18th World IMACS / MODSIM Congress, Cairns, Australia 13-17 July 2009
http://mssanz.org.au/modsim09

Multiscale mathematical modelling in medicine and biology

S.J. Chapman[1]
[1]OCIAM, Mathematical Institute, 24-29 St Giles', Oxford OX1 3LB

Abstract: The application of mathematical modelling to various problems arising in medicine and biology is considered. The benefits of mathematical modelling are highlighted, and the need for multiscale models in particular is discussed. Mathematical methods for formulating, simplifying and extracting key information from multiscale models are described. Examples are drawn from heart modelling, ultrasound contrast agents, the oxygenation of tissue and drug delivery.

Keywords: *Mathematical modelling, life sciences, multiscale, homogenisation, matched asymptotic expansions, integration.*

1 Why use a mathematical model?

Until relatively recently medicine and biology have been largely empirical sciences. Lacking some of the universal laws of the physical sciences, the life sciences are less amenable to mathematical models[1]. However, in the last forty years or so mathematical biology has become very popular, and in the last ten years or so the explosion in quantitative experimental data has meant that models are both more necessary and better validated/parameterised.

But why use a mathematical model? The development of any mathematical model has two main aims, (i) understanding; and (ii) prediction. A key question in the mind of any modeller is, what are the minimal ingredients needed to make the results of a model match with experiments? Which are the dominant effects, which are secondary, and which are negligible? In many respects the simpler the mathematical model, the greater the understanding. For example, if one were to incorporate all the currently available data on the heart, from structural geometry down to genetic pathways, into a mathematical model then the resulting complexity would be such that one has simply replaced a biological system one cannot understand by a computer model that one cannot understand. A good example of the way in which simplicity can give rise to understanding is the circuit diagram of a radio. For any commercial radio this would be quite complicated, containing many transistors, capacitors and resistors which are necessary for the robust working of the radio, but which make it hard to see *how* the radio works. Now strip the circuit diagram down to the familiar LCR circuit of a single inductor, capacitor, and resistor, and the mechanism for resonance at certain frequencies becomes apparent.

Simple mathematical models have other benefits over more complex ones. They tend to have fewer unknown parameters, and so are easier to fit to data (fewer experiments are needed). There is also less chance of "overfitting". With enough free parameters a model can be made to fit any data; however, at best the exercise may be little more than curve fitting (with little understanding gained), while at worst the model may give an overconfidence in its predictive ability. A simple example to illustrate this point is polynomial interpolation. Suppose we have 4 data points linking two variables, and we wish to find a "law" linking the variables, as illustrated in Figure 1. We can fit the data with a constant (one-parameter model), a straight line (two-parameter model), a quadratic curve (three-parameter model) or a cubic curve (four-parameter model), and the "error" between the curve and the data is reduced each time we increase the number of parameters. However, most people would quite rightly not expect the cubic curve to give a much more accurate prediction than the linear curve for additional data points.

This brings us onto the second main motivation for constructing a mathematical model, which is prediction. We can use a model to make predictions about the results of experiments we have yet to conduct. This may be used to forecast into the future (as in weather forecasting), or to conduct experiments which are too difficult or costly to carry out directly (for example by predicting the location of oil reserves through seismology).

As well as these two general reasons for undertaking mathematical modelling, there are other more specific benefits of mathematical modelling in the life sciences, as we now briefly discuss.

Diagnosis At present diagnosis of disease is usually made by a trained professional examining the available data (images, patient feedback, diagnostic tests) and coming to an informed estimate of the likelihood of a particular condition. Often gigabytes of imaging data is compressed into a single number—a score on a scale which measures severity of a condition for example. As even more and better data is becoming available it is getting harder to manually integrate all the necessary information. Mathematical models can help in turning observational data into a likelihood of disease. This can be in any number of ways, ranging from a simple extension of the scoring methodology to multiple key characteristics (multiple scores), to a translation of imaging data into clinically relevant parameters. For example, ultrasound measurements of

[1] Of course, at the right scale biology is simply physics (and beyond that chemistry), but that is often not the scale of interest.

