA+PVAr;

%Step2
MVO2=1.64*10^-5*PVA_total+0.015;  %Oxygen Demand of the Heart
                                    %provided by the coronaries
HR=w*(1/(2*pi)); %beat per second

%Step3
del_O2_cor=MVO2*HR/ssQc; %Oxygen content of blood required given flow
                          %Coronary A-V O2 difference

%-------------------------------------------------------------------------%


%% Second Law

T=310;

Qmet=n_dot_O2_sys*(1/6)*(77.7)*(1000); %1 glc per 6 O2
                                        %heat liberated per mole O2
entropy_sys=m_dot_a*cv*log(T3a/T2a)+Qmet/T;

entropy_pulm=m_dot_h*cv*log(T7/T6)+Qp/T;

entropy_MV=m_dot_h*cv*log(T8/T7);

entropy_PV=m_dot_h*cv*log(T6/T5);

entropy_TV=m_dot_h*cv*log(T4/T3);

entropy_AV=m_dot_h*cv*log(T2/T1);

entropy_heart=m_dot_c*cv*log(T3c/T2c)+m_dot_h*cv*(log((T1*T5)/(T8*T4));

entropy=entropy_sys+...
    entropy_pulm+...
    entropy_MV+...
    entropy_PV+...
    entropy_TV+...
    entropy_AV+...
    entropy_heart;
```

```
%% Outputs

thermo=zeros(1,12);

thermo(1)=entropy;
thermo(2)=entropy_sys;
thermo(3)=entropy_pulm;
thermo(4)=entropy_MV;
thermo(5)=entropy_PV;
thermo(6)=entropy_TV;
thermo(7)=entropy_AV;
thermo(8)=entropy_heart;
thermo(9)=P2;
thermo(10)=total_mheat_dis;
thermo(11)=m_dot_h;
thermo(12)=m_dot_c;
```

CVS_Model_Hyperspace_vco.m

```
% CVS_Model_Hyperspace_vco.m
% Niccole Schaible
% Nov 23, 2011

%%
%CVS_Model_Hyperspace.m modified to simulate vco experiment
%by using "cvs_vco.m" instead of "cvs_hemodynamics.m"
%%

%%
%Calls functions: CVS_ICs
%                 getLastBeat
%                 Calc_Thermo
%                 cvs_vco
%%


%Initialize Hemodynamic Model
clear all; clc; clf;

global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Ca2 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global P2 del_O2_sys del_O2_cor


%Define Hyperspace for Hemodynamic Model Simulation

Ra_array=[.2 .5 1 2 3];
Ca1_array=[.5 1 1.5 2 3];
Cv_array=[40 50 60 70 80];
Cp_array=[15 17.5 20 22.5 25];
w_array=[2 4 6 10.5 16];


%Analyze Hemodynamic Model with Numerical Solver over a timespan
%     (for normal state only)

for idx_ra=3:3
    Ra=Ra_array(idx_ra);

    for idx_ca=3:3
        Ca1=Ca1_array(idx_ca);
        Ca2=Ca1;

        for idx_cv=3:3
            Cv=Cv_array(idx_cv);
```

```
for idx_cp=3:3
        Cp=Cp_array(idx_cp);

        for idx_w=3:3
        w=w_array(idx_w);


        %skip states that are unstable: 5,1,1,1,4 % 5
        if (idx_ra==5 && idx_ca==1 && idx_cv==1...
            && idx_cp==1 && (idx_w==4 || idx_w==5))
            disp('51114&5 skipped');
        else


        % Display index of current simulation
        disp(['i = ',num2str(idx_ra)]);
        disp(['ii = ',num2str(idx_ca)]);
        disp(['iii = ',num2str(idx_cv)]);
        disp(['iv = ',num2str(idx_cp)]);
        disp(['v = ',num2str(idx_w)]);

        % Declare Initial Conditions
        CVS_ICs %dependent on adjustable param values

        % Settings for Numerical Solver
        options = odeset('RelTol',1e-3);
        y0 = [y01 y02 y03 y04 y05 y06 y07...
            y08 y09 y010 y011 y012 y013 y014];

        % Solve the Hemodynamic Model (from 0 to 20 sec)
        [t,Y] = ode23s(@cvs_vco,...
            [0 20],y0,options);

        % Find the last beat
        [t2, Y2] = getLastBeat(w,t,Y);


%Use results to calculate Thermodynamics

        % Calculate Entropy Generation
        [thermo] = Calc_Thermo(t2,Y2);
```

```
%Organize relevant variables according to CVS State: "cvs()."

cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).del_O2_sys=del_O2_sys;
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).del_O2_cor=del_O2_cor;

cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy=thermo(1);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_sys=thermo(2);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_pulm=thermo(3);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_MV=thermo(4);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_PV=thermo(5);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_TV=thermo(6);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_AV=thermo(7);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).entropy_heart=thermo(8);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).P2=thermo(9);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).total_mheat_dis=thermo(10);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).m_dot_h=thermo(11);
cvs(idx_ra,idx_ca,idx_cv,idx_cp,idx_w).m_dot_c=thermo(12);

                    end
                    end
            end
        end
    end
end


%Save all CVS states for entire Hyperspace to file:
%"vco_results.mat"
save vco_results cvs t Y
```

cvs_vco.m

```
function dy = cvs_vco(t,y)
global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Ca2 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv

%---------- Auxilary Equations ----------%

%VCO - increase Rp to progressively restrict venous return (preload)
Rp2=.005*t.^3+Rp;

%% Time-varying elastance (heart beat)

%Sine Wave
e_gen=sin(w*t-pi/2);

%Half-Wave Rectified (+ Derivative)
if e_gen >= 0
    e=e_gen;
    de=w*cos(w*t-pi/2);
else
    e=0;
    de=0;
end


%Left Ventricle
Elv=[alpha1+alpha2*y(1)]*e+alpha3*y(1);
dElv=(alpha2*e+alpha3)*(y(14)-y(4))+[alpha1+alpha2*y(1)]*de;

%Right Ventricle
Erv=[beta1+beta2*y(2)]*e+beta3*y(2);
dErv=(beta2*e+beta3)*(y(10)-y(12))+[beta1+beta2*y(2)]*de;

%% Nonlinear Resistances

Rlv=2*(k*y(3)/(1-k*(y(14)-y(4))));
Rrv=kr*y(11)/(1-kr*(y(10)-y(12)));
Rc=kc*y(3)/(1-k*(y(14)-y(4)));

D1=20*(1-.15./(.15+exp(-6*y(4))));
D2=20*(1-1./(1+exp(-6*y(10))));
D3=20*(1-.15./(.15+exp(-6*y(12))));
D4=20*(1-1./(1+exp(-6*y(14))));

z=1/(1+(Rv/Rc));
z2=1/(Rc+Rv);

Qoil = y(14)-y(4);
Qoir = y(10)-y(12);
```

```
%---------- State Equations ----------%
dy = zeros(14,1);    % a column vector

dy(1) = Qoil;
dy(2) = Qoir;
dy(3) = Qoil*Elv + y(3)*1/Elv*dElv;
dy(4) = (y(3)-y(5)+Rlv*y(14)-(Rlv+Rav+D1)*y(4))*1/Lav;
dy(5) = (y(4)-y(6)-z2*y(5)+z2*y(9)-z2*Rv*y(10))*1/Ca1;
dy(6) = (y(5)-y(7))*1/La1;
dy(7) = (y(6)-y(8))*1/Ca2;
dy(8) = (y(7)-y(9)-Ra*y(8))*1/La2;
dy(9) = (y(8)-z2*y(9)-z*y(10)+z2*y(5))*1/Cv;
dy(10)= (z*y(9)-y(11)+Rrv*y(12)+z*Rv/Rc*y(5)-...
    (z*Rv+Rrv+Rtv+D2)*y(10))*1/Ltv;
dy(11)= Qoir*Erv + y(11)*1/Erv*dErv;
dy(12)= (y(11)-y(13)+Rrv*y(10)-(Rrv+Rpv+D3)*y(12))*1/Lpv;
dy(13)= (y(12)-y(14))*1/Cp;
dy(14)= (y(13)-y(3)+Rlv*y(4)-(Rlv+Rp2+Rmv+D4)*y(14))*1/Lmv;
```

CVS_Plots.m

```
% CVS_Plots.m
% Niccole Schaible
% Nov 23, 2011

global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global Volv Vorv

load vco_results;

%CVS_ICs

Ra=1;
Ca1=1.5;
Cv=60;
Cp=20;;
w=6;

%Rename variables for convenience
LVV=Y2(:,1);
RVV=Y2(:,2);
HMP1=Y2(:,3);
Qol=Y2(:,4);
AoP1=Y2(:,5);
Qla1=Y2(:,6);
AoP2=Y2(:,7);
Qla2=Y2(:,8);
CVP=Y2(:,9);
Qir=Y2(:,10);
HMPr=Y2(:,11);
Qor=Y2(:,12);
PuP=Y2(:,13);
Qil=Y2(:,14);

t=t2;

Rlv=k*HMP1./(1-k*(Qil-Qol));
LVP=Rlv/k;

