Microvessel Chaste: A Library for Multi-Scale Agent-Based Simulation of Tissues with Microvessels

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Abstract

Microvessel Chaste is an open-source C++ and Python library for multi-scale agent-based modelling of tissues with microvessels. Development has focused on applications in spatial modelling of vascular tumours and wound healing. Problems of interest in these areas involve modelling blood flow, temporally evolving vessel network geometries and topologies and vessel interaction with diffusible chemicals. This code integrates discrete representations of microvessels with already re-usable components for agent-based modelling in Chaste, such as discrete cells, meshes and ordinary and partial differential equation (ODE/PDE) solvers. In addition, Python bindings and compile-time dimensional analysis are introduced to address two particular requirements in vascular tissue modelling, i) rapid model composition from a range of interchangeable sub-models and ii) management of a large number of input parameters from heterogenous literature sources. This article includes simple example applications of the library which can be run on a desktop computer. The source code is available to download under an open source Berkeley Software Distribution (BSD) licence at `https://chaste.cs.ox.ac.uk/trac/wiki/PaperTutorials/Angiogenesis`, together with details of a mailing list and links to documentation and tutorials.

Introduction

Cancer, Heart And Soft Tissue Environment (Chaste) is an open-source C++ library which has been developed to enable the study of novel problems in computational physiology and biology. As discussed in a dedicated article [1], the library has been designed to: i) facilitate the rapid development of computational models and methods through code re-use and documentation and ii) overcome challenges related to the reliability and reproducbility of computational results. Chaste has been widely used in cardiac electrophysiology [2], developmental biology [3] and cancer applications [4]. While some Chaste applications have focused on tumour modelling [5], it does not have functionality for modelling microvessels.

Multi-scale agent-based modelling of tissue with vessels, such as in Owen et al. [6], introduces several requirements beyond those faced by dedicated cell modelling software, of which there are many noticeable examples (such as CompuCell3D [7], EPISIM [8] and PhysiCell [9]). For example, i) line or surface based representations of vessels are needed in place of point or centre-based representations of cells, ii) blood flow and

chemical transport problems are solved in vessel networks with constantly evolving vessel diameters and connectivity and iii) new vessels may form and migrate based on mechanical and chemical cues. These requirements, which are additional to those of cell-only frameworks, such as cell-cycling, migration, proliferation and interaction with diffusible chemicals, lead to the use of a relatively large number of input parameters from heterogeneous literature sources and a variety of ways in which a model can be composed from interchangeable sub-models. Development of Microvessel Chaste aims to address these challenges, while adhering to the original Chaste design goals, by focusing on i) *extensibility*, ii) *documentation*, iii) *reproducibility* and iv) *efficiency* of both models and code. This is through the use of object oriented design, C++ for computational efficiency, Python bindings for model composition efficiency and Boost Units [10] for compile-time dimensional analysis.

The Microvessel Chaste library is distinguished from previous multi-scale agent-based models of tissue microvascaulture (notable examples are Secomb et al. [11], Anderson and Chaplain [12], Friboes et al. [13], Shirinifard et al. [14] and Welter and Rieger [15]) in that: i) it is available under a permissive open source license, ii) has API documentation and user tutorials, iii) has capability for on- and off-lattice modelling of vessels in arbitary geometries in two and three dimensions and iv) has focus on *extensibility* and code re-use. The authors have previously developed and applied a range of multi-scale agent-based microvessel models in the areas of cancer [16, 17] and angiogenesis [18]. However, they have not previously made the resulting code open-source with documentation and tutorials. The four previously mentioned distinguishing traits of Microvessel Chaste allow utilization of the library in addressing two outstanding challenges in tissue microvascaulture modelling. First, the importance of the development of software for rapidly constructing and cross-comparing multi-scale agent-based models of tissue microvascaulture is well recognized, as are the challenges of such an endeavour [19, 20]. One hurdle which the library helps overcome is the lack of open-source, documented software in the field. This has made it neccessary to re-implement each computational model before application, delaying comparison studies. Second, there is now a wealth of high resolution three-dimensional experimental imaging data against which model predictions can be compared [21]. To fully exploit this data it is neccessary that three-dimensional tissue regions of resonable volume with realistic geometries can be simulated, as per [22]. There are few approaches developed for this purpose in the literature. Such functionality is availble in this library, including several previously unpublished methods for three-dimensional off-lattice modelling of angiogenesis.

This article accompanies the first public release of the Microvessel Chaste library, although some elements have been used in previous studies [18, 22]. Code design and implementation are discussed in the next section, followed by a collection of simple sample applications. The sample applications are design to be quickly run on a desktop PC, in practice more expensive simulations are usually performed. Examples can be run and figures re-created by downloading the project from `https://chaste.cs.ox.ac.uk/trac/wiki/PaperTutorials/Angiogenesis`, as described in Text S1 (JG: to be added).

