A Differentiable, Periodic Function for Pulsatile Cardiac Output Based on Heart Rate and Stroke Volume *

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Abstract

Many mathematical models of human hemodynamics, particularly those which describe pressure and flow pulses throughout the circulatory system, require as specified input a modeling function which describes cardiac output in terms of volume per unit time. To be realistic, this cardiac output function should capture, to the greatest extent possible, all relevant features observed in measured physical data. For model analysis purposes, it is also highly desirable to have a model function that is continuous, differentiable, and periodic. This paper addresses both classes of needs by developing such a function. Physically, the present function provides an accurate model for flow into the ascending aorta. It is completely specified by a minimal number of standard input parameters associated with left ventricle dynamics, including heart rate, mean cardiac output, and an estimation of the peak-to-mean flow ratio. Analytically, it can be expressed as a product of two continuous, differentiable and periodic factors. Further, the Fourier expansion of this model function is shown to be a finite Fourier series, and explicit closed-form expressions are given for the non-zero coefficients in this series.

Key words: • Cardiac Output • Pulsatile Flow • Mathematical Model • Differentiable • Periodic • Finite Fourier Series

1 Introduction

Many mathematical studies of human hemodynamics, particularly those which seek to describe pressure and flow pulses throughout the circulatory system, employ cardiac output as a forcing term for the model's governing equations. The function used to model cardiac output in this context must strike a balance between two sometimes competing requirements. For physical realism, the model function should be sufficiently complicated that it captures to the greatest extent possible relevant features of observed physiological data. However, it must also be sufficiently "smooth" and simple that analysis of the overall model is not impractical. In particular, for analysis it is highly desirable for the function that models cardiac output to be continuous, differentiable, and periodic with a well-defined Fourier series expansion. The present work develops a function with these analytical properties which provides an accurate model for flow into the ascending aorta.

Cardiac output data measured in an animal model is displayed in Figure 1. This data trace was obtained at the International Heart Institute of Montana (IHIM) using a Transonic Flowmeter T201 (Transonic Systems Inc., Ithaca, NY, USA) placed on the ascending aorta of an anesthetized sheep. It is this type of data that must be modeled to provide input for many mathematical investigations of human hemodynamics.

Figure 1 illustrates some of the features typical of clinical recordings that complicate derivation of a model function for cardiac output. While the tracing is continuous, the presence of abrupt changes in flow rates suggests that there are points at which the physical relationship between cardiac output and time may not have a unique slope. Abrupt changes may also be noted in flow-meter recordings of cardiac output from humans and animals in Guyton and Hall (2000) [1], Nichols and O'Rourke (1998) [2], and Murgo *et al.* (1980) [3]. While it is not clear that abrupt changes in measured recordings can be smoothed without some effect on predicted hemodynamics, a lack of differentiability at isolated points can be dealt with in a straightforward manner. The curve in Figure 1 can easily be interpolated or approximated by a Fourier series expansion to produce a model function that is differentiable.

A further complication is that living heart dynamics are, at best, nearly periodic. For example, in Figure 1, the peak back-flow at the end of the second ejection period is significantly smaller in

