Uncertainty quantification reveals the physical constraints on pumping by peristaltic hearts

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Abstract

Most biological functional systems are complex, and this complexity is a fundamental driver of diversity. Since input parameters interact in complex ways, a holistic understanding of functional systems is key to understanding how natural selection produces diversity. We present uncertainty quantification (UQ) as a quantitative analysis tool on computational models to study the interplay of complex systems and diversity. We investigate peristaltic pumping in a racetrack circulatory system using a computational model and analyze the impact of three input parameters (Womersley number, compression frequency, compression ratio) on flow and the energetic costs of circulation. We employed two models of peristalsis (one that allows elastic interactions between the heart tube and fluid and one that does not), to investigate the role of elastic interactions on model output. A computationally cheaper surrogate of the input parameter space was created with generalized polynomial chaos expansion to save computational resources. Sobol indices were then calculated based the gPC expansion and model output. We found that all flow metrics were highly sensitive to changes in compression ratio and insensitive to Womersley number and compression frequency, consistent across models of peristalsis. Elastic interactions changed the patterns of parameter sensitivity for energetic costs between the two models, revealing that elastic interactions are likely a key physical metric of peristalsis. The UQ analysis created two hypotheses regarding diversity: favoring high flow rates (where compression ratio is large and highly conserved) and minimizing energetic costs (which avoids combinations of high compression ratios, high frequencies, and low Womersley numbers).

Keywords: valveless tubular hearts, immersed boundary method, tunicate, evolution

Introduction

Computational Modeling and Biodiversity

Most biological functional systems are complex. In these systems, variation in morphology and behavior leads to differences in performance at a variety of tasks, influencing individual fitness. Because functional systems are complex, variation in these input parameters do not have linear consequences to functional performance or fitness. Complexity often results in mechanical equivalence, or "many-to-one mapping," in which different combinations of parameters lead to the same or similar values of performance [1, 2]. In these ways, complexity may be a fundamental driver of morphological diversity [1, 3].

Therefore, understanding the connection between morphological and kinematic (input parameters) variation and functional performance (output) is key to understanding the evolution and diversity of complex functional systems [1, 4, 5]. Performance could be highly sensitive to variation in input parameters, meaning small changes in input could lead to disproportionately large changes in performance. On the other hand, performance could be insensitive to variation, leading to little change. Additionally, parameters rarely act independently, so understanding the system as a whole is important.

Computational modeling provides a solution to this problem. Complexity can be examined with models by decoupling parameters. Modeling can create structures and kinematics not naturally possible to isolate and control in biological systems, giving us a greater ability to test hypotheses of function. They can also explore variation by sampling a greater parameter space than what exists naturally in morphological diversity, providing a way to create full performance landscapes. Models can examine many-to-one mapping, genetic drift, and other synergies through output analysis in ways that traditional experimentation and morphometrics cannot [6–9].

However, many computational models are limited by qualitative analysis techniques [e.g. 10]. The difficulty in analyzing multi-parameter, multi-variable computational models curtails our ability to understand the practical implications of changing one parameter over another since qualitative analyses cannot directly compare the relative contribution of parameters to system performance. Typical analyses involve qualitative measures of performance by changing over only one variable (parameter sweeping), which can neglect effects of many-to-one mapping and synergy between parameters.

As a step towards connecting modeling and diversity of form, we apply a quantitative sensitivity analysis through uncertainty quantification (UQ) of a computational fluid dynamic (CFD) model of functional performance. UQ can help resolve these issues and broaden the impact of computational modeling on studies of evolution. Quantitative sensitivity analyses can improve our understanding of: 1) the effects of biologically important variation on the system, and 2) the relative importance of parameters that should be closely assessed. In addition, UQ can be used to make conclusions about the variation in existing morphological diversity (based on sensitivity analyses) and validate and improve models when compared to real measurements.

Uncertainty Quantification

Uncertainty quantification (UQ) studies the uncertainty in the deterministic modeling process of a physical system, and therefore makes it possible to provide more accurate, precise, and reliable model predictions. UQ accomplishes this by analyzing the effects of known variation of input parameters on the model's output.

Uncertainty in a model's input is normally represented using probability measures and uncertainty quantification frameworks that have been well established based on probability theory. Probability distribution functions (PDFs) represent the uncertainty in input parameters based on measured value ranges. Then the uncertainty in the model output can be quantified using its distribution or statistics instead of relying on a single deterministic value.

A common way to obtain this mathematical representation of uncertainty output is by using Monte Carlo (MC) method, which draws samples from a distribution of the deterministic model's input parameters, implements the simulations at the drawn samples, and then provides the corresponding samples (consequently the empirical distribution) of the model output. MC method is easy to implement and straightforward to understand. However, it can be computationally expensive since it may require a large number of full simulations to achieve a desired accuracy due to its slow convergence.

To represent the uncertainty in the output more efficiently than other techniques (i.e. Monte

Carlo), , one may construct a computationally cheaper surrogate of the input parameter space to approximate the full CFD model output. Generalized polynomial chaos (gPC) expansion method is an efficient way to construct this approximation. The gPC method expands the square integrable random functions in terms of orthogonal polynomials of the random variables. Hermite polynomials are first used to represent Gaussian processes based on the homogeneous chaos theory [11], then extended to the Askey scheme with different types of orthogonal polynomials for different random functions/processes [12]. By corresponding the PDF of random variables to the weighting function of the orthogonal polynomials from the Askey scheme, the gPC method reaches fast convergence for smooth functions.

