Simulation and Visualization of Medical Application to the Inner Ear of the Guinea Pig to Reduce Animal Experiments

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Abstract

We present a novel approach to simulate drug application to the inner ear of the guinea pig with the goal to reduce animal experiments and to increase the accuracy of measurements. The framework is based on a tetrahedral grid representing the individual compartments of the cochlea, associated with a finite element model used to simulate medical diffusion and clearance. In a first simulation scenario, we were able to compute transfer coefficients between the inner compartments of the ear, validating experiments from the literature, and to prove the existence of clearance at the inner scala tympani. In a second scenario, the cochlea was unwound to obtain a one-dimensional model for efficient simulation-based transfer coefficient identification. These coefficients are useful to predict the impact of novel medication application systems.

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1 Introduction

Hearing loss is still one of the most frequent chronic diseases and it may affect people of any age. Irreversible impairment of the sensory hair cells inside the human cochlea (inner ear), is often the reason for acute hearing loss. Due to the high sensibility of these hair cells, there is a wide range of possible causes for hearing loss, ranging from certain antibiotic treatments to simple aging processes. A drug therapy against hearing loss may only be successful when the right dosage is applied.

A promising alternative to systemic therapy, where medication is absorbed by the entire body, is the local delivery of drugs to the inner ear [7]. This is typically performed by injecting a small quantity of substance through the ear drum on top of the round window (purple region illustrated in Figure 3(a)), from where it will enter the scala tympani and will eventually reach the hair cells in the region where the hearing loss occurs, since hair cells at the front and at the end of the cochlea are associated with different frequency ranges. State of the art is round window application, i.e. placing a gel containing the drug on the round window. Alternatives to that may also help placing the medication closer to the target region, in the near future.

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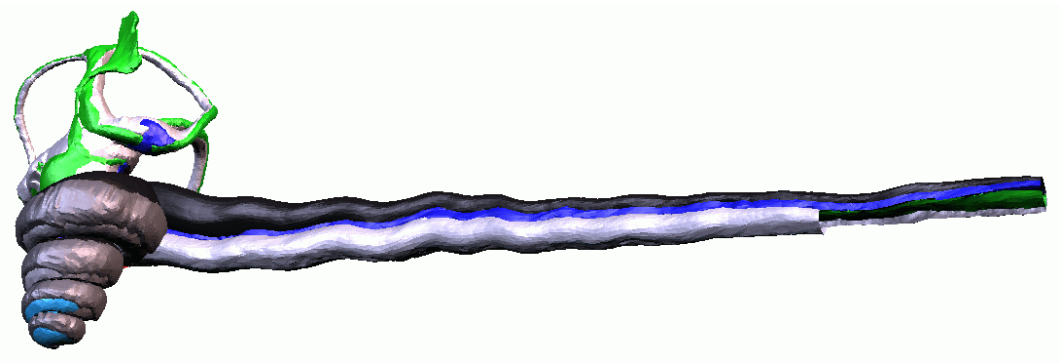


Figure 1 Unwinding the cochlea of a guinea pig, facilitating simulation and visualization of medical drug application to the inner ear.

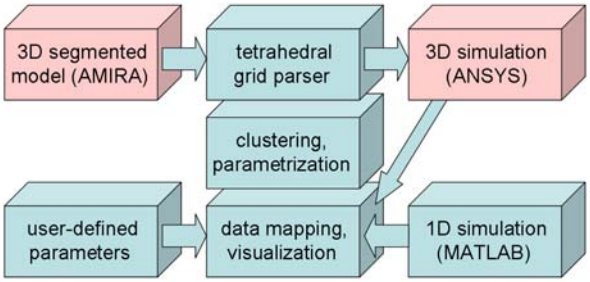


Figure 2 Simulation and modeling framework. The modules colored in blue belong to our own software, whereas red boxes denote commercial tools we used.

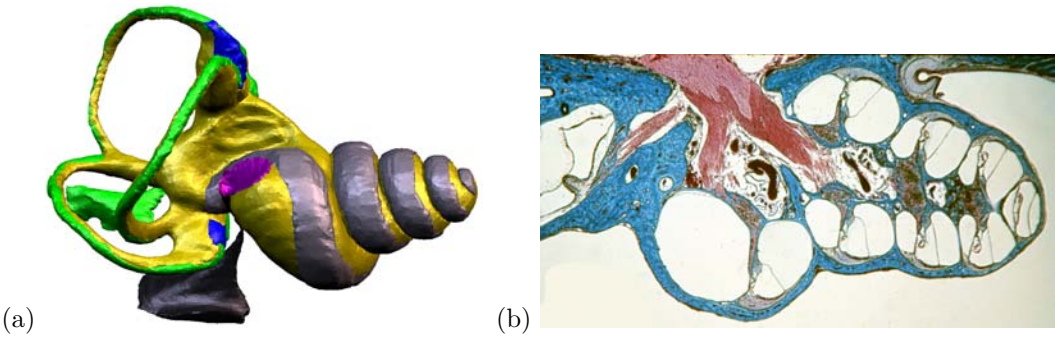


Figure 3 The cochlea (inner ear) of the guinea pig. (a) Segmented geometric model used for FEM-based simulation; (b) histological cross-section image of the cochlea, courtesy of Renate Lauf, Tübingen Hearing Research Center (THRC).