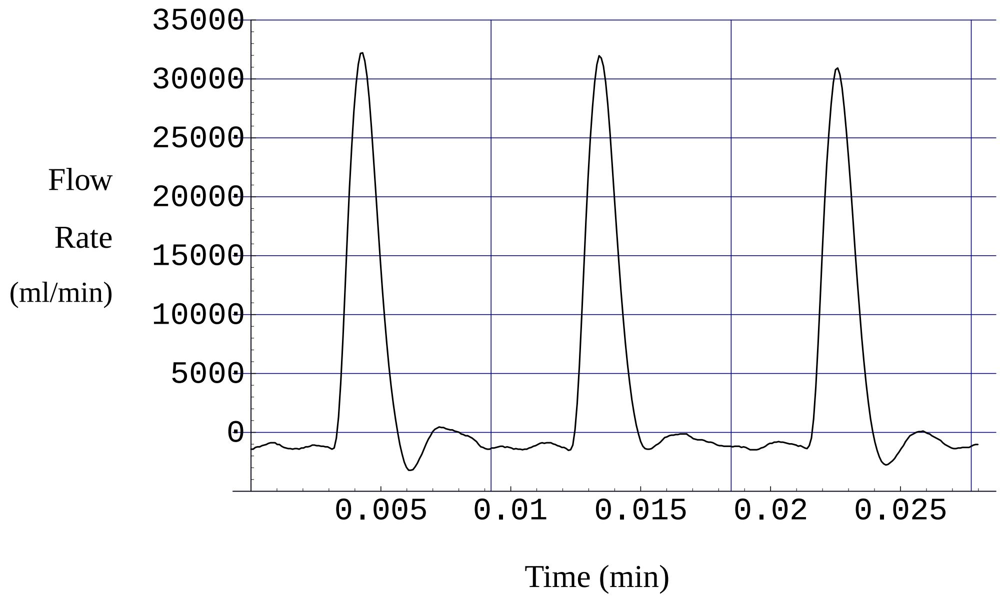

Figure 1: Measured data trace for the cardiac output of a sheep.

magnitude than the preceding or following peak back-flow. However, while this lack of periodicity indicates that the heart itself may be behaving differently in different cycles, a portion of the differences could also be due to the measurement technique, e.g. the temporal resolution of the flow-meter missing the peak back-flow. In either case, this non-periodicity must be resolved prior to any long term simulation that will extend beyond the time interval of a recorded data stream. Improvement may involve smoothly piecing together a typical segment of the recorded data to produce a continuous simulation of the data. In this case, an implicitly periodic model function results. A periodic model function that accurately models a segment of the cardiac output is also an attractive alternative in situations where there is no access to clinical flow data from humans or animals.

The model function developed in this work is continuous, differentiable, periodic, and accurately reflects the mean cardiac output, peak out-flow, peak back-flow, peak-to-mean flow ratio, and the duration of positive and negative flow into the ascending aorta with respect to the cardiac cycle. It has been formulated so that it is based on a minimal amount of preliminary data regarding ventricular dynamics. Specifically, the required calibration data includes the heart rate, either stroke volume or mean cardiac output, and an estimation of the peak-to-mean flow ratio.

For dynamical models in physiology that involve the solution of differential equations, it is particularly beneficial for analysis if the forcing terms in the model can be represented by Fourier expansions. A Fourier series is a method for describing a periodic waveform as the sum of a mean value and associated harmonics based on the underlying period of the oscillations. The general theory and how it applies to differential equations is discussed by Humi and Miller (1992) [4], and Nichols and O'Rourke (1998) [2] have shown how this approach pertains to hemodynamics. In a linearized model for pressure dynamics where the forcing term is a flow function given by a finite Fourier representation, the differential equations may be solved exactly without need for further approximation by assuming a Fourier representation of the solution and determining the coefficients of each harmonic algebraically, as depicted by Lakin *et al.* (1996) [5].

Although a Fourier expansion is usually an infinite series, terminating the series after a finite number of terms usually provides a good approximation of a physiologically-based function for use in a model. Little (1977) [6] suggests that a mean value plus only the first four or five harmonics are necessary to capture 80% of the cardiac pulse form, while Nichols and O'Rourke (1998) [2] suggest that use of the first six harmonics will provide a relatively close approximation. The model function developed in the present work is consistent with these observations. With the calibrated parameters, an excellent approximation to the model function is given by its mean value plus the first five harmonics of its Fourier representation. Indeed, the closed-form expressions derived for the Fourier coefficients of the model function show that its Fourier representation is a finite Fourier series that terminates after the seventh harmonic. Given the degree to which the model function in this case captures the behavior of measured data for the cardiac output, this feature is an unexpected strength that will considerably facilitate the use of this function in models involving differential equations.

The model function developed in this work gives a closed-form expression for the shape of the arterial flow rate (in ml/min) above the valve and is intended to provide an accurate approximation for the cardiac output into the ascending aorta as a source of cardiac forcing in hemodynamic models. In particular, it can provide cardiac forcing for a mathematical model that includes appropriate dynamics to predict the alteration of the waveform as the pulse propagates into the aorta and then into the other large arteries. However, the model function itself was not developed to represent the shape of a propagating flow-rate waveform at sites along these vessels. Measurements of the flow-rate waveform at a number of sites along the aorta indicate that the shape of the pressure pulse changes as the pulse propagates. In particular, the amplitude increases, the front becomes steeper, and the dicrotic notch disappears. While Nichols and O'Rourke (1998) [2] provide graphs for flow-rate waveforms that appear quite similar to the present model function in the ascending aorta and descending aortas, and data in [2] indicates that amplitude and backflow only begin to significantly diminish at and below the abdominal aorta and above the subclavian artery, it is not recommended that the present model function be calibrated with measured data for direct use at sites along the aortas beyond the heart valve.