Compared to Monte Carlo method, the gPC method requires far fewer model simulations to reach the same accuracy, and its efficiency can be orders of magnitude higher [13, 14]. Because of the computational demands of CFD modeling, the gPC method represents a huge improvement in our ability to study these complex systems. Therefore, the gPC method is adopted in our current work.

Based on the gPC expansion, global sensitivity analysis using Sobol indices can be implemented [15]. Sensitivity analysis studies the impact of different stochastic input variables on the quantity of interest, which helps to understand the important factors in functional performance and possibly reduce the complexity of the physical system [16]. The Sobol index (SI) is an important sensitive measure based on analysis of variance (ANOVA) decomposition [15, 17, 18]. It is defined as the ratio of the variance in the sub-dimensional problem to the total variance of the full-dimensional problem. The higher the SI ratio is, the more important the set of input parameters in that sub-dimensional space is.

In this study, we begin with a relatively simple model of a complex, biological system as proof of principle: peristaltic pumping in a simple racetrack circulatory system. We use the gPC expansion method to construct a surrogate of the input parameter space of peristaltic pumping and implement sensitivity analysis to determine how input variation in parameters impacts functional performance.

Driving Circulatory Flow with Peristalsis

Driving fluid with contractions of valveless tubes is widespread in animals and serves a variety of purposes, including pumping lymph and other fluids [19–22], driving fluid exchange in respiratory systems [23–26], and driving circulatory systems [27, 28]. Within the Chordata, valveless, tubular pumps (hearts) drive blood flow within circulatory systems in tunicates, cephalochordates, and embryonic vertebrates [28, 29]. In vertebrate embryos, a valveless, tubular heart is the first organ to function and the flow it generates impacts the development of all other organs [30].

Broadly, peristaltic pumps are classified as valveless, tubular pumps. Valveless, tubular pumps in animals are hollow, muscular tubes that produce flow through contractions of the walls. Such contractions reduce the diameter of the tube that drives fluid inside the lumen of the tube. Valveless, tubular pumps can be driven by peristalsis (rhythmic contractions of muscles within the walls of the tube that are propagated down the length of the tube) or Liebau pumping (where contractions at certain points on the tube travel in passive waves dictated by the material properties of the tube itself) [31, 32]. The direction of the flow inside the tube is controlled only by aspects of the pumping kinematics (e.g. the direction of the contracting wave), not by any physical means (e.g. one-way valves).

There is some debate as to whether the pumping mechanisms of tubular, valveless hearts in animals best fits with the definition of peristalsis or Liebau pumping (for a recent discussion, see [31, 33]). Recent work has suggested that peristalsis or some peristalsis-like mechanism bests fits the available data and theoretical understanding of each mechanism [32, 34–36]. Here, we simplify the situation by focusing exclusively on peristaltic pumping by tubular hearts.

Despite their simple outward appearance, pumping by peristaltic hearts is a complicated functional system. This mechanical system has a variety of parameters, including:

- *Morphology of the heart.* Parameters associated with morphology which possibly influence flow include the tube's relative resting diameter and length [32], the mechanical properties of the myocardium and surrounding structures [34, 37, 38], and the resistivity of the circulatory system. These morphological features show variation among animals within the Chordata [27, 28], but the role of such features in functional performance is not well understood.

- *Kinematics of tube compression.* The frequency of compressions can have a complicated, non-linear relationship with flow speeds [32, 39]. Compression ratio, the percent occlusion of the tube, can affect flow speeds in non-linear ways [32, 37]. Feedback between the action potentials and mechanical properties of the myocardium also impact flow features [34, 35, 37].

- *Size and scaling.* Fluid flow undergoes a critical transition between small sizes and speeds, where the viscosity of fluid damps out unsteady effects, to large sizes and speeds, where inertia is relatively more influential to the character of fluid flow than viscosity and unsteady effects are important. For pulsatile flow, a ratio between inertial and viscous forces is called the Womersley number Wo help to define the transition (at $Wo \approx 1$):

$$Wo = d\sqrt{\frac{f\rho}{\mu}}, \tag{1}$$

where f is the frequency of the pulse, d is the resting diameter of the tube, μ is fluid dynamic viscosity, and ρ is fluid density. Embryonic vertebrates possess circulatory systems that grow through this transitional range with tubular hearts that transform into chambered hearts with valves during development. Other groups of animals explore size through evolutionary time, retaining a tubular heart throughout their lives.

Performance of hearts can be assessed in several ways. Volume flow rate may be an important performance output, as flow produced by the heart transports key nutrients and waste [40]. However, this fluid transport comes at a cost, as work must be done by the myocardium to force viscous fluid through a resistive circulatory system. It is likely that performance trade-offs exist in this system, and these trade offs are inevitably mediated by variation in input parameters.