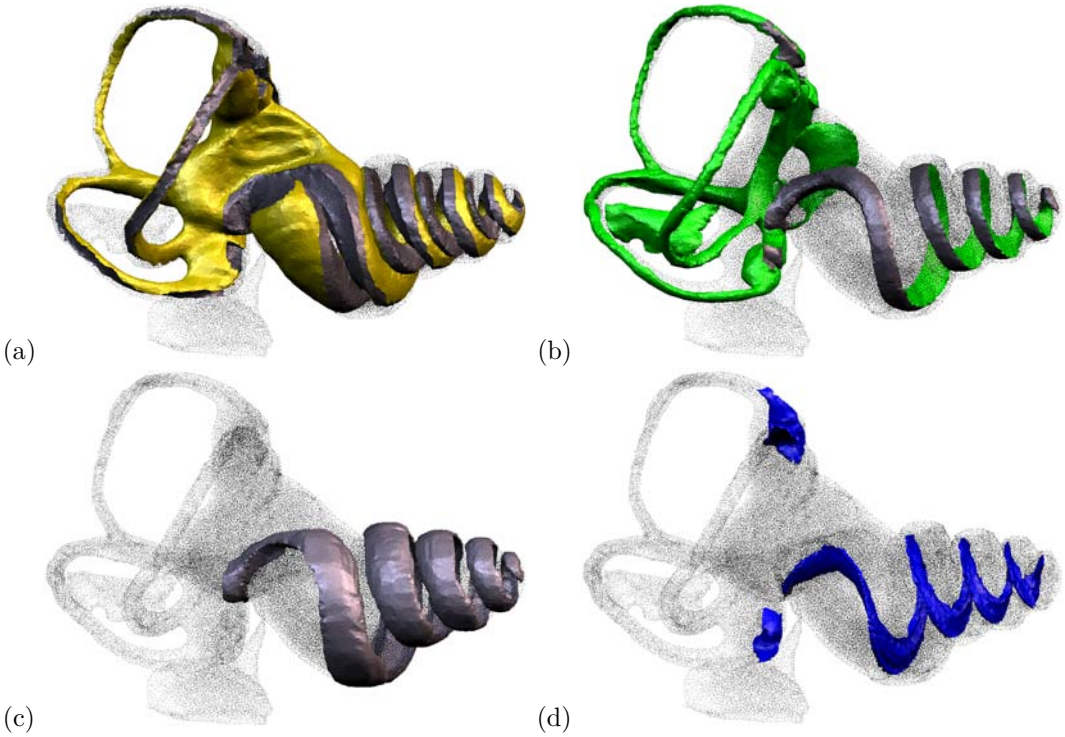


Figure 4 Segmented volume compartments: (a) scalae tympani and vestibuli; (b) endolymphic space; (c) spiral ligament; (d) organ corti.

Care must be taken not to cause further damage to the inner ear when locally applying medication. An over dosage of applied medication may increase hearing loss, as well as inner tissues may suffer from surgery. With under dosage, incorrect application frequency, or faulty medication formulation (e.g. too large molecules to penetrate round window tissue), no significant quantity will enter the cochlea. Due to these risks, at the current state approval of new application systems requires a large number of animal experiments.

The cochlea of the guinea pig (Figure 1) is shaped in a similar way as the human cochlea, except that it is much smaller and variations in size and shape are rather limited [3, 13]. Animal experiments required by law are used to assess the effect of drug application. The results are scaled up to the human ear without understanding the physical fundamentals of this process. Measurements of drug concentration are very difficult to perform due to the small size of a guinea pig's cochlea. Substances that cannot be measured with micro CT or magnetic resonance microscopy [11] may require destruction of the cochlea when measured. Unfortunately, the visible marker substances may have different transfer coefficients than the medication to be investigated.

In our present work, we contribute a simulation and modeling framework with the goal to reduce and replace animal experiments. Besides the ethical advantage of computer-simulated approaches, there are virtually no limitations in measuring results and in the accuracy for transforming the underlying physics into mathematical models. The only loss of precision is due to (small) numerical simulation errors and due to differences between the virtual model and reality, both in geometry and the physical phenomena developed here. Our algorithm simulates and visualizes the application process for the cochlea of a guinea pig with much greater accuracy than can be obtained with any state of the art animal experiment, provided

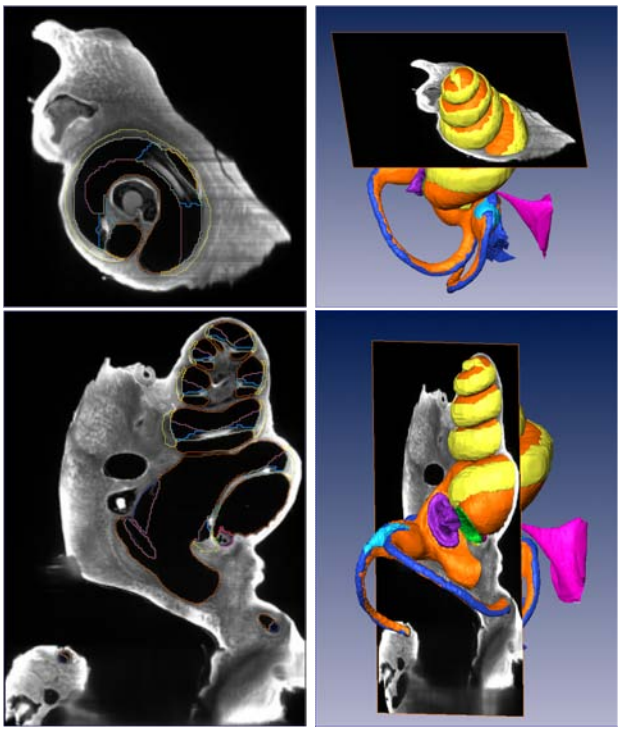


Figure 5 Volume modeling by cross-sectional segmentation with AMIRA.

that transfer and diffusion coefficients are known. We anticipate that similar methods will be available in the near future to simulate analogous processes in the human ear.

