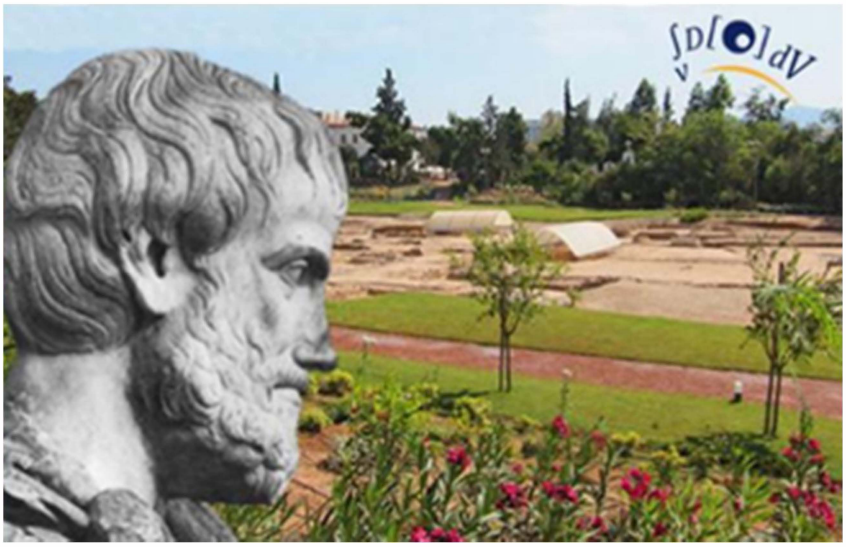

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The CHIC Project Workshop
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Simulating Tumour Vasculature at Multiple Scales*

J. A. Grogan, P. K. Maini, J. Pitt-Francis and H. M. Byrne

Abstract— **The vasculature plays an important role in tumour development and treatment, acting as a conduit for nutrients, waste products and therapeutics. Simulating transport and network structure evolution in malformed tumour networks is a challenging multi-scale problem. Current approaches for modelling the vasculature at distinct size scales are described here, followed by a discussion of current efforts in developing integrated multi-scale modelling approaches for simulating the growth and treatment of vascular tumours.**

I. Introduction

The vessel network transports nutrients such as glucose and oxygen to tissues and provides a mechanism for waste product removal. In tumours the vasculature can become dysfunctional, losing its hierarchical structure and increasing in permeability. The resulting poor perfusion of tumour tissue can lead to hypoxia, which is associated with malignancy [1].

Current therapeutic strategies rely on tumour tissue perfusion, either directly for chemotherapeutic drugs to reach diseased regions or indirectly due to the dependence of radiotherapy effectiveness on tissue oxygenation. Normalization strategies, which improve the transport efficiency of the tumour vessel network prior to subsequent treatments, are showing promise in the clinic [2].

One of the challenges when adopting individual or combined therapies is predicting suitable dosings and timings for individual patients. Particularly in the case of combined therapies there may be periods of time during which synergistic effects can be exploited [3-4]. Imaging forms an important role in identifying such time periods, however the spatial resolution of functional imaging is relatively coarse, meaning information about the state of the vasculature can be limited.

Simulation of transport and network evolution in the vasculature in response to tumour cells or the application of normalization therapies allows more detailed predictions of suitable dosing strategies for patients. This is particularly the case when simulations are closely linked with functional imaging data, such as with PET and fMRI [3]. One of the challenges in developing simulations which can utilise the information given by functional imaging is that the length scales are significantly larger than those associated with individual cells or small capillaries. Since it is at this scale that the physical mechanisms used in the simulations are characterized, multi-scale approaches are required to link imaging and cell scales. This work is focused on the development of such approaches.

We first briefly overview existing macro-scale (imaging or tissue scale) and micro-scale (cell and capillary scale) modelling strategies. Efforts in developing multi-scale modelling approaches are then discussed, in particular those being developed as part of the Computational Horizons in Cancer (CHIC) Project.

II. MICRO-SCALE VASCULATURE MODELLING

The diameters of vessels in capillary beds are on the order of 10 μm, similar to the size of most surrounding cells [5]. It is within this micro-vasculature that species exchange primarily takes place in tissue. At this size scale individual cells and vessels can be modelled as discrete entities.