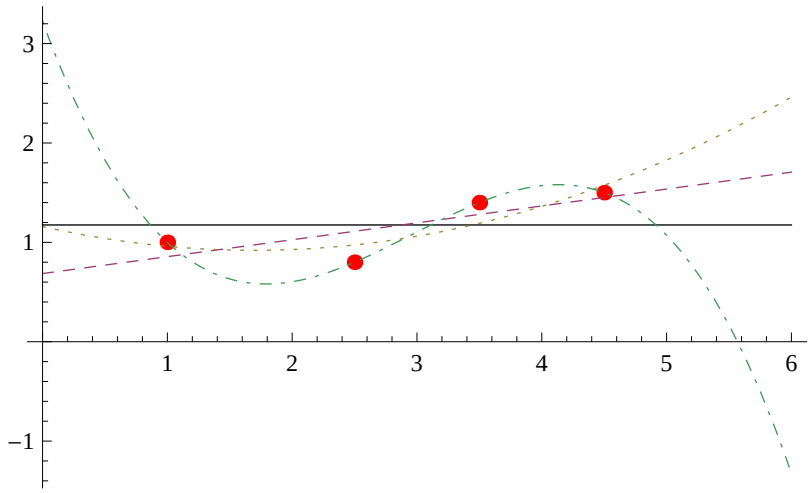

Figure 1: Polynomial interpolation through four points, showing a constant (solid), linear (dashed), quadratic (dotted) and cubic (dot-dashed) interpolation. The mean equare error for these is 0.57, 0.37, 0.28 and 0 respectively.

tissue displacements can be converted to tissue stiffness, which may be a better indicator of tumour location [7]; or perfusion images of the heart can be converted to effective permeabilities, giving a better idea of possible occlusions.

Mathematical methods can also be used to integrate the range of data from different sources (some of which may be contradictory) to give an overall probability of disease.

Technology transfer Mathematics is a universal language, and as such there are many opportunities for the transfer of knowledge from one field to another. For example, a modern technique for imaging blood vessels consists of injecting microbubbles into the blood stream before imaging with ultrasound. The bubbles oscillate in response to the insonification, and this oscillation produces further sound waves. Crucially the response of the bubbles is nonlinear, while scattering and reflection from changes in tissue stiffness within the body is linear. Thus if equal and opposite ultrasound pulses are used, and the corresponding returning waves summed, any linear response will cancel leaving only the nonlinear response of the bubbles, which are then clearly identifiable. Mathematical models for acoustic waves through bubbly fluids have been developed since the 1940s, with the application being sonar use in the ocean. Though the scales between this application and acoustic contrast agents are quite different, the mathematical models are very similar.

A second example concerns flow through blood vessels, and in particular those inside a tumour, which tend to be poorly formed and leaky. Models for flow through a porous material containing channels have been developed in the oil industry for modelling fractured rock. The result is a double-porosity model, in which two porous materials are supposed to coexist, one representing the fine scale of the rock pores, and one the fissures, with fluid transfer possible between the two. Here again, the scales are very different, but the mathematical models are very similar.

Framework Mathematical models provide a framework for interpreting and integrating data. New data can be interpreted by its implication after passing it through the model.

A good example of the way in which a model has become the main way for interpreting data is the Black-Scholes model in mathematical finance. This is a model for calculating the theoretical fair price of

Figure 2: Schematic diagram of the hierarchy of scales involved in (for example) modelling the heart.

a security derivative (usually an option) given the drift and volatility of the underlying security (usually a share). This model is so ubiquitous in financial circles that market-driven option prices are often quoted by their implied volatility, that is, what the volatility of the stock would have to be if the market price was to be equal to the theoretical Black-Scholes price.

Extracting information Mathematical models allow us to extract information from data by integrating it into a biological framework. We have already used a simple example of this above: a mathematical model can be used to convert ultrasound images of displacement (data) into estimates of tissue stiffness (information).

In silico experiments Armed with a good mathematical model we can interrogate it in ways which may be expensive, unethical or even impossible in the laboratory. We can test out the results of clinical procedures or drug administration before they are carried out. Models can also be used to suggest new drug targets and treatment protocols.

Inform biological experiments Mathematical models can be used to select appropriate biological experiments and to rule out inappropriate ones. As well as reducing cost (which is one of the main reasons mathematical models are used in this way in technological industries) this can help to reduce and replace animal experiments.

In this context it is important to appreciate that all experimental models present a compromise between relevance (man would be the ideal subject for study), reproducibility (test-tube type work with the fewest degrees of freedom would be ideal) and cost. This means that modern research work requires experimentation at a multitude of levels of complexity to be successful. Model selection, interrelation between levels of investigation, and interpretation is vastly improved by application of the matching theoretical models.