The section which follows contains the derivation of the present model function for cardiac output and describes its dependence on a small group of physical parameters. Section 3 compares the model function with clinical data. Details of the derivation of the closed forms for the coefficients in the Fourier representation of the model function and an explicit demonstration that this representation is a finite Fourier series are presented in the Appendix.

2 Derivation

The present model function for cardiac output is formulated by defining an interior function which oscillates with the frequency of the heart pulse as well as an envelope function for these interior oscillations, normalizing the product of these two functions, and calibrating the associated model parameters with physical data. The envelope function is defined by

$$Q_1(t,n) = \sin^n(\omega t) \quad \text{where } n \text{ is odd,} \tag{1}$$

while the interior function is of the form

$$Q_2(t,\phi) = \cos(\omega t - \phi) \tag{2}$$

where ω is one half the basic frequency of the heart pulse and ϕ is a phase angle. For $n = 13$ and $\phi = 0$, these two functions are shown in Figure 2. The preliminary flow function $Q_3(t,n,\phi)$ is produced by multiplying the envelope and interior functions to give

$$Q_3(t,n,\phi) = Q_1(t,n) \cdot Q_2(t,\phi). \tag{3}$$

This function is shown in Figure 3 for $n = 13$ and the non-zero phase angle $\phi = \frac{\pi}{10}$.

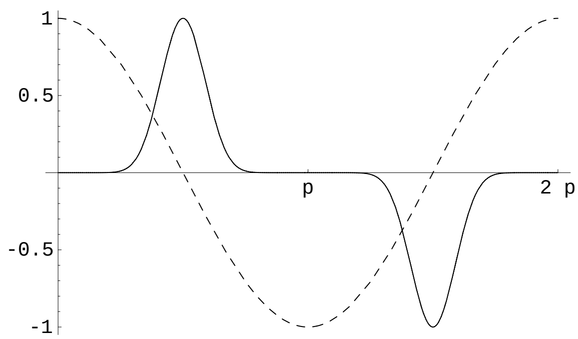

Figure 2: The envelope function $Q_1(t,n)$ (solid curve) and the interior function $Q_2(t,\phi)$ (dashed curve) for $n = 13$ and $\phi = 0$.

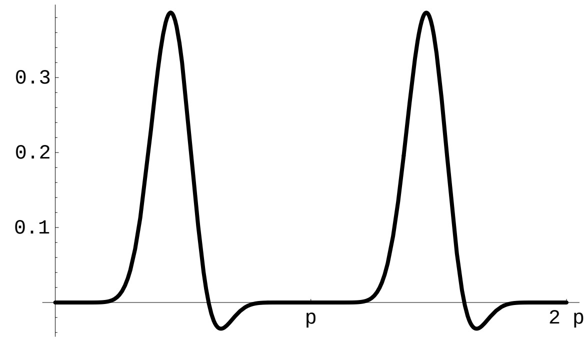

Figure 3: The preliminary flow function $Q_3(t, 13, \dfrac{\pi}{10})$.

Although the shape of Q_3 is clearly similar to the data trace in Figure 1, Q_3 must now be normalized and calibrated to produce an appropriate model function for cardiac output. The set of calibration variables for the present model function includes the mean cardiac output $\overline{Q}$, the heart rate b, and the peak-to-mean flow ratio σ. Typical literature values for these variables are $\overline{Q} = 6900$ ml/min (Murgo *et al.*, 1980 [7]), $b = 76$ beats per minute (Murgo *et al.*, 1980 [7]), and $\sigma = 5.95$ (Murgo *et al.*, 1980 [7]), 6.00 (Gabe *et al.*, 1969 [8]) and 6.25 (Nichols *et al.*, 1977 [9]). Once appropriate values of these calibration variables are chosen, it is now possible to determine the output per stroke $v = \dfrac{\overline{Q}}{b}$, the period $p = \dfrac{1}{b}$ of the cycle, the frequency $\omega = \frac{\pi}{p}$, and the phase angle ϕ.

