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Finite-element modelling: a new tool for the biologist

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Most types of behaviour, from muscle contraction to conscious thought, are mediated at the cellular level between thousands, if not millions, of cells within a single biological organ. Technological advances over the next decade will make it feasible to simulate these interactions on a computer, providing an invaluable tool for predicting how an organ behaves when presented with particular stimuli. Finite-element modelling techniques are particularly suited to this task, since, by dividing a system into a large number of small elements, they mimic the physical reality by which cell interactions, even over large distances, result from a large number of localized interactions between adjacent units. Finite-element techniques have been used in engineering for some time, and they are already being applied to a variety of biological organs. One example is the mammalian cochlea, where sound is transformed into electrical signals that are subsequently passed to the auditory nerve. The cochlea contains an amplifier of mechanical motion that operates on a microsecond time-scale at sub-nanometre displacements, and it enables the auditory system to respond over a dynamic range in excess of 120 dB. A simple finite-element model that represents the cochlea at a cellular level has already demonstrated the potential value of this approach by providing an explanation for contradictory experimental observations. Developing structurally realistic cell-level models of biological organs will improve our ability to properly characterize and quantify experimental observations, and dramatically reduce the need for animal experimentation. The finite-element approach could also provide a valuable tool in the design of new, simpler, cellular structures that would mimic the known operation of a biological organ. Given the impressive specifications of such organs, these new devices—manufactured in carbon or silicon—could have numerous research, clinical and industrial applications in the new millennium.

Keywords: computer modelling; biological organs; finite-element analysis; cochlea; cell motility; distributed computing

1. Introduction

Car manufacturers do not destroy thousands of prototypes when designing crashworthiness into their vehicles. Instead, they spend most of their time building and analysing models on computers. Only once a computer model is found to be consistent with statutory requirements do they resort to expensive and time-consuming physical testing. This beneficial relationship between modelling and experimentation is still in its infancy in biological research, thanks partly to the great complexity of biological organs. In this paper I claim that by the end of the first decade of the new

millennium, computer modelling will have revolutionized research into the operation of biological organs in the same way that experimental techniques have over the past century. This will be achieved by applying a technique that is used widely in engineering, known as finite-element analysis, to model complete biological organs at a cellular level. I put forward the following arguments.

(1) Both experimentation and modelling are vital in virtually all fields of scientific and industrial endeavour. While modern experimental techniques make it possible to characterize the operation of individual cells, understanding the mechanisms of the interactions between thousands, if not millions, of cells within an organ is only possible using a computer model.

(2) The processing power available from inexpensive commodity computers will continue to increase exponentially for at least another decade, even if technological breakthroughs in computing hardware are not forthcoming. The computing power will then be sufficient to model complete biological organs at a cellular level.

(3) Applications of finite-element techniques to the modelling of organs have provided insights that would not have been possible experimentally. The specific application to modelling of the mechanics of the inner ear is described in detail.

(4) Beyond the first decade of the millennium, these developments could lead to the manufacture of new types of biological or synthetic organs. They could be used to either replace their defective counterparts or to perform entirely new tasks with efficiencies that are impossible using current technologies.

2. Striking a balance between experimentation and modelling

(*a*) *Modelling in industry*

Computer modelling is now used extensively in many manufacturing industries. Its use decreases both the time required to design and manufacture a product, and the financial costs of doing so. One familiar application is in the design of car crashworthiness. Cars must both protect the occupants from physical intrusions into the passenger compartment, and minimize the deceleration forces that act upon them. The first of these requirements could be achieved easily by making the car body rigid. Unfortunately, the deceleration forces would then be intolerably large, so instead the design aim is to make the expendable parts of the vehicle (i.e. those outside the passenger compartment) absorb as much of the impact energy as possible by deforming them in a predefined time-dependent manner so as to minimize peak deceleration levels. It is impossible to achieve this without extensive experimentation or modelling.

In the past, when car crashworthiness was designed entirely experimentally, full-sized prototypes were subjected to the crash scenarios required by the relevant authorities. If the performance was unacceptable, the shape deformations of the components making up the prototype were examined. A new prototype was engineered empirically to overcome the identified weaknesses before being built and then destroyed in a subsequent test. These tests would be repeated many times before an appropriate design was found. The cost of the process was enormous. Nowadays, car manufacturers do not survive unless they rely heavily upon computer modelling—and, especially, finite-element analysis—in the design of crashworthiness (figure 1).

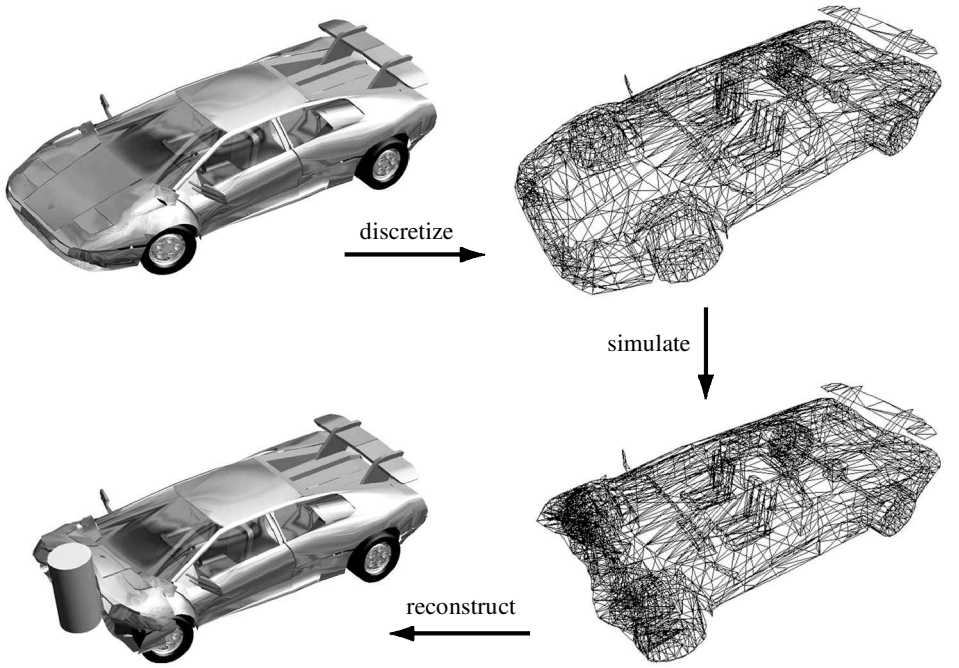

Figure 1. Designing car crashworthiness using finite-element modelling. The intact car is first divided into a large number of small elements (discretization). The equations describing the interactions between adjacent elements are then solved (simulation), with the stimulus in this example being an obstacle at the front of the vehicle. The resulting deformations and deceleration forces are then investigated in detail (reconstruction), in order to predict how best to modify the design to improve its performance.

