WILLIAM HOLMES RESEARCH STATEMENT

1. Introduction

My dissertation work thus far has broadly been in applied mathematics and scientific computing with a specialization in cochlear mechanics/hearing sciences. This work has been performed under the supervision of Jacob Rubinstein and Michael Jolly. On a more specific level this work has dealt with the development of a fully 3D, non-local model of the passive (linear) cochlea and a numerical procedure for solving it. The purpose of this work is two fold. First, we seek to better understand the physical mechanisms which produce the salient features of the passive cochlea. Second, we seek to provide a computational platform onto which models of the active (possibly non-linear) cochlea can be built. To this end, this work has involved a healthy dose of both asymptotic analysis and time domain solutions of a coupled system of PDE's using hybrid finite difference/spectral methods.

In addition to my dissertation work, I have also had the opportunity to work on models of salivary function as an NSF funded visitor with James Sneyd at the University of Auckland. This work was performed in the context of a larger (NIH) project run jointly at the University of Auckland and the medical school at the University of Rochester. The overarching goal of this work is to better understand the signaling and control mechanisms in salivary production with the hope of understanding the cause of salivary dysfunction. My work on this project dealt primarily with extending an existing point cell ODE based model [2] to a more realistic spatially heterogeneous model in a standard reaction diffusion formulation.

2. A Cochlear Model

A brief discussion of hearing function is in order. The mammalian ear is broken into three parts (outer, middle, inner). We concentrate our discussion on the inner ear as this is the focal point of our work. The inner ear consists primarily of the cochlea, the organ which converts sound pressure waves into neural signals. The basis of hearing function is that sound pressure waves create vibrations of the eardrum which through mechanical linkage causes excitation of the cochlea. At a basic level, the cochlea can be viewed as a long, thin, coiled tube consisting of three fluid filled cavities and a complex micro-structure which is forced at one end by the input from the eardrum [10]. Separating these cavities is a cochlear partition comprised of the basilar membrane among other structures. Vibrations emanating from the eardrum cause pressure fluctuations in the cochlear fluid which in turn force the cochlear partition. It is the motion of the cochlear partition which is of interest as this is known to be the neural transducer of the cochlea [1]. This is the focal point of our work.

We work with a simplified form of the cochlea consisting of a single fluid filled rectangular cavity depicted in Figure 1. We assume the eardrum forces the system at the $x = 0$ face and that the cochlear partition fills the $z = 0$ face. For further discussion of the simplifications

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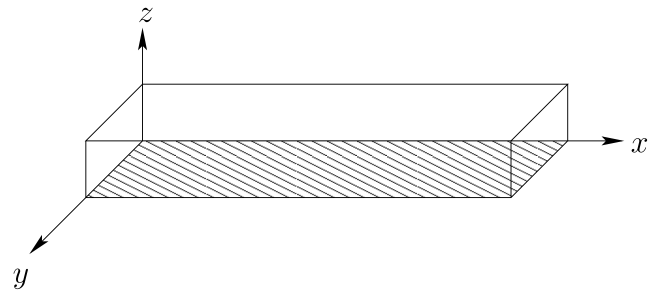

FIGURE 1. The geometrically simplified single cavity cochlea. The forcing is understood to occur at the $x = 0$ boundary and the cochlear partition fills the $z = 0$ face.

and assumptions applied see [3]. The two systems which must be modeled are the fluid and the cochlear partition. We take our fluid to be linear, incompressible, irrotational, and inviscid. For further discussion of the validity of these assumptions see [3], [7], [6], [4]. The cochlear partition is taken to be a thin elastic plate. This is a novel approach as most historical models ([9] for example) are of transmission line type which consider the partition to be a system of uncoupled oscillators.