Analytical models and approximations of peristalsis have been used to describe many aspects of peristaltic transport, including the average flow as a function of the wave speed and contraction amplitude [41–44]. These models typically assume contraction amplitudes are small, inertia is negligible, there is no flow in the radial direction, and/or any effects of elastic storage are negligible. Furthermore, metrics such as the cost of transport and the amount of mixing are not readily obtainable. Few, if any, studies have examined this flow in the context of resistive circulatory systems, a key evolutionary development in vertebrate circulation.

Computational modeling of flow produced by valveless, tubular hearts has improved our understanding of biological pumps, since many of the assumptions made in analytical models are not required and metrics such as the cost of transport and mixing dynamics can be readily quantified. These models have also helped clarify the mechanism of pumping of hearts such as those of vertebrate embryos [32–36], as well as our understanding of other important developmental morphological changes including the development of cardiac cushions, the presence of trabeculae, and the presence of blood cells [33, 45–47].

Study Objectives

In the current work, we implement UQ techniques to explore peristalsis in a circulatory system driven by peristalsis using the immerse boundary method, a computational fluid dynamics (CFD) model. We present two mechanisms of peristalsis in this work: peristalsis driven by opposing sine waves and peristalsis driven by opposing sharp, Gaussian peaks. Our aims are to (1) demonstrate the effectiveness of the UQ method for assessing the impact of input variation on a functional system modeled computationally; (2) assess the impacts of elastic interactions using two models of peristalsis; and (3) use the results and sensitivity analyses to make prediction of morphology and kinematic combinations that make especially effective pumps.

We constructed two-dimensional models of peristalsis in a heart tube which drive flow through a closed racetrack circulatory system. We then constructed a surrogate to replace the full input space of the CFD model using gPC expansion. Using sensitivity analysis, we explore the interactive effects on performance outputs (flow in the system, work, and cost of transport) of morphology, kinematics, and size through three input parameters: the dimensionless Womersley number Wo, compression ratio of the tube CR, and compression frequency f with constant wave speed. Based on these results, we make conclusions about the diversity of these parameters in extant groups of animals with peristaltically driven circulatory flow.

Materials and Methods

Computational Model of Peristalsis

Immersed Boundary Method

The models of peristalsis (presented in [32]) were implemented using the immersed boundary method (IBM) and with the C++ library Immersed Boundary with Adaptive Mesh Refinement (IBAMR) [48]. IBM allows a direct, numerical simulation of the Navier-Stokes equations of fluid flow interacting with flexible boundaries moving either freely or with preferred motion. IBAMR incorporates adaptive mesh refinement, which allows the Eulerian grid on which the Navier-Stokes equations are solved to be rougher away from the boundaries and finer close to boundaries to save computational resources (Fig. 1). Additional details of the IBM are located in the supplemental information to this paper.

The circulatory model consisted of a racetrack that was effectively made rigid through the use of tether points with an inner lumen, two straight sections connected by two curved regions, and a moving region at the bottom of the racetrack, representing the heart tube that moved with a preferred motion (see Figs. 1 and 2). The racetrack design was used to stay consistent with past designs for easier comparison to other analyses [32, 34, 38, 49].

The elastic region had a 4:1 length:diameter ratio with the inner 3/4 of the tube length consisting of points tethered to target points, which drove the preferred peristaltic motion (Fig. 1). The rest of the racetrack were tethered to target points which remained still throughout the simulations. Target point stiffness (k_{targ}) was chosen as 30.0 to remain consistent with the model in [32]. Table 1 summarizes parameter values of the models.

The force equation used to drive peristalsis in the model is:

$$\mathbf{f}(r,t) = k_{targ}(\mathbf{Y}(r,t) - \mathbf{X}(r,t)) \tag{2}$$

where $\mathbf{Y}(r,t)$ is the preferred position of the boundary. Only the preferred motion of the boundary in each model of peristalsis differed. Each model of driving peristalsis is described below.

Opposing sine-wave peristalsis model

The sine-wave model defines the motion of the boundary as two opposing sine waves:

$$y_{top,bot} = R_{top,bot} \pm A\sin(2\pi f t + 2\pi c x_t) \tag{3}$$

where f is the compression frequency, c is the compression-wave speed (held constant throughout the study at a non-dimensional speed of 3.0), A is the amplitude of the contraction, and x_t is the horizontal distance from the beginning of the prescribed motion section. The compression ratio gives the percent occlusion and is equal to $2A$. The peristaltic waves created by Eq. 3 propagated from left to right, therefore driving fluid flow counter-clockwise in the lumen of the racetrack. The stiffness of the boundary and target point stiffness ($k_{targ} = 30.0$) allowed for very little independent elastic motion in the peristaltic region of the tube.

For additional details on the opposing sine-wave peristalsis model, see [32].

Opposing Gaussian-peak peristalsis model

The pinch model defines the motion of the boundary as two sharp, Gaussian peaks, with the remainder of the boundary being free to flex with little restriction by the target points:

$$y_{top,bot} = R_{top,bot} \pm A\exp((-0.5(x_t - \gamma)/\sigma)^2) \tag{4}$$

Where γ is the position of the pinch on the x-axis of the center of the tube and σ is the width of the pinch. The pinch was advanced by altering γ depending on the time step of the simulation. For the points within the region of the Gaussian wave, the target point stiffness was chosen to be extremely stiff ($k_{targ} = 2500$) so that the target points adhered closely to the programmed waveform. Outside the peak region, the target points were tethered very loosely ($k_{targ} = 0.7$) with a spring constant about two orders of magnitude stiffer to allow for elastic interactions between fluid and the heart tube.