Having sung the praises of mathematical modelling, we finish this section with a brief warning about the dangers of mathematical modelling. The main pitfalls are overfitting and overinterpretation. We have already discussed the problem of overfitting. Overinterpretation arises when too much faith is placed in a model. A model is only as good as its underlying assumptions and most models have a very limited range of applicability. Often the developer of the model is acutely aware of its limitations. But once a model is in the open literature it may be taken up by others and used outside its real range of validity. All models, especially in the life sciences, should be treated with a degree of healthy scepticism.

2 Multiscale modelling

2.1 Need

To understand function and disease in biology requires modelling and coupling phenomena which occur on many different length and time scales, as illustrated in Table 1. The mathematical challenges are (i) developing models at each scale; (ii) integrating models at different scales; (iii) extracting minimal models without oversimplifying; and (iv) extracting macroscopic variables from microscopic models and vice versa.

As an illustrative example, consider the heart. Its primary function, to pump blood around the body, emerges from a long chain of processes beginning with the genetic regulation of transporting proteins within

Lengthscales	
1 m	person
1 mm	electrical length scale of cardiac tissue
1μm	cardiac sarcomere spacing
1 nm	pore diameter of a membrane protein
Range = 10^9	

Timescales	
109 s (70 years)	human lifetime
106 s (10 days)	protein turnover
103 s (1 hour)	digest food
1s	heart beat
1 ms	ion channel gating
1μs	Brownian motion
Range = 10^{15}	

Table 1: Length and timescales of mathematical modelling in the life sciences

cardiac cells. This ensures that the ion transport mechanisms via the cell membrane proteins function correctly, and leads to the propagation of an action potential throughout the cardiac muscle fibres. The fibres contract in the appropriate sequence in response to this potential, giving rise to the pumping action. In fact, even this description is simplified—the electrical and mechanical processes are highly interdependent with feedback mechanisms in place throughout the hierarchy of lengthscales.

The description at the organ scale involves macroscopic quantities from continuum mechanics: blood flow, active and passive changes in stress and strain, chemical concentrations, and electric potentials. The quantities that are measured clinically, such as the ECG, do not usually allow reverse mapping to underlying chemo-electro-mechanical mechanisms. On the other hand, our understanding of the processes occurring at the cellular and especially subcellular level has grown enormously over the past few years, and will continue to do so. The challenge is to link this detailed finescale information, through processes occurring at a hierarchy of different length and time scales, to macroscale effects of function and pathology of tissues and organs, as illustrated in 2.

At present there is a need for a transfer of technology from scientific areas in which modelling of multiscale phenomena is well-developed into biology and medicine. This is crucial to research in the life sciences and provides a wealth of new and exciting challenges to the mathematician, since biological processes interact over such a vast range of time and length scales. For example, the rhythm of the heart may both be disturbed and corrected by mechanical means (mechanically-induced sudden cardiac death, precordial thump for resuscitation). This clinically highly relevant issue needs to be reconciled with experiments at lower levels of functional integration (cells, tissues, isolated hearts) as these experiments can, for obvious reasons, not be performed on patients. This requires a consideration of length scales from at least micron to decimeter (i.e. from sarcomere length to organ dimensions) and time scales from milliseconds to minutes (i.e. from impact duration to clinically relevant cessation/restoration of heart rhythm). A similar range of length scales is relevant to cancer growth, with timescales ranging at least from seconds to years (i.e. from drug delivery timescales to tumour growth and metastasis).

At each scale more and more data is being generated daily. If one were to incorporate all the data at each level, the complexity of the model would increase exponentially and, as we have already mentioned above, one would simply replace a biological system one cannot understand by a computer model that one cannot understand (nor compute in any feasible time). Instead it is necessary to develop a hierarchy of models, each of which significantly reduces the model at a finer scale and extracts only key coarse grained information. In

this way, the complexities at one level of the hierarchy can be encompassed in a small number of parameters (or, more generally, functions or equations) and these can then be incorporated into the next scale in the hierarchy. Such an approach leads to a greater intuition and understanding of key phenomena at each level.