A schematic view of our framework is depicted in Figure 2. We used the AMIRA software to construct a segmented geometric model of the cochlea compartments. The resulting tetrahedral mesh is parsed by our system and exported for simulation with ANSYS. After the model and a number of ANSYS simulation runs used for validation have been established, our system forms a stand-alone application, as we obtain a parametrized 1D-representation by unwinding the cochlea and the simulation model. The 1D-version of the simulation is now implemented in MATLAB, whereas C++ with OpenGL was used for the remaining modules. Based on user-defined parameters, 3D ANSYS and 1D MATLAB simulations are mapped to the geometric model for visualization purposes.

The remainder of our paper is structured as follows: The next section summarizes previous and related work. Section 3 contains the parameter identification process determining transfer coefficients and validating them based on results from previous work. Section 4 is devoted to the model reduction process, unwrapping the cochlea geometry into a one-dimensional model. Segmentation and visualization of the geometry facilitates the construction of a parametrized 1D simulation approach that accurately matches the results of the full 3D finite element simulation. Section 5 presents a concluding discussion of the results obtained.

2 Previous and Related Work

An initial study of the cochlea geometry for the guinea pig has been described by Fernandez [3]. A more recent work by Shepherd and Colreavy [13] presents geometric examples for the micro structure of the main compartments of the human cochlea (inner ear), the scala tympani

and the scala vestibuli (cavities in Figure 3(b)). Approaches directed at surgery planning propose segmentation of computer tomography data [2] and direct volume rendering [5]. Modeling of the human middle ear has been described for dynamic and acoustic simulation [4, 1].

The compartments of the inner ear are mostly filled with a liquid, such that the distribution of medical substances is mostly due to **diffusion** within homogeneous liquid and **transfer** across boundary tissues. Further effects are **clearance** (advection) due to blood flow and bio-chemical **degradation**, which also reduces the concentration on a longer time scale.

Recent work is concerned with localizing the most important transfer (communication) routes between individual scalae [7, 9]. Knowing these transfer routes, (and corresponding transfer coefficients) it is possible to locate and quantify the clearance due to blood flow. Compartments that are densely connected to blood flow, like the spiral ligament at the outer boundary (gray surface in Figure 3(a)) cause a reduction of medication substance. For controlling medication dosage, it is important to fully understand the interplay between diffusion, transfer, and clearance.

An early study based on animal experiments measuring the transfer between scalae tympani and vestibuli is described in [12]. In our present work, we used these results for validation and for parameter identification, i.e. specifying the transfer coefficients based on a 3D finite element model. A mathematical FEM-based diffusion approach has been described in [8], using an analytic snake-like shape as geometric model. For a more complete overview of the physical modeling, we refer to [6].

In the present work, an accurate 3D model of the cochlea is used for FEM-based simulation of medication concentration. Data sets for reconstructing the geometry of the guinea pig inner ear were obtained from computed tomography (CT) and orthogonal plane fluorescence optical sectioning (OPFOS; A. Voie, G. Saxon; Spencer Technologies). Fluid spaces of the inner ear were segmented using the AMIRA software system (MERCURY Computer Systems Inc.). The 3D construction of the geometric cochlea model was published in [10] and is illustrated in Figure 5.

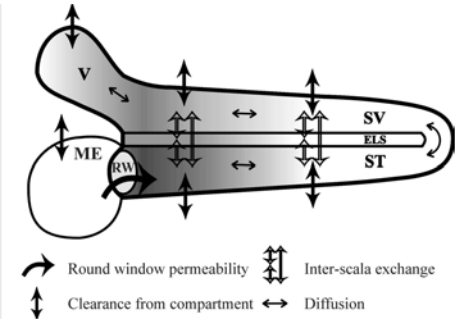


Figure 6 Schematic view of middle ear (ME), round window (RW), scala tympani (ST), scala vestibuli (SV), and vestibule (V). Both scalae are connected in the apex and also exchange material due to their proximity.

3 FEM-based Simulation and Parameter Identification

3.1 Simulation Model

The segmented geometric model constructed with AMIRA is composed of 117,773 vertices and 586,674 tetrahedra, each of which is marked with a label denoting its compartment.

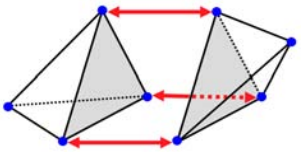
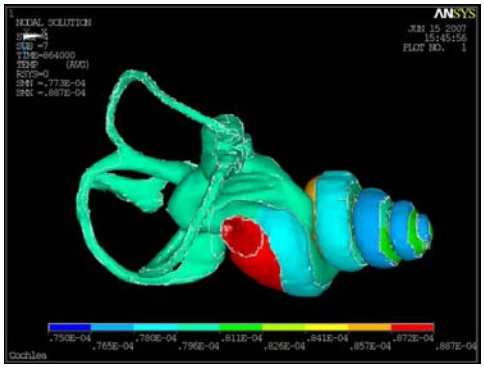


Figure 7 Duplicating inner compartment boundary vertices. Diffusion is based on linear ansatz functions associated with the ANSYS nodes (blue dots). Transfer across boundary surfaces is defined by ANSYS link elements (red arrows) between duplicated nodes.

