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Chaste: Cancer, Heart and Soft Tissue Environment

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Summary

Chaste (Cancer, Heart And Soft Tissue Environment) is an open source simulation package for the numerical solution of mathematical models arising in physiology and biology.

To date, Chaste development has been driven primarily by applications that include continuum modelling of cardiac electrophysiology ('Cardiac Chaste'), discrete cell-based modelling of soft tissues ('Cell-based Chaste'), and modelling of ventilation in lungs ('Lung Chaste'). Cardiac Chaste addresses the need for a high-performance, generic, and verified simulation framework for cardiac electrophysiology that is freely available to the scientific community. Cardiac chaste provides a software package capable of realistic heart simulations that is efficient, rigorously tested, and runs on HPC platforms. Cell-based Chaste addresses the need for efficient and verified implementations of cell-based modelling frameworks, providing a set of extensible tools for simulating biological tissues. Computational modelling, along with live imaging techniques, plays an important role in understanding the processes of tissue growth and repair. A wide range of cell-based modelling frameworks have been developed that have each been successfully applied in a range of biological applications. Cell-based Chaste includes implementations of the cellular automaton model, the cellular Potts model, cell-centre models with cell representations as overlapping spheres or Voronoi tessellations, and the vertex model. Lung Chaste addresses the need for a novel, generic and efficient lung modelling software package that is both tested and verified. It aims to couple biophysically-detailed models of

airway mechanics with organ-scale ventilation models in a package that is freely available to the scientific community.

Chaste is designed to be modular and extensible, providing libraries for common scientific computing infrastructure such as linear algebra operations, finite element meshes, and ordinary and partial differential equation solvers. This infrastructure is used by libraries for specific applications, such as continuum mechanics, cardiac models, and cell-based models. The software engineering techniques used to develop Chaste are intended to ensure code quality, re-usablity and reliability. Primary applications of the software include cardiac and respiratory physiology, cancer and developmental biology.

The software

Chaste is available on GitHub (https://github.com/Chaste/Chaste), and the current stable release is version 2019.1. Please see the Readme.md file on the Github repository for links to the Chaste wiki and install guides.

Previous publications about Chaste have detailed the rationale for, and design principles behind, Chaste (Pitt-Francis et al., 2009), as well as the main application areas of Chaste up to 2013 (Mirams et al., 2013).

Chaste places an emphasis on reproducibility and verification and, as such, extensive automated testing is used to ensure software quality and reliability. A series of test suites must all pass before any commit is considered a release-candidate. Most testing is performed on Long Term Support (LTS) versions of Ubuntu Linux, with unit tests additionally being run on macOS.

Testing includes compilation of all libraries with GCC, clang and Intel C++ compilers; extensive unit testing; performance profiling to identify any slowdowns over time; memory testing with valgrind; verification of code coverage; and running unit tests with different combinations of dependencies to ensure portability. The output of these tests is available at https://chaste.cs.ox.ac.uk/buildbot/

Installation

Installation of Chaste has been greatly simplified through the development of a Docker image (https://github.com/chaste/chaste-docker). Docker is a lightweight, open-source virtualisation technology for running encapsulated applications ('containers') on all major operating systems at near-native speed. This enables Chaste (including all dependencies, environment settings, convenience scripts and the latest precompiled release) to be downloaded and installed with just a single command. Isolating Chaste within a container also means that its dependencies and those installed on the user's host system can coexist without interference or version conflicts.

In addition to simplifying the setup and execution of Chaste, importantly this also enhances its reproducibility by providing a homogeneous computational environment regardless of the underlying operating system and hardware. Not only is the Chaste source code version-controlled, but so too are the dependencies, configuration settings and environment variables used to build and run it. This means that collaborators and reviewers can easily and consistently reproduce results (to within machine precision) on any platform while developers can seamlessly migrate and scale-up their simulations from a laptop to a workstation or HPC cluster.

Example usage

Chaste has tutorials to walk users through basic functionality for each application area. Tutorial examples are bundled for each specific release version, and examples for this release are available at https://chaste.cs.ox.ac.uk/chaste/tutorials/release_2019.1.

Tutorials take the form of C++ header files that each define 'tests' in the Chaste testing infrastructure. These tests must be compiled and run to produce an output, which can be visualised using ParaView.

In the following sections we showcase a specific tutorial for each of cardiac, cell-based, and lung Chaste, with minimal commands necessary to reproduce the output shown.

Cardiac example

Here we demonstrate how to run and visualise a three-dimensional monodomain cardiac simulation. This follows the tutorial `TestMonodomain3dRabbitHeartTutorial` which simulates the result of an electrical stimulus being applied to a realistic rabbit heart geometry. Assuming that 1. Chaste has been installed on Ubuntu Linux (or is running within a Docker container), 1. the Chaste source code exists at `$CHASTE_SOURCE_DIR`, 1. the environment variable `$CHASTE_TEST_OUTPUT` is set to a valid directory,

a minimal set of commands to build and run the tutorial is as follows:

```
mkdir build && cd build
cmake $CHASTE_SOURCE_DIR
make TestMonodomain3dRabbitHeartTutorial
ctest -R TestMonodomain3dRabbitHeartTutorial
```

This will produce output in the following directory:

```
$CHASTE_TEST_OUTPUT/Monodomain3dRabbitHeart
```

To view the results evolving over time as an animation in ParaView it is necessary to post-process the results with the following command:

```
cd $CHASTE_TEST_OUTPUT/Monodomain3dRabbitHeart/vtk_output
python $CHASTE_SOURCE_DIR/python/utils/AddVtuTimeAnnotations.py results.vtu annota
```

To visualise the output, open the file `annotated_results.vtu` in ParaView, and select to colour by `V` (voltage).