Design and Implementation

This section briefly summarizes available algorithms, with reference to a typical multi-scale agent-based problem for tissue with microvessels, and also code layout and design. An dedicated article should be consulted for further details on algorithms for core Chaste functionality, such as linear algebra and input/output, and discrete cell modelling [1]. It is noted that development of the MicroVessel Chaste library has not

strictly followed the Test-Driven Development and Agile-Programming practices adopted by the Chaste project, although it aims for full unit-test and API documentation code coverage.

The present library can be used with Linux only, with virtual machines required for use on Microsoft Windows and Max OSX. The Python interface can be quickly installed as an anaconda package from `https://chaste.cs.ox.ac.uk/trac/wiki/PaperTutorials/Angiogenesis`. The C++ interface requires building from source after downloading and setting up dependencies, which can take on the order of hours the first time.

Algorithm Overivew

The library is designed for multi-scale agent-based problem for tissue with microvessels using on- and off-lattice representations of cells and vessels. A typical model is shown in Fig 3, simplified from more detailed versions in [6], along with a schematic of available algorithms.

Code Layout And Design

The components of the library are as follows:

- geometry – code for generating and describing 2D and 3D geometries using piece-wise linear complex (PLC) descriptions for direct use in Triangle and Tetgen meshing software.
- mesh – code for automated finite element meshing of 2D and 3D geometries and interpolation of vessel and cell locations onto meshes and regular grids.
- ode – ode models for describing cell-cycles of interest in vascular tumour problems.
- pde – descriptions and solvers for steady state linear and non-linear PDEs with discrete sinks and sources for vessels and cells. Solvers use finite differences, finite element methods and Green's function methods [11] based on Boost uBLAS and PETSc for vector and matrix operations.
- population – code for describing, reading, writing and generating vessel networks.
- simulation – flow, structural adaptation and angiogenesis solvers. Also code for managing integration of discrete vessel simulations with discrete cell populations from Cell Based Chaste.
- utility – dimensional analysis and collection of literature parameters of interest for tissue microvascualture simulations.

As per the remainder of Chaste, object oriented programming, including templating in C++ are heavily utilized. Distinct from Chaste, shared pointers are used throughout to ease memory management. Input and output of vessel networks, regular grids, meshes and PDE results are in VTK (Paraview) format, which offer standard methods for visualization and post-processing.

Python bindings are generated automatically using Py++ with a CASTXML backend. Automated generation is neccessary to account for the high degree of templating used in Chaste and Boost libraries and greatly eases code maintenance. A significant advantage of the provision of Python bindings for multi-scale agent-based models of this type is that compiled C++ classes can be overloaded in Python, without the need to re-compile the code. This gives allows for rapid and automatic model (or