A summary of our model equations is

$$\triangle P(x, y, z, t) = 0 \tag{2.1}$$

$$r(x)w_t(x, y, t) + \triangle(k(x)\triangle w(x, y, t)) = -2P(x, y, 0, t) \tag{2.2}$$

where P, w is the plate displacement, and r, k are the friction and stiffness coefficients of the plate. We take clamped plate boundary conditions for the plate system as it is rigidly connected. For further discussion of thin plates and boundary conditions see [5]. We take boundary conditions for our fluid pressure to be

$$P(0, y, z, t) = f(t), \qquad P(L_x, y, z, t) = 0, \tag{2.3}$$

$$P_y(x, 0, z, t) = 0 \qquad P_y(x, L_y, z, t) = 0, \tag{2.4}$$

$$P_z(x, y, 0, t) = -\rho w_{tt}(x, y, t), \qquad P_z(x, y, L_z, t) = 0 \tag{2.5}$$

where f is the forcing supplied by the eardrum. Note the lack of spatial dependence of the forcing. This piston like treatment is not strictly necessary. However it simplifies the resulting model and there is little reason to think the spatial profile of the forcing effects the function of the system, particularly so in light of the large aspect ratio of the cochlea.

At this juncture we can reformulate the model in a way that will make the numerical solution simpler. Recall that we are primarily interested in observing the motion of the plate. As can be seen in (2.5) and (2.2), the plate only sees the pressure and its normal derivative at the $z = 0$ face. So it is unnecessary to carry the full fluid throughout the problem. Instead we analytically eliminate the pressure and end up with a non-local equation for the plate's deflection w. (2.5) can be reformulated as

$$\rho w_{tt}(x, y, t) = \bar{T}P(x, y, 0, t) \tag{2.6}$$

where $\bar{T}$ is a Dirichlet to Neumann (DtN) operator. This operator can be defined through the use of a separation of variables argument for (2.1), (2.3)-(2.4). Considering (2.2) and (2.6) together and eliminating pressure between them yields a wave type equation for w

$$2\rho w_{tt} - \bar{T}(r(x)w_t + \triangle(k(x)\triangle w) + 2q(x,t)) = 0 \tag{2.7}$$

where ρ is the fluid density and

$$q(x,t) = f(t)\frac{x - L_x}{L_x} \tag{2.8}$$

is a remnant of the DtN reformulation.

This reformulation is interesting independent of the numerical simplification it provides. The prevailing theory of the function of the cochlea is that the partition motion exhibits wave like characteristics [1]. In the model development, we specifically neglected the inertia of the plate (2.2). It is clear from (2.7) that the inertia of the fluid provides the necessary resonance structure for the partition to exhibit wave like characteristics. This is not surprising, however it is the most apparent manifestation we have seen to date.

3. Numerical Implementation

The close relation of (2.7) to the wave equation suggests a forward Euler scheme inspired by the decomposition

$$w_t = v \tag{3.1}$$

$$v_t = \frac{1}{2\rho}\bar{T}\left(r(x)w_t + \triangle(k(x)\triangle w + 2q(x,t))\right). \tag{3.2}$$

For simplicity, we supply initial conditions of the form $w(x,y,0)$ and $w_t(x,y,0) = v(x,y,0)$. In light of (2.2), it would be sufficient to supply $P(x,y,0)$ in place of $w_t(x,y,0)$. There are two primary computational difficulties associated with any computational procedure dealing with (2.7). First, one has to be able to compute the non-constant bi-harmonic operator $\triangle(k(x)\triangle w)$ efficiently. This is dealt with using an augment form of a compact second order discretization of $\triangle^2$ developed by Stephenson [11].

The second computational difficulty associated with this model is the DtN operator $\bar{T}$. The primary feature of this operator which makes it useful is that it can be computed efficiently with the use of a FFT through the decomposition

$$\bar{T} = \mathcal{F}^{-1}D\mathcal{F} \tag{3.3}$$

where $\mathcal{F}$ is a Fourier transform, and D is a linearly unbounded, negative definite, diagonal weighting operator. The primary downside is its unboundedness. A simplified analog of our system is the canonical rod equation (aka Euler-Bernoulli equation). A forward Euler scheme for this fourth order equation exhibits a quadratic stability condition [12]. The presence of $\bar{T}$ in (2.7) essentially adds an extra derivative and leads to the experimentally observed stability condition

$$\Delta t \propto \frac{\Delta x^{\frac{5}{2}}}{max(k)}. \tag{3.4}$$

Unfortunately this is a difficulty that cannot be avoided under any reasonable circumstances due to (2.5). With these tools to deal with computational difficulties, the resulting numerical scheme has been experimentally shown to be second order convergent with respect to the spatial mesh size.