Analysis of Flow and Pressure Fields

Several calculations of non-dimensional fluid flow and pressure were made for each simulation in VisIt 2.9.1 [50] and R [51], similar to the analyses in [32]. Positive flow speeds indicate fluid motion in the counter-clockwise direction in the racetrack, the same direction as the traveling peristaltic wave. All values presented in the analysis are dimensionless, and more information about nondimensionalizing values can be found in the supplemental information to this paper.

At each time step in the simulation, the magnitude of dimensionless fluid velocity was recorded and then spatially averaged across each area indicated in Fig. 2A to find $|\mathbf{u}'|$ across four rigid sections of the racetrack: the upper position, a connecting vertical position, the inflow region (vena cava) and outflow region (aorta). The mean speeds $|\mathbf{u}'|$ were then temporally averaged to find the average flow speed across each simulation (U_{avg}). The maximum value of flow speed, $\mathbf{u'_m}$, was also taken at each time step, and the maximum of these in a simulation represents the peak flow speed (U_{peak}). Fig. 3A and B reports $|\mathbf{u}'|$, $\mathbf{u'_m}$, U_{avg}, and U_{peak} for a sample simulation.

Non-dimensional pressure was also recorded for each time step of the simulation and spatially averaged at each time step near the inflow area (vena cava position) and the outflow area (aorta position) of the elastic region (see Fig. 2A for positions). For each simulation, the vena cava and aorta positions' pressures were averaged temporally to find p_{in} and p_{out}, respectively. (See Fig. 3C and D for sample simulation.) Each inflow pressure was subtracted from the outflow pressure at each time step to find their difference, and these differences were averaged over simulation time to find ΔP.

Volume flow rate was calculated using the velocity profile across the upper position of the racetrack for each simulation. At each time step during a simulation, the velocities were sampled across the diameter of the tube to create a velocity profile across the tube. Each value was then used to calculate the volume of a concentric ring of fluid that passed through the tube during the time step based on the velocity at that position in the tube. These rings were then summed to find the volume flow rate at that time step, then these volume flow rates were averaged temporally to find the average volume flow rate of the simulation, Q.

Cost of Transport

The cost of transport was computed in the following manner:

$$COT = \frac{1}{N}\frac{1}{U_{avg}}\sum_{i=1}^{N}\left|F_i^{tube}\right|\left|U_i^{tube}\right|, \tag{5}$$

where N is the total number of time points analyzed, U_{avg} is the mean flow speed, $\left|F_i^{tube}\right|$ is the average force magnitude at each Lagrangian point in the peristaltic tube at time point i, and $|U_i^{tube}|$ is the average peristaltic contraction velocity magnitude of the tube at time point i. The contraction velocity was computed using two successive timepoints' Lagrangian positions, e.g.,

$$\left|U_{j,i}^{tube}\right| = \frac{||\mathbf{X}_{j,i}^{tube} - \mathbf{X}_{j,i-1}^{tube}||}{\Delta t}, \tag{6}$$

where Δt is the time between successive time points, not time-steps, and $\mathbf{X}_{j,i}^{tube}$ is the position of the j^{th} Lagrangian point along the peristaltic contraction region of the tube at the i^{th} time point. The quantity $\left|U_i^{tube}\right|$ is the average of all of the magnitude of velocities along the tube at time point i.

Parameter Selection

Parameters of interest were selected based on potential effects on functional performance, the ability of the parameter to vary in animals with valveless, tubular hearts, and their representation in the model. Compression ratio (CR), a measure of the percent occlusion of the tube during a compression event, varied from 0.4 (reduction of 40% of the tube's diameter) to 0.95 (reduction of 95% of the tube's diameter). Compression ratio was varied by changing the amplitude (A) of Eq. 3. Compression frequency (f) of Eq. 3 reflects the number of compression events per unit time and was varied between 0.5 and 2.0, reflective of a range of values seen in tunicates and other animals with valveless, tubular hearts. Compression wave speed was chosen to be constant and decoupled from compression wave frequency because this is reflective of the speed at which muscle can contract, which typically does not vary in individual animals at a constant temperature. Finally, Womersley number (Wo) was allowed to vary between 0.1 and 10 by changing ν in Eq. 1, which reflects roughly the fluid regime of many tubular hearts.

All other model parameters were kept constant throughout the study. A list of these parameters and their values in this study can be found in Table 1. The target point stiffness k'_{targ}, bending stiffness k'_{bend}, and the spring constant k' were kept constant because in the previous study these were found not to meaningfully affect flow in this model given that the heart walls move with preferred kinematics [32]. The length and resting diameter of the contracting region of the tube, although they can vary in animals, were chosen to remain constant for convenience in comparing this analysis to the previous study.

