Component Model for Macroscopic Tumour Biomechanics

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CHIC

The Computational Horizons in Cancer (CHIC) [1] project addresses the challenge of **personalised clinical decision support** for **cancer** treatment, based on the integration of multi-modality, multi-scale data. Computational models are developed for this purpose, as well as a secure infrastructure for data and model access, and reuse. CHIC focuses on selected clinical scenarios: **Nephroblastoma**, **Glioblastoma**, **Non-Small-Cell Lung Cancer** and **Prostate Cancer**.

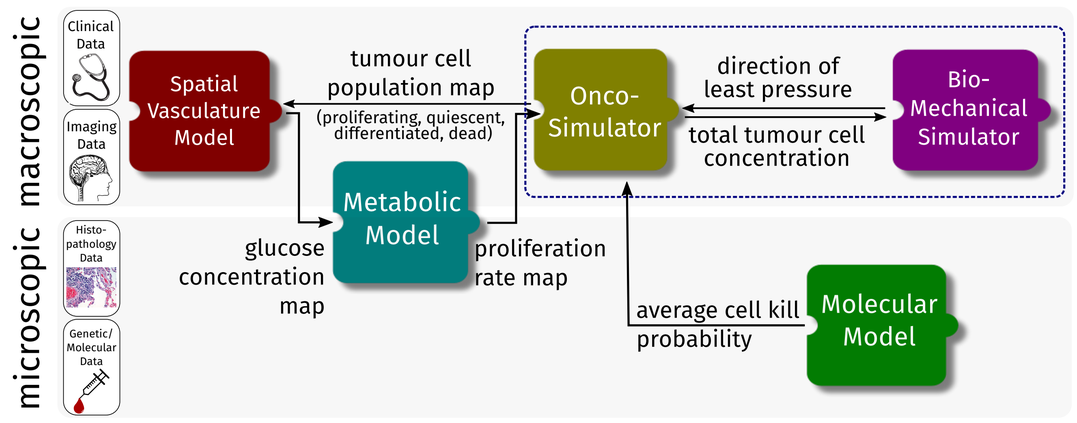
Cancer is a complex condition involving a large variety of processes on different length and time scales. Challenges related to the development, validation and maintenance of suitable **multi-scale models** are addressed through **hyper-modeling**.

Hyper-Modeling in CHIC

Hyper-modeling has been defined as the "general theory and practice of linking system models and their components" [2]. Here, a hyper-model represents a disease model which emerges from the **composition** of **multiple component models**, each of which captures existing knowledge about a portion of the process and operates at characteristic space-time intervals.

This approach facilitates the **collaborative development** of complex disease models and the **re-use of validated simulation components**.

In CHIC, **five mechanistic component models** are used. The main **model outcomes refer to** the **cell / tissue scale** and are **influenced by processes on molecular** and **tissue / body scale**.



Biomechanical Simulator

Biomechanical Simulator

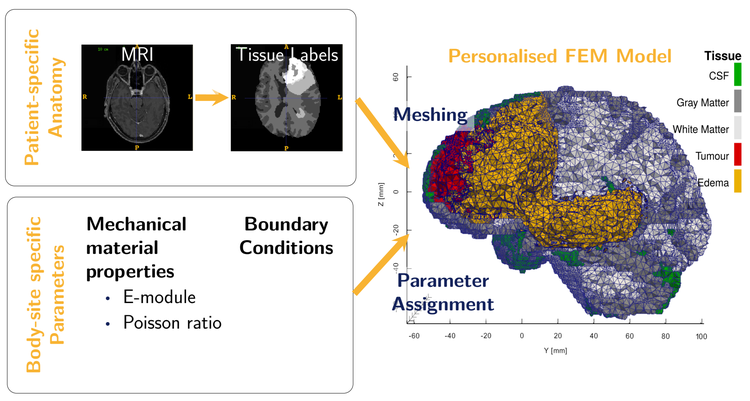
The Biomechanical Simulator (BMS) is a **component model** for the simulation of **bio-mechanical aspects** of **macroscopic tumour growth**. It relies on the Finite Element Method (FEM) to compute mechanical stresses and strains resulting from tumor growth or shrinkage in a patient-specific anatomy [3]. In CHIC, its output is used to **guide** the **direction of tumour expansion** by iterative coupled execution with a cellular-automaton based model of tumour cell proliferation and treatment effects, the Onco-Simulator (OS) [4]. Simulation involves two processes:

1. **Pre-processing**: Creation of personalised FEM model.
2. **Iterative coupled execution** with model of tumour growth dynamics.