(*b*) *Experimentation in biology*

Car crashworthiness design involves the manufacture of a new system, but each stage of the process requires an understanding of the operation of an existing system. This is analogous to most research in biology. However, in contrast to crashworthiness design, investigations into the operation of biological organs are still dominated by experimental approaches, partly because most organs are much more complex than a car. Computer modelling is already used widely in some specialized applications: in the development of therapeutic drugs to combat disease, for example. In the past this was performed purely in a brute-force trial-and-error manner. Cell cultures, animals or humans—or all three—were subjected to many variations of a likely candidate for a drug, with the final choice being chosen on the basis of best performance with the minimum adverse side effects. This is analogous to building thousands of car prototypes simultaneously, each with slight differences in design, and then subjecting them all to the rigours of experimental crash testing. The best model is that which, largely by chance, survives best. If car crashworthiness was still designed in this way, only the very rich would be able to afford the end product. Fortunately, computer models are now being used to 'experiment' with the effects that changes in structure will have on the potency of the drug, with corresponding reductions in production costs.

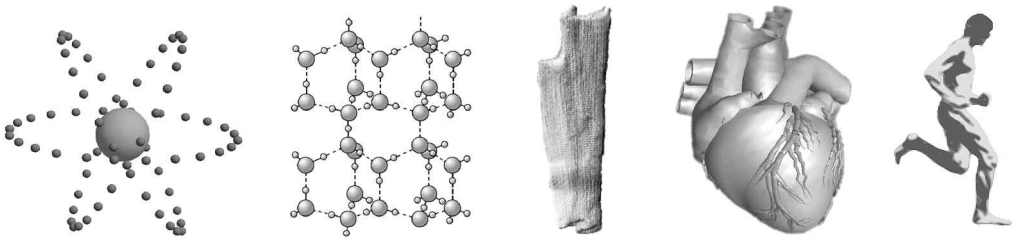

Figure 2. The biological hierarchy. It is natural to describe function at any level in terms of the component at the next level down. Both the behaviour of the component in isolation and interactions between components must be considered. (Cell image courtesy of Allan Levi; heart image courtesy of Peter Hunter).

The application of computer modelling techniques to biology is most beneficial if an appropriate level of complexity is chosen. Assemblies of carbon, hydrogen and oxygen atoms combine to form molecules that, when linked together, form proteins, carbohydrates and fats. These three fundamental types of biological molecule combine to form cells that are typically 10 μm in diameter and have the mass of 30 trillion hydrogen atoms. Cells can be independent organisms, as in a bacterium, or, by cooperating with other cells, form tissues. By acquiring specialized functions, assemblies of tissues form the next distinct structural and functional unit, the organ. At the highest level, a human comprises 75 trillion cells divided into ten major organ systems. Each organ plays a crucial life-sustaining role, and understanding how each works is of profound interest for many reasons, from the possibility of widespread treatment, or even the prevention of disease, to the possible engineering applications of the unique types of signal-processing employed by each organ.

Considering this biological hierarchy, it is natural to describe the function at each level in terms of the components at the next level down (figure 2). Sometimes it may be necessary to consider processes occurring two levels down, but further subdivision is seldom beneficial. Schrödinger's equation, for example, is useful when modelling the behaviour of atoms in a molecule, but it would be absurd to model car crashworthiness using this level of detail. When we are interested in the operation of a complete organ, a description at the level of the cell is the natural choice. The model must incorporate both the operation of the cell in isolation and the interactions between cells since, by analogy, we could not predict the load-bearing capacity of the Forth rail bridge by considering only the strength of the individual cantilevers in isolation.

3. Modelling strategies

The ability to predict how a system behaves when presented with particular stimuli is the realistic goal of most research into the 'understanding' of system function. If the laws of physics that control the behaviour of the system can be described in terms of mathematical equations, it is possible to simulate, or model, the operation of the system to an arbitrary stimulus by solving those equations. Modelling also gives us the ability to perform 'experiments' that would be difficult, or even impossible,

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with the real system, for reasons of safety (e.g. designing new types of nuclear power station), expense (e.g. car crashworthiness), or technical impossibility (e.g. observing the individual interactions between tens of thousands of cells simultaneously).

(*a*) *Finite-element analysis*

Finite-element analysis is a numerical technique that involves dividing a system up into a large number of small elements. It is self-consistent and accurate even when a number of different physical phenomena act simultaneously. The quantity of interest within each element (be it, for example, motion, voltage, temperature, chemical concentration, magnetic-field strength, or any combination of these) is described in terms of its values at several points, called nodes, on, or within, the element boundary. If, for example, we are interested in the motion of a mechanical system, the strain within each element can be expressed mathematically in terms of nodal displacements. These equations are derived while ensuring that the displacement is continuous across element boundaries for any choice of the nodal displacements. The stresses associated with these strains are then calculable from the material properties of the element (e.g. Young's modulus and Poisson's ratio). This results in the generation of a set of simultaneous equations that encapsulates the system under investigation.

Finite-element analysis is very flexible. The system of interest may be a continuum, as in a fluid, or it may comprise separate, discrete components. The basic principle of finite-element modelling—to simulate the operation of a system by deriving equations only on a local scale—mimics the physical reality by which interactions within a system, even over large distances, are usually the result of a large number of localized interactions between adjacent elements. These interactions are often bi-directional, in that the behaviour of each element is also affected by the system of which it forms a part. The finite-element method is particularly powerful because, with the appropriate choice of elements, it is feasible to accurately model complex interactions between large numbers of elements, provided that it is possible to create a reasonably simple mathematical description of the physical behaviour of each element.

Determining the optimal complexity of a finite-element model is largely down to the skill of the modeller. If the model is too simplistic, it will not embody the important processes of the real system. If the model is too complex, the computational round-off errors associated with finite-precision arithmetic become large, and the analysis time becomes prohibitive. The complexity and number of the individual equations is determined partly by the formulation method: namely 'true' finite-element, finite-volume, finite-difference, or boundary-element methods. All of these share the principle of dividing the system into a number of discrete elements, the only difference is in the method used in the discretization process. Some purists would argue that these are quite different types of analysis. Here, in common with some standard textbooks (see, for example, Zienkiewicz 1975), the term 'finite element' is rather loosely applied to all of these variations to emphasize the common, overriding principle of dividing the system into a large number of small elements.

(*b*) *Distributed parallel computing*

The maximum size of a finite-element model is limited mainly by acceptable analysis times, which, in turn, are determined largely by the available computer processing

power. The speed of commodity microprocessors has increased exponentially since their introduction three decades ago, doubling every 18 months. If this were to continue, within the first decade of the new millennium they would be 100 times more powerful than they are today. They would also be cheaper in real terms. Physical limitations to both transistor density and switching speed may prevent such an increase; instead, distributed parallel-processing techniques could provide the necessary computing power, by dividing the task of analysing the finite-element model between several processors that are housed in separate computers. By using commodity computers at the inexpensive end of the market, we would benefit from the economies of mass production that are associated with sales of tens of millions of units annually. Their price-to-performance ratios far exceed those of any other type of computing platform, so it will always be more cost effective to buy several of these machines than, say, half the number of computers that are twice as powerful.