Rrv=kr*HMPr./(1-kr*(Qir-Qor));
RVP=Rrv/kr;

Rc=kc/k*Rlv;

z=1./(1+(Rv./Rc));
CVP2=z.*CVP-z.*Rv.*Qir+z.*Rv./Rc.*AoP1;

Qc=(AoP1-CVP2)./Rc;
```

```
%Plot Cardiac Cycle (Left Heart)
figure(1); clf;
subplot(2,1,1); plot(t,LVP,t,AoP1,t,PuP); title('Left Heart');
legend('LVP', 'AoP', 'PuP','Location','EastOutside');
ylabel('Pressure (mmHg)');
axis([t2(1) 20 -5 120]);
subplot(2,1,2); plot(t,Qol,t,Qil);
legend('Qol', 'Qil','Location','EastOutside');
xlabel('Time (sec)'); ylabel('Flow (mL/sec)');
axis([t2(1) 20 -50 2000]);

%Plot Cardiac Cycle (Right Heart)
figure(2); clf;
subplot(2,1,1); plot(t,RVP,t,PuP,t,CVP); title('Right Heart');
legend('RVP', 'PuP', 'CVP','Location','EastOutside');
ylabel('Pressure (mmHg)');
axis([t2(1) 20 -5 40]);
subplot(2,1,2); plot(t,Qor,t,Qir);
legend('Qor', 'Qir','Location','EastOutside');
xlabel('Time (sec)'); ylabel('Flow (mL/sec)');
axis([t2(1) 20 -50 1100]);

%Plot PV Domain (Left Heart)
figure(3); clf;
plot(LVV,LVP,'k'); axis([ -20 350 -20 200]);
xlabel('Left Ventricular Volume (mL)');
ylabel('Left Ventricular Pressure (mmHg)');

%Plot PV Domain + PV envelopes (Left Heart)
figure(4); clf;
plot(LVV,LVP,'k'); axis([ -20 350 -20 200]);
xlabel('Volume (mL)'); ylabel('Pressure (mmHg)');
hold on;

%% Envelopes %%
x=0:.1:450;

Pmin=0.5*.0003*x.^2;
Pmax=0.5*-.0083*x.^2+3.1*x;

Edia=.001*x;
Esys=-.0166*x+3.1;

Pminr=0.5*.00025*x.^2;
Pmaxr=0.5*-.0016*x.^2+.624*x;

Ediar=.0005*x;
Esysr=-.006*x+1.09;

plot(x,Pmax,'r',x,Pmin,'LineWidth',2);
xlabel('Volume (mL)'); ylabel('Pressure (mmHg)');
title('Left Heart');
```

VCO_Plots.m

```
% VCO_Plots.m
% Niccole Schaible
% Nov 23, 2011

global alpha1 alpha2 alpha3 beta1 beta2 beta3 k kr kc
global Ra Ca1 Cv Cp w
global La1 La2 Rv Rp Lmv Rmv Ltv Rtv Lav Rav Lpv Rpv
global Volv Vorv

%Load vco_results (simulation workspace)

%CVS_ICs

Ra=1;
Ca1=1.5;
Cv=60;
Cp=20;;
w=6;

%Rename variables for convenience
LVV=Y(:,1);
RVV=Y(:,2);
HMP1=Y(:,3);
Qol=Y(:,4);
AoP1=Y(:,5);
Qla1=Y(:,6);
AoP2=Y(:,7);
Qla2=Y(:,8);
CVP=Y(:,9);
Qir=Y(:,10);
HMPr=Y(:,11);
Qor=Y(:,12);
PuP=Y(:,13);
Qil=Y(:,14);
Rlv=k*HMP1./(1-k*(Qil-Qol));
LVP=Rlv/k;
Rrv=kr*HMPr./(1-kr*(Qir-Qor));
RVP=Rrv/kr;

Rc=kc/k*Rlv;

z=1./(1+(Rv./Rc));
CVP2=z.*CVP-z.*Rv.*Qir+z.*Rv./Rc.*AoP1;

Qc=(AoP1-CVP2)./Rc;
```

```
%Plot Results (3 Figures)
figure(1); clf;
plot(t,LVP); xlabel('Time (sec)'); ylabel('LVP (mmHg)');
title('Venal Caval Occlusion Experiment Response');

figure(2); clf;
plot(LVV,LVP,'k'); axis([ -20 350 -20 200]);
EW=polyarea(LVV,LVP); %mL, mmHg
Volv=20; pva2=polyarea([Volv min(LVV) min(LVV)], [0 max(LVP) 0]);
PVA=EW+pva2;
title('Venal Caval Occlusion Experiment Response');
xlabel('Volume (mL)'); ylabel('Pressure (mmHg)');

figure(3); clf;
plot(LVV,LVP,'k'); axis([ -20 350 -20 200]);
EW=polyarea(LVV,LVP); %mL, mmHg
Volv=20; pva2=polyarea([Volv min(LVV) min(LVV)], [0 max(LVP) 0]);
PVA=EW+pva2;
title('VCO Experiment Response with Operating Envelopes');

xlabel('Volume (mL)'); ylabel('Pressure (mmHg)');
hold on;