The mathematical approach to multiscale modelling has been very successful in materials science, in which many of the same questions arise. There it is important to be able to predict the bulk properties of a material given a detailed knowledge of its microstructure. One important example is the hierarchy of models from atomistic simulations, through models of individual dislocations in elastic crystals, dislocations densities, and finally models of crack propagation and plasticity. The mechanics community has not as yet attempted a similar approach with biological materials, which are far more complicated than even the most difficult of those normally considered in materials science, not least because the cells are mechanically active, and in the case of cancer may grow and divide or die over timescales of interest. Moreover, while in materials science one is homogenising over identical entities, in biology, each entity has its own highly dynamic characteristics (for example, even cells of specific type are not identical to each other). This means that an over-arching framework of an integrated model must be developed in such a way that "modules" describing each level of complexity can be fitted in as they are required. It also means that one can not simply address the issue within a single research project or team. Rather, progress will arise as the result of a large integrated effort in which teams of researchers investigate different levels, and where theoretical and experimental studies iterate at every step.

An illustration of the success of the multiscale approach is the Hunter-Noble heart model, which integrates many different aspects of cardiac function, from the subcellular to whole organ levels [6, 8].

2.2 Methods

We now describe briefly some of the methods of multiscale modelling which have been applied in mathematics.

The simplest problems to homogenise are those in which a fine scale model can be coarsened (averaged) to produce key data for a coarser level model. Here the averaging is done just once, and then we are done with the fine scale model (until such time as we require the more detailed information it provides). For an example of this type of coarse graining, an atomistic model of a metal could be used to evaluate, ab initio, its shear and bulk moduli. Having found these two parameters the coarse grained model (the equations of elasticity) can then be solved, without further reference to the fine scale atomistic model.

Many multiscale problems do not decouple so easily—the microscale problem depends on the macroscale variables, so that the fine scale problem cannot be decoupled from the coarse scale problem. For example, for fluid flow through a network of vessels the fine scale structure of the flow depends on the (coarse scale) pressure gradient. Or, for the propagation of acoustic waves through a bubbly fluid, the amplitude of oscillation of the bubbles depends on the (coarse scale) background pressure.

In such cases there are two basic approaches to homogenisation. If the individual units (the bubbles or blood vessels) are small by comparison to their separation (so that they occupy a small volume fraction), then the method of matched asymptotic expansions can be used. This method is illustrated in Figures 3 and 4.

In each example there are three scales to consider. On the fine scale the geometry is much simplified, and we have a single isolated unit (bubble or blood vessel). By solving these canonical problems we can determine the response of the unit to external forcing. If we zoom out a bit to the intermediate scale (b), then we see a discrete set of units, with each unit having a response function which has been determined in (a). If we zoom out further then the units become more and more densely packed, and on the coarse scale (c) we lose the details of the geometry and see only the effective material properties. The method is applied to microbubbles in [1, 9] and blood flow in [3].

This method works well providing there is a good separation of scales between (a) and (b), that is, between the size of an individual unit and the distance between neighbouring units. This means that the units must occupy a small volume fraction.

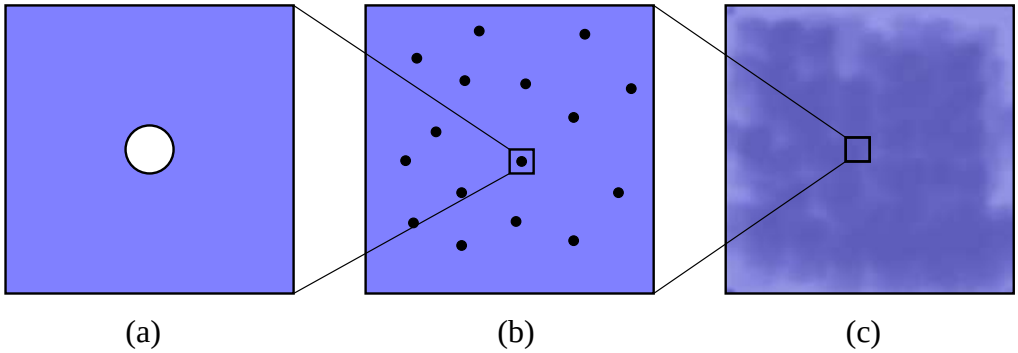

Figure 3: An illustration of the method of matched asymptotic expansions for the propagation of acoustic waves through a bubbly fluid. The fine scale (a) corresponds to the oscillation of a single bubble; on the intermediate scale (b) the bubbles acts as discrete point sources of acoustic waves; on the coarse scale (c) the bubbles act as an effective compressible material medium.