Determination of the appropriate phase angle ϕ from a given value for the peak-to-mean flow ratio σ and the power n in equation (1) will be considered shortly. Generally, ϕ will lie in the range $0 < \phi \leq \dfrac{\pi}{2}$. If $\phi = 0$, cardiac outflow will equal backflow. There will also be nearly zero backflow if $\phi > \frac{\pi}{6}$.

With the frequency ω defined as above, the preliminary flow function Q_3 will have the desired period p. The model function for cardiac output is now obtained from Q_3 by normalizing the preliminary flow function so that the total outflow over one period is v. This gives $Q(t,n,\phi)$ as

$$Q(t,n,\phi) = \frac{v}{A(n,\phi)} Q_3(t,n,\phi) = \frac{v}{A(n,\phi)} \sin^n(\omega t)\cos(\omega t - \phi) \tag{4}$$

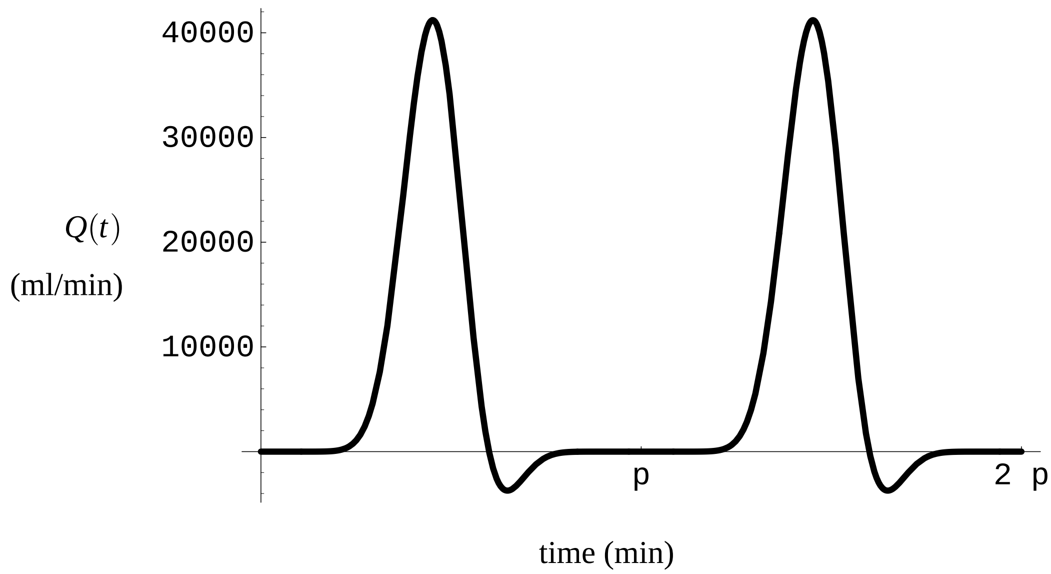

Figure 4: The normalized model flow function $Q(t, 13, \dfrac{\pi}{10})$.

where

$$A(n,\phi) = \int_0^p Q_3(t,n,\phi)\; dt. \tag{5}$$

Recalling that $\omega = \frac{\pi}{p}$, the denominator in (4) may be calculated by noting that

$$\mathscr{A}(n,\phi) = \int_0^\pi \sin^n(t)\cos(t-\phi)\; dt = \frac{\sqrt{\pi}\;\; \Gamma(1+\frac{n}{2})\;\; \sin(\phi)}{\Gamma(\frac{3+n}{2})} \tag{6}$$

where Γ is the Euler gamma function. This now implies that

$$A(n,\phi) = \int_0^p Q_3(t,n,\phi)\; dt = \int_0^{\frac{\pi}{\omega}} \sin^n(\omega t)\cos(\omega t-\phi)\; dt = \frac{\mathscr{A}(n,\phi)}{\omega}. \tag{7}$$

Figure 4 depicts the model function described by equations (4) through (7) for $b = 76$, $\overline{Q} = 6900$, $n = 13$, and $\phi = \frac{\pi}{10}$. The narrowness of the output function is determined by the choice of n. A large n represents a small systole period. Using a value of $n = 13$ results in a systole period approximately 1/3 of the cardiac cycle, consistent with values given by many of the standard texts in physiology.

