Automatically Finding the Average Output of a Steadily Beating Ventricle

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ABSTRACT: The repetitive behavior of a device or system can be described in two ways: a detailed description of one iteration of the behavior, or a summary description of the behavior over many repetitions. In this paper, an implemented program called AIS is applied to a model of a steadily beating ventricle (part of the heart). AIS transforms the first type of description into the second type. The output consists of the symbolic average rates of change in parameter values and how those rates would be different if various constants and functions had been different. AIS's results are compared to results in the literature.

INTRODUCTION: A program called AIS (short for Analyzer of Iterated Sequences) has been developed and applied to a model of a steadily beating ventricle. When given a state-description of a system and a sequence of actions or transformations on that state, AIS symbolically finds some of the time-averaged effects of continually iterating that sequence. The specific effects found at present include 1) the symbolic average rate of change in parameters, and 2) an assessment of how those rates of change would be different with different values for various constants and functions (sensitivity analysis). The sequences handled by AIS are ones which have the following "constancy": the sequence always repeats the same actions in the same order and each occurrence of a given action changes the parameters by the same amounts. Such an iterated sequence of actions is exemplified by the beat cycle of a heart at steady-state. Effects to be found include the average rate at which blood enters the heart and how increasing that entering blood's pressure affects that rate.

A motivation for finding such effects is that many periodic sub-systems iterate at such a fast rate that the other parts of a system respond only to the behavior of such a sub-system β averaged over many iterations. Then a steady-state model for the entire system would only require a description of β's averaged behavior; β can be modeled as a constant iteration of the same sequence of parameter value changes. In this paper, the sub-system and system combination is the heart and the human circulatory system.

Some other approaches of finding the behaviors of a continually iterating sequence have combined qualitative simulation with cycle detection [1]. For complicated systems (such as the heart), these simulations predict many possible sequences of actions besides the actual sequence. *Aggregation* [9] and *comparative analysis* [10] are useful after isolating the actual sequence.

Another approach [6] takes in a system description that consists of a single set of differential equations that are always applicable. Creating such a description may often be hard, such as when doing so for a heart.

The next two sections summarize the methodology behind AIS. More details are given in [11]. Afterwards is a section giving the results of AIS for a ventricle. The paper ends with a summary.

METHOD (AIS Input): An input description consists of three parts: the parameters which describe the system state, static conditions on those parameters, and the sequence of actions (transformations) that gets iterated.

Parameters are divided by the model-builder into 4 types. The first 3 types are classified by how a parameter behaves as the sequence of actions is iterated:

1. *Constant parameters* do not change in value at all.
2. *Periodic parameters* change in value, but the sequence of values repeats exactly with each sequence iteration.
3. *Accumulating parameters* monotonically change in value with each sequence iteration.

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In general, parameters are represented by symbols. The constant parameter type also includes numbers and arbitrary functions of expressions of constant parameters. The fourth parameter "type" has only one parameter: the rate at which the sequence of actions is iterated. At present, the rate must be expressed as a constant parameter that is a symbol or number.

The second part of the input is a set of static conditions between constant parameters. These conditions are inequalities between numbers and expressions made up of constant parameters. The expressions can have algebraic and the more common transcendental functions. Also permissible are (partial) derivatives of constant parameters which are arbitrary functions.

The last part of the input gives the sequence of actions (transformations) that is iterated. The sequence is partitioned into *phases* so that 1) every part of a sequence is put in exactly one phase, and 2) during each phase, every parameter is either monotonically non-decreasing or non-increasing in value.

For each phase, the input description needs to supply an expression for every parameter that changes in value during that phase. For a periodic parameter, the corresponding expression gives that parameter's value at the end of the phase.[1] For an accumulating parameter, the expression gives the change in that parameter's value each time that phase occurs. An expression may have algebraic and the more common transcendental functions. The expression's arguments can consist of constant parameters, periodic parameters' values at the beginning or end of that phase, and/or accumulating parameters' change in values[2] each time that phase occurs.

The limitations on describing parameter changes are to assure that each occurrence of a phase alters the parameters by the same constant amount. Without some restrictions on how phases alter parameters, it will be hard to impossible for AIS to determine the effects of steadily iterating the sequence of actions.

Each phase also has a list of the conditions that are inequalities between expressions and numbers.

METHOD (AIS Output): AIS takes the input equations, solves them and checks for inconsistencies (using the Bounder system [6]). Bounder is also used to find the numeric bounds mentioned below.