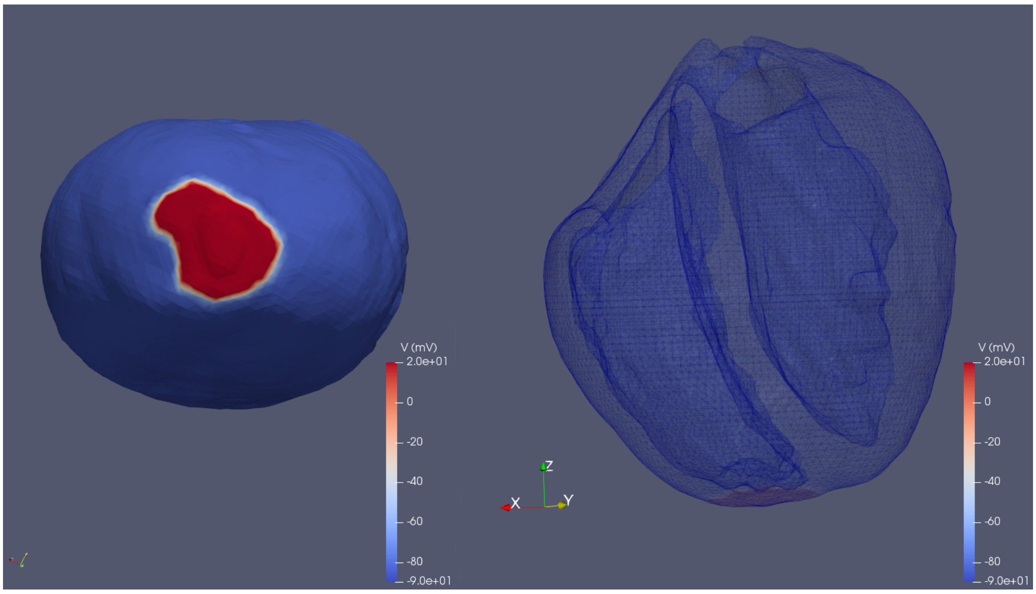

Figure 1: Trans-membrane voltage on the rabbit heart mesh at the end of the simulation. As viewed on the surface from the apex of the heart (left) and on a wireframe showing the ventricular cavities (right).

Cell-based example

Here we demonstrate how to run and visualise a cell sorting simulation using Chaste's vertex model implementation. This follows the tutorial `TestRunningDifferentialAdhesionSimulationsTutorial`. Assuming that 1. Chaste has been installed on Ubuntu Linux (or is running within a Docker container), 1. the Chaste source code exists at `$CHASTE_SOURCE_DIR`, 1. the environment variable `$CHASTE_TEST_OUTPUT` is set to a valid directory,

a minimal set of commands to build and run the tutorial is as follows:

```
mkdir build && cd build
cmake $CHASTE_SOURCE_DIR
make TestRunningDifferentialAdhesionSimulationsTutorial
ctest -R TestRunningDifferentialAdhesionSimulationsTutorial
```

This will produce output in the following directory:

```
$CHASTE_TEST_OUTPUT/TestVertexBasedDifferentialAdhesionSimulation
```

To visualise the simulation, open the file `results.pvd` in ParaView, choose to colour by 'Cell types', and display 'Surface With Edges'.

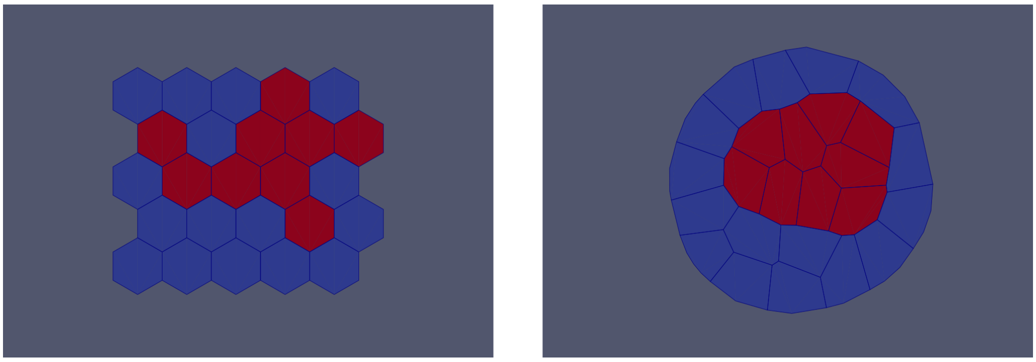

Figure 2: The initial configuration of cells (left), and the final configuration of cells after sorting has occurred (right).

Lung example

Here we demonstrate how to run and visualise the lung airway generation tutorial. This follows the tutorial `TestAirwayGenerationTutorial` which statistically generates lung airways given initial geometry segmented from a CT scan. Assuming that 1. Chaste has been installed on Ubuntu Linux (or is running within a Docker container), 1. the Chaste source code exists at `$CHASTE_SOURCE_DIR`, 1. the environment variable `$CHASTE_TEST_OUTPUT` is set to a valid directory,

a minimal set of commands to build and run the tutorial is as follows:

```
mkdir build && cd build
cmake $CHASTE_SOURCE_DIR
make TestAirwayGenerationTutorial
ctest -R TestAirwayGenerationTutorial
```

This will produce output in the following directory:

```
$CHASTE_TEST_OUTPUT/TestAirwayGenerationTutorial
```

To visualise the generated airway geometry, open the file `example_complete_conducting_airway.vtu` in ParaView. Application of an 'Extract Surface' filter followed by a 'Tube' filter allows the centreline and radius information to be viewed as a series of tubes.

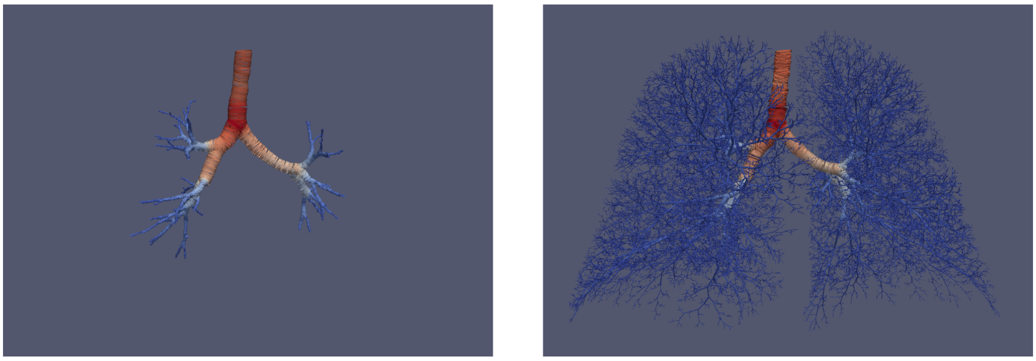

Figure 3: The initial geometry of major airways segmented from a CT scan (left), and an example of a complete generated airway tree (right).