Generalized Polynomial Chaos Expansion

In the current work, we assume that uncertainty is due to the inherent random nature of the system and consequently can be represented using random parameters of interest: compression ratio CR, compression frequency f, and Womersley number Wo. With the assumption of the uniform distributions for the uncertain inputs, generalized Polynomial Chaos (gPC) expansion method is implemented for stochastic uncertainty propagation to quantify the uncertainty in the model output (e.g., U_{avg}, U_{peak}). The exact model output $q(\boldsymbol{\xi})$ (with $\boldsymbol{\xi}$ denoting the input) is approximated by a gPC expansion as

$$q_p(\boldsymbol{\xi}) = \sum_{i=0}^{N-1} q_i \Phi_i(\boldsymbol{\xi}), \tag{7}$$

Where p is the polynomial order, Φ_is are the Legendre polynomials, q_is are gPC coefficients to be determined in the algorithm. N is the number of terms. Details for gPC expansion for a similar CFD model is detailed in Waldrop et al. [7] and more details are located in the supplementary information to this paper.

The three input parameters with uniform distributions have the ranges: Womersley number $Wo = [0.1, 10]$, Compression ratio $CR = [0.4, 0.95]$, Compression frequency $f = [0.5, 2]$. The parameter space based on gPC expansion consisted of $M = 681$ combinations of the three parameters which were run as separate simulations. To determine the gPC coefficients, we run 681 full simulations and extract a set of quantities of interest corresponding to the inputs as $\{\boldsymbol{\xi}^{(j)}, q^{(j)}\}_{j=1}^{M}$, then solve the Least Squares problems for the coefficient vector $\mathbf{q} = [q_1, q_2, \ldots, q_N]$ as

$$\mathbf{q} = \arg\min_{\tilde{\mathbf{q}}} \| \sum_{i=0}^{N-1} \tilde{q}_i \Phi_i(\boldsymbol{\xi}) - q(\boldsymbol{\xi}) \|_2 \tag{8}$$

where $\tilde{\mathbf{q}} = [\tilde{q}_0, \tilde{q}_1, \ldots, \tilde{q}_N]$ is an arbitrary gPC coefficient vector which converges to the desired coefficient vector $\mathbf{q}$ through the minimization. With the gPC expansion of the model output q_p, one can efficiently obtain the empirical distribution or statistics for the quantify of interest and consequently quantify its uncertainty.

Sensitivity Analysis

As mentioned earlier, sensitivity analysis studies the impact of different stochastic input variables on the quantity of interest, which helps to understand the important factors in functional performance and possibly reduce the complexity of the physical system. In the current work, we consider global sensitivity analysis and calculate the Sobol indices [15, 17, 18]. Here are the formulas.

We first introduce ANOVA (analysis of variance) decomposition of a function $q(\boldsymbol{\xi})$, based on which the Sobol sensitivity indices are calculated [17, 18]

$$q(\boldsymbol{\xi}) = q_0 + \sum_i q_i(\xi_i) + \sum_{i<j} q_{ij}(\xi_i, \xi_j) + \ldots + q_{1,\ldots,n}(\xi_1, \xi_2, \ldots, \xi_n). \tag{9}$$

where

$$\int q(\boldsymbol{\xi}) d\boldsymbol{\xi} = q_0, \qquad \int q(\boldsymbol{\xi}) \Pi_{k\neq i} d\xi_k = q_0 + q_i(\xi_i),$$
$$\int q(\boldsymbol{\xi}) \Pi_{k\neq i,j} d\xi_k = q_0 + q_i(\xi_i) + q_j(\xi_j) + q_{i,j}(\xi_i, \xi_j),$$

and so on.

From Eq. 9, the so called variance of each sub-function $q_{i_1,i_2,\ldots,i_r}$ is defined as

$$D_{i_1,i_2,\ldots,i_r} = \int q^2_{i_1,i_2,\ldots,i_r} d\xi_{i_1,i_2,\ldots,i_r},$$

and the total variance is

$$D = \int q^2(\boldsymbol{\xi}) d\boldsymbol{\xi} - q_0^2 = \sum_{r=1}^{n} \sum_{i_1<\ldots<i_r}^{n} D_{i_1,i_2,\ldots,i_r}. \tag{10}$$

Following that, the global sensitivity indices are calculated as the ratio of variances

$$S_{i_1,i_2,\ldots,i_r} = D_{i_1,i_2,\ldots,i_r}/D. \tag{11}$$

Take $r = 1$, the first order Sobol indices are

$$S_i = D_i/D, \qquad , i = 1, \ldots, n, \tag{12}$$

which measure the sensitivity of the quantity of interest to each single variable ξ_i alone.

We calculate the Sobol indices more efficiently based on gPC expansion in the current work [16]. Additional details of Sobol index calculations can be found in the supplemental information to this paper. With the calculated Sobol indices (SI), one can analyze how sensitive the quantity of interest is with respect to the variation of individual parameters and their interactions, and also rank the importance of the uncertain parameters. SI's across a single output value will sum to 1, and higher values of SI indicate greater sensitivity of the output value to the specific parameter or combination of parameters. Fig. 4 gives a graphical overview of the UQ and SA analysis problem from raw data to SI for volume flow rate Q for the sine-wave model.