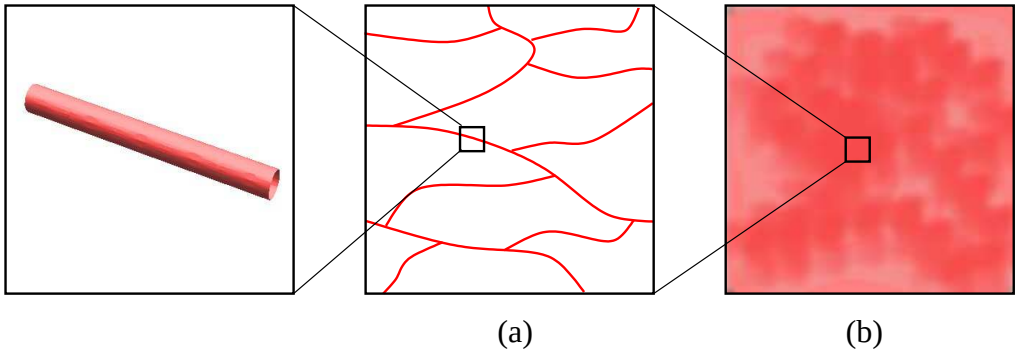

Figure 4: An illustration of the method of matched asymptotic expansions for the flow of blood through a vascular network. The fine scale (a) corresponds to the flow down a single vessel; on the intermediate scale (b) the vessels act as a discrete network; on the coarse scale (c) the vessels act as an effective porous material.

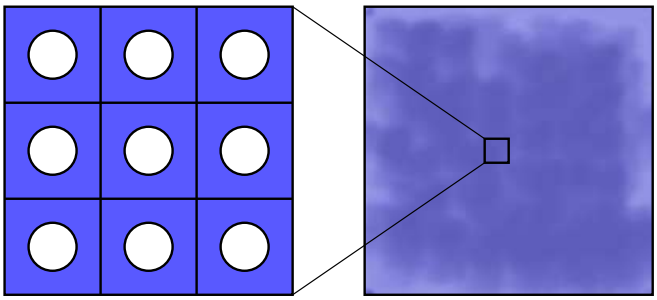

Figure 5: An illustration of the method of multiple scales for the propagation of acoustic waves through a bubbly fluid. The fine scale (a) corresponds to wave propagation through a periodic array of bubbles; on the coarse scale (b) the bubbles act as an effective compressible material.

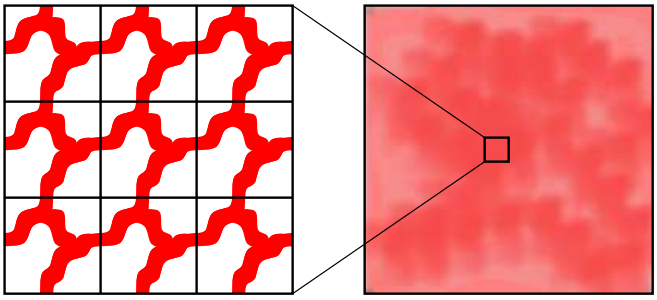

Figure 6: An illustration of the method of multiple scales for the flow of blood through a vascular network. The fine scale (a) corresponds to the flow through a periodic network of vessels; on the coarse scale (b) the vessels act as an effective porous material.

If the volume fraction of units is not small, so that the separation of units is comparable to the size of an individual unit, then we need to turn instead to the method of multiple scale, illustrated in Figures 5 and 6.

Now there are only two scales to consider. On the fine scale (a) the medium is assumed to be periodic, though the "unit cell" may vary from place to place on the coarse scale, as illustrated in Figure 7. The procedure is then to separate the fine and coarse scales in the solution, treating them as independent. The extra freedom this gives is removed by imposing that the solution is periodic on the fine scale, so that any modulation is captured by the coarse scale. The method is applied to microbubbles in [2] and blood flow in [4].

Sometimes the fine scale problem (known as the cell problem) can be "factorised", so that the solution becomes a product of a function of the coarse variable and a function of the fine variable. In this case a canonical cell problem can be formulated, independent of the macroscale variable. This canonical problem can then be solved just once, analytically or numerically, and the coarse gained model decouples from the fine scale model—effectively it has been possible to integrate out the fine scale. Both fluid flow through blood vessels and acoustic propagation through microbubbles are of this form. For example, for the blood flow problem, given the geometry of the unit cell a single cell problem can be solved (usually numerically) which then determines the effective porosity of the coarse scale porous medium problem.