Recent publications enabled by Chaste

Since our last publication on Chaste (Mirams et al., 2013), over 70 peer-reviewed publications have been enabled, which we mention briefly below.

Publications using Cardiac Chaste have included scientific studies relating to: basic mechanisms of cardiac electrophysiology in healthy and diseased settings (Walmsley, Rodriguez, et al., 2013, pp. @Passini2013Computational, @Sadrieh2014Multiscale, @Bartolucci2014Linking, @Samanta2015Ca, @Pathmanathan2015, @cardone2016human, @Zhou2016, @Mahoney2016Connexin43, @Corsi2017Noninvasive, @Dutta2016, @Reilly2016, @Dutta2017, @Lyon2018, @Xin2019); the effects of realistic tissue structure on simulated cardiac electrical activity (Walmsley et al., 2013, pp. @Lekadir2014Effect, @Lekadir2016Statistically, @Zacur2017); the sources and consequences of inter-subject electrophysiological variability (Dutta, Mincholé, Walmsley, & Rodriguez, 2013, pp. @Britton2013Experimentally, @Elkins2013Variability, @Walmsley2015Application, @Britton2017, @Muszkiewicz2018); predicting the effects of drugs on cardiac activity, including safety assessment (Beattie et al., 2013, pp. @Zemzemi2013Computational, @Wallman2014Computational, @Mirams2014Prediction, @Passini2014Late, @Cardone-Noott2014Computational, @Zemzemi2015Effects, @Moreno2015New, @Davies2016Recent, @Hill2016Computational, @Passini2016, @britton2017quantitative, @McMillan2017, @passini2017human, @Lim2018Role); and the development of associated web-based tools (Williams & Mirams, 2015, pp. @Cooper2015Cellular, @Cooper2016Cardiac, @Daly2018). Other studies enabled by Cardiac Chaste have advanced the methodologies for parameter identifiability and inference, model selection and uncertainty quantification for in cardiac electrophysiology models (Daly, Gavaghan, Holmes, & Cooper, 2015, pp. @Mirams2016White, @Johnstone2016Uncertainty, @Daly2017Comparing); and for the verification and efficient numerical simulation of such models (Marsh, Ziaratgahi, & Spiteri, 2012, pp. @Agudelo–Toro2013Computationally, @Pathmanathan2014Verification, @Corrado2016Stability, @Campos2016Lattice, @Spiteri2016Godunov, @Cervi2018HighOrder, @Cardone2018, @Green2019LUT). The continuum-mechanics solvers in Chaste have been used for studies of dielectric elastomers (Langham, Bense, & Barkley, 2018); and our electro-mechanics code as used in (Carapella et al., 2014), has also been used to verify new numerical methods (Gurev et al., 2015).

Work using Cardiac Chaste has also been published on mesh generation and model simulation in the area of gastric electrophysiology, in particular focusing on interstitial cell of Cajal network structure and function (Sathar, Trew, Du, O'Grady, & Cheng, 2014, pp. @Gao2014Developmental, @Sathar2015Tissue, @Sathar2015Comparison, @Sathar2015Multiscale, @Gao2015Stochastic).

Publications enabled by Cell-based Chaste have focused on: the cellular mechanisms and dynamics of intestinal homeostasis and carcinogenesis (Dunn, Näthke, & Osborne, 2013, pp. @Hu2014Epidermal, @Baker2014Quantification, @Osborne2015Multiscale, @Dunn2016Combined, @Langlands2016Paneth, @Carroll2017Interkinetic, @Almet2018Multicellular, @Muraro2018TNF); the mechanisms underlying vascular tumour growth and response to therapy in the Microvessel Chaste project (Grogan, Connor, et al., 2017, pp. @Grogan2017Predicting, @Grogan2018Importance); the biomechanical characterization of skin lesions (Franzetti et al., 2015); the organisation and proliferation of stem and pluripotent cells in development (Atwell et al., 2015, pp. @Koke2014Computational, @Godwin2017Extended); the dynamics of developing epithelial tissues (Kursawe, Brodskiy, Zartman, Baker, & Fletcher, 2015, pp. @Tetley2016Unipolar, @Abdullah2017Universal, @Finegan2018Tissue, @Waites2018Information); the spread of sexually-transmitted infections (Nelson et al., 2014); vascular remodelling (Osborne & Bernabeu, 2018); the similarities and differences between competing cell-based modelling approaches (Figueredo, Joshi, Osborne, Byrne, & Owen, 2013, pp. @Davit2013Validity, @Fletcher2013Implementing, @Osborne2017Comparing); the calibration and parameterisation of such models (Cooper & Osborne, 2013, p. @Kursawe2018Approximate); and their efficient numerical solution (Harvey, Fletcher, Osborne, & Pitt-Francis, 2015, pp. @Rubinacci2015Cognac, @Kursawe2017Impact, @Cooper2017Numerical).

Papers on Lung Chaste describe its use for patient-specific airway tree generation and flow modelling (Bordas et al., 2015, pp. @soares2017evaluation, @burrowes2017combined).