Discrete modelling approaches for cells at this scale typically involve representing them using cellular automata [4] or lattice free approaches, with the latter being able to account for mechanical interactions [6]. Since cells are modelled individually there is scope for including sub-cellular details such as cell-cycle and signalling pathway models [4] and for characterising cell behaviours based on mutation status. This allows detailed predictions of how specific mutations, or therapies targeted at cells at specific stages in their cycle, affect tumour development [7].

For the vessels, a typical approach at this scale is to model them as 1-D pipes with blood flow within the system approximated as Hagen-Poiseuille flow [8]. Within this framework flow rates, red blood cell concentrations (haematocrit) and wall shear stresses can be predicted in individual capillaries. Since individual vessels are being modelled it is possible to predict the influence of network topology on tumour development.

The vessels and surrounding cells form an interdependent system, which is relatively straightforward to model at the micro-scale. In a general sense, cells require nutrients from the vasculature. If they are deficient their cycle can be altered and they release angiogenic factors that stimulate new vessel formation. Through modelling the transport of nutrients and growth factors at the micro-scale it is possible to couple the vessel and cell layers [4].

The vessel network adapts according to the metabolic needs of the surrounding tissue, perfusion or in response to therapeutics [9]. This can be done through the change of vessel diameters, the regression of existing vessels or the development of new vessels. New vessels can form through angiogenesis and vasculogenesis. At the micro-scale these processes can be modelled explicitly [4]. Angiogenesis can be stimulated by growth factors secreted by individual hypoxic cells. Individual sprouts can be tracked as endothelial tip cells respond to mechanical and chemical gradients in their environment. Micro-scale modelling of this type gives useful

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J.A.G., H.M.B. and P.K.M. are with the Wolfson Centre for Mathermatical Biology (WCMB), Mathematical Institute, University of Oxford, UK (corresponding author phone: +44-1865-615162; fax: +44-1865-273583; e-mail: james.grogan@maths.ox.ac.uk).

H.M.B and J.P.F. are with the Computational Biology Group, Dept. of Computer Science, University of Oxford, UK.

predictions of tumour behaviour in a confined volume [10], however it is infeasible to apply the same approach when predicting the behaviour of an entire tumour or when comparing predictions with clinical imaging, both of which operate on size scales on the order of 10 mm or more.

III. Macro-scale vasculature modelling

At the size scale of a whole tumour or at the resolution provided by current functional imaging technology it is not practical to model individual capillaries and cells. Instead a number of approaches exist in which the vasculature is described in a continuum sense [11-12]. In [11] the vasculature is treated as a diffusible species within a continuum reaction-diffusion framework. The spreading of the vasculature is captured through a diffusion term and the proliferation is captured through a source term dependent on the local concentration of angiogenic factor. Interaction with cells is mediated by allowing the rate at which cells become hypoxic to depend on local vessel concentration. A limitation of this approach is that the mechanics of the spreading tumour and phases are neglected, however for applications in modelling diffuse tumours such as glioblastoma this may not be significant. Due to the macro-scale nature of this approach it is natural to combine it with functional imaging data [13].

In [12] multi-phase continuum mechanics approaches are used to model the vasculature and tumour. In this approach the constituents of the tumour are divided into distinct spatial regions with uniform properties (phases) representing the vasculature, healthy cells, cancer cells and extra-cellular matrix. A volume of space may contain multiple phases, which are described through their relative volume fractions and which can interact mechanically and chemically. The interdependence of vascular and cellular phases is treated in a similar manner to that in [11], however in addition to species transport these models also allow the mechanical environment of the tumour to be included by applying momentum balances to the individual phases. This is important given the relatively high interstitial pressures known to exist in typical tumour environments. This approach also allows simulation of tumour growth in confined environments.

A challenge in the development of tissue scale models is investigating the scenarios and size scales at which a continuum level description of a discrete vessel network is appropriate [14]. Given that current continuum descriptions do not account for hierarchy and heterogeneity in vessel networks their predictive capability remains to be established. A further challenge is the development of suitable rules at the tissue scale to account for complex structural changes in the network at the micro-scale, such as branching and anastamosis [15].