Distributed parallel processing also provides the potential to use a wasted resource. Within a university department, which is one likely setting for biological modelling, most people have in their office a computer that spends more than 99% of its time doing little more than providing low levels of background heating and noise. It makes sense to give them something to do when they are not being used as expensive typewriters or desktop calculators. In a department with 50 commodity computers, with virtually no capital investment a distributed parallel application would enable access to the processing performance that a single-processor computer will not be able to match within the next 10 years. And, of course, as individuals upgrade their computers, the distributed application will have immediate access to the increased processing power. The main obstacle to distributed computing is dividing the analysis task itself onto multiple machines, where each processor has efficient access only to the memory on its own machine. The magnitude of this difficulty depends heavily upon the type of problem, but because of the localized way in which the equations are formulated, the task of solving the equations associated with a finite-element analysis is ideally suited to parallelization.

4. Modelling tissues, gap junctions and the heart

The predicted growth in commodity microprocessor-based computing power over the next decade will make finite-element modelling of complete biological organs feasible at a cellular level. Work has already begun in a number of areas, including bone, skin and brain mechanics, intercellular communication within tissues, and heart contraction.

(*a*) *Bone and soft-tissue mechanics*

One obvious biological application of finite-element modelling, given the popularity of the technique in mechanical engineering, is in bone mechanics. The structural properties of bone are determined by non-cellular organic and inorganic components. It is only these components that are included in the simplest models. The potential exists to quantitatively assess an individual patient's risk of bone fracture, which has significant clinical implications in an ageing population. Currently, estimates of this risk are limited by the inability to cope with complex structural features within the bone. However, if the internal structure of a bone was determined *in vivo*,

using X-ray-based computed tomography, an accurate finite-element model could be built to estimate the maximum load that can be borne before fracture (Keyak *et al.* 1998). Finite-element models can aid surgical spine-stabilization procedures (Goel & Seenivasan 1994), thanks to their ability to cope well with the irregular geometry and composite nature of the vertebrae and intervertebral discs.

The acellular structure of real bone is modified continuously according to the internal stresses caused by applied loads. This process, which represents an attempt to optimize the strength-to-weight ratio in a biological structure, is achieved by interaction between two types of cell: the osteoclasts, which absorb bone; and the osteoblasts, which synthesize new bone. Finite-element modelling of this process is possible by combining the mechanical stresses that occur within bone with the ongoing process of density change that is driven by these internal stresses (Weinans *et al.* 1992). An accurate model of this combined process could be used clinically to determine the course of traction that will maximize bone strength during recovery from a fracture.

Another well-established area of mechanical finite-element analysis is in the motion of the structures of the mammalian middle ear. The geometry of the eardrum, combined with the three bones of the middle ear (the malleus, incus and stapes), ensures the efficient conduction of sound from the ear canal (which is filled with air) to the inner ear (which is filled with a liquid). Of particular interest are comparisons between the vibration pattern of the eardrum and the mode of vibration of the middle-ear bones under normal and diseased conditions. Serious middle-ear infections and blows to the head can cause partial or complete detachment of the incus from the stapes, and infected products can restrict the motion of the stapes itself. Draining of the middle ear, to remove these products, is usually achieved by cutting a hole in the eardrum. This invariably results in the formation of scar tissue. Finite-element models of the dynamic motion of the eardrum (Lesser & Williams 1988) can help to determine better ways of achieving drainage without significantly affecting the motion of the eardrum. Finite-element models can also be used to optimize prostheses when replacement of the middle-ear bones is necessary (Funnell *et al.* 1992).

Finite-element techniques can cope with large, highly nonlinear deformations, making it possible to model soft tissues such as skin. When relatively large areas of skin are replaced during plastic surgery, there is a problem that excessive distortion of the applied skin will prevent adequate adhesion. Finite-element models can be used to determine, either by rapid trial-and-error modelling or by mathematical optimization, the best way of covering a lesion with the available skin graft (Kirby *et al.* 1998). The brain is another organ that is mechanically soft. Certain brain disorders are associated with variations in pressure in the cerebrospinal fluid, which protects the brain from the hard skull. Imaging techniques can provide information about the resulting changes in brain shape, but finite-element models of the fluid–structure interactions have the potential to provide quantitative information about the forces exerted on the tissue itself (Tada & Nagashima 1994).

(*b*) *Electromagnetic fields in and around cells*

Of growing interest worldwide is the possible carcinogenic effect of low-frequency non-ionizing electromagnetic radiation, such as that emitted from power lines. Pos-

sible candidates for explaining sensitivity to electromagnetic fields are the gap junctions that exist between cells in many types of tissue. These junctions are similar to the protein-based channels that enable ions to pass across cell membranes, except that they span the extracellular space between adjacent cells. Gap junctions provide cells with a direct means of intercellular communication to coordinate the physiology of large populations of cells. Their properties also influence the regulation of cell growth and the cell's membrane potential and frequency response. There is some experimental evidence to suggest that the properties of gap junctions change in the presence of electromagnetic fields. Finite-element models provide a flexible and accurate way of assessing the effects of such changes on the operation of large systems of cells (Fear & Stuchly 1998).

(*c*) *Electromechanical interactions in the heart*

Given that heart disease is the single largest cause of death in North America and Europe, finite-element models of the mammalian heart have great potential clinical significance. The heart relies on interactions between several different physical phenomena, but many current models consider only, say, the electrical or the mechanical operation in isolation. Models that incorporate a heart into a complete body and include electromagnetic interactions are being developed.

The heart wall consists mostly of cardiac muscle, comprising millions of electrically activated contractile cells, called myocytes, that are typically 100 μm long and 15 μm wide (see figure 2). The myocytes are organized into fibre-like structures that are arranged at different orientations within discrete layers, resulting in a general anisotropy in the tissue's conductivity. Cardiac contraction is activated by an electrical impulse that is generated by cells in the heart's pacemaker. This impulse spreads rapidly through the tissue due to the high degree of electrical coupling between the myocytes (via gap junctions), ensuring that the whole organ contracts in a synchronized fashion.

A number of factors, including electric shock, deprivation of oxygen, or abnormally high levels of potassium or low levels of calcium in the blood, can cause malfunction of the conduction system. The resulting irregular contraction of the heart wall, or fibrillation, can be stopped by applying controlled electric shocks to the heart, either internally or externally. Patients at risk may be fitted with internal devices for supplying such shocks when they are needed. Maximizing battery life reduces the frequency of invasive surgery. Purely electrical finite-element models of the heart can aid optimization of the type of stimulation and positioning of such devices (Province *et al*. 1993), so as to minimize the energy required to arrest fibrillation. External defibrillation can be simulated in whole-body finite-element models (Sepulveda *et al*. 1990). Whole-body models can also be used in reverse, to aid in the interpretation of the skin-surface voltages induced by cardiac activity (i.e. the electrocardiogram). Unfortunately, the body does not behave simply as a solution of electrolytes in a leathery container. The huge variation in the conductivity of the intervening tissues (e.g. the resistivity of bone is 100 times greater than that of blood) greatly influences how energy passes between the heart and the skin. Performing subject-specific analyses could reduce existing discrepancies between models and experiments in both types of whole-body model. Unfortunately, the typical requirement for millimetre resolutions produces several million model nodes, and the resulting analysis times are currently too long to make this clinically useful (Schimpf *et al*. 1998).