(a) 

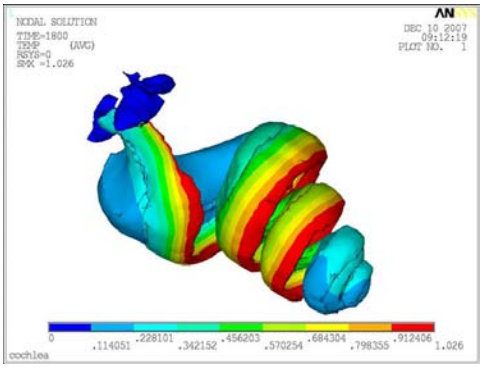
(b) 

Figure 8 Simulation scenarios using ANSYS. (a) Round window application scenario; (b) validation of transfer coefficients for clearance estimation.

The four major compartments are illustrated in Figure 4. Most tetrahedra belong to the complex containing scala tympani, scala vestibuli, and the vestibule. The round window, where medication is usually applied, is located in front of the scala tympani (seen from the middle ear), which is twisted to a snake-like shape together with the other scalae. At the very end, the apex, it is connected to the scala vestibuli, as depicted in Figure 6. For the ANSYS simulation, this complex is split into two labels ST and SV (scala tympani and scala vestibuli).

The three other compartments illustrated in Figure 4 are the endolymphic space (ES, green) between the scalae, the spiral ligament (SL, gray) causing a clearance at the outside boundary due to blood flow, and the organ corti (OC, blue), which is part of the hearing nerve system. Our simulation model assumes that each compartment has a unique diffusion coefficient and that material can also be exchanged between the common boundaries, based on transfer coefficients. While the diffusion coefficients mostly depend on the medium, the transfer coefficients heavily depend on the molecule size of the drug and of the tissue. Modeling the tissue as a surface rather than a volumetric shape is already a simplification. The simulation model has been described earlier [8] using a simple spiral-like shape model. The equations are defined as follows:

Diffusion of medical concentration c_i ($i = ST, SV, ES, OC, SL$) in a compartment, due to its diffusion constant k_i:

$$\frac{\partial c_i}{\partial t} = k_i \Delta c_i, \tag{1}$$

where Δ denotes the Laplace operator.

Transfer between concentrations c_i and c_j in adjacent scalae linked by (directed) area n

with transfer coefficient k_{ij}:

$$k_i \frac{\partial c_i}{\partial n} = k_{ij}(c_i - c_j). \tag{2}$$

Inflow of medication concentration from the round window into the scala tympani, due to concentration D at round window:

$$k_{ST} \frac{\partial c_{ST}}{\partial n} = -\beta(c_{ST} - D). \tag{3}$$

Clearance at the outer boundary of spiral ligament:

$$k_{SL} \frac{\partial c_{SL}}{\partial n} = -\gamma c_{SL}. \tag{4}$$

The only well known quantities in the above model are the diffusion coefficients k_i. The transfer coefficients k_{ij} depend on the structure of the tissue between each pair of neighboring scalae and on the molecular size of the drug. We note that the transfer constraints in equation (2) are symmetric, seen from both sides. The coefficients β and γ are one-sided transfer coefficients for inflow and clearance, respectively. We assume that the drug concentration in the blood is zero, since the volume of the cochlea is much smaller than the volume of the entire body. An additional term for bio-chemical degradation reducing the drug concentration over time may be added when considering long time scales.

We assume that the drug or marker substance is either placed on the round window surface or (in secondary experiments) directly ejected into the scala tympani. The overall concentration drops down over time, mostly due to a clearance at tissues connected to major blood flow. In regions such as the spiral ligament, the drug is partially advected by blood flow into the entire body, where it does not play a significant role for ours simulation. We note that this effect is reversed when a systemic therapy is simulated, i.e. the drug is contained in the blood and gets into the cochlea via diffusion.

For the solution of above equations, we used ANSYS, a FEM-based simulation package mostly used for calculating heat transfer. Our diffusion model in fact differs from heat transfer only in the physical units used. The drug concentration inside the scalae is represented by a piecewise linear representation,

$$c(x, y, z) = \sum_i a_i \phi_i(x, y, z), \tag{5}$$

where a_i are coefficients and ϕ_i linear ansatz functions associated with ANSYS nodes located at the vertices of our tetrahedral mesh.

For the transfer between adjacent scalae, ANSYS link elements are employed. These couple the corresponding nodes and take into account a transfer coefficient and the directed surface i.e. an averaged normal vector times the orthogonal surface area. To properly specify these link elements, our preprocessor needs to duplicate all triangles (and the corresponding vertices) belonging to inner tissues, see Figure 7. The link element between two ANSYS nodes corresponding to a split vertex takes one third of the directed areas of all tissue triangles connected to this vertex. Directed areas are accumulated by summing up the corresponding vectors.

After the tetrahedral model has been preprocessed and exported for ANSYS, the simulation is started, based on an ANSYS script. Figure 8 depicts two simulation scenarios, (a) round window application where the concentration decays along the scala tympani and also spreads into the adjacent compartments and (b) a scenario to estimate transfer coefficients, described below.

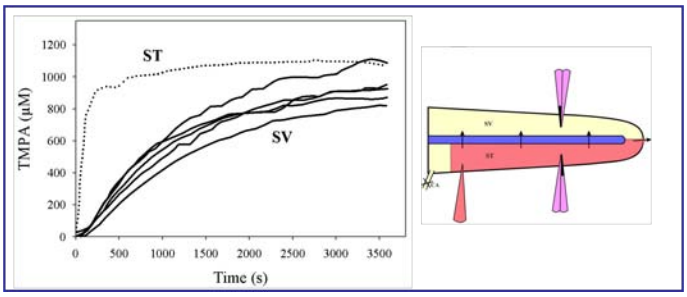


Figure 9 Results from first experiment [12] filling scala tympani with an ionic marker (TMPA) and measuring concentration in scala vestibuli.