Then, to derive the average rate of change in an accumulating parameter a, AIS locates the change in that parameter's value during each phase of a sequence, adds all those changes together, and then multiplies the sum by the rate of cycle repetition. Next AIS finds numeric bounds on this rate.

After deriving an average rate for a, AIS can observe how that rate would be different if any one constant symbol or function were different. For each symbol, AIS takes the first two (symbolic) derivatives of the rate with respect to that symbol and obtains numeric bounds on those derivatives. Each constant symbol is considered to be independent of all other symbols.

At present, AIS also tries to plot a "qualitative" graph of the rate versus each constant symbol. The first derivative described above provides slope information and the second provides convexity information. AIS makes the assumption that the rate versus constant function is smooth (differentiable). If the second derivative can be both more or less than zero, AIS gives up. Otherwise, depending on how the second derivative is bounded by zero and on how the first derivative's bounds relate to zero, AIS determines which of the following shapes the curve may possibly have: , , , , , , , and/or . For example, if the first derivative is < 0 and the second is $= 0$ (such as when the rate is $-3x$ and the symbol is x), then the curve shape is .

Afterwards, AIS derives the effects of functions having different values by performing some symbolic substitution & subtraction and some expression value bounding to observe how the rates would be different if a function were larger in value.

RESULTS for Ventricle Model: This section describes the current version of AIS running on a model of the beating of the left ventricle.[3] The ventricle is a chamber with two one-way valves: one valve lets in blood from the lungs at a pressure of Pi, and the other valve lets out blood going to the rest of the body at a pressure of Po. The chamber consists of muscle which can either relax or contract. When relaxed (*diastole*), the ventricle volume (V) versus pressure (P) curve ($Vd[P]$) is roughly as shown in Figure 1a (the P and V axes are interchanged from their usual positions). When contracted (*systole*), the V versus P curve ($Vs[P, HR]$) is roughly as shown in Figure 1b. The symbol HR appears because with Vs, V decreases as the rate at which the ventricle contracts and relaxes increases. This rate is known as the heart rate (HR). Figure 1c shows with a dashed line the V versus P path that ventricle takes as it contracts and relaxes

[1] Due to the requirements on choosing phases, a periodic parameter's value at a phase's beginning and the preceding phase's end is the same. And because the sequence iterates, the last phase in the sequence is also deemed to "precede" the 1st phase.

[2] Only the change in value can be referred to because it stays the same from one iteration of the sequence to the next. The actual value changes with each iteration of the sequence.

[3] The description is based on various texts and articles [5, 8] [2, Ch. 13: Mechanisms of Cardiac Contraction and Relaxation] and makes many assumptions. One assumption is that blood is an incompressible fluid without inertia.

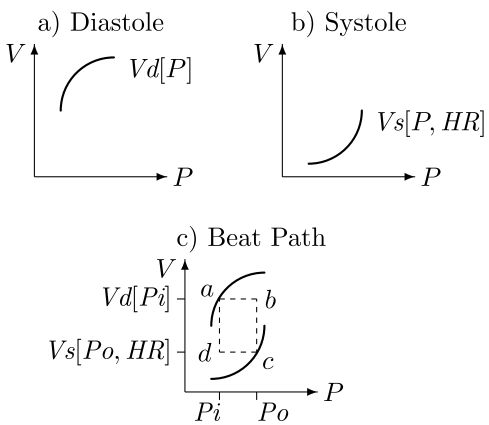

Figure 1: Curves for a Left Ventricle

once (a beat sequence): 1) The ventricle contracts, but no blood moves. So, V stays the same while P increases to Po. Move from a to b in the diagram. 2) The ventricle continues contracting, but now, blood ejects out the output valve. P stays the same while V decreases to $Vs[Po, HR]$. Move from b to c. 3) The ventricle now starts to relax and the blood stops moving. V becomes constant as P decreases to Pi. Go from c to d. 4) The ventricle continues relaxing, but now blood enters from the input valve. P stays the same while V increases to $Vd[Pi]$. Return from d to a.