Purely electrical models of the heart are only a start. Combined electromechanical finite-element models of the heart (LeGrice *et al.* 1997) take into account the close relationship that exists between the electrical and mechanical properties of individual myocytes (Kohl *et al.* 1998). The mechanical operation of the heart is also influenced by the fluid–structure interactions between the blood and the blood vessels (Balar *et al.* 1989), heart walls (Dubini & Redaelli 1997), and valves (Kunzelman *et al.* 1998). All of these interactions would need to be included in a complete description of the operation of the heart. The predicted growth in computing power should makes this feasible within the next decade.

5. A finite-element model of cochlear mechanics

While finite-element modelling of gap junctions occurs at a sub-cellular level, these models do not consider the operation of an entire organ. Conversely, in models of the complete heart, the discretization is usually on a millimetre scale. There is one organ that is being simulated on a 10 μm (i.e. cellular) scale: the mammalian cochlea.

(*a*) *The role of the cochlea in hearing*

The cochlea is the microphone of the auditory system, where mechanical motion at sound frequencies is converted into electrical signals in the auditory nerve. Although cochlear malfunction is not life threatening, damage to it adversely affects the ability of almost 1 billion people to communicate. Like the heart, the cochlea is an electromechanical device, but its operation occurs largely at a purely mechanical level, controlled by fluid–structure interactions on length-scales ranging from microns to millimetres.

In most mammals, the cochlea consists of approximately three turns of a circular duct, wound in a manner similar to that of a snail shell (figure 3*a*); hence the name, from the Greek word *kochlias*. The coiling is not thought to influence its operation. When stretched out, the duct is 25–35 mm long and has a cross-sectional area of 1 mm^2. The duct is divided lengthways into two chambers by the flexible cochlear partition. Sound stimulation is provided by the piston-like motion of the stapes bone, which is connected to the eardrum via the bones of the middle ear. This leads to a pressure differential across the partition that causes it to move. This motion commences near the stapes end of the cochlea, and is followed by motion at positions progressively further away, thereby giving the appearance of a travelling wave propagating away from the stapes (figure 3*b*). As this wave travels along the length of the cochlea, it increases in amplitude before reaching a peak and then dying away rapidly. The stiffness of the partition decreases away from the stapes, so that lower-frequency stimuli produce a peak further from the stapes. The cochlea thereby acts as a Fourier transformer.

The cochlear partition has three main components (figure 4): the basilar membrane, tectorial membrane and the organ of Corti. The organ of Corti contains two types of sensory hair cell: outer and inner, and a number of supporting cells. At each position along the cochlea, the supporting pillar cells couple vertical motion of the basilar membrane to a shearing motion between the tectorial membrane and the reticular lamina. This bends the stereociliary bundles that project from the top of both types of hair cell. These bundles contain ion channels whose electrical conductance changes with mechanical stimulation. The mechanical motion of the bundle

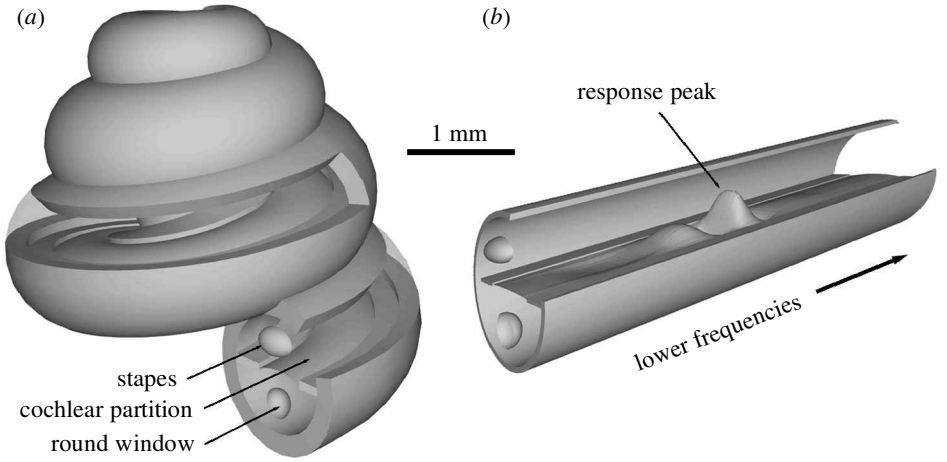

Figure 3. (*a*) The mammalian cochlea converts mechanical stimuli at sound frequencies into electrical signals in the auditory nerve. The cochlea consists of a liquid-filled duct, typically 30 mm long and 1 mm in diameter, which is wound into a spiral and embedded in the temporal bone. The duct is divided lengthways into two chambers by the flexible cochlear partition. Sound stimulation is provided by motion of the stapes bone, which sets up a pressure differential across the partition. The incompressibility of the cochlear liquid means that the stapes and the round window move in anti-phase. (*b*) An unwound portion of the cochlea nearest the stapes, showing the instantaneous displacement of the partition during sound stimulation at a single frequency. This wave of transverse motion propagates away from the stapes, reaching a peak before dying away. The stiffness of the partition decreases with distance, so, for lower-frequency stimuli, the response peak is further from the stapes. This enables the cochlea to act as a spectrum analyser by decomposing complex sounds into their individual frequency components. The sensory cells that convert partition motion into electrical signals in the auditory nerve are present along the entire length of the cochlea.

thereby modulates the flow of ions into the cell, causing changes in the potential across the cell membrane. This in turn modulates the release of neurotransmitter onto the nerve fibres that innervate the cell. Due to the pattern of innervation, it is the inner hair cells that are primarily responsible for providing the higher auditory centres with information about basilar membrane motion, whereby different frequencies are encoded onto different nerve fibres.

When the cochlea is functioning normally, the motion of the basilar membrane near the peak is boosted upto 1000 fold by forces exerted on it by the so-called cochlear amplifier (Davis 1983). The forces driving cochlear amplification most probably come from the outer hair cells. Like myocytes, these cells change their length in accordance with the electrical potential across the cell membrane. Motility in outer hair cells, however, is much faster (operating on a microsecond time-scale) than in myocytes, and it is bi-directional. It has been studied extensively, both *in vitro* (Ashmore 1987; Evans & Dallos 1993) and *in situ* (Mammano *et al*. 1995), but observations of the effects *in vivo* are severely hampered by the inaccessibility of the cochlea, which is embedded deep in the temporal bone, and its physiological vulnerability to surgical trauma. Modelling, therefore, has a potentially important role to play.