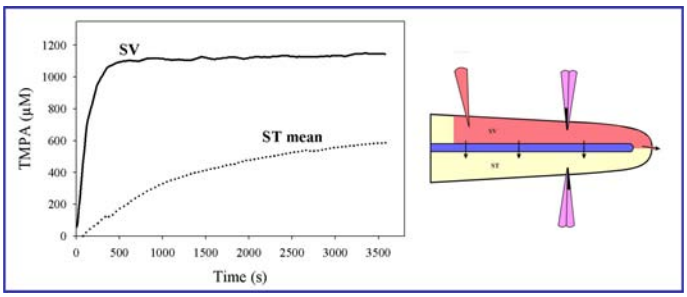


Figure 10 Results from second experiment [12] filling scala vestibuli and measuring concentration in scala tympani.

3.2 Clearance Estimation

The main difficulty in our simulation approach is the estimation of transfer and clearance coefficients. These are not known from the literature (like diffusion coefficients) and may depend on the molecular shape of a drug or marker substance. The only way of estimating these coefficients is a time-consuming parameter-identification process, where the FEM solver is iteratively being used with different parameter sets until the most proper solution has been found. This process requires some knowledge about the data, for example measurements.

In the following, we describe this parameter identification process validating measured results from the literature [12]. These measurements are taken from two experiments. First, the scala tympani of a guinea pig had been filled with a ionic marker (TMPA) substance and the concentration had been measured over time at two points inside the scalae tympani and vestibuli, see Figure 9. In the second experiment, the scala vestibuli was filled with the ionic marker and the concentration inside the scala tympani was measured. It is observed that this concentration does not reach the full level, since the clearance via the spiral ligament constantly reduces the concentration, while that one in the scala vestibuli is artificially kept at the same level.

Based on the data from the first experiment, we were able to estimate the clearance coefficient for the spiral ligament, see Figure 11. Without any clearance (left), the scala vestibuli is eventually filled up completely, i.e. with the same concentration as inserted. By adding clearance from the spiral ligament to the systemic blood flow the calculated final concentration at the measurement site (third winding of scala vestibuli) can be matched to the measured concentration (right of Figure 11). With this method, the transfer coefficient for the outer clearance is determined.

It is conjectured that also a clearance inside the cochlea due to blood vessels near the

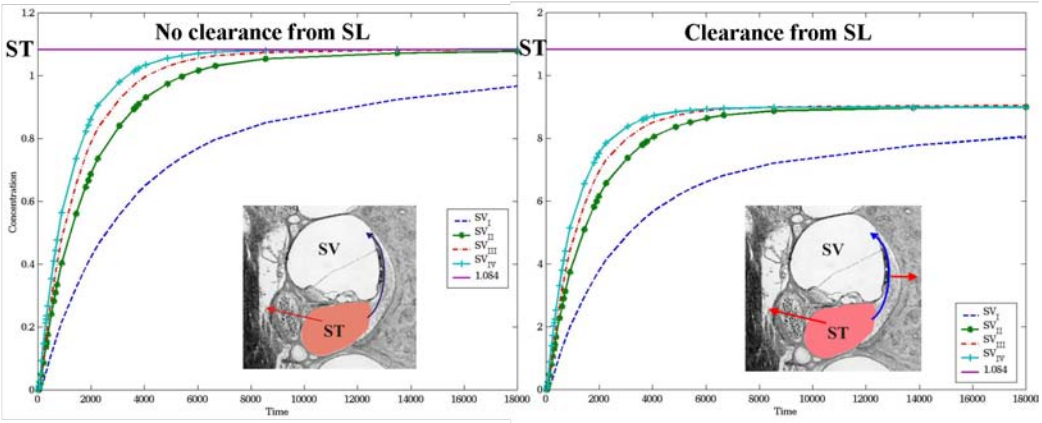


Figure 11 Validation of results of first experiment without clearance from spiral ligament (left) and with outer clearance identified by matching experimental results (right).

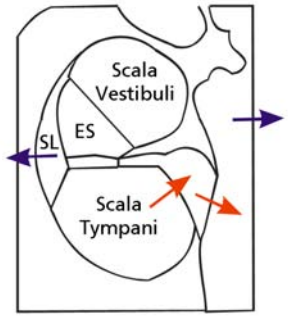


Figure 12 Schematic view of medication clearance due to blood flow. It is conjectured that in addition to the spiral ligament (SL), a second clearance must apply at the inner scala tympani.

scala tympani exists [9], see Figure 12. With our simulation we were able to prove this hypothesis. The corresponding transfer coefficient can be estimated, provided that the exact region of the inner clearance is known. Figure 13 shows the calculated concentration at pipette location in the third turn of the scala tympani while holding the level inside the scala vestibuli constant. When only adjusting the clearance coefficient for the spiral ligament, the actually measured concentration cannot be reached. An additional clearance of substance to the modiolus is needed to explain the data. The link nodes where we assumed that the clearance takes place are highlighted in Figure 14.