The input to AIS has the following: The symbol HR gives the rate at which the ventricle beat sequence repeats. The constants are Pi, Po, $Vd[Pi]$ and $Vs[Po, HR]$.[4] The periodic parameters are P and V. The accumulating parameters are the amount of work done by the blood in moving through the ventricle (W), and the amount of blood that has entered the ventricle (Bi) and left the ventricle (Bo). The static conditions on the constants are:

$$Pi < Po, \quad Vd[Pi] > Vs[Po, HR], \quad 0 \leq Vd[Pi],$$
$$0 \leq Vs[Po, HR], \quad 0 < d(Vd[Pi])/d(Pi),$$
$$0 > d^2(Vd[Pi])/d(Pi)^2, \; 0 < \partial(Vs[Po, HR])/\partial(Po),$$
$$0 < \partial^2(Vs[Po, HR])/\partial(Po)^2,$$
$$0 > \partial(Vs[Po, HR])/\partial(HR).$$

Most of the conditions help describe the shape of $Vd[Pi]$ and $Vs[Po, HR]$. There are four phases in the sequence. Each phase has a name, condition(s), and equation(s) for value changes. The notation is: X_b stands for parameter X's value at the beginning of a phase, X_e for the value at the end, and X_c for X's change in value when the phase occurs. In order, the phases are:

[4] Pi and Po are assumed to be constant during the ventricle beats. These assumptions then force $Vd[Pi]$ and $Vs[Po, HR]$ to be also constant during the beats.

1. Isovolumetric Contraction: $0 \leq V, \quad P_e = Po$.
2. Ejection: $0 \leq V_b, \quad 0 \leq V_e, \quad V_e = Vs[Po, HR]$, $W_c = -P \cdot Bo_c, \quad Bo_c = V_b - V_e$.
3. Isovolumetric Relaxation: $0 \leq V, \quad P_e = Pi$.
4. Filling: $0 \leq V_b, \quad 0 \leq V_e, \quad V_e = Vd[Pi]$, $W_c = P \cdot Bi_c, \quad Bi_c = V_e - V_b$.

After solving these phases' equations, AIS discovers the following average rates of change for the accumulating parameters and bounds on those rates:

$$\begin{aligned} dW/dt &= ((Pi \cdot (Vd[Pi] - Vs[Po, HR])) + \\ &\quad (-Po \cdot (Vd[Pi] - Vs[Po, HR]))) \cdot HR \\ d(Bi)/dt &= HR \cdot (Vd[Pi] - Vs[Po, HR]) > 0 \qquad (1) \end{aligned}$$

Also, $d(Bo)/dt = d(Bi)/dt$. One can show that $dW/dt < 0$, but the bounding mechanism misses this.

After finding the rates, AIS derives and bounds the first two derivatives of those rates with respect to each constant symbol, and tries to give the shape of the curve of each rate versus each constant. For $d(Bi)/dt$, its first derivative with respect to HR is > 0, but no bounds are found for the second derivative. No curve shape is deduced. With respect to the constant Pi, the first derivative is > 0 but the second is < 0. Assuming smoothness, AIS deduces a shape for $d(Bi)/dt$ versus Pi. This shape is consistent with the Frank-Starling mechanism [5, p. 212]. With respect to Po, both derivatives are < 0, so the curve has a shape. These results also apply to $d(Bo)/dt$. As a check on the ventricle model, these rate shape results are compared to experimental results. The results for Pi and Po agree [7] in that the corresponding AIS and experiment curves have the same general shapes (signs of the first and second derivatives are the same). For HR, the AIS and experimental results are incomparable because the latter came from intact systems where changing HR can change Pi and Po.

For the rate dW/dt, the only bound AIS can derive is that this rate's second derivative with respect to either Pi or Po is > 0. So for dW/dt versus either Pi and Po, the possible curve shapes are , or .

As for the Vd and Vs functions, AIS deduces that if Vd were larger, both $d(Bi)/dt$ and $d(Bo)/dt$ would be also. But if Vs were larger, these rates would be smaller. These results agree with the description in [8].

When modeling a circulatory system that has been averaged over many heart beats and is in a steady-state, such as done in [3, 4, 8], most of the system's mechanics can be modeled by using direct current electrical circuit analogies, such as [pressure drop]

= [resistance]·[flow]. Too complicated to be modeled this way is the part of the mechanics that relates the *Pi*, *Po*, *HR*, *Vs*, and *Vd* for each ventricle to the rate at which blood flows through that ventricle ($d(Bi)/dt = d(Bo)/dt$). Current modeling efforts either directly use empirically derived relationships (like [7]) or derive the needed equations by hand from an AIS-input-like description (done in [8]). AIS can perform the latter derivations automatically: equation (1) found by AIS for $d(Bi)/dt$ provides the desired relationship for the left ventricle. The right ventricle is similar. Actually, to use this relationship numerically, one must be more specific about the *Vs* and *Vd* curves, such as specifying that $Vd[x] = \log x$.