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References

Abdullah, A., Avraam, D., Chepizhko, O., Vaccari, T., Zapperi, S., La Porta, C. A. M., & Vasiev, B. (2017). Universal statistics of epithelial tissue topology. *arXiv preprint arXiv:1710.08527*. Retrieved from https://arxiv.org/abs/1710.08527

Agudelo-Toro, A., & Neef, A. (2013). Computationally efficient simulation of electrical activity at cell membranes interacting with self-generated and externally imposed electric fields. *J Neural Eng*, *10*(2), 026019. doi:10.1088/1741-2560/10/2/026019

Almet, A. A., Hughes, B. D., Landman, K. A., Näthke, I. S., & Osborne, J. M. (2018). A multicellular model of intestinal crypt buckling and fission. *Bull Math Biol*, *80*(2), 335–359. doi:10.1007/s11538-017-0377-z

Atwell, K., Qin, Z., Gavaghan, D., Kugler, H., Hubbard, E. J. A., & Osborne, J. M. (2015). Mechano-logical model of C. elegans germ line suggests feedback on the cell cycle. *Development*, *142*(22), 3902–3911. doi:10.1242/dev.126359

Baker, A.-M., Cereser, B., Melton, S., Fletcher, A. G., Rodriguez-Justo, M., Tadrous, P. J., Humphries, A., et al. (2014). Quantification of crypt and stem cell evolution in the normal and neoplastic human colon. *Cell Rep*, *8*(4), 940–947. doi:10.1016/j.celrep.2014.07.019

Bartolucci, C., Moreno, C., Cruz, A. de la, Lambiase, P., Severi, S., & Valenzuela, C. (2014). Linking a novel mutation to its short QT phenotype through multiscale computational modelling. In *Computing in cardiology 2014* (pp. 1017–1020). IEEE.

Beattie, K. A., Luscombe, C., Williams, G., Munoz-Muriedas, J., Gavaghan, D. J., Cui, Y., & Mirams, G. R. (2013). Evaluation of an in silico cardiac safety assay: using ion channel screening data to predict QT interval changes in the rabbit ventricular wedge. *J Pharmacol Toxicol Methods*, *68*(1), 88–96. doi:10.1016/j.vascn.2013.04.004

Bordas, R., Lefevre, C., Veeckmans, B., Pitt-Francis, J., Fetita, C., Brightling, C. E., Kay, D., et al. (2015). Development and analysis of patient-based complete conducting airways models. *PloS one*, *10*(12), e0144105.

Britton, O. J., Abi-Gerges, N., Page, G., Ghetti, A., Miller, P. E., & Rodriguez, B. (2017). Quantitative comparison of effects of dofetilide, sotalol, quinidine, and verapamil between human ex vivo trabeculae and in silico ventricular models incorporating inter-individual action potential variability. *Frontiers in physiology*, *8*, 597.

Britton, O. J., Bueno-Orovio, A., Van Ammel, K., Lu, H. R., Towart, R., Gallacher, D. J., & Rodriguez, B. (2013). Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology. *Proc Natl Acad Sci USA*, *110*(23), E2098–E2105. doi:10.1073/pnas.1304382110

Britton, O. J., Bueno-Orovio, A., Virág, L., Varró, A., & Rodriguez, B. (2017). The electrogenic na+/k+ pump is a key determinant of repolarization abnormality susceptibility in human ventricular cardiomyocytes: A population-based simulation study. *Frontiers in Physiology*, *8*, 278. doi:10.3389/fphys.2017.00278

Burrowes, K., Doel, T., Kim, M., Vargas, C., Roca, J., Grau, V., & Kay, D. (2017). A combined image-modelling approach assessing the impact of hyperinflation due to emphysema on regional ventilation–perfusion matching. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization*, *5*(2), 110–126.

Campos, J. O., Oliveira, R. S., Santos, R. W. dos, & Rocha, B. M. (2016). Lattice Boltzmann method for parallel simulations of cardiac electrophysiology using GPUs. *J Comput Appl Math*, *295*, 70–82. doi:10.1016/j.cam.2015.02.008

Carapella, V., Bordas, R., Pathmanathan, P., Lohezic, M., Schneider, J. E., Kohl, P., Burrage, K., et al. (2014). Quantitative study of the effect of tissue microstructure on contraction in a computational model of rat left ventricle. *PLOS ONE*, *9*(4), e92792. doi:10.1371/journal.pone.0092792

Cardone-Noott, L., Bueno-Orovio, A., Minchole, A., Zemzemi, N., & Rodriguez, B. (2016). Human ventricular activation sequence and the simulation of the electrocardiographic QRS complex and its variability in healthy and intraventricular block conditions. *EP Europace*, *18*(suppl_4), iv4–iv15.

Cardone-Noott, L., Bueno-Orovio, A., Mincholé, A., Burrage, K., Wallman, M., Zemzemi, N., Dall'Armellina, E., et al. (2014). A computational investigation into the effect of infarction on clinical human electrophysiology biomarkers. In *Computing in cardiology* (pp. 673–676). IEEE.

Cardone-Noott, L., Rodriguez, B., & Bueno-Orovio, A. (2018). Strategies of data layout and cache writing for input-output optimization in high performance scientific computing: Applications to the forward electrocardiographic problem. (R. S. Oliveira, Ed.)*PLOS ONE*, *13*(8), e0202410. doi:10.1371/journal.pone.0202410

Carroll, T. D., Langlands, A. J., Osborne, J. M., Newton, I. P., Appleton, P. L., & Näthke, I. (2017). Interkinetic nuclear migration and basal tethering facilitates post-mitotic daughter separation in intestinal organoids. *J Cell Sci*, *130*(22), 3862–3877. doi:10.1242/jcs.211656

Cervi, J., & Spiteri, R. J. (2018). High-order operator splitting for the bidomain and monodomain models. *SIAM Journal on Scientific Computing*, *40*(2), A769–A786.

Cooper, F. R., Baker, R. E., & Fletcher, A. G. (2017). Numerical analysis of the Immersed Boundary Method for cell-based simulation. *SIAM J Sci Comput*, *39*(5), 943–967. doi:10.1137/16M1092246

Cooper, J., & Osborne, J. (2013). Connecting models to data in multiscale multicellular tissue simulations. *Procedia Comput Sci*, *18*, 712–721. doi:10.1016/j.procs.2013.05.235

Cooper, J., Scharm, M., & Mirams, G. R. (2016). The cardiac electrophysiology web lab. *Biophys J*, *110*(2), 292–300. doi:10.1016/j.bpj.2015.12.012

Cooper, J., Spiteri, R. J., & Mirams, G. R. (2015). Cellular cardiac electrophysiology modeling with Chaste and CellML. *Front Physiol*, *5*, 511. doi:10.3389/fphys.2014.00511

Corrado, C., Lassoued, J., Mahjoub, M., & Zemzemi, N. (2016). Stability analysis of the POD reduced order method for solving the bidomain model in cardiac electrophysiology. *Math Biosci*, *272*, 81–91. doi:10.1016/j.mbs.2015.12.005