4 1D Model Reduction

In the above section we have described the parameter identification process. Since the full-resolution ANSYS simulation takes about 30 minutes (regardless of the simulation time, since time steps are adapted to the rate of change in "temperature"), this process is not very efficient. On the other hand, our model still contains a number of transfer coefficients that are not really accurate. For calculating these parameters, the FE-model needs to be reduced into a more efficient, yet accurate approach. Exploiting the one-dimensional shape of the scalae, we propose a 1D-parametrization of these, such that we obtain five univariate concentration functions $c_i(s)$, interconnected by corresponding transfer functions. This

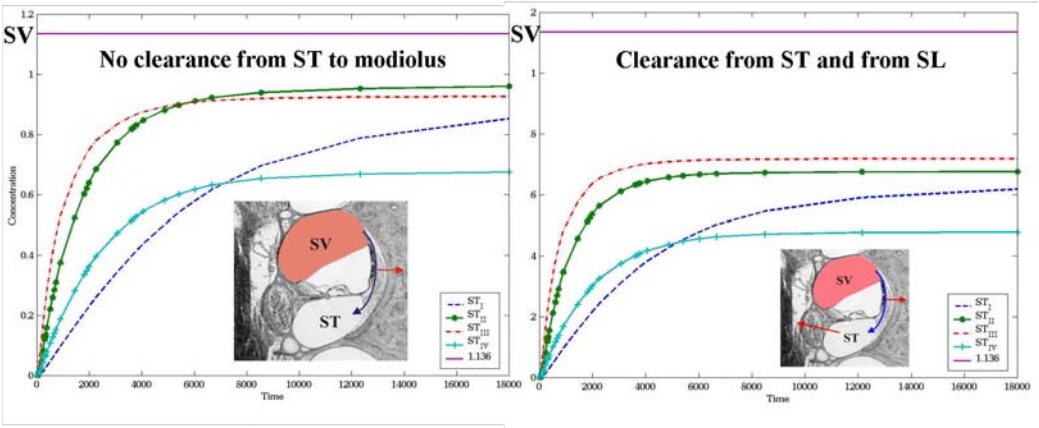
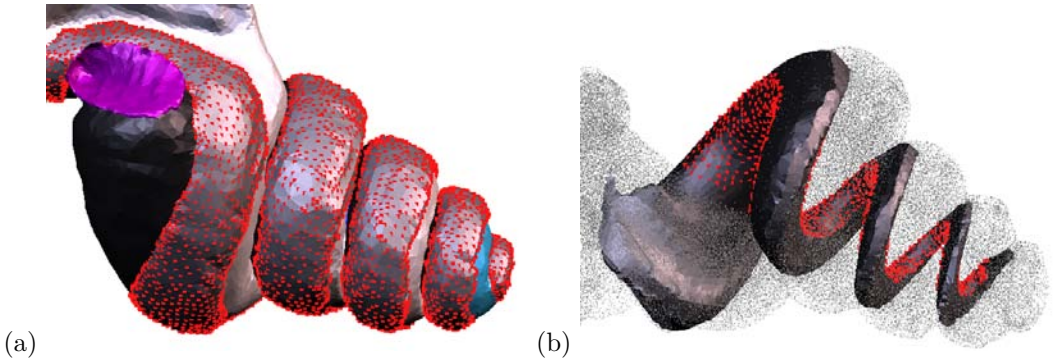


Figure 13 Validation of results of second experiment without clearance from inner scala tympani (left) and with inner clearance identified by matching experimental results.



(a) (b)

Figure 14 Link nodes used for clearance. (a) outside spiral ligament; (b) inside scala tympani.

approach corresponds to unwrapping and stretching the cochlea, as illustrated in Figure 1. With a one-dimensional parametrization of the individual scalae, also the simulation model is projected onto the topologically simpler 1D model space, according to Figure 15.

Unfortunately, to our knowledge no commercial tool for unwinding inner ear models exists. Hence, we extended our own modeling and visualization system (previously used to link AMIRA with ANSYS; all implemented in C++ based on OpenGL rendering) to also support these geometric operations (Figure 2).

In a first approach, we approximated the four main compartments (leaving scalae tympani and vestibuli connected) by polylines. These where obtained by a graph clustering approach in the following way:

- create a graph node for every tetrahedron
- connect the nodes of adjacent tetrahedra by edges
- repeatedly collapse shortest edges merging two nodes

For collapsing, we admit only edges that do not connect different compartments. Each node is associated with the center of a polyhedral complex and each edge carries the accumulated directed area of its corresponding surface. Based on this approach (with few more constraints eliminating small cycles) we obtained the clustering in Figure 16.

Though this cluster graph still contains enough information for simulation, its representation is too coarse to obtain accurate results. However, we could use the resulting polylines to

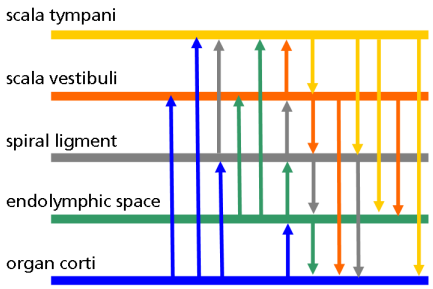


Figure 15 Schematic view of 1D model.