Other than needing more specific curve shapes, the AIS $d(Bi)/dt$ equation is similar to the equations derived by others. The differences are caused by modeling with slightly different sets of assumptions and beliefs on what relationships exist and are important.

Sagawa [7] experimentally measured the effects of different *Pi* and *Po* values on the flow of blood ($d(Bi)/dt = d(Bo)/dt$) through the left ventricles of dogs. The results were numerically fitted to a relationship (curve) of the following form (translated to the notation used in this paper): $d(Bi)/dt =$

$$K_1 \cdot (Pi - Pi_0) \cdot$$
$$(1 - \exp[-(1 - Po/Po_{max})/(K_2 \cdot (Pi - Pi_0))]),$$

where K_1, Pi_0, Po_{max} and K_2 are constants. This result agrees with AIS's result in that both have a positive first derivative for rate $d(Bi)/dt$ with respect to *Pi* and a negative first and second derivative for that rate with respect to *Po*. The major difference between this result and AIS's result is that this result does not consider the effects of *HR* at all. This omission is not surprising given that *HR*'s effects were never tested in the experiments. Another difference is that with Sagawa, the minimum *Pi* and maximum *Po* needed to keep $d(Bi)/dt$ above zero are given by the simple thresholds Pi_0 and Po_{max} respectively. With the AIS result, the minimum *Pi* is a more complex function of *Po*, and similarly with the maximum *Po* and *Pi*. A possible reason for this difference is that Sagawa determined the effects of *Pi* and *Po* on $d(Bi)/dt$ separately in the experiments and then combined the resulting equations. A third difference is that the effects of *Pi* have been linearized somewhat to simplify the relationship: the actual data in the reference indicates that at large values of *Pi*, $d(Bi)/dt$ starts to increase sublinearly with respect to *Pi*, which agrees with AIS's result rather than the equation fitted in the reference.

Sato and associates [8] have built a simultaneous equation model of the cardiovascular system at steady-state. The model was built to show the effects of heart failure (the heart muscle gets weaker or less elastic) and to help find the optimum drug dosages for heart failure therapies. Among the equations are the ones that give $d(Bi)/dt$ for each ventricle (as before, the $d(Bo)/dt$ equations are equivalent). These equations have the form (translated to the notation used in this paper):

$$d(Bi)/dt = K \cdot \ln(Pi - Pi_0) - H \cdot Po + M,$$

where K, Pi_0, H and M are constants. As mentioned above, these $d(Bi)/dt$ equations were derived by essentially carrying out what AIS does by hand. The shape of the $d(Bi)/dt$ versus *Pi* curve from these equations is , which is the same shape as the one given by the AIS results. A difference between these equations and the ones found by AIS are due to Sato *et al.* having more specific forms for the *Vd* and *Vs* functions:

$$\begin{aligned} Vd[Pi] &= (K \cdot \ln(Pi - Pi_0) + Md)/HR \\ Vs[Po, HR] &= (H \cdot Po - Ms)/HR, \end{aligned}$$

where $M = Md + Ms$, so their equations have those more specific forms in place of the *Vd* and *Vs* functions. Also, their *Vs* function has been linearized with respect to *Po*, so the resulting $d(Bi)/dt$ versus *Po* curve has a shape instead of the shape found by AIS. Another difference is that their versions of the *Vd* and *Vs* functions are proportional to $1/HR$, so their $d(Bi)/dt$ is independent of *HR* instead of increasing with increases in *HR*. In experiments on intact circulatory systems at rest, this independence does hold for a wide range of *HR* values [5, p. 222, 294]. However, the latter source attributes the constancy of $d(Bi)/dt$ as *HR* increases to a decline in *Pi*. In [8], as *HR* increases, *Pi* stays the same while *Vd* and *Vs* decrease.