4. Asymptotic Reduction

Given the difficulties associated with studying a fully 3D cochlear model, most past work has dealt with models of the transmission line type [9], [13]. These models have been helpful in understanding many features of the cochlea. However the asymptotic arguments which lead to this class of models leave something to be desired. As such, we seek to provide a more rigorous asymptotic reduction of the full model based on physically motivated assumptions. For purposes of asymptotics we will return to the full formulation of the model given by (2.1), (2.2), (2.3)-(2.5).

It is experimentally observed that the human cochlear partition has an aspect ratio in the range of 70×1 [1]. As such we shall assume the cochlear box seen in Figure 1 has dimensions $1 \times \epsilon \times \epsilon$ where ϵ is assumed to be small. We now make the scalings

$$x^* = \frac{x}{\epsilon} \qquad y^* = \frac{y}{\epsilon} \tag{4.1}$$

$$z^* = \frac{z}{\epsilon} \qquad t^* = \frac{t}{\epsilon} \tag{4.2}$$

along with the following scalings for the dependent variables

$$f = \frac{f^*}{\epsilon} \qquad P = \frac{P^*}{\epsilon} \qquad w = \epsilon^2 w^*. \tag{4.3}$$

The scalings (4.3) are inspired by the clamped plate boundary conditions. Recall that our plate is now thin and rigidly clamped. Such a plate will require a large forcing to induce substantial motion. In addition, it is known that the deflection of the plate is very small in relation to the depth of the cochlea. The time scaling is not well motivated. It turns out to be necessary to maintain dominant balances in the asymptotics. However it is this scaling that will provide insight into the relationship between the form and function of cochlea.

After making these substitutions and drooping the $*$, the Laplace problem for P becomes

$$\epsilon^2 P_{xx} + P_{yy} + P_{zz} = 0 \qquad P_z(x, y, 0, t) = -\epsilon^2 \rho w_{tt} \tag{4.4}$$

$$P(0, y, z, t) = f(t) \qquad P(1, y, z, t) = 0 \tag{4.5}$$

Suppose now that $P = P^0 + \epsilon^2 P^1$. Then it can be determined from the $O(1)$ terms that

$$P^0 = P^0(x, t) \qquad P^0(0, t) = f(t) \qquad P^0(1, t) = 0. \tag{4.6}$$

It can also be determined from the $O(\epsilon^2)$ terms that

$$P^0_{xx}(x, t) = -\rho \int_0^1 w_{tt}(x, y, t)\, dy. \tag{4.7}$$

Let us now move to the elasticity equation. Upon making the above mentioned substitutions and dropping the $*$, the meaningful terms that persist are

$$r(x)\epsilon w_t + \frac{1}{\epsilon^2}k(x)w_{yyyy} = -\frac{1}{\epsilon}2P^0. \tag{4.8}$$

Let us now make the following scalings for k and r

$$k = \epsilon k^* \qquad\qquad r = \frac{r^*}{\epsilon^2}. \tag{4.9}$$

Upon substituting and dropping the $*$, the dominant balance becomes

$$r(x)w_t(x,y,t) + k(x)w_{yyyy}(x,y,t) = -2P^0(x,t). \tag{4.10}$$

The reduced model given by (4.7), (4.8) is similar to a transmission line type model with the exception that it has maintained the lateral (y) direction.

5. Results

A successful model of the cochlea must at the very least exhibit a place principle. That is, it must exhibit the dispersive relation where by low input frequencies produce maximum response near the apical ($x = 1$) end of the partition and high frequencies produce maximum response near the basel ($x = 0$) end of the partition. Simulations of the full and reduced models show that both indeed exhibit this place principal. Evidence of this can be seen in 2. These are plots of maximal deflection as a function of input forcing frequency. This set of plots pertains to the full model (2.7) at a value of $\epsilon = \frac{1}{16}$. This is the smallest aspect ratio we can consider at the moment due computational limitations. Similar results have been seen in simulations of the reduced model.