We now know that the remarkable sensitivity and frequency selectivity exhibited by the cochlea are properties that are established by the mechanical motion of the

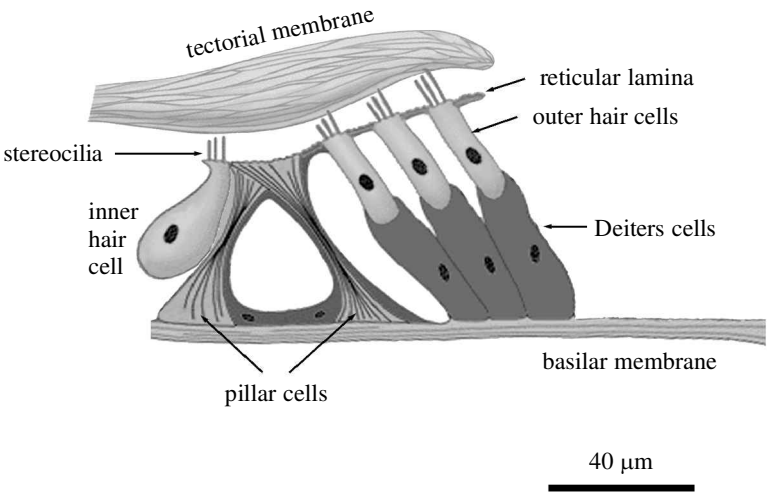

Figure 4. A cross-section of the partition at one position along the length of the cochlea, showing the organ of Corti sitting on top of the basilar membrane, and an overlying tectorial membrane. The organ of Corti contains two types of sensory cell (inner and outer hair cells) and two main types of supporting cell (pillar and Deiters cells). The triangular arrangement of the supporting pillar cells couples vertical motion of the basilar membrane, caused by hydrodynamic pressure across it, with the radial shearing motion between the reticular lamina and the tectorial membrane. This activates mechanical-to-electrical transduction within the stereociliary bundle of the sensory hair cells, leading to excitation of the nerve fibres. The supporting Deiters cells transmit the forces associated with outer hair cell motility to the basilar membrane. The structure depicted is repeated thousands of times along the length of the cochlea.

basilar membrane (Narayan *et al*. 1998). Eighty per cent of the significant hearing losses suffered by the population are attributable to pathological changes in this motion (Davis 1998), so an accurate understanding of the cochlear amplifier would have profound clinical significance. This requires characterization of the role played by each of the structures of the cochlear partition *in vivo*, while taking into account loading by the fluids that surround them. In comparison with the heart, the development of structurally realistic finite-element models of cochlear mechanics is in its infancy. Most cochlear models resemble the transmission line that finds applications in many areas of electrical engineering. Many of them are able to realistically simulate the gross mechanical response of the basilar membrane, but their formulation reduces the complex structure of the cochlea to just a handful of independent variables. The extreme vulnerability to trauma exhibited by the real cochlea prevents the experimental observations that could confirm the validity of the assumptions inherent in this process.

Finite-element techniques have already been applied to problems associated with cochlear mechanics, including the motion of the hair cell stereociliary bundle (Duncan & Grant 1997), and the stiffness of individual outer hair cells (Ulfendahl *et al*. 1998). They have also been used in complete cochlear models, with very simple representations of the organ of Corti, to investigate gross fluid motion both in two dimensions (Miller 1985) and three dimensions (Kagawa *et al*. 1987). Another study has modelled the organ of Corti with high structural accuracy and included nonlinear

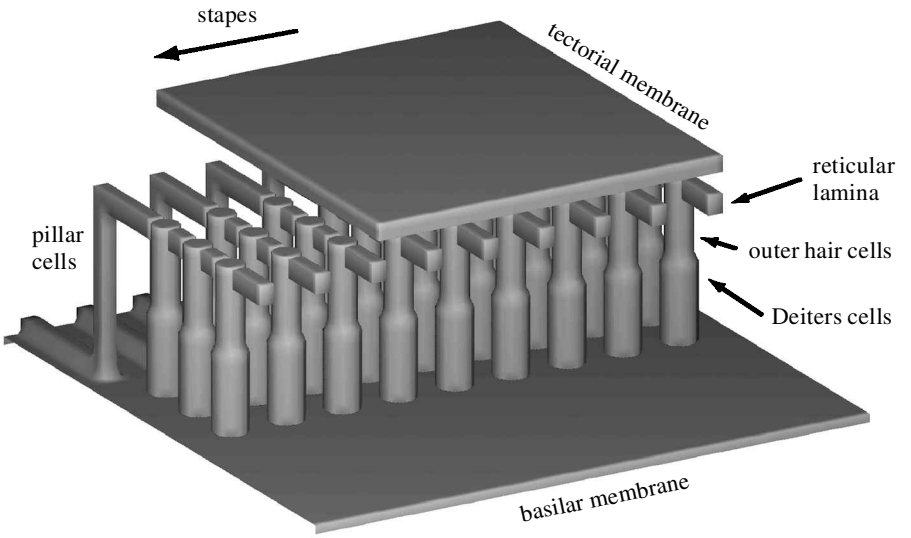

Figure 5. An oblique view of a 150 μm long portion of the partition of the finite-element cochlear model (the complete model is 30 mm long). The tectorial membrane has been partly removed to reveal the tops of the outer hair cells and the reticular lamina. Inner hair cells are not included as they play no role in cochlear amplification. An orthogonal discretization is used, with a resolution of 10 μm within the organ of Corti in all three dimensions. The basilar membrane is 180 μm wide, and the outer hair cells and Deiters cells are each 40 μm long. The cochlear partition is embedded within an inviscid, linear and incompressible fluid, and longitudinal fluid coupling is included over the entire cross-section of the model.

behaviour (Böhnke & Arnold 1998), but their analyses were limited to only a short (60 μm) section of the cochlea, and, most significantly, fluid–structure interactions were not included.

(*b*) *Model formulation*

The crucial question is: what simplifications should we use to retain as much structural realism as possible while ensuring that the model is solvable on present-day computers? My approach is to embed an orthogonal organ of Corti into the cochlear fluids (figure 5), which allows the use of a (relatively simple) finite-difference formulation. This model, referred to here as the 3-DOC model to emphasize the three-dimensional organ of Corti, is linear, since it is intended to simulate the effects of the cochlear amplifier during low-intensity stimulation only. Furthermore, stimulation is limited to pure tones, consistent with most experimental investigations. All of these simplifications mean that the model difference equations can be formulated in the frequency domain. This has made discretization possible at a cellular level: the complete cochlea is divided into 10 μm sections along its length, and 10 μm sections

Figure 6. (*Cont.*) membrane, driven by outer hair cell motility, is the characteristic of the cochlear amplifier that serves to increase both the sensitivity and frequency selectivity of the auditory system. With motility, the bottom of each outer hair cell moves more than the top (5), indicating that the basilar membrane is moving considerably more than the tectorial membrane. However, the uniform motion along the length of each Deiters and pillar cell is unchanged, due to their high axial stiffnesses.