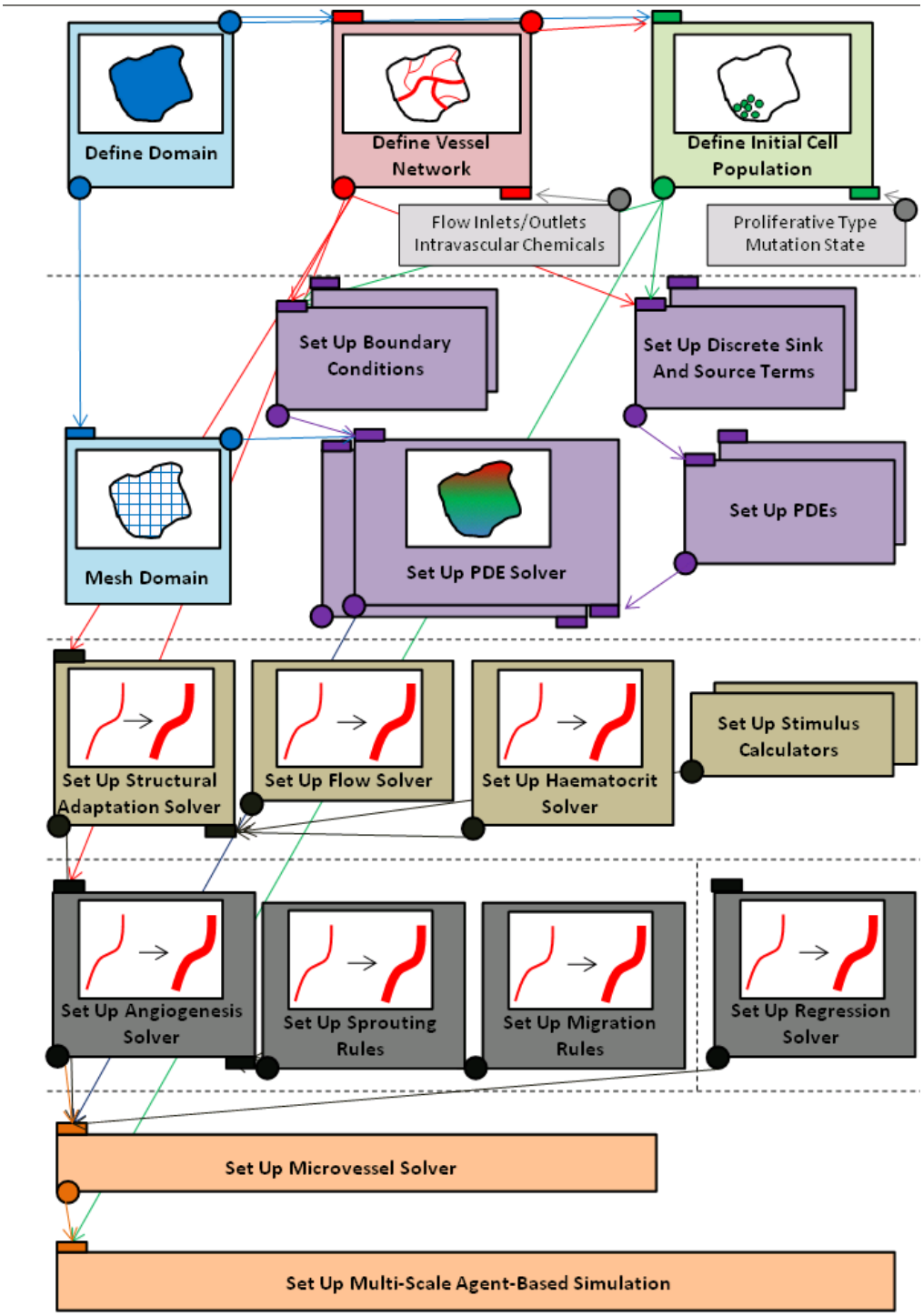

Fig 1. Bold the figure title. Figure caption text here, please use this space for the figure panel descriptions instead of using subfigure commands. A: Lorem ipsum dolor sit amet. B: Consectetur adipiscing elit.

sub-model) generation based on mark-up language descriptions (e.g. over-riding a cell cycle model based on an SBML description scraped from a web database).

During the development of the library it became apparent that there was significant potential for mis-use of units when quantities are passed into solvers which a modeller may not be familiar with, but would like to use none-the-less. As a simple example, oxygen consumption rates are often quoted as amount per cell per time (e.g. moles per second). If one is solving an oxygen reaction-diffusion PDE with oxygen partial pressure as the solution quantity (e.g. mmHg) it may be tempting to insert the literature oxygen consumption rate as a discrete sink term, per cell. A result will be produced, but our inputs have had dimensional incompatibilities. How do we convert from a partial pressure (mmHg) to an amount (moles)? A solubility term (mole per mmHg per metre cubed) is needed to convert partial pressure to concentration and a volume term to convert concentration to amount. Where does the volume term come from? It is an integral over a point source (or delta function) with a value depending on the chosen numerical method for solving the PDE (e.g. cube of the grid spacing in a 3D finite difference method). With compile-time dimensional analysis the code will not compile in C++ (or throw a type conversion exception in Python) if the user attempts to use incompatible dimensions, forcing a re-think regarding what they are actually modelling.

Results

A 2D Lattice Based Vascular Tumour Simulation

Replicate an Alarcon model, but with 'Chaste cells'

Fig 2. Bold the figure title. Figure caption text here, please use this space for the figure panel descriptions instead of using subfigure commands. A: Lorem ipsum dolor sit amet. B: Consectetur adipiscing elit.

A 3D Off-Lattice Angiogenesis Simulation

Finite element PDE solve on curved domain.

Fig 3. Bold the figure title. Figure caption text here, please use this space for the figure panel descriptions instead of using subfigure commands. A: Lorem ipsum dolor sit amet. B: Consectetur adipiscing elit.

Availability and Future Directions

Microvessel Chaste is available to download from the Chaste website `https://chaste.cs.ox.ac.uk/trac/wiki/PaperTutorials/Angiogenesis`. The software is available under an open source Berkeley Software Distribution (BSD) licence.

Additional functionality for semi-automated 2D and 3D image segmentation and meshing is under development to aid integration with experimental studies. Porting to Windows and Mac OSX are of interest, with future availbaility of Python packages for each likely. At present, alrogithms operate in serial only, however there is much scope for distributed memory parallelisation for both C++ and Python interfaces. All PDE, Green's function and flow solvers are based on PETSc structures and vessel network components may be communicated using existing serialization functionality in Chaste [**?**] or through VTK based serialization.

How to Become and Active Developer

As discussed in [1] contributions are welcome via the main Chaste website, which includes a developer wiki, mailing list details and the ability to open and comment on work tickets. A new git based version control system has recently been introduced for Chaste, which may further aid contribution in future.

Supporting Information

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Acknowledgments

Chaste team. Possibly contributors of vessel networks (e.g. Bostjan and co). Secomb for Greens Function code (our code has a re-write but maybe should also contact for general feedback).

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