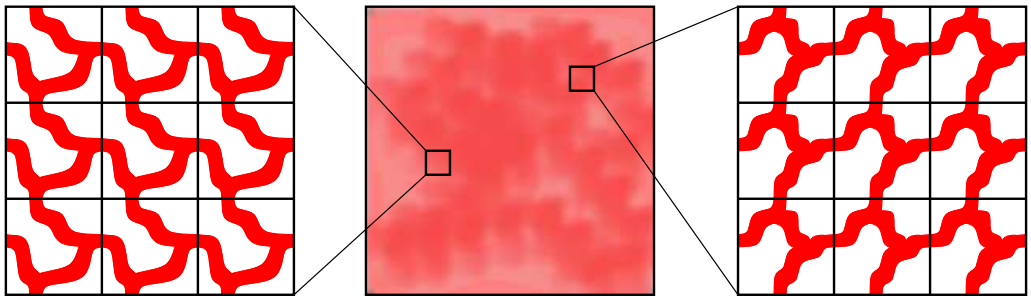

Figure 7: An illustration of the way the unit cell in the method of multiple scales may vary from place to place on the coarse scale. Looking locally near each point in the coarse model the fine scale structure is assumed to be periodic, but the details of this structure may vary from point to point.

It is important to note that the fine details are not lost in this averaging process—if we are really interested in the fine scale solution it can be reconstructed from the coarse scale solution and the cell problem.

If the cell problem does not factorise then we are left with solving a different fine scale cell problem at each point of the coarse scale—the two scales are intrinsically linked. In this case the cell problems must be solved at the same time as the coarse scale problem, rather than being solved first and used as input data. The number of cell problems depends on the numerical discretisation of the coarse model. For example, if we imagine solving the coarse scale model by finite element methods, then on each element we need to know parameters which are given by the fine scale model. Thus we have to solve a cell problem for each element. This method has been named the heterogeneous multiscale method [5].

A similar approach is used in heart modelling, in which a set of ordinary differential equations representing the currents flowing through the ion channels are solved not in each biological cell but in each element of the discretisation of the macroscale model, effectively assuming that neighbouring cells are behaving in the same way.

3 Conclusion

The life sciences are becoming data rich and cover a wide range of length and time scales. Integrating all this information requires the use of mathematical models. We have only touched on the mathematical challenges involved in developing and integrating models at each scale. Furthermore, the problems we have used as illustrations have been relatively clean, in that a fine scale model exists but is simply too complicated to use. However, for many problems in biology the all-singing-all-dancing fine scale model does not exist, and models at different scales need to be developed, simplified and coupled in a more ad hoc fashion.

References

[1] Caflisch, R.E., Miksis, M.J., Papanicolaou, G.C. & Ting, L. (1985), Effective equations for wave propagation in bubbly liquids. *J . Fluid Mech.* **153**, 259–273.

[2] Caflisch, R.E., Miksis, M.J., Papanicolaou, G.C. & Ting, L. (1985), Effective equations for wave propagation in bubbly liquids. *J . Fluid Mech.* **160**, 1–14.

[3] Chapman, S.J., Shipley, R.J. & Jawad, R. (2008), Multiscale modelling of fluid flow in tumours, *Bull. Math. Biol.* **70**, 8, 2334–2357.

[4] Chapman, S.J. & Shipley, R.J., Multiscale modelling of fluid and drug transport in vascular tumours, preprint.

[5] E, Weinan, Enquist, B., Xiantao, Li, Ren, Weiqing & Vanden-Eijnden, E. (2007), Heterogeneous multiscale methods: a review. *Comm. Comp. Phys.* **2**, 367–450.

[6] Hunter, P.J., McCulloch, A.D. & ter Keurs, H.E.D.J. (1998), Modelling the mechanical properties of cardiac muscle. *Prog. Biophys. Mol. Biol.* **69**, 289-331.

[7] Li, J.B., Noble, A., Han, L.G. & Burcher M., Inversion elasticity reconstruction of soft tissue using split-and-merge strategy from strain map of ultrasound image sequence. IEEE International Ultrasonics Symposium 2003 Honolulu Proceedings, vols 1 and 2, 1927–1930 (2003).

[8] Noble, D., Modeling the heart - from genes to cells to the whole heart. (2002) *Science* **295**, 1678-1682.

[9] van Wijngaarden, L. (1972), One-dimensional flow of liquids containing small gas bubbles. *Ann. Rev. Fluid Mech.* bf 4, 369–394.