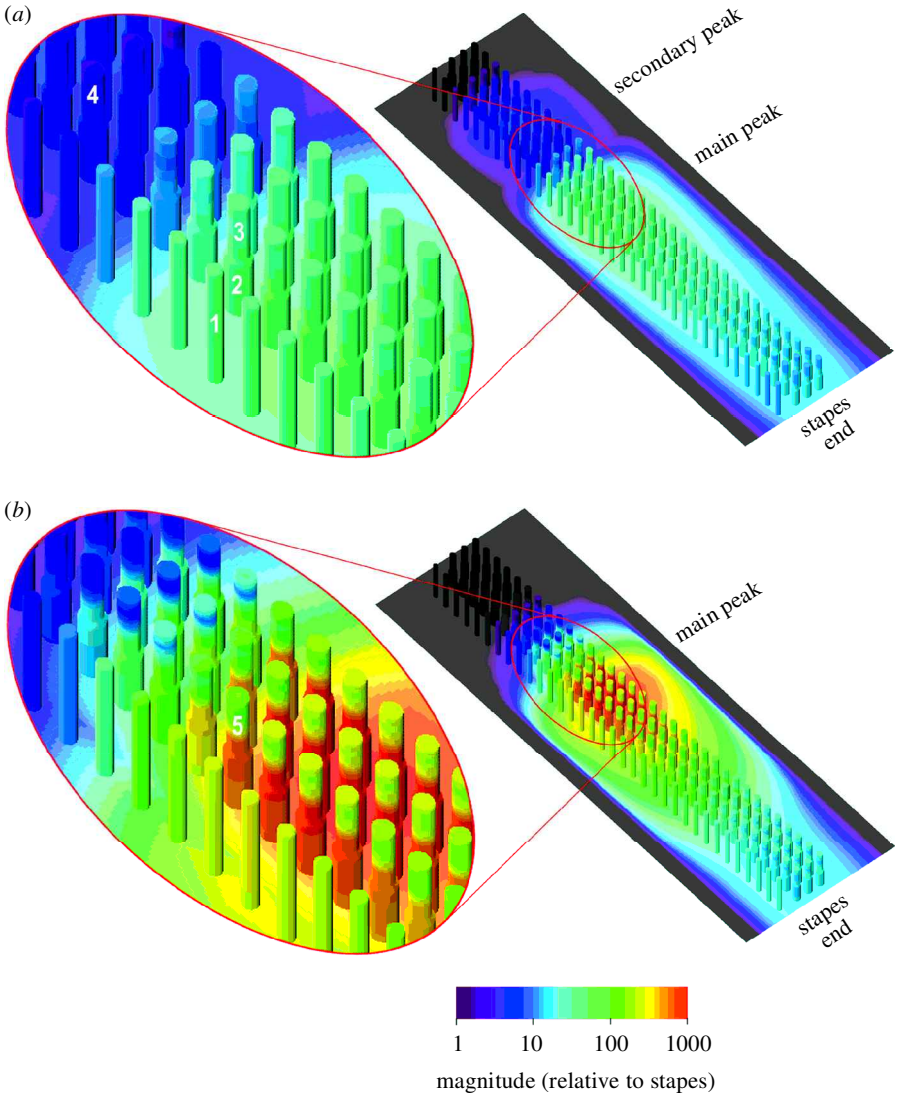

Figure 6. Magnitude of the motions of the basilar membrane, Deiters cells, pillar cells and outer hair cells, relative to that of the stapes, in the 3-DOC model during sound stimulation at 30 kHz, in the absence (*a*) and presence (*b*) of normal outer hair cell motility (330 pN nm^{-1}, expressed as axial force versus deflection of the stereociliary bundle). The reticular lamina and tectorial membrane have been figuratively peeled away. The viewing angle is different from that in figure 5; here we are looking down on the basilar membrane from above and behind the pillar cells. Scale varies in the figures, with only the first 5 mm of the model basilar membrane shown since no significant motion occurred beyond this point. Only a small fraction of the 5000 cells present in this region of the model are displayed. With no motility (*a*), the motion throughout the model is the same along the length of each pillar cell (1), Deiters cell (2), and outer hair cell (3), except in the transition region between the main and secondary peaks, where there is a slight variation along the length of the outer hair cells (4). The main effect of the addition of outer hair cell motility (*b*) is to dramatically increase the motion near the peak, with little change occurring near the stapes. This place-dependent increase in motion of the model basilar