Recall from the discussion of asymptotics that we we had to make an unfounded scaling of time in order for the asymptotics to work. This inspired us to use forcing functions of the form

$$f(t) = \frac{1}{\epsilon}\sin(2\pi\frac{\Omega}{\epsilon}) \tag{5.1}$$

as inputs to the full model. We found that, in line with the asymptotics, the location of the point of maximum deflection was independent of ϵ. This to some extent validates the previously described asymptotic model. Additionally this suggests that the aspect ratio of the cochlea plays an integral role its function. Consider two values of ϵ differing by a factor of 2 and a single value of Ω. It has been observed that the location of the point of maximum deflection and the general structure of the solution at that value of Ω is the same for both values of ϵ. The striking feature of this is that these two cases are acting at different real frequencies. This suggests that the size of the effective hearing band, which we will denote $|HB|$, is directly related to the inverse of the aspect ratio

$$|HB| \propto \frac{1}{\epsilon}. \tag{5.2}$$

In order to test this we have found data relating to five mammals with comparably sized hearing bands. Table:1 shows that for these five mammals, the cochlear aspect ratios are in the same range. The fact that all five species have aspect ratios in the same range lends some credence to this statement. When considering this data, keep in mind that the stated aspect

	$\|HB\|$ (Octaves)	BM Length (mm)	BM Apex Width (μm)	ϵ
Gerbil	10	12.1	250	.0207
Chinchilla	9	18.5	310	.0168
Cat	10	25.8	420	.0163
Guinea Pig	10	18.5	245	.0132
Human	9+	33.5	504	.0150

TABLE 1. This table represents hearing band and aspect ratio data for five mammal species. Aspect ratio data was taken directly from [8].

ratios relate to the width of the basillar membrane at the apex only. The actual cochlear partition has a tapered shape where our model assumes a constant width partition.

6. A 3D Radially Symmetric Salivary Model

This work was primarily an extension of [2]. The work of Gin et.al. produced a 0-D ODE based model of a single parotid acinar cell. It posited that an agonist induced Ca^{2+} oscillation induces the flow of Na^+, Cl^-, and K^+ through the cellular membrane creating an osmotic pressure. These ionic flows are controlled by highly non-linear ion channels/pumps/exchangers. My work on this project dealt with the extension of this 0-D model to a more realistic 3-D radially symmetric model in a reaction diffusion formulation.

The primary conclusion of this work is that the given model assumptions are not sufficient to produce a well posed problem in a spatially heterogeneous environment. The original 0-D model, while successful, brushes over one of the primary features of the system. The basic function of a salivary cell is to produce an ion driven fluid flow. As such, much of the interesting dynamics of the system are going to involve boundary flows through the cell membrane. This is something that a 0-D model cannot account for as all flows are treated as reaction terms in a ODE based model.

When moving to a reaction diffusion formulation, many of the terms which were originally considered as reaction terms are embedded into the boundary conditions of the new model. In fact, the resulting model turns out to be almost entirely boundary condition dominated. The remaining reaction terms of interest are essentially linear. This turns out to be problematic. Due to the structure of the physiological system, the given model naturally uses Neumann boundary conditions. The pure diffusion problem with Neumann boundary conditions suffers from a degeneracy problem where solutions can only be determined up to a constant. The addition of reaction terms typically anchors a reaction diffusion system providing uniqueness of solutions. However, this is not occurring in this problem. The reaction terms are in no way related to the primary dynamics of the system, and as such they are not providing an anchor for the model. The non-linear dynamics are embedded into the boundary conditions of the system, however it appears that this is not sufficient to provide a unique solution either.

This degeneracy in the system is numerically observed. Consider the numerical solutions of the heat equation with homogeneous Neumann boundary conditions. Numerical solutions eventually move to what could be called a floating steady state. That is the resulting solution is constant across the domain, but this constant is slowly changing with time due to discretization errors. This phenomenon is seen in our salivary system. The numerical solution is quickly moving to a solution which resembles what the steady state solution of the system should look like. However this solution is slowly shifting by a constant in time. This float is due to the degeneracy inherent in the structure of the system. As such, the model assumptions are insufficient to produce a unique solution. Unfortunately this visit ended before we had a chance to explore ways to correct this.