Data Accessibility Statement

The immersed boundary code for this study can be found publicly at https://github.com/lindsaywaldrop/peri-gPC-git for the opposing sine wave model and at https://github.com/lindsaywaldrop/peri-gPC-pinch for the opposing Gaussian peak model. The raw simulation data produced by the code can be found at the following locations: Visualization Data for Pinch model: [52, 53]; Hierarchy Data for Pinch model: [54, 55]; Visualization Data for Sine-wave model: [56, 57]; and Hierarchy Data for Sine-wave model: [58, 59]. The analyzed data of this paper can be found publicly at [60] the pinch model and [61] for the sine-wave model.

Results

Flow produced by peristalsis models

Across flow output measurements, there were large ranges of values indicating a substantial potential for differential performance with input parameter variation. Average dimensionless flow speeds (U_{avg}) at all positions in the circulatory system ranged between 0.0816 and 3.30 diameters per beat for sine-wave and 0.0840 and 2.45 diameters per beat for pinch model, 36- and 29-fold ranges in speeds between simulations, respectively. Dimensionless volume flow rates (Q) also ranged broadly, from 0.144 to 5.52 for the sine-wave (Fig. 4) and 0.180 and 4.22 for the pinch model (Fig. 5 top row), representing 24- and 38-fold differences between simulations, respectively.

All measures of flow speed (U_{avg}, U_{peak}, Q) are highly sensitive to compression ratio CR; higher values of CR lead to higher flow rates (Fig. 6A, B, D, respectively). Sobol indices (Fig. 6A, B) illustrate the outsized impact of CR to flow speed at all positions on the racetrack.

In contrast, measures of flow speed were largely insensitive to the other parameters in this study, Wo and f (Fig. 6A, B, D). Note that although it may be surprising that the frequency did not affect the flow speed, recall that the wave speed is held constant such that the change in frequency simply affects the shape of the waveform. All three measures have very small SI's for Wo (SI's < 0.05) and slightly higher values for f (SI's < 0.10). Flow speeds were generally insensitive to the influence of parameter interactions (SI's < 0.05).

There were few differences in flow produced by the two pumping mechanisms (sine-wave and pinch peristalsis). Values of volume flow rates Q were slightly higher for sine-wave peristalsis (maximum of 5.52) versus pinch peristalsis (maximum of 4.22). Peak flow speeds (U_{peak}) were up to 20% higher for sine-wave peristalsis than pinch peristalsis, but the differences in average flow speeds (U_{avg}) were small between the two mechanisms.

Pressures, Work and Cost of Transport produced by peristalsis models

In addition to flow metrics, the large ranges in pressures, cost of transport, and work metrics existed across simulations. Dimensionless pressures (p_{in}, p_{out}) varied in the circulatory system from -1140 to 1370 for both mechanisms, with values of non-dimensional instant difference of pressure ΔP varying between 10.4 and 6,000 (Fig. 7). Cost of transport varied between 1.25×10^5 to 2.67×10^6 for sine-wave peristalsis and 4.37×10^5 to 6.87×10^6 for pinch peristalsis, representing 21- and 16-fold differences, respectively. The range for work done to produce flow were similar; 183 to 3,550 for the sine-wave model, and 930 to 19,000 for the pinch model, both representing a 20-fold range.

Non-dimensional pressure within the system was very sensitive to f at both the vena cava and aorta positions with CR playing a smaller role (Fig. 6C). Pressures tended to increase with increasing values of f for both peristalsis mechanisms. Pressures were generally insensitive to Wo, with the exception of the aorta pressure p_{out} (SI: 0.093).

The pressure differential between the aorta and vena cava positions ΔP reflects the pressure required to drive fluid through the resistive racetrack circulatory system. ΔP is highly sensitive to Wo (SI sine-wave: 0.77, SI pinch: 0.39), with CR showing a small influence for sine-wave peristalsis (SI sine-wave: 0.097) and a much larger sensitivity for pinch peristalsis (SI pinch: 0.39). For very small values of Wo, values ΔP are very high, indicating the increased resistance to flow due to size and/or viscosity. Other parameters and interactions are less influential on ΔP (SI's < 0.06).

Similar to pressure, the cost of transport of fluid within the racetrack circulatory system is strongly influenced by f and Wo (Fig. 9). Cost of transport was sensitive to f (SI sine: 0.54, SI pinch: 0.59) and Wo (SI sine: 0.26, SI pinch: 0.23) and not sensitive to CR (SI sine: 0.05, SI pinch: 0.04). Cost of transport was somewhat sensitive to the interaction between Wo and f (SI sine: 0.14, SI pinch: 0.13), and not sensitive to other interactions (SIs < 0.01).

Work done on the tube during pumping diverged substantially between the two models in terms of sensitivity. For the sine-wave model of peristalsis, work was sensitive to f (SI: 0.39) and CR (SI: 0.34) and to a lesser extent Wo (SI: 0.18), with no sensitivity for interactions (SI's < 0.05). For the pinch peristalsis model, work was sensitive to Wo (SI: 0.41) and to a lesser extent CR (SI: 0.15) and the interaction between Wo and f (SI: 0.10). Work was not sensitive to other interactions (SIs < 0.04).

Discussion

Flow and costs associated with peristalsis

In this study, we used uncertainty quantification on a computational model of fluid flow to quantify the sensitivity of performance to three parameters associated with peristaltic pumps: Womersley number Wo (eq. 1), compression ratio CR, and compression frequency f. Performance was quantified as various aspects of fluid flow (average flow speed, peak flow speed, volume flow rate, pressures) and the energetic costs of driving flow (work and cost of transport).