Corsi, C., Cortesi, M., Callisesi, G., De Bie, J., Napolitano, C., Santoro, A., Mortara, D., et al. (2017). Noninvasive quantification of blood potassium concentration from ECG in hemodialysis patients. *Sci Rep*, *7*, 42492. doi:10.1038/srep42492

Daly, A. C., Clerx, M., Beattie, K. A., Cooper, J., Gavaghan, D. J., & Mirams, G. R. (2018). Reproducible model development in the cardiac electrophysiology Web Lab. *Progress in Biophysics and Molecular Biology*, *139*, 3–14. doi:10.1016/j.pbiomolbio.2018.05.011

Daly, A. C., Cooper, J., Gavaghan, D. J., & Holmes, C. (2017). Comparing two sequential Monte Carlo samplers for exact and approximate Bayesian inference on biological models. *JR Soc Interface*, *14*(134), 20170340. doi:1098/rsif.2017.0340

Daly, A. C., Gavaghan, D. J., Holmes, C., & Cooper, J. (2015). Hodgkin-Huxley revisited: reparametrization and identifiability analysis of the classic action potential model with approximate Bayesian methods. *R Soc Open Sci*, *2*(12), 150499. doi:10.1098/rsos.150499

Davies, M. R., Wang, K., Mirams, G. R., Caruso, A., Noble, D., Walz, A., Lavé, T., et al. (2016). Recent developments in using mechanistic cardiac modelling for drug safety evaluation. *Drug Discovery Today*, *21*(6), 924–938. doi:10.1016/j.drudis.2016.02.003

Davit, Y., Osborne, J. M., Byrne, H. M., Gavaghan, D. J., & Pitt-Francis, J. M. (2013). Validity of the Cauchy-Born rule applied to discrete cellular-scale models of biological tissues. *Phys Rev E*, *87*, 042724. doi:10.1103/PhysRevE.87.042724

Dunn, S.-J., Näthke, I. S., & Osborne, J. M. (2013). Computational models reveal a passive mechanism for cell migration in the crypt. *PLOS ONE*, *8*(11), e80516. doi:10.1371/journal.pone.0080516

Dunn, S.-J., Osborne, J. M., Appleton, P. L., & Näthke, I. (2016). Combined changes in Wnt signaling response and contact inhibition induce altered proliferation in radiation-treated intestinal crypts. *Mol Biol Cell*, *27*(11), 1863–1874. doi:10.1091/mbc.E15-12-0854

Dutta, S., Mincholé, A., Quinn, T. A., & Rodriguez, B. (2017). Electrophysiological properties of computational human ventricular cell action potential models under acute ischemic conditions. *Progress in Biophysics and Molecular Biology*, *129*, 40–52. doi:10.1016/j.pbiomolbio.2017.02.007

Dutta, S., Mincholé, A., Walmsley, J., & Rodriguez, B. (2013). Ionic mechanisms of variability in electrophysiological properties in ischemia: A population-based study. In *Computing in cardiology* (pp. 691–694). IEEE.

Dutta, S., Mincholé, A., Zacur, E., Quinn, T. A., Taggart, P., & Rodriguez, B. (2016). Early afterdepolarizations promote transmural reentry in ischemic human ventricles with reduced repolarization reserve. *Progress in Biophysics and Molecular Biology*, *120*(1-3), 236–248. doi:10.1016/j.pbiomolbio.2016.01.008

Elkins, R. C., Davies, M. R., Brough, S. J., Gavaghan, D. J., Cui, Y., Abi-Gerges, N., & Mirams, G. R. (2013). Variability in high-throughput ion-channel screening data and consequences for cardiac safety assessment. *J Pharmacol Toxicol Methods*, *68*(1), 112–122. doi:10.1016/j.vascn.2013.04.007

Figueredo, G. P., Joshi, T. V., Osborne, J. M., Byrne, H. M., & Owen, M. R. (2013). On-lattice agent-based simulation of populations of cells within the open-source Chaste framework. *Interface focus*, *3*(2), 20120081. doi:10.1098/rsfs.2012.0081

Finegan, T. M., Na, D., Skeeters, A. V., Cammarota, C., Nadasi, T. J., Dawney, N. S., Fletcher, A. G., et al. (2018). Tissue tension and not interphase cell shape determines cell division orientation in the Drosophila follicular epithelium. *EMBO Journal*, *38*, e100072. doi:10.15252/embj.2018100072

Fletcher, A. G., Osborne, J. M., Maini, P. K., & Gavaghan, D. J. (2013). Implementing vertex dynamics models of cell populations in biology within a consistent computational framework. *Prog Biophys Mol Biol*, *113*, 299–326. doi:10.1016/j.pbiomolbio.2013.09.003

Franzetti, G., Crippa, F., Cutrì, E., Spatafora, G., Montin, E., Mainardi, L., Spadola, G., et al. (2015). Combined approach for the biomechanical characterization of skin lesions. In *37th annual international conference of the ieee engineering in medicine and biology society (embc)* (pp. 913–916). doi:10.1109/EMBC.2015.7318511

Gao, J., Sathar, S., O'Grady, G., Archer, R., & Cheng, L. K. (2015). A stochastic algorithm for generating realistic virtual interstitial cell of Cajal networks. *IEEE Trans Biomed Eng*, *62*(8), 2070–2078. doi:10.1109/TBME.2015.2412533

Gao, J., Sathar, S., O'Grady, G., Han, J., & Cheng, L. K. (2014). Developmental changes in postnatal murine intestinal interstitial cell of Cajal network structure and function. *Ann Biomed Eng*, *42*(8), 1729–1739. doi:10.1007/s10439-014-1021-9

Godwin, S., Ward, D., Pedone, E., Homer, M., Fletcher, A. G., & Marucci, L. (2017). An extended model for culture-dependent heterogenous gene expression and proliferation dynamics in mouse embryonic stem cells. *NPJ Syst Biol Appl*, *3*(1), 19. doi:10.1038/s41540-017-0020-5

Green, B., Kevin R., & Spiteri, R. J. (n.d.). Direct function evaluation vs. lookup tables: When to use which? *SIAM J. Sci. Comput.*