Another simultaneous equation model of the cardiovascular system at steady-state was built earlier by Greenway [3]. This model was built to show the effects of a multitude of drugs on the cardiovascular system. Greenway uses some of the same relationships given to AIS as input. But a relationship[5] comparable to equation (1) is never explicitly derived. Instead, *Po* is solved out by the addition of the parameters for the arterial capacitance and the body's resistance to blood flow. However, by noting that $d(Bi)/dt = HR \cdot SV$, where *SV* is the stroke volume, one can rearrange Greenway's equations into one comparable to equation (1) to derive (translated to the notation used in this paper) the following: $d(Bi)/dt =$

$$HR \cdot ((Pi + K \cdot F_A) \cdot C_{DV} - Po/E_{max} - V_D),$$

[5] $d(Bi)/dt$ as a function of *HR*, *Pi*, *Po*, *Vd* and *Vs*.

where K, F_A and V_D are constants, and C_{DV} is a "constant" that decreases as Pi gets very large. This equation matches the ones produced by AIS and Sato *et al.* in that all three predict a shape for the $d(Bi)/dt$ versus Pi curve (C_{DV} decreases in size as Pi increases). And like with Sato and associates, this equation has more specific forms in the place of the Vd and Vs functions in AIS's result. In this equation:

$$
\begin{aligned}
Vd[Pi] &= (Pi + K \cdot F_A) \cdot C_{DV} \\
Vs[Po, HR] &= Po/E_{max} + V_D.
\end{aligned}
$$

Also like Sato *et al.* and unlike AIS's result, the Vs function in this equation has been linearized with respect to Po, so the resulting $d(Bi)/dt$ versus Po curve also has a shape. On the other hand, this equation predicts that $d(Bi)/dt$ will increase as HR increases, which is what the AIS result predicts but not Sato *et al.*'s result. A difference between this equation and the ones given by both Sato *et al.* and AIS is that this one has some terms to account for the affects of the atria (the $K \cdot F_A$ term) while the other two do not (they were given models that assume that the atrial effects are either negligible or can be folded into the expressions for the ventricles). Also, unlike the AIS result, Vs in this equation is independent of HR.

This comparison of AIS's results to existing steady-state ventricle models shows that the former are fairly similar to the latter. Furthermore, the existing differences are due to different assumptions being made about the ventricles, not to deficiencies in AIS itself. Two major differences between AIS's results and the existing models are that the latter have more specific relationships for the volume versus pressure curves than the former and that these more specific curves are also more linearized. In addition, in two of the existing ventricular models, the blood flow rate is independent of the heart rate, which is often not true, especially during exercise or other times of increased venous return [2, p. 414] [5, p. 222].

SUMMARY: A program called AIS has been applied to a description of a ventricle. AIS takes in a description of the parameter changes in a heart-beat sequence and finds the symbolic average rate of change for various parameters. These rates form a steady-state model of a ventricle, and this model is similar to existing ones. The differences that exist can be traced back to differing assumptions one can make about a ventricle. A major difference is that two of the existing models have the shortcoming of letting the blood flow rate be independent of the heart rate.

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References

[1] D. G. Bobrow, ed.. *Qualitative Reasoning about Physical Systems.* MIT Press, 1985.

[2] Eugene Braunwald, editor. *Heart Disease.* W. B. Saunders Co., Philadelphia, third edition, 1988.

[3] C. Greenway. Mechanisms and quantitative assessment of drug effects on cardiac output with a new model of the circulation. *Pharmacological Reviews*, 33(4), 1982.

[4] W. Long, *et al.* Using a physiological model for prediction of therapy effects in heart disease. In *Proc. of the Computers in Cardiology Conf.* IEEE, October 1986.

[5] J. Ross. Cardiovascular system. In *Best and Taylor's Physiological Basis of Medical Practice.* Williams & Wilkins, Baltimore, 11th ed., 1985.

[6] E. Sacks. Automatic qualitative analysis of ordinary differential equations using piecewise linear approximations. TR 416, MIT-LCS, 545 Tech. Sq., Cambridge, MA, 02139, 1988.

[7] Kiichi Sagawa. Analysis of the ventricular pumping capacity as a function of input and output pressure loads. In E. Reeve & A. Guyton, editors, *Physical Bases of Circulatory Transport: Regulation and Exchange*, chapter 9. W. B. Sanders Co., Philadephia, 1967.

[8] T. Sato, *et al.* Computer assisted instruction for therapy of heart failure based on simulation of cardiovascular system. In *MEDINFO 86: Proc. of the 5th Conf. on Medical Informatics*, p. 761–765, Washington, Oct. 1986. North-Holland.

[9] D. Weld. The use of aggregation in causal simulation. *Artificial Intelligence*, 30(1):1–34, 1986.

[10] Daniel Weld. Theories of comparative analysis. AI-TR 1035, MIT, AI Laboratory, 545 Technology Square, Cambridge, MA, 02139, May 1988.

[11] A. Yeh. Finding the average rates of change in repetitive behavior. In *Proc. of the National Conf. on Artificial Intelligence.* Am. Assoc. for Artificial Intelligence, 1990.