CR stands out as the dominating feature of driving flow in peristaltic systems. Our results are consistent with previous research on experimental and analytical studies of peristalsis [44, 62, 63]. These studies found that back flow from low CR reduced the flow speed downstream of a pump driving flow with sine-wave peristalsis. The result from our analysis shows that the sensitivity of flow to compression ratio is independent of f, size and scaling (through Wo), and the mechanism of peristalsis used to drive flow.

Non-dimensional measures of flow speed were insensitive to the other parameters chosen for this study (Fig. 6A, B, D). f is commonly understood to be highly influential to flow speeds and volume flow rates in systems with tubular hearts [39], except when compression frequency is decoupled from the speed of the compression wave [32]. This study employs the latter, since compression-wave speed and frequency are not explicitly coupled in animal hearts.

Driving flow is costly for animals. Higher relative viscosity of the fluid (lower Wo) and higher pumping frequencies (f) within the circulatory system require the contracting region of the tube to generate larger pressure differentials. The cost of transport (COT) and work done on the contracting regions of the tube are a reflection of the energy required to drive fluid through the racetrack circulatory system. COT and work were both sensitive to f and Wo and the interaction of these two parameters, attaining their highest values at combinations of low Wo and high f (Fig. 5 bottom row).

The two mechanisms of peristalsis used to drive flow in each models represent peristalsis where elastic interactions were allowed (pinch model) and not allowed (sine-wave peristalsis). Although these models produces extremely similar flows, their COT and work deviated sharply (Fig. 8). Sensitivity analysis between the two models show that elastic interactions fundamentally alter the effects of input parameters (Fig. 9), indicating that material properties may be a fundamental feature of assessing the costs of peristaltic transport.

Predictions of Morphological Diversity based on Parameter Sensitivity

Evolution has tested the performance of biological functional systems over millions of years. Evolution has had ample time to explore the combined parameter space of many functional systems, and its diversity, in part, reflects its own sensitivity analysis of the functional system on that space [3, 7, 64].

If a model of a biological system is accurate in the most important components of the functional system, UQ analysis can be used in two ways to better understand that system. First, the output surrogate provides a way to estimate the performance landscape associated with the system, identifying possible adaptive peaks and valleys and providing output estimates for animals that fall within the space. Second, a sensitivity analysis on the model can inform our understanding of biological diversity and the mechanistic function of the system.

For our models of peristalsis, UQ analyses create two hypotheses of selective pressures: flow speeds (U_{avg}, U_{peak}, Q) (Fig. 5 top row) and measures of energetic costs (ΔP, COT, Work) (Fig. 5 bottom row).

1. **Flow is highly sensitive to CR.** The highest flow speeds, and therefore the best performance, occur at high compression ratios. CR should then be both of large values to maximize flow (Fig. 5 top row) and highly constrained, exhibiting very low variability amongst species compared to other morphological or kinematic measurements. In contrast, flow was insensitive to changes in Wo, a proxy for body size (eq. 1), and f. Wide variation in these parameters does little to affect flow speeds, therefore these parameters should exhibit a wide variation in extant animals.

2. **Energetic costs exhibit a complicated relationship with input parameters.** Costs incurred by the contracting section of tube were sensitive to both CR, Wo, and f and their interactions in different combinations (Figs. 6 & 9). Low values of Wo and high f lead to extreme values of work and cost of transport (Figs. 8 and 5 bottom row), and high values of CR lead to very high values of work. Since energetic measures have a complicated relationship with each parameter, it is likely that patterns of variation would also be complicated, although parameter combinations mostly likely avoid areas that combine high f, low Wo, and very high or very low CR.

Ultimately, these predictions can be tested using the distribution of animals with peristaltic pumps in the three-dimensional input space of the model.

Model Limitations and Improvements

There are several potentially influential parameters that our study did not take into consideration, two prominent ones being the length to width ratio of the heart tube and the resistivity of the attached circulatory system. These are likely influential for the characteristics of fluid flow produced by peristalsis, considering long-wave approximations [32, 42, 44, 63]. Additionally, increases in pressure may be required to drive fluid through a more resistive circulatory system. Since pressure is sensitive to compression frequency and the pressure differential is highly sensitive to Wo, these parameters may have substantial interactive effects when a more resistive circulatory system is added.

In addition, fluid flow and cost of transport are not the only performance outputs that could be the focus natural selection. Circulatory flow is a means for mass transport, and circulatory structures also rely on diffusion, mass transport is likely not captured by fluid motion alone. Addition of a diffusion component to the model to quantify the effects of flow on mass transport will further clarify the performance of the system.