The value of the phase angle ϕ is determined by the requirement that the peak-to-mean flow ratio equals σ. Thus, ϕ is a solution of the implicit equation

$$\sigma = \frac{Q(t^*,n,\phi)}{\overline{Q}} = \frac{Q(t^*,n,\phi)}{b\; v} \tag{8}$$

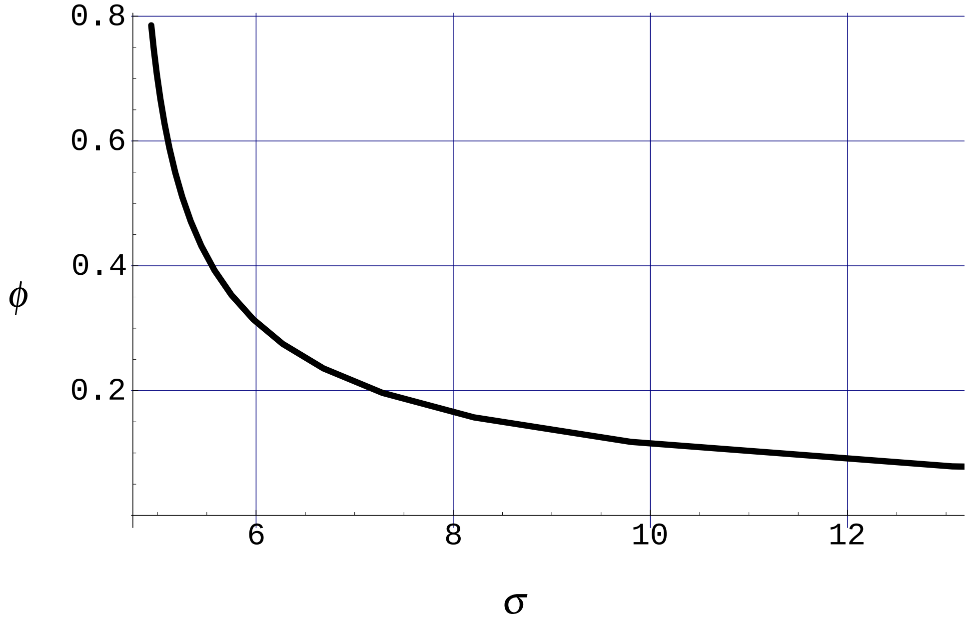

Figure 5: ϕ as a function of the peak-to-mean flow ratio σ for $n = 13$.

where t^* is the value between 0 and p where Q has its maximum value, i.e. $Q > 0$, $\frac{dQ}{dt} = 0$, and $\frac{d^2Q}{dt^2} < 0$ at t^* . In general, equation (8) must be solved numerically. The value of ϕ is independent of both $\overline{Q}$ and b, but it does depend on the choice of n. Figure 5 shows the computed relationship for ϕ as a function of the peak-to-mean flow ratio for $n = 13$. In general a peak-to-mean flow ratio below 5 cannot be associated with a value of ϕ unless n is reduced so that systole takes up a much greater portion of the cardiac cycle.

As noted above, for resting adults, typical literature values for the peak-to-mean flow ratio σ lie in the range 5.95 to 6.25. For a peak-to-mean flow ratio of 6.25 (Nichols *et al.*, 1977 [9]) the corresponding value of ϕ is 0.279 radians. For a peak-to-mean flow ratio of 6.00 (Gabe *et al.*, 1969 [8]) the corresponding value of ϕ is 0.310 radians. For a peak-to-mean flow ratio of 5.95 (Murgo *et al.*, 1980 [7]) the corresponding value of ϕ is 0.318 radians. The model function for cardiac output shown in Figure 4 was calibrated using data from Murgo *et al.* (1980) [7], i.e. , $p = 76$ bpm and $\overline{Q} = 6900$ ml/min, with ϕ approximated by $\frac{\pi}{10}$ and $n = 13$.