Grogan, J. A., Connor, A. J., Markelc, B., Muschel, R. J., Maini, P. K., Byrne, H. M., & Pitt-Francis, J. M. (2017). Microvessel chaste: an open library for spatial modeling of vascularized tissues. *Biophys J*, *112*(9), 1767–1772. doi:10.1016/j.bpj.2017.03.036

Grogan, J. A., Connor, A. J., Pitt-Francis, J. M., Maini, P. K., & Byrne, H. M. (2018). The importance of geometry in the corneal micropocket angiogenesis assay. *PLoS Comput Biol*, *14*(3), e1006049. doi:10.1371/journal.pcbi.1006049

Grogan, J. A., Markelc, B., Connor, A. J., Muschel, R. J., Pitt-Francis, J. M., Maini, P. K., & Byrne, H. M. (2017). Predicting the influence of microvascular structure on tumor response to radiotherapy. *IEEE Trans Biomed Eng*, *64*(3), 504–511. doi:10.1109/TBME.2016.2606563

Gurev, V., Pathmanathan, P., Fattebert, J.-L., Wen, H.-F., Magerlein, J., Gray, R. A., Richards, D. F., et al. (2015). A high-resolution computational model of the deforming human heart. *Biomechanics and modeling in mechanobiology*, *14*(4), 829–849. doi:10.1007/s10237-014-0639-8

Harvey, D. G., Fletcher, A. G., Osborne, J. M., & Pitt-Francis, J. (2015). A parallel implementation of an off-lattice individual-based model of multicellular populations. *Comput Phys Commun*, *192*, 130–137. doi:10.1016/j.cpc.2015.03.005

Hill, A. P., Perry, M. D., Abi-Gerges, N., Couderc, J.-P., Fermini, B., Hancox, J. C., Knollmann, B. C., et al. (2016). Computational cardiology and risk stratification for sudden cardiac death: one of the grand challenges for cardiology in the 21st century. *J Physiol*. doi:10.1113/JP272015

Hu, S., & Cucinotta, F. A. (2014). Epidermal homeostasis and radiation responses in a multiscale tissue modeling framework. *Integr Biol*, *6*(1), 76–89. doi:10.1039/C3IB40141C

Johnstone, R. H., Chang, E. T. Y., Bardenet, R., De Boer, T. P., Gavaghan, D. J., Pathmanathan, P., Clayton, R. H., et al. (2016). Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models? *J Mol Cell Cardiol*, *96*, 49–62. doi:10.1016/j.yjmcc.2015.11.018

Koke, C., Kanesaki, T., Grosshans, J., Schwarz, U. S., & Dunlop, C. M. (2014). A computational model of nuclear self-organisation in syncytial embryos. *J Theor Biol*, *359*, 92–100. doi:10.1016/j.jtbi.2014.06.001

Kursawe, J., Baker, R. E., & Fletcher, A. G. (2017). Impact of implementation choices on quantitative predictions of cell-based computational models. *J Comput Phys*, *345*, 752–767. doi:10.1016/j.jcp.2017.05.048

Kursawe, J., Baker, R. E., & Fletcher, A. G. (2018). Approximate Bayesian computation reveals the importance of repeated measurements for parameterising cell-based models of growing tissues. *J Theor Biol*, *443*, 66–81. doi:10.1016/j.jtbi.2018.01.020

Kursawe, J., Brodskiy, P. A., Zartman, J. J., Baker, R. E., & Fletcher, A. G. (2015). Capabilities and limitations of tissue size control through passive mechanical forces. *PLoS Comput Biol*, *11*(12), e1004679. doi:10.1371/journal.pcbi.1004679

Langham, J., Bense, H., & Barkley, D. (2018). Modeling shape selection of buckled dielectric elastomers. *J Appl Phys*, *123*(6), 065102. doi:10.1063/1.5012848

Langlands, A. J., Almet, A. A., Appleton, P. L., Newton, I. P., Osborne, J. M., & Näthke, I. S. (2016). Paneth cell-rich regions separated by a cluster of lgr5+ cells initiate crypt fission in the intestinal stem cell niche. *PLOS Biology*, *14*(6), 1–31. doi:10.1371/journal.pbio.1002491

Lekadir, K., Lange, M., Zimmer, V. A., Hoogendoorn, C., & Frangi, A. F. (2016). Statistically-driven 3D fiber reconstruction and denoising from multi-slice cardiac DTI using a Markov random field model. *Med Image Anal*, *27*, 105–116. doi:10.1016/j.media.2015.03.006

Lekadir, K., Pashaei, A., Hoogendoorn, C., Pereanez, M., Albà, X., & Frangi, A. F. (2014). Effect of statistically derived fiber models on the estimation of cardiac electrical activation. *IEEE Trans Biomed Eng*, *61*(11), 2740–2748. doi:10.1109/TBME.2014.2327025

Lim, H., Cun, W., Wang, Y., Gray, R. A., & Glimm, J. (2018). The role of conductivity discontinuities in design of cardiac defibrillation. *Chaos*, *28*(1), 013106. doi:10.1063/1.5019367

Lyon, A., Bueno-Orovio, A., Zacur, E., Ariga, R., Grau, V., Neubauer, S., Watkins, H., et al. (2018). Electrocardiogram phenotypes in hypertrophic cardiomyopathy caused by distinct mechanisms: apico-basal repolarization gradients vs. Purkinje-myocardial coupling abnormalities. *EP Europace*, *20*(suppl_3), iii102–iii112. doi:10.1093/europace/euy226

Mahoney, V. M., Mezzano, V., Mirams, G. R., Maass, K., Li, Z., Cerrone, M., Vasquez, C., et al. (2016). Connexin43 contributes to electrotonic conduction across scar tissue in the intact heart. *Sci Rep*, *6*, 26744. doi:10.1038/srep26744

Marsh, M. E., Ziaratgahi, S. T., & Spiteri, R. J. (2012). The secrets to the success of the rush–larsen method and its generalizations. *IEEE Transactions on Biomedical Engineering*, *59*(9), 2506–2515.