IV. Developing integrated multi-scale models

The CHIC project is focused on the development of integrated multi-scale cancer models (hypermodels) which can ultimately be used as a clinical tool. In this framework models developed at different scales (from molecular to compartment models) and by different research groups are linked to provide insight into clinical problems. An example of the planned framework is shown in Fig. 1, with the angiogenesis and vasculature component being developed in the present work highlighted.

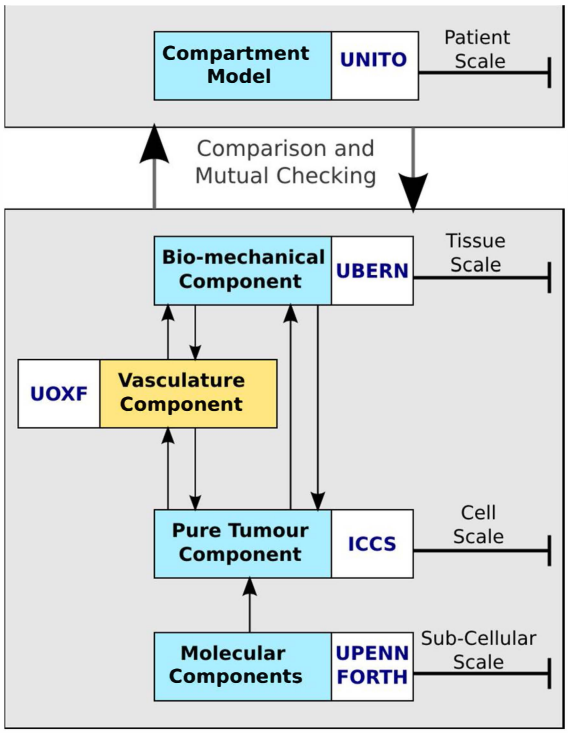

Figure 1. Schematic of the planned modelling framework for the CHIC project with the angiogenesis/vascular component highlighted. The project partners included here are the University of Oxford (UOXF), the Institute of Communications and Computer Systems (ICCS) Greece, the University of Bern (UBERN), the University of Turin (UNITO), the Foundation for Research and Technology, Helas (FORTH), and the University of Pennsylvania (UPENN).

The development of an integrated model of this type brings new challenges. In addition to the need to link tissue and cell scale vasculature models, each vasculature model must also link with models representing different aspects of the tumour environment. In particular, as shown in Fig. 1, the vasculature modelling component communicates with a macro-scale bio-mechanical component, currently being developed at UBERN and a micro-scale tumour growth component being developed at ICCS. Addressing the challenge of linking across size scales and model domains will require the development of new theoretical and computational strategies. Two approaches currently being considered are now described.

In the first approach, shown in Fig. 2 the tumour and its environment are divided into three domains. Ω_B is the domain of tissue surrounding the diseased region and is modelled as an isotropic elastic material using the model of UBERN. Ω_o is the domain of diseased tissue and is modelled using the previously described multiphase-fluid model of Hubbard and Byrne [12], implemented by UOXF. To realise this implementation careful consideration of the interface $\partial\Omega_{OB}$ is required. The macro-scale multi-phase model and micro-scale discrete model are linked by discretising the macro-scale model into subdomains Ω_I. Within each subdomain the macro-scale model provides an average vascular oxygenation and growth factor uptake rate while the micro-scale model provides summed cellular oxygen uptake and growth factor release rates for a unified time step.

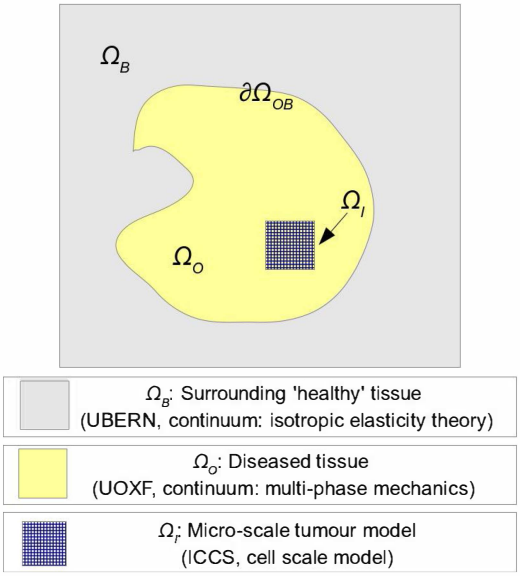

Figure 2. Schematic showing how to interface the macro-scale vasculature model with the bio-mechanical and cell scale models.