Finally, let F_k denote the finite Fourier approximation for the model function $Q(t)$ consisting of a mean value and the first k harmonics. Then, consistent with the observations of Little (1977) [6] and Nichols and O'Rourke (1998) [2], $Q(t)$ may be well-represented by its mean value and first

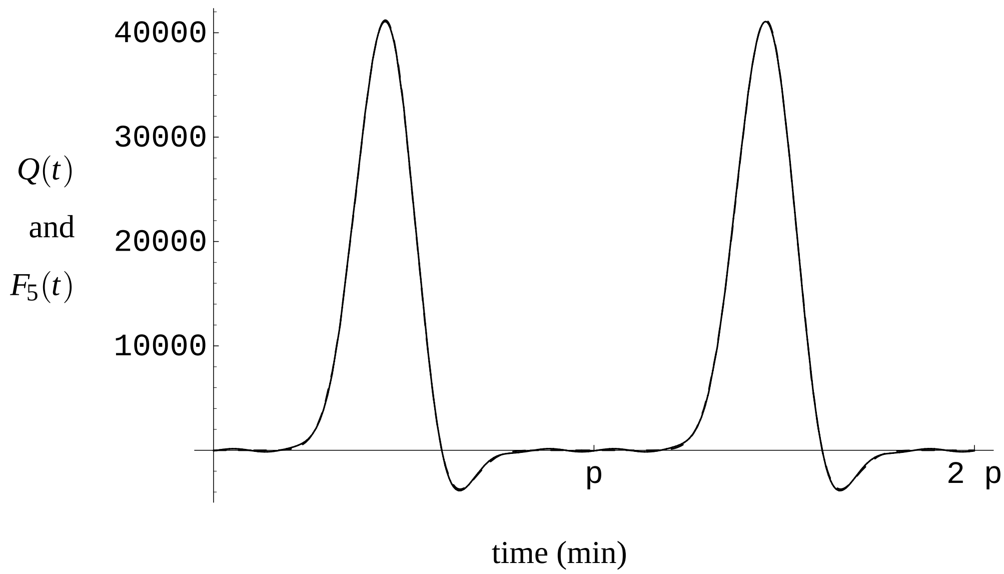

Figure 6: Comparison of the model function $Q(t)$ (dashed) and its five term Fourier approximation $F_5(t)$ (solid) with $n = 13$ and $\phi = \pi/10$.

5 harmonics. Figure 6 shows the approximating finite Fourier series $F_5(t)$ superimposed on the $Q(t)$ from Figure 4. With the exception of some minor oscillations during diastole, the two curves are nearly indistinguishable. Indeed, as is shown in the Appendix, the exact Fourier expansion of $Q(t,n,\phi)$ for general values of n and ϕ is a finite Fourier series which terminates after the first $\frac{n+1}{2}$ harmonics. Consequently, when $n = 13$, by including only two additional harmonics in the Fourier series the present model function for cardiac output can be used as a forcing function without introducing any additional approximation.

3 Results: Comparisons with Clinical Data

The model function $Q(t)$ shown in Figure 4 was calibrated relative to the peak-to mean flow ratio $\sigma = 5.95$ provided by Murgo *et al.* (1980) [7]. The phase angle $\phi \equiv \pi/10$, used for simplicity in generating Figure 4, differs fractionally from the exact value of $\phi = 0.318$ that corresponds to this calibration value. Calculations show that $\phi = \pi/10$ produces a peak-to-mean flow ratio of $\sigma = 5.97$ rather than 5.95. If the actual value of $\phi = 0.318$ is used in equation (4), then the model indeed generates a peak-to-mean flow ratio of 5.95. However, even with this slight variance in

σ, the model produces good agreement with physical data. The peak flow from the model with $\phi = \pi/10$ is calculated at 41,205 ml/min. This is nearly identical to the clinical value for peak flow of 41,040 ml/min quoted by Murgo *et al.* (1980) [7].

The peak back-flow calculated using the Fourier approximation $F_5(t)$ for $Q(t)$ is found to be approximately 3723 ml/min, slightly less than 10% of the peak out-flow. This matches well with data from animal models, including the data from sheep shown in Figure 1 and data collected from monkeys and dogs by Nichols and O'Rourke (1998) [2] and Milnor (1989) [3]. This value also appears to be consistent with the velocity profiles (in distance/time) presented by these same authors for flow in the ascending aorta of humans.

The time intervals for positive and negative flow in the cardiac cycle are very similar in the animal data of Figure 1 and the model function $Q(t)$ in Figure 4. The minor oscillations during diastole observed in the Fourier approximation $F_5(t)$ are also typical of the clinical measurements presented in Guyton and Hall (2000) [1], Nichols and O'Rourke (1998) [2], Milnor (1989) [3], and are also present in the sheep data depicted in Figure 1. An obvious negative flow during diastole can be noted in Figure 1. This feature is not present in either $Q(t)$ or $F_5(t)$, but appears to be an artifact of the measurement technique. In the collection of the data trace in Figure 1, the flow-meter was placed directly above the coronary arteries. Hence, the blood supply to the heart produces a minor negative flow during diastole.