McMillan, B., Gavaghan, D. J., & Mirams, G. R. (2017). Early afterdepolarisation tendency as a simulated pro-arrhythmic risk indicator. *Toxicology Research*, *6*(6), 912–921. doi:10.1039/C7TX00141J

Mirams, G. R., Arthurs, C. J., Bernabeu, M. O., Bordas, R., Cooper, J., Corrias, A., Davit, Y., et al. (2013). Chaste: an open source C++ library for computational physiology and biology. *PLoS Comput Biol*, *9*, e1002970. doi:10.1371/journal.pcbi.1002970

Mirams, G. R., Davies, M. R., Brough, S. J., Bridgland-Taylor, M. H., Cui, Y., Gavaghan, D. J., & Abi-Gerges, N. (2014). Prediction of thorough QT study results using action potential simulations based on ion channel screens. *J Pharmacol Toxicol Methods*, *70*(3), 246–254. doi:10.1016/j.vascn.2014.07.002

Mirams, G. R., Pathmanathan, P., Gray, R. A., Challenor, P., & Clayton, R. H. (2016). Uncertainty and variability in computational and mathematical models of cardiac physiology. *J Physiol*. doi:10.1113/JP271671

Moreno, C., Oliveras, A., Cruz, A. de la, Bartolucci, C., Muñoz, C., Salar, E., Gimeno, J. R., et al. (2015). A new KCNQ1 mutation at the S5 segment that impairs its association with KCNE1 is responsible for short QT syndrome. *Cardiovasc Res*, cvv196. doi:10.1093/cvr/cvv196

Muraro, D., Parker, A., Vaux, L., Filippi, S., Almet, A. A., Fletcher, A. G., Watson, A. J. M., et al. (2018). Chronic TNFα-driven injury delays cell migration to villi in the intestinal epithelium. *J R Soc Interface*, *15*(145), 20180037. doi:10.1098/rsif.2018.0037

Muszkiewicz, A., Liu, X., Bueno-Orovio, A., Lawson, B. A. J., Burrage, K., Casadei, B., & Rodriguez, B. (2018). From ionic to cellular variability in human atrial myocytes: an integrative computational and experimental study. *American Journal of Physiology-Heart and Circulatory Physiology*, *314*(5), H895–H916. doi:10.1152/ajpheart.00477.2017

Nelson, M. R., Sutton, K. J., Brook, B. S., Mallet, D. G., Simpson, D. P., & Rank, R. G. (2014). STI-GMaS: an open-source environment for simulation of sexually-transmitted infections. *BMC Syst Biol*, *8*(1), 1. doi:10.1186/1752-0509-8-66

Osborne, J. M. (2015). Multiscale model of colorectal cancer using the cellular Potts framework. *Cancer Inform*, *14*(Suppl 4), 83. doi:10.4137/CIN.S19332

Osborne, J. M., & Bernabeu, M. O. (2018). A fully discrete open source framework for the simulation of vascular remodelling. In *2018 40th annual international conference of the ieee engineering in medicine and biology society (embc)* (pp. 4552–4555). doi:10.1109/EMBC.2018.8513223

Osborne, J. M., Fletcher, A. G., Pitt-Francis, J. M., Maini, P. K., & Gavaghan, D. J. (2017). Comparing individual-based approaches to modelling the self-organization of multicellular tissues. *PLoS Comput Biol*, *13*(2), 1–34. doi:10.1371/journal.pcbi.1005387

Passini, E., Britton, O. J., Lu, H. R., Rohrbacher, J., Hermans, A. N., Gallacher, D. J., Greig, R. J., et al. (2017). Human in silico drug trials demonstrate higher accuracy than animal models in predicting clinical pro-arrhythmic cardiotoxicity. *Frontiers in physiology*, *8*, 668. doi:10.3389/fphys.2017.00668

Passini, E., Mincholé, A., Coppini, R., Cerbai, E., Rodriguez, B., Severi, S., & Bueno-Orovio, A. (2016). Mechanisms of pro-arrhythmic abnormalities in ventricular repolarisation and anti-arrhythmic therapies in human hypertrophic cardiomyopathy. *Journal of Molecular and Cellular Cardiology*, *96*, 72–81. doi:10.1016/j.yjmcc.2015.09.003

Passini, E., Pellegrini, A., Caiani, E., & Severi, S. (2013). Computational analysis of head-down bed rest effects on cardiac action potential duration. In *Computing in cardiology* (pp. 357–360). IEEE.

Passini, E., Rodriguez, B., Mincholé, A., Coppini, R., Cerbai, E., Severi, S., & Bueno-Orovio, A. (2014). Late sodium current inhibition counteracts pro-arrhythmic mechanisms in human hypertrophic cardiomyopathy. In *Computing in cardiology* (pp. 861–864). IEEE.

Pathmanathan, P., & Gray, R. A. (2014). Verification of computational models of cardiac electro-physiology. *Int J Numer Meth Biomed Eng*, *30*(5), 525–544. doi:10.1002/cnm.2615

Pathmanathan, P., & Gray, R. A. (2015). Filament Dynamics during Simulated Ventricular Fibrillation in a High-Resolution Rabbit Heart. *BioMed Research International*, *2015*, 720575. doi:10.1155/2015/720575

Pitt-Francis, J., Pathmanathan, P., Bernabeu, M. O., Bordas, R., Cooper, J., Fletcher, A. G., Mirams, G. R., et al. (2009). Chaste: A test-driven approach to software development for biological modelling. *Comput Phys Commun*, *180*(12), 2452–2471. doi:10.1016/j.cpc.2009.07.019

Reilly, S. N., Liu, X., Carnicer, R., Recalde, A., Muszkiewicz, A., Jayaram, R., Carena, M. C., et al. (2016). Up-regulation of miR-31 in human atrial fibrillation begets the arrhythmia by depleting dystrophin and neuronal nitric oxide synthase. *Science Translational Medicine*, *8*(340), 340ra74–340ra74. doi:10.1126/scitranslmed.aac4296

Rubinacci, S., Graudenzi, A., Caravagna, G., Mauri, G., Osborne, J., Pitt-Francis, J., & Antoniotti, M. (2015). CoGNaC: a Chaste plugin for the multiscale simulation of gene regulatory networks driving the spatial dynamics of tissues and cancer. *Cancer Inform*, *14*(Suppl 4), 53. doi:10.4137/CIN.S19965