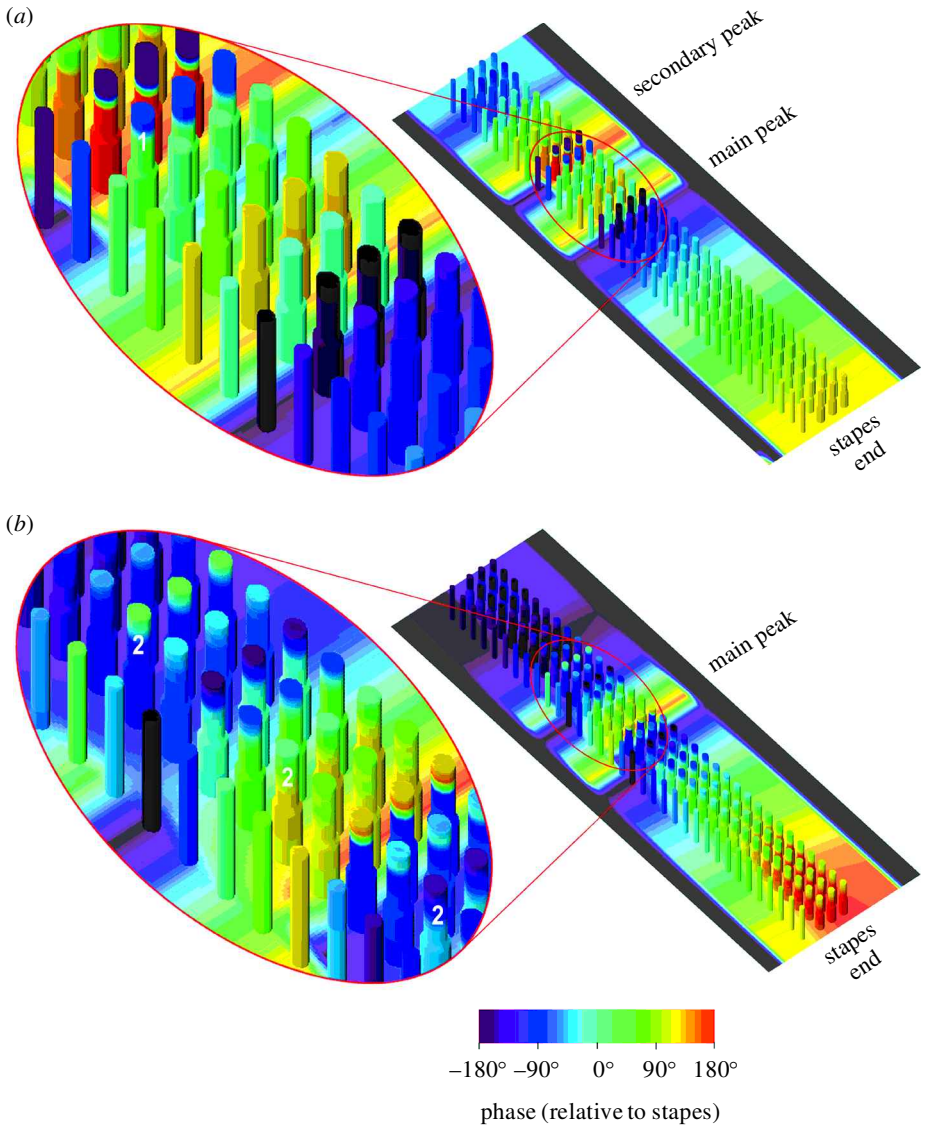

Figure 7. Phase of the motions of the basilar membrane, Deiters cells, pillar cells and outer hair cells, relative to that of the stapes, in the 3-DOC model during sound stimulation at 30 kHz, in the absence (*a*) and presence (*b*) of normal outer hair cell motility. The positions of the main and secondary magnitude peaks (from figure 6) are indicated. With no motility (*a*), the longitudinal accumulation of phase exceeds 360°, indicating the presence of a travelling wave. There is no variation of phase across the width of the basilar membrane except in the transition region between the main peak and the secondary peak. Here, the phase also varies along the length of each outer hair cell (1), due to the radial motion of the tectorial membrane being greater than, and not in phase with, that of the reticular lamina (data not shown). This behaviour is consistent with the tectorial membrane mass-loading hypothesis. With motility (*b*), the significant variation in phase across the width of the basilar membrane throughout the model is reflected in a difference between the top and the bottom of each outer hair cell (2). There is no variation in phase along the length at each pillar and Deiters cell.

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vertically and radially within the organ of Corti. When the resulting 1 000 000 (or so) system equations are expressed in matrix form, most of its entries are equal to zero. This is typical of finite-element formulations, and makes analysis of the matrix particularly amenable to distributed, parallel algorithms. The parameters used for the individual model structures in the 3-DOC model are based on recent experimental measurements *in vitro* and *in situ* (see Kolston (1999) for a full listing). The model was simulated using self-written software running on a commodity computer (see Kolston & Ashmore (1996) for full details).

(*c*) *Response of the model*

It is crucial to understand the effect that outer hair cell motility has on motion within the organ of Corti. The high spatial resolution of the 3-DOC cochlear model enables the visualization of this motion at a cellular level. Figures 6 and 7 show, respectively, the magnitude and the phase of the motion in the model during sinusoidal sound stimulation, with each figure divided into two parts relating to the presence and absence of normal outer hair cell motility. Comparing the responses under these two conditions can give valuable insight into how the cochlear amplifier operates.

Figure 6*a* shows that with no motility the magnitude of the model basilar membrane increases gradually with distance from the stapes, before reaching a peak and rapidly dying away. Beyond the main peak, the presence of a smaller secondary peak is consistent with the hypothesis that the tectorial membrane contributes mass rather than stiffness loading to the organ of Corti (Zwislocki 1980; Gummer *et al*. 1996). Figure 6*b* shows that the main effect of the addition of outer hair cell motility is to dramatically increase the motion near the main peak. The place-dependent increase in motion of the model basilar membrane, driven by outer hair cell motility, is the characteristic of the cochlear amplifier that serves to increase both the sensitivity and frequency selectivity of the mammalian auditory system. Figure 7*a* shows that with no motility the phase of the basilar membrane motion increases monotonically with longitudinal distance, and there is no variation in phase radially across the width of the basilar membrane. Figure 7*b* shows that the addition of outer hair cell motility produces a significant variation in the phase of the motion, both radially across the basilar membrane and between the top and the bottom of each outer hair cell throughout the model.

(*d*) *Comparisons with experimental data*

The gross motion of the model basilar membrane is consistent with experimental observations made at this level *in vivo* (see, for example, Narayan *et al*. 1998), but there are several much simpler models that share this attribute (de Boer 1996). The uniqueness of the 3-DOC model is that the addition of the cochlear amplifier results in complex motion both on the basilar membrane and within the organ of Corti. Comparable experimental data are not yet available, but variations in the motion of the basilar membrane across its width have been observed recently *in vivo* (Nilsen & Russell 1999). More importantly, perhaps, the model's behaviour is consistent with unresolved experimental observations of the effects of the efferent neurotransmitter acetylcholine. In the real cochlea, the amount of cochlear amplification decreases during stimulation of the efferent fibres (Murugasu & Russell 1996). Paradoxically,

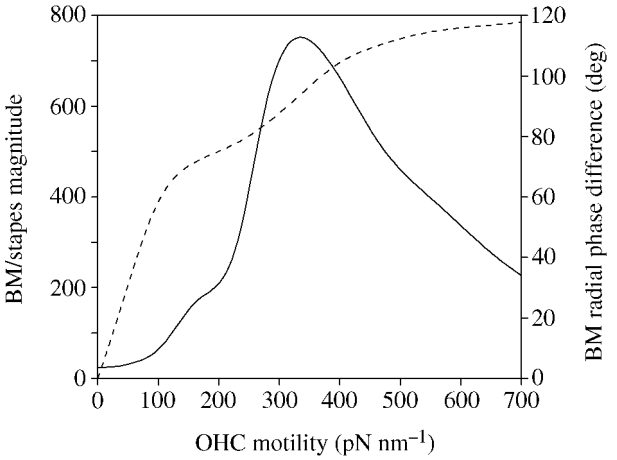

Figure 8. Motion of the model basilar membrane (BM) at the main peak during sound stimulation to the stapes (30 kHz), as a function of outer hair cell (OHC) motility. The solid line shows the magnitude of the motion, relative to that of the stapes, beneath the outer row of outer hair cells. The dashed line shows the phase difference between motion at the outer edge of the pillar cells and motion beneath the furthest row of outer hair cells. The non-monotonic variation of magnitude with motility in the model is consistent with paradoxical experimental observations of the effects of the efferent neurotransmitter acetylcholine *in vitro* versus *in vivo*.

application of acetylcholine onto outer hair cells *in vitro* increases motility (Dallos *et al*. 1997). These experiments were simulated in the 3-DOC model by increasing motility above its normal value of 330 pN nm^{-1} (expressed as the axial force at each of the cells divided by the displacement of the stereociliary bundle). Surprisingly, the model's response is entirely consistent with the experimental observations, in that enhanced motility leads to a decrease in the gain of the cochlear amplifier (figure 8). This behaviour is the direct result of the radial asymmetry exhibited in the response of the 3-DOC model in the presence of outer hair cell motility, whereby increased motility leads to an increase in radial phase variation.