7. Future Work

In relation to the cochlear modeling work, there are a few directions which can and should be explored. First and foremost, the existing numerical method while sufficient, needs to be improved. At the moment, the given numerical procedure cannot handle parameters in physiological ranges. As such, while qualitative information can be gained from this model, it is not yet able to provide quantitative information. One room for improvement is in improving the treatment of the bi-harmonic operator. The current treatment requires the mesh spacing in the x and y directions be the same. This produces a computational bottleneck at large aspect ratios. Additionally, an implicit solution method with improved stability properties should be produced.

On a more phenomenological level, there are a few model simplifications which could possibly be unwound. This would involve looking at more realistic cochlear geometries as well as more realistic models of the cochlear fluid. In addition, one of the stated goals of this work is to provide a platform on which models of the active cochlea can be built. The model and computational procedure are now at a point where it is reasonable to start looking at the effect of including various active components. There is much to be done with this work that would be of interest to both the mathematical and audiological communities.

Beyond my dissertation work, I am broadly interested in the application of mathematics to interesting problems arising from natural and life sciences. In the past I have had the opportunity to dabble in problems relating to ecology, climate sciences, cellular physiology, and fundamental physics. All have been fascinating problems. As such, in addition to my current work, I would like the opportunity to explore new directions. This would hopefully involve building relationships with other scientific departments. There is a wealth of interesting questions to be explored. Such relationships provide access to these questions as well as the physical and experimental expertise necessary to make headway on them.

My short term research goals are two fold. First, I would like to extend my dissertation work. As stated there are a few plausible directions to take this work. Secondly, I would like to explore other directions which build upon and extend the skill set developed over the past few years. This would involve both the development of interesting scientific question(s) and the mathematical tools necessary to approach them. I have numerous particular interests and as such would base any future directions on the expertise of the faculty and departments I would have access to.

References

[1] G. V. Bekesy. *Experiments in Hearing*. McGraw-Hill, New York, 1960.

[2] E. Gin, E. J. Crampin, D. A. Brown, T. J. Shuttleworth, D. I. Yule, and J. Sneyd. A mathematical model of fluid secretion from a parotid acinar cell. *Journal of Theoretical Biology*, (248):64–80, 2007.

[3] J. Keener and J. Sneyd. *Mathematical Physiology*. Springer, 2001.

[4] J. B. Keller and J. C. Neu. Asymptotic analysis of a viscous cochlear model. *J. Acoust. Soc. Am.*, 77(6):2107–2110, 1985.

[5] L. Landau and E. Lifshitz. *Theory of Elasticity*, volume 7 of *Course of Theoretical Physics*. Elsevier, third edition, 1986.

[6] R. J. Leveque, C. S. Peskin, and P. D. Lax. Solution of a two-dimensional cochlea model with fluid viscosity. *SIAM J. Appl. Math*, 48(1):191–213, 1988.

[7] J. Lighthill. Energy flow in the cochlea. *Journal of Fluid Mechanics*, 106:149–213, 1981.

[8] D. Manoussaki, R. S. Chadwick, D. R. Ketten, J. Arruda, E. K. Dimitriadis, and J. T. O'Malley. The influence of cochlear shape on low-frequency hearing. *PNAS*, 105(16):6162–6166, 2008.

[9] L. C. Peterson and B. P. Bogert. A dynamical theory of the cochlea. *J. Acoust. Soc. Am.*, 22(3):369–381, 1950.

[10] J. O. Pickles. *An Introduction to the Physiology of Hearing*. Emerald, third edition, 2008.

[11] J. W. Stephenson. Single cell discretizations of order two and four for biharmonic problems. *Journal of Computational Physics*, (55):65–80, 1984.

[12] J. C. Strickwerda. *Finite Difference Schemes and Partial Differential Equations*. SIAM, second edition, 2004.

[13] J. Xin, Y. Qi, and L. Deng. Time domain computation of a nonlinear nonlocal cochlear model with applications to multitone interaction in hearing. *Comm. Math Sci.*, 1(2):211–227, 2003.