%% PV Envelopes %%
x=0:.1:450;

Pmin=0.5*.0003*x.^2;
Pmax=0.5*-.0083*x.^2+3.1*x;

Edia=.001*x;
Esys=-.0166*x+3.1;

Pminr=0.5*.00025*x.^2;
Pmaxr=0.5*-.0016*x.^2+.624*x;

Ediar=.0005*x;
Esysr=-.006*x+1.09;

plot(x,Pmax,'r',x,Pmin,'LineWidth',2);
```

Search_SigmaDot.m

```
% Search_SigmaDot.m
% Niccole Schaible
% Nov 23, 2011

%%
%Check for Physiological O2 Demand
%Enforce Constraints over Hyperspace
%Given constraints, find the CVS state with min sigma dot
%Display results for min CVS state plus nearest neighbors
%%

Ra_array=[.2 .5 1 2 3];
Cal_array=[.5 1 1.5 2 3];
Cv_array=[40 50 60 70 80];
Cp_array=[15 17.5 20 22.5 25];
w_array=[2 4 6 10.5 16];

%Check for Physiological O2 Demand
%at Command Line
%If all values are within range, then max < 0.2
%CORONARIES
[max_cor_value,max_cor_index]=max([cvs.del_O2_cor]);
[i ii iii iv v] = ind2sub([5,5,5,5,5], max_cor_index);
%SYSTEMIC
[max_sys_value,max_sys_index]=max(cvs.del_O2_sys]);
[i ii iii iv v] = ind2sub([5,5,5,5,5], max_sys_index);

%Enforce Constraints over Hyperspace
limited_list=find([cvs.P2] > 0);

%Given constraints, find the CVS state with min sigma dot
[min_entropy_value,min_entropy_index]=...
    min([cvs(limited_list).entropy]);

[i ii iii iv v] = ind2sub([5,5,5,5,5], min_entropy_index);
```

```
%Check min_entropy_value at command line
%and pick nearby value (save as variable "threshold")
%Display results for min CVS state plus nearest neighbors
list=find(([cvs(limited_list).entropy] < threshold));
n=length(list);

for idx=1:n
    [i ii iii iv v] = ind2sub([5,5,5,5,5], limited_list(list(idx)));

    results_table(idx,1)=Ra_array(i);
    results_table(idx,2)=Ca1_array(ii);
    results_table(idx,3)=Cv_array(iii);
    results_table(idx,4)=Cp_array(iv);
    results_table(idx,5)=w_array(v);

    results_table(idx,6)=cvs(i,ii,iii,iv,v).entropy;
    results_table(idx,7)= cvs(i,ii,iii,iv,v).m_dot_h;
    results_table(idx,8)=cvs(i,ii,iii,iv,v).del_O2_sys;
    results_table(idx,9)=cvs(i,ii,iii,iv,v).m_dot_c;
    results_table(idx,10)=cvs(i,ii,iii,iv,v).del_O2_cor;
    results_table(idx,11)=cvs(i,ii,iii,iv,v).P2;

end

header={'Ra  ';'Ca1';'Cv   ';'Cp';'w';' sigma ';'mh ';...
    ' O2s';'mc ';'O2c ';'AoP'};
disp(header')
disp(sortrows([results_table],5))
```

Distribution_SigmaDot.m

```
% Distribution_SigmaDot.m
% Niccole Schaible
% Nov 23, 2011

load simulation_results

nonzero=find([cvs.entropy] ~= 0);
limited_list=find([cvs.P2] > 80);
leftover=find(([cvs.entropy] ~= 0)&([cvs.P2] < 80));

figure(1);
hist([CVS(nonzero).entropy],50); axis([0 .05 0 180]);
xlabel('Entropy Generation (J/K/sec)');

figure(2);
hist([CVS(limited_list).entropy],50); axis([0 .05 0 180]);
xlabel('Entropy Generation (J/K/sec)');
ylabel('For AoP > 80mmHg');

figure(3);
hist([CVS(leftover).entropy],50); axis([0 .05 0 180]);
xlabel('Entropy Generation (J/K/sec)');
ylabel('For AoP < 80mmHg');
```