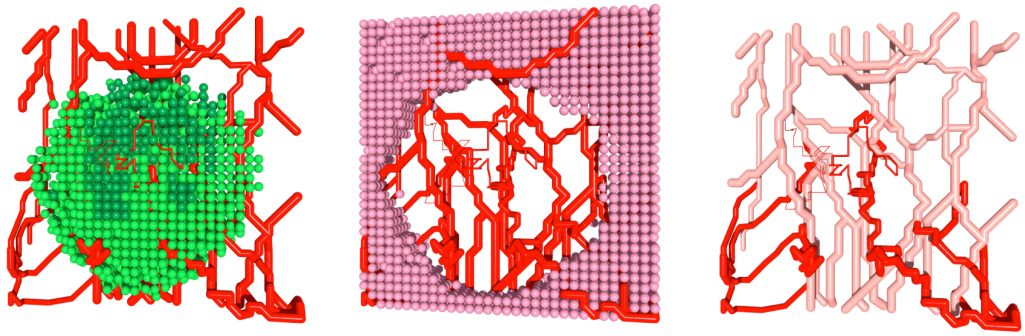
VPH 2012 Conference

Abstract Title: Vascular Tissue Modelling Environment (VTME)



Track: Systems Medicine: bridging Physiome / VPH and Systems Biology

Category: 10- to 15-minute oral presentation in the main conference

Keywords: Cancer, Multiscale modelling, Angiogenesis, Tiissue growth

Topics: 1. Tissue modelling: missing link between cells and organs.
2. PDE-ODE integration in tissue-cell multiscale models

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Blood vessel growth, death and remodelling are fundamental processes in health and disease. During vasculogenesis, endothelial progenitor cells migrate, cluster and differentiate to form new blood vessels. The resulting vascular trees are then extended via angiogenesis. Flow-dependent vessel pruning, nutrient demands and intercellular signalling contribute further to vascular tissue remodelling. Inappropriate vascular development can lead to severe birth defects. Later in life, angiogenesis is crucial for the female reproductive cycle and the repair of damaged tissues. Angiogenesis also plays a key role in pathologies such as diabetes, macular degeneration and rheumatoid arthritis. Tumour growth is crucially dependent on the co-option and expansion of the host blood supply, and inadequate vascularisation in solid tumours leads to nutrient deprivation and hypoxia, which can be responsible for cancer cell resistance to many common therapies. Clearly, the multiscale and interlinked dynamics of vascular tissues require a physiome modelling approach to increase understanding of normal physiology and pathology, and to predict optimal therapeutic interventions.

There is now a strong need for curated and sustainable multiscale models to investigate the complex interplay between subcellular signalling (e.g. the cell cycle, responses to hypoxia), growth factor and nutrient distributions, and vascular dynamics at the network level. For example, local nutrient shortages can stimulate growth factor release, leading to new vessel connections which can have implications for blood flow in the wider vessel network. We have developed models that combine (A) fluid flow in a vessel network; (B) partial differential equations for the transport, release and uptake of diffusible substances such as oxygen; (C) cell division and reinforced random walks of cells on a regular lattice; (D) ordinary differential equations for the subcellular networks regulating the cell cycle and factors such as VEGF; and (E) integration of angiogenic and vasculogenic endothelial cells into the vascular network [1, 2]. A 2D implementation has been used to predict synergistic anti-tumour effects

of combining a macrophage-based, hypoxia-targeted, gene therapy with chemotherapy, recently published in Cancer Research [3]. Extension of the model to 3D has also recently been accomplished, and we have begun to explore simulations of tumour growth in vascular networks extracted from in vivo [4]. We are now reinforcing these developments with a VPH NoE Exemplar Project that will enable re-use, integration and sharing of the model and relevant data. This exemplar project will implement a user-friendly Vascular Tissue Modelling Environment (VTME) within the "Cancer, Heart and Soft Tissue Environment" (Chaste, http://web.comlab.ox.ac.uk/ chaste/), already part of the VPH ToolKit (http://toolkit.vph-noe.eu/). VTME will allow biologists and clinicians to test hypotheses on the mechanisms of vascular tissue growth and homeostasis, and to test potential new treatments for various pathologies. In this presentation we will outline the VTME model framework and the progress made on implementation within the VPH ToolKit.

References

[1] T. Alarcón, H. M. Byrne, and P. K. Maini. A cellular automaton model for tumour growth in inhomogeneous environment. *J. Theor. Biol.*, 225(2):257–274, 2003.

[2] M. R. Owen, T. Alarcón, P. K. Maini, and H. M. Byrne. Angiogenesis and vascular remodelling in normal and cancerous tissues. *J Math Biol*, 58(4-5):689–721, Apr 2009.

[3] M. R. Owen, I. J. Stamper, M. Muthana, G. W. Richardson, J. Dobson, C. E. Lewis, and H. M. Byrne. Mathematical modeling predicts synergistic antitumor effects of combining a macrophage-based, hypoxia-targeted gene therapy with chemotherapy. *Cancer Res*, 71(8):2826–2837, Apr 2011.

[4] H. Perfahl, H. M. Byrne, T. Chen, V. Estrella, T. Alarcón, A. Lapin, R. A. Gatenby, R. J. Gillies, M. C. Lloyd, P. K. Maini, M. Reuss, and M. R. Owen. Multiscale modelling of vascular tumour growth in 3d: The roles of domain size and boundary conditions. *PLoS ONE*, 6(4):e14790, 2011.