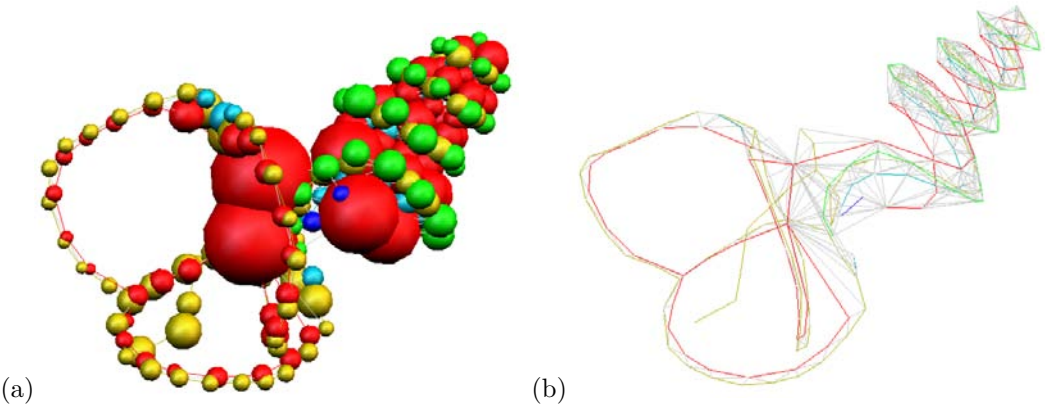


Figure 16 Clustering results. (a) visualization of associated polyhedral volumes; (b) connectivity graph for parametrization of scalae.

parametrize the different compartments. Thus, the clustering provided a (nearly) automatic way of separating the scalae tympani, vestibuli and the apex by simply marking tetrahedra associated with the nodes of corresponding polylines, see Figure 17.

In a second attempt, for each compartment a set of cross-sectional slices following a midpoint-curve (cubic interpolating spline for graph nodes) was constructed. Besides the matching problem for parametrizations of different scalae, this approach did not provide smooth transitions of the coordinate frame (Bishop Frame). One of the most significant reasons for this is that the normal plane of a guiding curve (i.e. a plane whose normal vector is tangential to the curve) is not the optimal choice for minimal cross sections. In some cases, these intersection planes produced connected 2D regions from multiple windings.

A clean approach to parametric cross sections was found by interpolating a linear axis inside the cochlea. With two fixed points on this axis and one parametrized point on a guiding curve (midpoint of spiral ligament), a smooth parametrization of cutting planes is obtained. The polygonal regions of the individual scalae can be combined to a tubular structure, as depicted in Figure 18.

Starting with a resolution of 500 slices, the region where scalae tympani and vestibuli are disconnected (408 slices) was identified. Interestingly, the scala vestibuli already ends at slice 324, where it enters the apex, see white tube in Figure 1 and compare to Figure 17. What on the first glance looks like a flaw in our visualization is caused by the fact, that this scala has one winding less than the other scalae.

The parametrization of cross-sectional slices of the five scalae allowed us to transform

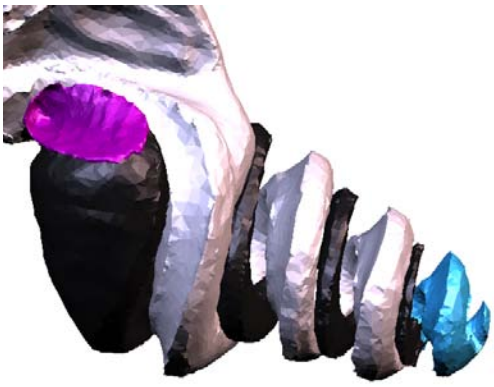
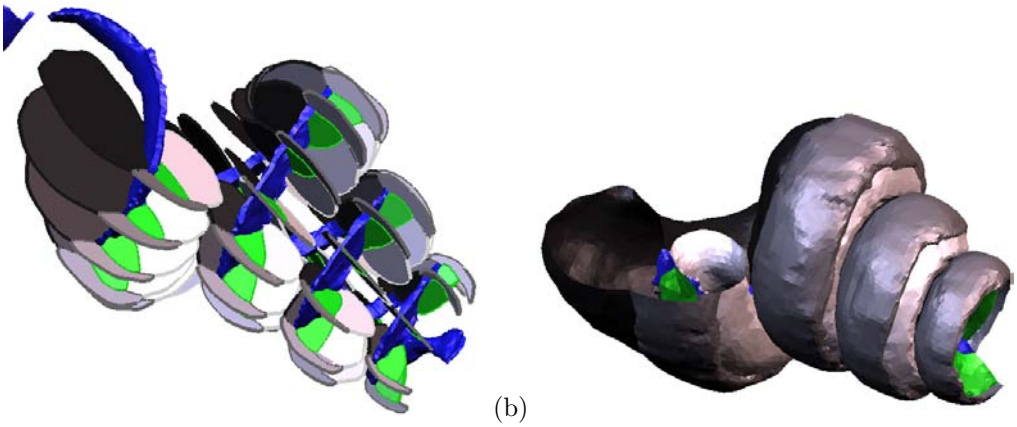


Figure 17 Automatic separation of scala tympani (black), scala vestibuli (white), and apex (cyan), based on clustering graph.