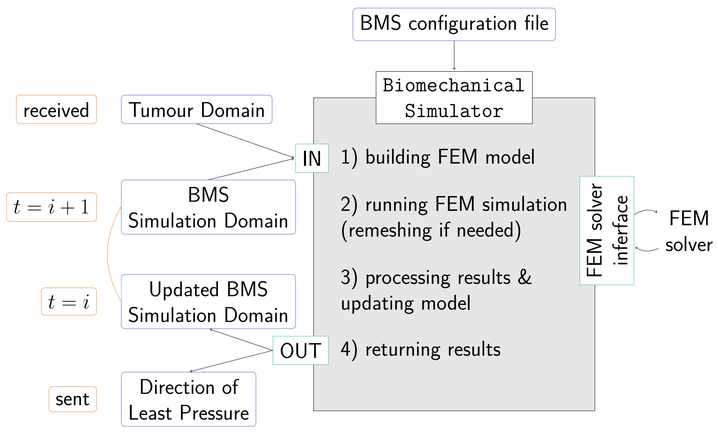
Model and pre-processing pipeline are implemented using **Open Source** libraries and software packages (CGAL, VTK, FEBio).

Pre-processing

A pre-processing pipeline **automates** the model **configuration process**, including the **assignment of** body-site specific **material properties** and **boundary conditions** from simple configuration options. In combination with automatic segmentation tools, this pipeline permits **rapid generation of patient-specific FEM** models for personalized simulations.



Simulation Tool



- Standalone or MUSCLE-enabled [5]
- Data I/O in VTK format
- FEBio [6] as FEM-backend

Coupled Execution

Interaction between BMS and OS component models:

- **Mechanical pressure informs growth direction.**
- Steps repeated in each iteration.

- Receiving **updated** map of tumour **cell concentrations** from OS.
- **Mapping** from OS domain to BMS simulation domain:

	OS	BMS
Tissues	tumour	tumour & close-by healthy tissue
Discretisation	regular grid	unstructured mesh

- Computation of elements' **growth** from cell concentration c:

$$\epsilon_{\text{growth}} = \left(\frac{c}{c_0}\right)^{1/3} - 1\,,$$

with cell-carrying capacity of tissue c_0.

- Growth assumed to result in **uniform and isotropic strain** in tissue:

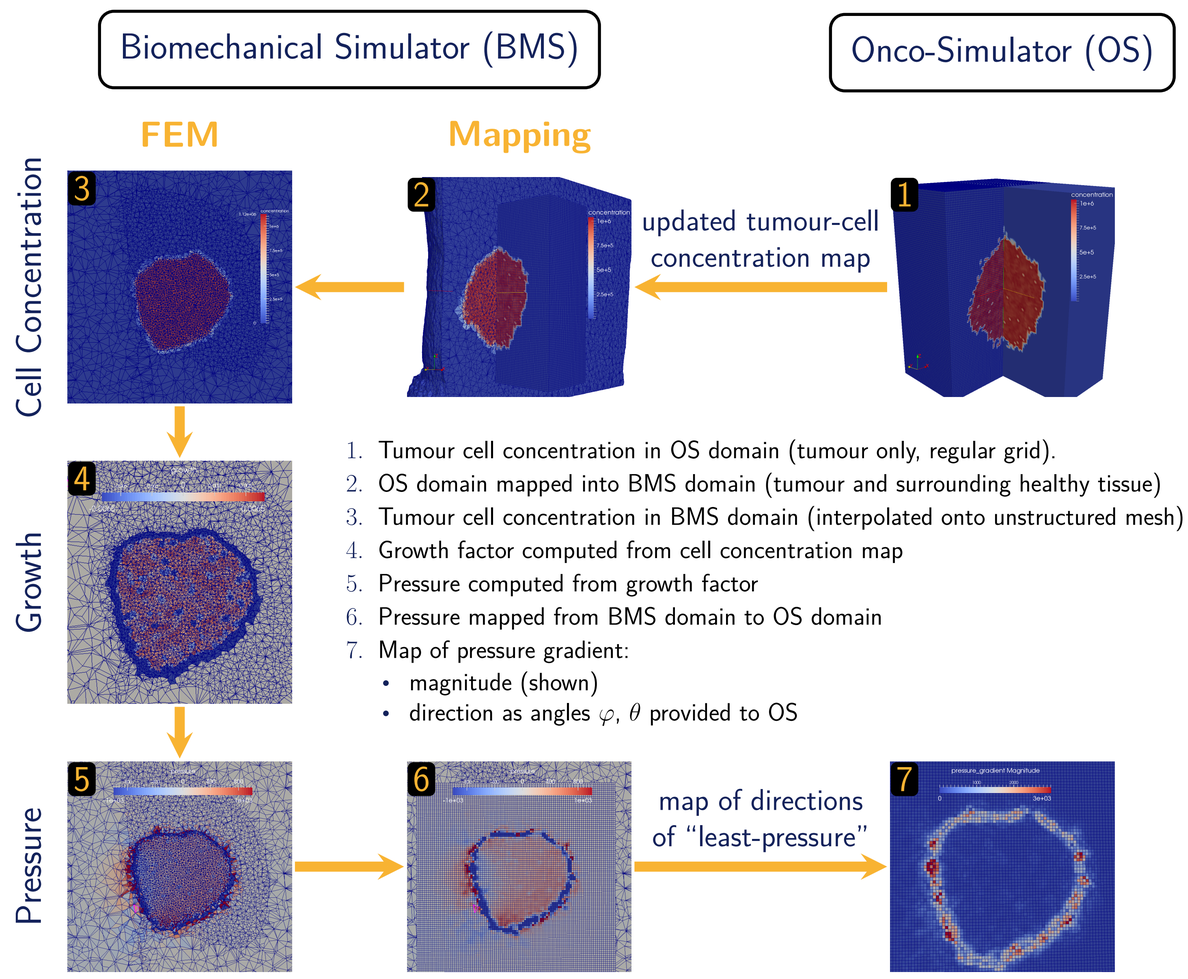
$$\hat{\boldsymbol{\epsilon}} = \hat{\boldsymbol{\epsilon}}_{\text{mech}} - \mathbb{I}\,\epsilon_{\text{growth}}$$