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Tables

Parameter	Sine-wave	Pinch	
		Guassian peak region	Non-peak regions
Maximum time step (dt)	1×10^{-5}	1×10^{-5}	1×10^{-5}
Minimum Eulerian spatial step (dx)	0.020	0.020	0.020
Lagrangian spatial step (ds)	9.8×10^{-5}	9.8×10^{-5}	9.8×10^{-5}
Refinement ratio	4:1	4:1	4:1
Domain size	10×10	10×10	10×10
Resting diameter of tube (d)	1.0	1.0	1.0
Length of pumping section (L_{tube})	4.0	4.0	4.0
Wave speed	3.0	3.0	3.0
Spring constant (k')	30	510	6.8
Target point stiffness (k_{targ})	30	2500	0.68
Bending stiffness (k'_{bend})	0.30	0.8	0.8
Contraction Frequency (f)**	$0.5 - 2.0$	$0.5 - 2.0$	$0.5 - 2.0$
Womersley number (Wo)**	$0.1 - 10$	$0.1 - 10$	$0.1 - 10$
Compression ratio (CR)**	$0.4 - 0.95$	$0.4 - 0.95$	$0.4 - 0.95$

Table 1: Summary table of parameters used for the numerical simulations, all values are non-dimensional. ** indicates input parameters of interest.

Figures

Figure 1: **Racetrack model showing adaptive meshing.** Full racetrack showing the R_{top} and R_{bot} used to generate prescribed motion in red and adaptive meshing of domain: roughest mesh (32×32 grid) in dark blue, intermediate mesh (16×16 grid) in teal, and finest mesh (8×8 grid) in gold, black box highlights inset a. Inset a: close up of region including part of the tube and racetrack showing meshes, black box highlights inset b. Inset b: close up of tube showing relation of finest mesh and target points of the racetrack.

Figure 2: **Racetrack model of peristalsis with two pumping mechanisms.** Initial conditions (A) and snapshots of a sample simulation ($CR = 0.675,\ Wo = 0.35,\ f = 1.25$) for two peristalsis mechanisms: opposing sine waves (B) and pinch (C,D). Background color is magnitude of velocity, scale on right top indicates values in non-dimensional speed for B and scale on right bottom indicates values of non-dimensional speed for C and D. Black dots are passive markers that indicate the pumping region in A. A: Initial conditions of racetrack circulatory system with prescribed motion peristalsis. Transparent boxes indicate areas where measurements were recorded. B: sine-wave simulation at $t' = 0.5$, C: pinch simulation at $t' = 0.5$, D: simulation at $t' = 1.5$. Arrows indicted direction of wave propagation.

Figure 3: **Non-dimensional speeds and pressures during a sample simulation (**$CR = 0.675,\ Wo = 0.35,\ f = 1.25$**) for both pumping models.** A: Non-dimensional flow speeds for sine-wave peristalsis, B: non-dimensional flow speeds for pinch peristalsis, non-dimensional pressure for C: sine-wave peristalsis and D: pinch peristalsis at two positions (aorta, vena cava). U_{avg} (solid, black lines) and U_{peak} (solid, red lines) and the mean of U_{avg} (dashed, black line) and the maximum value of U_{peak} (dashed, red lines) were for the simulation used in the sensitivity analysis. Pressure is reported at two positions: vena cava (VC, solid, blue lines) and aorta (solid, orange lines). The mean of pressure values (p_{in}, p_{out}) used in the sensitivity analysis are dashed for each position.

Figure 4 *(following page)*: **UQ study of volume flow rate (**Q**) and three parameters.** Top: Simulation results showing volume flow rate as color on a 3D plot of parameter space (Womersley number (Wo), Compression Frequency (f), and Compression ratio (CR)) for sine-wave model of peristalsis; left - values from the 681 simulation set created by generalized polynomial chaos; and right - surrogate produced from UQ analysis. Gray slices at $CR = 0.7$ and $f = 1.25$ are represented as 2D graphs in the middle row, left and right respectively. Bottom: Sobol indices calculated for volume flow rate of the sine-wave model for each parameter and their interactions. Color bar indicates scale in non-dimensional units of volume flow rate for all panels.

Figure 5: **Non-dimensional volume flow rate (**Q**, top) and cost of transport (**COT**, bottom).** Left: three-dimensional surrogates; middle: two-dimensional slice of each surrogate at $Wo = 1$; right: two-dimensional slice of each surrogate at $Wo = 9$.

Figure 6: **Sobol Indices for flow and three parameters.** Womersley number Wo, Compression ratio CR, and Compression frequency f and their interactions at four positions in the tube (Aorta=gray, Connecting = gold, Upper = blue, Vena Cava = green) for mean non-dimensional speed U_{avg} (A), peak non-dimensional speed U_{peak} (B), pressure p_{in} , p_{out} (C), and volume flow rate Q (D). Darker colors represent sine-wave peristalsis values and lighter colors indicate pinch peristalsis values.

Figure 7: **Non-dimensional values of change in pressure (ΔP) for two positions in the circulatory system and two pumping mechanisms.** Non-dimensional pressure versus compression frequency (Wo) and compression ratio (CR) for two pumping mechanisms (A: sine-wave peristalsis; B: pinch peristalsis). Color enhances the z-axis values.

Figure 8: **Non-dimensional cost of transport and work.** Cost of transport (A, B) and work (C, D) values calculated from each simulation against relevant input parameters for the sine-wave (A, C) and pinch (B, D) models of peristalsis. Color highlights values of z-axis.

Figure 9: **Sobol Indices for energetic costs.** Sobol indices against three parameters (Womersley number Wo, Compression ratio CR, and Compression frequency f) and their interactions at across the contracting region of the tube for cost of transport (COT) and work for each pumping mechanism.