In the second approach, shown in Fig. 3, the tumour and its environment are again divided into three domains. In this case the macro-scale mechanics of both the tumour and the environs are modelled using the macro-scale bio-mechanical model of UBERN. The macro-scale model calculates the pressure field in the tumour based on the local density of cells, given by the micro-scale cell model of ICCS. This approach has previously been described in [16]. Within this framework a micro-scale model of the vasculature developed at UOXF, based on [4], is used to provide spatial oxygen and growth factor sink and source information to the ICCS cell model, as well as evolving constraints on cell movement. In turn the cell model supplies growth factor distributions to the vessel model, while the macro-scale model provides an average interstitial pressure. This pressure can be used to predict vessel collapse.

Another important aspect of integration when developing models of the type proposed in the CHIC project is the incorporation of experimental data. The vasculature component of the model is being developed in tandem with real-time micro-scale imaging studies of vessel network development in diseased mice. This allows validation of individual components of the model which has in the past not been possible, for example blood flow rate and haematocrit distribution predictions in tumour vessel networks. Combining modelling and experimental imaging in this manner also facilitates the assessment of the overall predictive capabilities of the model with reference to a relatively controlled tumour environment. For example, available imaging data allows for side-by-side comparisons of model predictions of tumour growth and network development with experimental images right from the time of injection of the initial tumour cells through to the development of a malformed tumour vasculature.

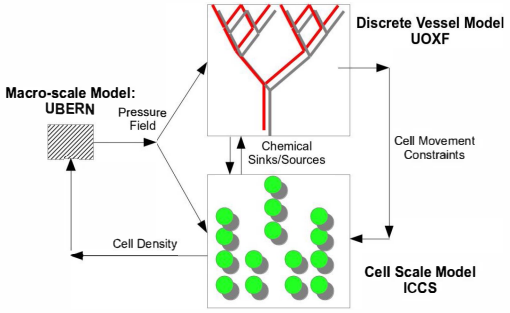

Figure 3. Schematic showing how to interface the macro-scale bio-mechanical model with the discrete vessel and cell models.

When integrating the experimental data in the modelling framework care must be taken to ensure that the effects of per-processing operations, performed on the images in order to make them suitable for modelling, are quantified relative to model predictions. In this sense it is useful to explicitly integrate image analysis and processing directly within the modelling framework. This is currently being explored for the micro-scale modelling approach, as shown in Fig. 4. Subsequent work will focus on the incorporation of macro-scale imaging data such as CT and functional imaging.

V. CONCLUSIONS

The difference in length scales between clinical imaging data and that of individual cells and capillaries makes predicting suitable therapeutic strategies challenging. Computer simulations can aid in resolving this difference, however challenges remain in linking discrete and continuum representations of vessel networks and the surrounding tissue. These challenges are being investigated as part of the modelling component of the CHIC project with the aim of facilitating the integration of different models at different length scales and over different domains.

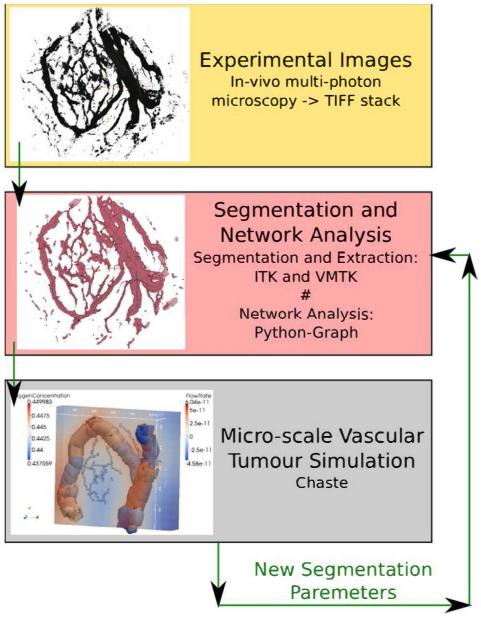

Figure 4. Integrating image analysis and processing with modelling, a sample workflow.

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