Sadrieh, A., Domanski, L., Pitt-Francis, J., Mann, S. A., Hodkinson, E. C., Ng, C.-A., Perry, M. D., et al. (2014). Multiscale cardiac modelling reveals the origins of notched T waves in long QT syndrome type 2. *Nat Commun*, *5*. doi:10.1038/ncomms6069

Samanta, K., Kar, P., Mirams, G. R., & Parekh, A. B. (2015). Ca2+ channel re-localization to plasma-membrane microdomains strengthens activation of Ca2+-dependent nuclear gene expression. *Cell Rep*, *12*(2), 203–216. doi:10.1016/j.celrep.2015.06.018

Sathar, S., Cheng, L. K., & Trew, M. L. (2015a). A comparison of solver performance for complex gastric electrophysiology models. In *37th annual international conference of the ieee engineering in medicine and biology society (embc)* (pp. 1452–1455). IEEE. doi:10.1109/EMBC.2015.7318643

Sathar, S., Trew, M. L., & Cheng, L. K. (2015b). Tissue specific simulations of interstitial cells of cajal networks using unstructured meshes. In *37th annual international conference of the ieee engineering in medicine and biology society (embc)* (pp. 8062–8065). doi:10.1109/EMBC.2015

Sathar, S., Trew, M. L., Du, P., O'Grady, G., & Cheng, L. K. (2014). A biophysically based finite-state machine model for analyzing gastric experimental entrainment and pacing recordings. *Ann Biomed Eng*, *42*(4), 858–870. doi:10.1007/s10439-013-0949-5

Sathar, S., Trew, M. L., O'Grady, G., & Cheng, L. K. (2015c). A multiscale tridomain model for simulating bioelectric gastric pacing. *IEEE Trans Biomed Eng*, *62*(11), 2685–2692. doi:10.1109/TBME.2015.2444384

Soares, M., Owers-Bradley, J., Foy, B., Kay, D., & Siddiqui, S. (2017). The evaluation of frequency dependence of resistance using a patient-specific 3D physical model and a computational model, *50*, PA2476. doi:10.1183/1393003.congress-2017.PA2476

Spiteri, R. J., & Torabi Ziaratgahi, S. (2016). Operator splitting for the bidomain model revisited. *J. Comput. Appl. Math.*, *296*, 550–563. doi:10.1016/j.cam.2015.09.015

Tetley, R. J., Blanchard, G. B., Fletcher, A. G., Adams, R. J., & Sanson, B. (2016). Unipolar distributions of junctional Myosin II identify cell stripe boundaries that drive cell intercalation throughout Drosophila axis extension. *eLife*, *5*, e12094. doi:10.7554/eLife.12094

Waites, W., Cavaliere, M., Cachat, É., Danos, V., & Davies, J. A. (2018). An information-theoretic measure for patterning in epithelial tissues. *IEEE Access*, *6*, 40302–40312. doi:/10.1109/ACCESS.2018.2853624

Wallman, M., Smith, N. P., & Rodríguez, B. (2014). Computational methods to reduce uncertainty in the estimation of cardiac conduction properties from electroanatomical recordings. *Med Image Anal*, *18*, 228–240. doi:10.1016/j.media.2013.10.006

Walmsley, J., Mirams, G. R., Efimov, I. R., Burrage, K., & Rodriguez, B. (2013). Estimation of conductivity tensors from human ventricular optical mapping recordings. In *International conference on functional imaging and modeling of the heart* (pp. 224–231). Springer. doi:10.1007/978-3-642-38899-6_27

Walmsley, J., Mirams, G. R., Pitt-Francis, J., Rodriguez, B., & Burrage, K. (2015). Application of stochastic phenomenological modelling to cell-to-cell and beat-to-beat electrophysiological variability in cardiac tissue. *J Theor Biol*, *365*, 325–336. doi:10.1016/j.jtbi.2014.10.029

Walmsley, J., Rodriguez, J. F., Mirams, G. R., Burrage, K., Efimov, I. R., & Rodriguez, B. (2013). mRNA expression levels in failing human hearts predict cellular electrophysiological remodelling: A population- based simulation study. *PLOS ONE*, *8*(2). doi:10.1371/journal.pone.0056359

Williams, G., & Mirams, G. R. (2015). A web portal for in-silico action potential predictions. *J Pharmacol Toxicol Methods*, *75*, 10–16. doi:10.1016/j.vascn.2015.05.002

Zacur, E., Minchole, A., Villard, B., Carapella, V., Ariga, R., Rodriguez, B., & Grau, V. (2017). MRI-Based Heart and Torso Personalization for Computer Modeling and Simulation of Cardiac Electrophysiology. In (pp. 61–70). Springer, Cham. doi:10.1007/978-3-319-67552-7_8

Zemzemi, N., Bernabeu, M. O., Saiz, J., Cooper, J., Pathmanathan, P., Mirams, G. R., Pitt-Francis, J., et al. (2013). Computational assessment of drug-induced effects on the electrocardiogram: from ion channel to body surface potentials. *Br J Pharmacol*, *168*(3), 718–733. doi:10.1111/j.1476-5381.2012.02200.x

Zemzemi, N., & Rodriguez, B. (2015). Effects of L-type calcium channel and human ether-a-go-go related gene blockers on the electrical activity of the human heart: a simulation study. *Europace*, *17*(2), 326–333. doi:10.1093/europace/euu122

Zhou, X., Bueno-Orovio, A., Orini, M., Hanson, B., Hayward, M., Taggart, P., Lambiase, P. D., et al. (2016). In Vivo and In Silico Investigation Into Mechanisms of Frequency Dependence of Repolarization Alternans in Human Ventricular Cardiomyocytes. *Circulation Research*, *118*(2), 266–278. doi:10.1161/CIRCRESAHA.115.307836

Zhou, X., Bueno-Orovio, A., Schilling, R. J., Kirkby, C., Denning, C., Rajamohan, D., Burrage, K., et al. (2019). Investigating the complex arrhythmic phenotype caused by the gain-of-function mutation kcnq1-g229d. *Frontiers in Physiology*, *10*, 259. doi:10.3389/fphys.2019.00259