Summary

The goal of this work has been to develop a function that can model cardiac output and capture the relevant features of the human cardiac cycle, yet is sufficiently smooth and simple that it can provide a robust forcing term in mathematical models of human hemodynamics. The functions $Q(t)$ described by equation (4) require only a small set of physical quantities for calibration. The calibrated function then provides a representation for cardiac output which accurately describes mean cardiac output, peak out-flow, peak back-flow, the peak-to-mean flow ratio, and the duration of positive and negative flow within the cardiac cycle. The model function is continuous, differentiable, and periodic, facilitating analysis of the hemodynamic model's governing equations. Its exact Fourier representation is a finite series consisting of a mean value and $\frac{n+1}{2}$ harmonics, but it can be well-approximated by stopping after only five harmonics.

Acknowledgement

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4 Appendix – Derivation of the Fourier Expansion

The Fourier series for the output function $Q(t,n,\phi,\nu,p)$ in (4) on the interval $0 < t < p$ has the form

$$Q(t,n.\phi,\nu,p) = \frac{A_0}{2} + \sum_{k=1}^{\infty}[A_k \cos(2k\omega t) + B_k \sin(2k\omega t)] \quad \text{where} \quad \omega = \frac{\pi}{p} \tag{9}$$

and the Fourier coefficients A_k and B_k are given by the definite integrals

$$A_k = \frac{2}{p}\int_0^p Q(t)\cos(2k\omega t)dt \tag{10}$$

and

$$B_k = \frac{2}{p}\int_0^p Q(t)\sin(2k\omega t)dt. \tag{11}$$

Determining expressions for these two coefficients for a given index k thus requires evaluating the non-standard definite integrals

$$C_k(n,\phi) = \int_0^{\pi} \sin^n(t)\cos(t-\phi)\cos(2kt)dt \tag{12}$$

and

$$S_k(n,\phi) = \int_0^{\pi} \sin^n(t)\cos(t-\phi)\sin(2kt)dt \tag{13}$$

where n is an odd positive integer.

As an initial step in evaluating the integrals in (12) and (13), the trigonometric identity for the cosine of the difference of two angles can be used to give

$$C_k(n,\phi) = \cos(\phi)\int_0^{\pi} \sin^n(t)\cos(t)\cos(2kt)dt + \sin(\phi)\int_0^{\pi} \sin^{n+1}(t)\cos(2kt)dt \tag{14}$$

and

$$S_k(n,\phi) = \cos(\phi)\int_0^{\pi} \sin^n(t)\cos(t)\sin(2kt)dt + \sin(\phi)\int_0^{\pi} sin^{n+1}(t)\sin(2kt)dt. \tag{15}$$

Integrating the first integral in equation (14) by parts using $u = \cos(2kt)$ and $dv = \sin^n(t)\cos(t)dt$ now yields

$$\int_0^{\pi} \sin^n(t)\cos(t)\cos(2kt)dt = \frac{2k}{n+1}\int_0^{\pi} \sin^{n+1}(t)\sin(2kt)\, dt. \tag{16}$$

Similarly, integrating the first integral in equation (15) by parts using $u = \sin(2kt)$ and $dv = sin^n(t)\cos(t)dt$ yields

$$\int_0^{\pi} \sin^n(t)\cos(t)\sin(2kt)dt = \frac{-2k}{n+1}\int_0^{\pi} \sin^{n+1}(t)\cos(2kt)\, dt. \tag{17}$$

Substituting these expressions back into equations (14) and (15) now shows

$$C_k(n,\phi) \;=\; \frac{2k\cos(\phi)}{n+1}\, I_1(n,k) + \sin(\phi)\, I_2(n,k) \tag{18}$$

$$S_k(n,\phi) \;=\; \frac{-2k\cos(\phi)}{n+1}\, I_2(n,k) + \sin(\phi)\, I_1(n,k) \tag{19}$$