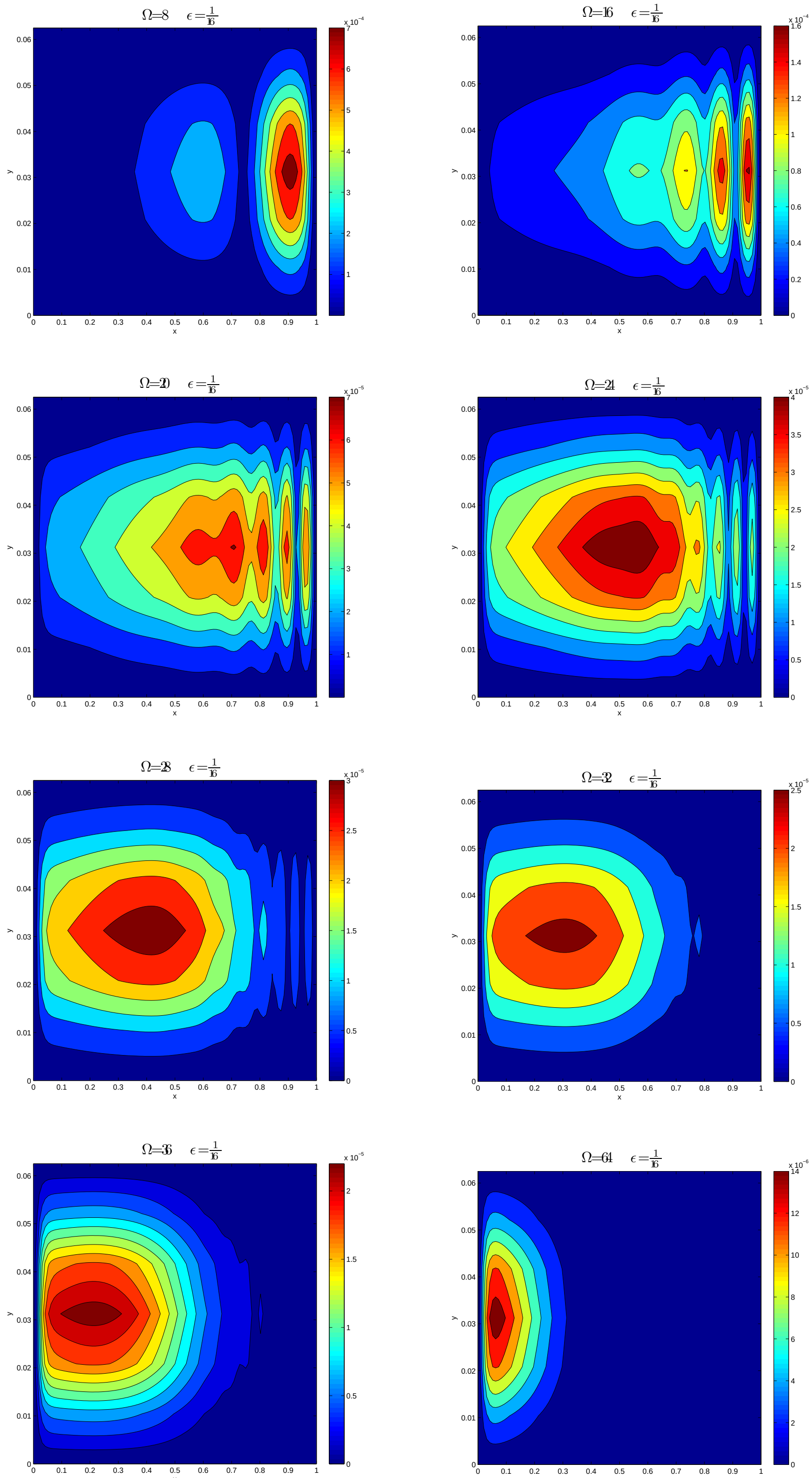

FIGURE 2. These figures represent maximal deflection as a function of location for the cochlear problem with $\epsilon = \frac{1}{16}$ and input frequency values of $\Omega = 8, 16, 20, 24, 28, 32, 36, 64$. For this simulation we take the number of points in the y-direction to be $N = 6$ and we choose M so that $\Delta x = \Delta y$. Friction and stiffness were taken to be $k(x) = \epsilon \exp(-4x)$ and $r(x) = \frac{1}{\epsilon^2} \exp(-4x)$ as inspired by (4.9) and physiological literature.