(a) (b)

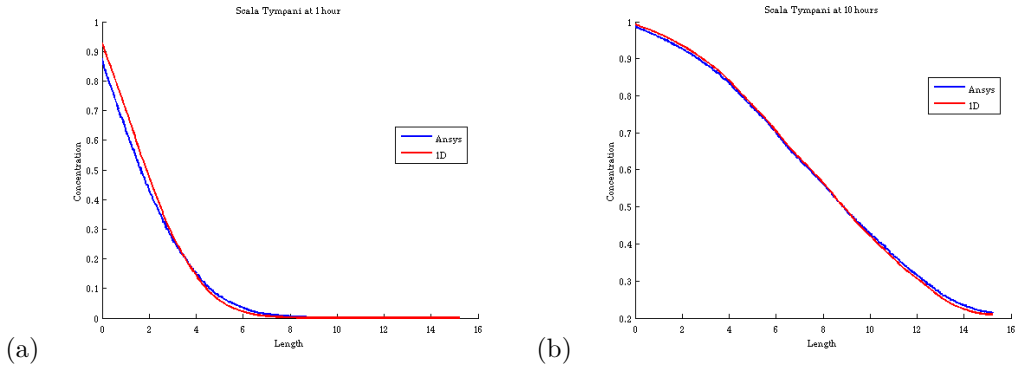
Figure 18 Construction of slices. (a) moving slices around organ corti (blue); (b) slices connected to tubes.

the equations (1–4) of the 3D model into a one-dimensional approach. This means that the system of equations is now a banded system with five equations for every cross-sectional slice. In order to transform the equations properly, we needed to calculate for every two consecutive slices the volume of the compartments in between and the common surface areas for every pair of compartments.

The simulation results for a round-window application scenario based on our reduced 1D model and the full 3D ANSYS simulation are compared in Figure 19. Therefore, we have re-loaded the ANSYS simulation into our own viewer and averaged it over the cross-sectional area for each scala. A 3D comparison of both results is depicted in 20. Despite of the much greater efficiency of the 1D approach, the solution is nearly as accurate as the 3D approach. The computation time for one simulation has dropped down from 30 minutes to a few seconds, which is efficient enough for sophisticated parameter identification.

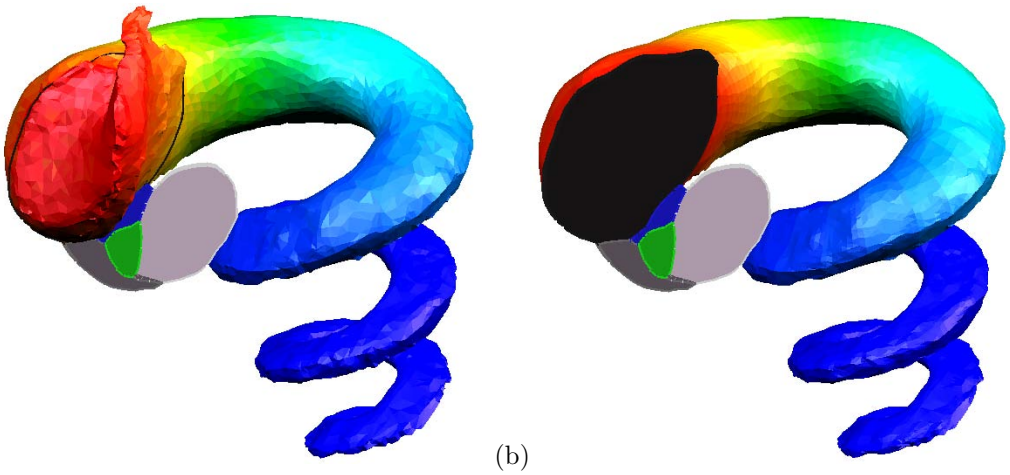
5 Concluding Discussion

In the present work, we have combined previous constructions of accurate cochlea geometry [10] with a physical simulation method [8] for medical application to the inner ear. The model is accurate enough to validate measurement results from the literature [12] and to



(a) (b)

Figure 19 1D Comparison of 3D ANSYS simulation and 1D model reduction. (a) Simulated concentration inside scala tympani after one hour of application; (b) after 10 hours.



(a) (b)

Figure 20 3D Comparison for scala tympani after one hour application time. (a) ANSYS-result; (b) reduced 1D simulation. The 1D simulation nearly coincides with the full 3D simulation, since concentration gradients are mostly oriented along the scalae in typical application scenarios. We used a similar color map as ANSYS, here without quantization. Alternative color maps are available (since rainbow colors work well for comparative visualization but do not convey gradient magnitude).

prove a hypothesis [9] that also a clearance at the inner boundary of the scala tympani exists.

The benefit of our modeling and visualization system to achieve this task is that simulation results obtained with ANSYS and with MATLAB can be integrated into the same system and compared on the same geometric model. For this case study, even simple visualization methods were extremely helpful to understand the entire process. For example, when unwinding the cochlea, we observe that the scala vestibuli (white in Figure 1) is shorter than the others, since it is connected earlier to the apex. Also the location and quantification of clearances is very convenient with the aid of a 3D visualization with user interaction.

A limitation of the simulation model is still that the exact values for a number of parameters are still unknown. These are mostly related to the material-dependent transfer coefficients that also may have local variations. A further increase of accuracy would be obtained by knowing the exact regions where clearance can occur. In order to determine these parameters, we have reduced our finite element model to a more efficient one-dimensional approach that matches the FEM-based simulation results for round window application

scenarios. Simulation scenarios with steep concentration gradients across scalae boundaries may cause greater errors of the 1D approach. However, when using this efficient method for parameter identification (where the simulation is run hundreds of times with various parameters), the resulting parameter set can be validated by a single 3D simulation.

Our ultimate goal is the reduction of animal experiments required for approval of novel application systems designed for the human ear. This includes a more reliable method for predicting such processes compared to "up-scaling" results from animal experiments to the human ear geometry. The present work is a small step towards this goal, providing a methodology composed of geometric modeling, visualization, simulation, and validation. In the near future, a lot of work will be necessary for modeling and simulating human cochleas where the variation in geometric shape is somewhat greater than for the guinea pig. A further challenge is the validation of the results, based on non-invasive measurements.

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