The model can provide unique insights into how the response of the cochlea is produced, due to the comparative ease with which its response can be analysed, for example, by studying pressure and velocity in the model with a 10 μm resolution. Analysis of the model (Kolston 1999) reveals that the cochlear amplifier works by adding mechanical energy to the basilar membrane beneath the outer hair cells and increasing the resistance beneath the pillar cells. The relative importance of these two processes varies with the amount of outer hair cell motility, which is, in turn, responsible for the paradoxical observation.

A crucial issue in cochlear mechanics is the identification of the processes responsible both for hearing disorders and the extreme vulnerability of the cochlea to surgical trauma. This could be addressed by systematically modifying the model parameters in order to determine which most directly affect the normal operation of the cochlea. Pharmacological interventions could then be used in animal models to replicate the observations. The results of preliminary investigations of this type suggest that the response of the 3-DOC model is most sensitive to the stiffness of the stereociliary bundle and to the properties of the tectorial membrane. Antibodies raised to the

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real tectorial membrane could be used to alter its properties, and the effects may be observed *in vivo*. If this verifies the model-based hypothesis, the 3-DOC model could be used to see if modifications to other structures could offset the negative effects of the vulnerable process. Any promising results could again be tested *in vivo*.

(*e*) *An advanced model for the new millennium*

The paradoxical effects of acetylcholine in the 3-DOC model are consistent with the hypothesis that behaviour at organ level is impossible to predict from that of individual cells in isolation. This reinforces the view that finite-element models can provide insights into the operation of biological organs that are impossible to obtain using simpler modelling strategies. However, the 3-DOC model is not the definitive description of the real cochlea. Several aspects of the model will need modification as more data on both the structural parameters and motion within the organ of Corti become available.

The most demanding improvement needed will be switching analysis from the frequency domain to the time domain. Time-domain analysis will extend the model's capabilities greatly, enabling the inclusion of nonlinear behaviour, simulation of the response to non-steady-state stimuli such as speech, and the generation of sounds by the ear. These sounds, that are emitted from the ear, have properties that are related directly to the operation of the cochlear amplifier. A full understanding of the mechanisms responsible for their generation would be of great importance clinically, since they can be monitored without the need for invasive surgery. The main problem with time-domain analysis is that the model equations must be solved hundreds, if not thousands, of times for each stimulus. This contrasts to frequency-domain analyses, in which they are solved only once. Given that each simulation of the model takes several hours (on a processor capable of 300 million instructions per second), it is not feasible to use time-domain methods on a computer of moderate cost without severely compromising the spatial resolution. However, the predicted 100 fold improvement in computing power over the next decade will make time-domain finite-element analysis of the cochlea at a cellular level an affordable proposition.

6. Looking further into the future

We are at the threshold of a new era in biological research. Finite-element computer models are transforming our understanding of complete organs. Some organs, such as the cochlea, are already being modelled at a cellular level. Other organs, such as the heart, are represented by models that are more structurally accurate, they incorporate interactions between different forms of energy, and they are analysed in the time domain (Kohl *et al*., this issue). These different strategies for balancing structural realism against spatial resolution will converge as computing power increases over the coming decade. The resulting structurally realistic cell-level models will improve our ability to properly characterize and quantify experimental observations, and dramatically reduce the need for animal experimentation.

(*a*) *2020*

It is difficult to predict developments beyond the first decade of the new millennium. However, there are two arenas in which modelling and biology may converge

even further: developmental biology and carbon-based computing. Developmental biology is an area of experimental research that is expanding rapidly. Current tissue-based work on cochlear regeneration highlights the difficulties of artificially controlling the development of structurally complex biological systems. Rather than attempting to replicate the existing organ of Corti, we could use finite-element models to predict the degree of mechanical amplification that could occur in regenerated hair-cell-based sensory epithelia, whose structure and properties are quite different from those of the normal organ of Corti. Biological, carbon-based implementations of the simplified organ could be constructed using genetic techniques, both by manipulating the function of individual cells and controlling the way in which the developing cells form the structure. The development process itself is amenable to finite-element analysis (Hardin & Keller 1988), since it is driven mainly by local effects. The replacement organ could be constructed from cells obtained from the eventual organ recipient, bypassing the problems associated with tissue rejection during transplantation. Conversely, silicon-based implementations of the simplified model could be used in signal-processing applications. For example, a silicon cochlea could form the front-end of a speech-recognition system with a performance superior to any designed by an electrical engineer.

Our ability to model replacement organs will depend critically upon the availability of sufficient computing power. In the second decade of the new millennium, it is highly likely that silicon-based computing will have reached fundamental technological or physical limits. Computers will, therefore, be based on substrates that exhibit superior performance characteristics. One possibility is the photon. Optoelectronic devices, which use substrates such as gallium arsenide, permit the interconversion of electrons and photons. Hybrid computers, which may already be available commercially by 2010, would use silicon for computation and photons for data transfer. The coherent modulation of very-high-frequency light beams (5×10^{14} Hz) enables many high-bandwidth signals to be multiplexed onto a single beam, taking up little space and not interfering with cooling air. In, say, 20 years, a fully optical computer would integrate lasers with optical modulators and photodetectors, and could operate at clock rates into the terahertz region.

(*b*) *2050*

Decades beyond the new millennium we may see the ultimate combination of biology and modelling: finite-element models being implemented on carbon-based computing platforms. Carbon shares silicon's electron valency, making it a viable semiconductor. But carbon's real potential lies in its unrivalled ability to form compounds of very high molecular weight, which has made it suitable for the encoding and processing of the huge amount of information required to construct a human being. It is a logical step to consider using DNA code and associated enzymes, which have been developed and refined over billions of years of evolution, to construct a carbon-based computer. Such a device could exist in a test tube, into which DNA-like molecules containing the input data would be placed, and recombinant DNA techniques used to perform the processing function. The output would be the resulting new 'genetic' combinations. A carbon-based computer would be compact (information on DNA is stored at a density of 1 billion bits per cubic micron), fast (trillions of strands of DNA could be processed in a single biochemical operation), and efficient (10 trillion operations per microjoule of energy, close to the theoretical limit

dictated by the second law of thermodynamics; see Adleman (1994)). These performance levels represent a one-million fold improvement over present-day computers, which means that the current rate of exponential growth in computing power will be sustained for another half century if carbon-based computers do become commodity items by 2050. It may then be feasible to implement a finite-element model of a complete human at a cellular level.

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Born in Wellington, New Zealand, Paul Kolston studied at Canterbury University (NZ), where he graduated in 1985 with first class honours in electrical and electronic engineering. He obtained his PhD there in 1989, having spent one year of his PhD studies at the Delft University of Technology, The Netherlands. After a one-year postdoctoral position at the University Hospital, Utrecht, The Netherlands, he moved to Bristol University (UK). In 1995 Paul was awarded a Royal Society University Research Fellowship, which he transferred to Keele University in 1999. Aged 37, he is married with four infant children. Paul's favourite scientific interest is computer modelling of biological systems; his favourite recreational pursuit is body-surfing.

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