where

$$I_1(n,k) \;=\; \int_0^{\pi} \sin^{n+1}(t)\sin(2kt)\,dt \tag{20}$$

$$I_2(n,k) \;=\; \int_0^{\pi} \sin^{n+1}(t)\cos(2kt)\,dt \tag{21}$$

Relations that connect $\sin(2kt)$ and $\cos(2kt)$ to powers of $\sin(t)$ and $\cos(t)$ may be used to extract the explicit dependence on k from these integrals. This approach leads to expressions (Gradshteyn & Ryzhik (1965),§3.6.31 [10]) for the similar integrals

$$\int_0^{\pi} \sin^m(x)\;\sin(2kx)\,dx = 0 \tag{22}$$

and

$$\int_0^{\pi} \sin^{2m}(x)\;\cos(2kx)\,dx = \begin{cases} \pi\,\frac{(-1)^k}{2^{2m}}\binom{2m}{m-k} & \text{for} \quad m \geq k \\ 0 & \text{for} \quad m < k \end{cases}, \tag{23}$$

where $\binom{2m}{m-k}$ is the binomial coefficient and $\binom{q}{r} = \frac{q!}{r!\,(q-r)!}$. Relation (22) with $m = n+1$ can be used in (20). Further, if n is odd, then $n+1$ is even. Thus, setting $2m = n+1$ in equation (23) and using this relation in equation (21) gives

$$I_1(n,k) \;=\; 0 \tag{24}$$

$$I_2(n,k) \;=\; \begin{cases} \pi\,\frac{(-1)^k}{2^{n+1}}\binom{n+1}{\frac{n+1}{2}-k} & \text{for} \quad k \leq \frac{n+1}{2} \\ 0 & \text{for} \quad k > \frac{n+1}{2} \end{cases}. \tag{25}$$

Substituting these values for I_1 and I_2 into equations (18) and (19) now shows

$$C_k(n,\phi) \;=\; \sin(\phi)\, I_2(n,k) \tag{26}$$

$$S_k(n,\phi) \;=\; \frac{-2k\cos(\phi)}{n+1}\, I_2(n,k). \tag{27}$$

Consequently, relations (4) through (7) and the above development give the Fourier coefficients for the model cardiac output function as

$$A_k = \frac{2\,\overline{Q}}{\mathscr{A}(n,\phi)} C_k(n,\phi) = \frac{2\,\overline{Q}\,\Gamma(\frac{3+n}{2})}{\sqrt{\pi}\,\Gamma(1+\frac{n}{2})\,\sin(\phi))}\,C_k(n,\phi) \tag{28}$$

and

$$B_k = \frac{2\,\overline{Q}}{\mathscr{A}(n,\phi)} S_k(n,\phi) = \frac{2\,\overline{Q}\,\Gamma(\frac{3+n}{2})}{\sqrt{\pi}\,\Gamma(1+\frac{n}{2})\,\sin(\phi))}\,S_k(n,\phi). \tag{29}$$

for $k \leq \frac{n+1}{2}$ while $A_k = B_k = 0$ for $k > \frac{n+1}{2}$.

Having explicit closed-form expressions for the Fourier coefficients of $Q(t)$ is clearly a distinct advantage, particularly in a modeling context. In the present case, equations (24) through (29) also explicitly show that the Fourier expansion of the model cardiac output function is, in fact, a finite Fourier series where the number of non-zero terms depends on the odd integer chosen for the parameter n in equation (1). In particular, equations (24) and (25) show that the Fourier expansion will terminate after the mean value plus $\frac{n+1}{2}$ harmonics.

For the parameter values associated with Figure 6 ($n = 13$, $\phi = \frac{\pi}{10}$, $\overline{Q} = 6900$, and $b = 76$), numerical values of the Fourier coefficients for $Q(t)$ are given in Table 1. Even though A_k and B_k vanish identically for $k > 7 = \{(13+1)/2\}$ with this choice of n, the rapid decrease in the magnitudes of the non-zero coefficients in Table 1 as k increases indicates why it is sufficient to use $F_5(t)$ as a finite series approximation for $Q(t)$.

index	A_k	B_k
k = 0	13800.00	0
k = 1	-12075.00	5309.00
k = 2	8050.00	-7078.67
k = 3	-4025.00	5309.00
k = 4	1463.64	-2574.06
k = 5	-365.91	804.40
k = 6	56.30	-148.50
k = 7	-4.02	12.38
k $\geq$ 8	0.00	0.00

Table 1: Numerical values of Fourier coefficients for $n = 13$, $\phi = \frac{\pi}{10}$, $\overline{Q} = 6900$, and $b = 76$