- Computation of **mechanical stress** $\hat{\boldsymbol{\sigma}}$ assuming **hyperelastic material**

$$\hat{\boldsymbol{\sigma}} = \lambda \text{Tr}(\hat{\boldsymbol{\epsilon}}) + 2\mu\hat{\boldsymbol{\epsilon}}\,,$$

with Lamé constants $\lambda(E,\nu)$ and $\mu(E,\nu)$.

- Computation of **pressure** $p = \frac{1}{3}\text{Tr}(\hat{\boldsymbol{\sigma}})$
- Computation of **direction of "least pressure"**: $-\frac{\boldsymbol{\nabla}_p}{\|\boldsymbol{\nabla}_p\|}$



1. Tumour cell concentration in OS domain (tumour only, regular grid).
2. OS domain mapped into BMS domain (tumour and surrounding healthy tissue)
3. Tumour cell concentration in BMS domain (interpolated onto unstructured mesh)
4. Growth factor computed from cell concentration map
5. Pressure computed from growth factor
6. Pressure mapped from BMS domain to OS domain
7. Map of pressure gradient:
   - magnitude (shown)
   - direction as angles φ, θ provided to OS

Summary

- **Macroscopic-continuum model of tumour biomechanics** (BMS) introduces **directionality** in otherwise isotropic tumour growth process (OS).
- Simulator **adaptable to different body-sites**, provided segmentations and estimates for bio-mechanical parameters.
- **Uncertainty in parameter assumptions**, boundary conditions and minimum size of simulation domain for most body-sites.

Outlook

- **Model evaluation** ongoing:
  BMS component model and composite hyper-model.
- **Model development**:
  simulation of tumour **mass-effect** & healthy tissue **invasion** as mechanically-coupled reaction-diffusion model.
- **Simulator improvements**:
  accuracy of parameter exchange between models, remeshing in case of large deformations.

Further Information

[1] *Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology*. URL: http://chic-vph.eu/project/.

[2] P. A. Fishwick. "Hypermodelling: an integrated approach to dynamic system modelling". In: *Journal of Simulation* 6.1 (02/2012). 00000, pp. 2–8.

[3] C. P. May et al. "Coupling biomechanics to a cellular level model: An approach to patient-specific image driven multi-scale and multi-physics tumor simulation". In: *Progress in Biophysics and Molecular Biology*. Experimental and Computational Model Interactions in Bio-Research: State of the Art 107.1 (10/2011). 00016, pp. 193–199.

[4] G. Stamatakos et al. "An advanced discrete statediscrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study". In: *Journal of Theoretical Biology* 266.1 (09/2010), pp. 124–139.

[5] J. Borgdorff et al. "Distributed multiscale computing with MUSCLE 2, the Multiscale Coupling Library and Environment". In: *J. Comput. Sci.* 5.5 (09/2014), pp. 719–731.

[6] S. A. Maas et al. "FEBio: finite elements for biomechanics". In: *J Biomech Eng* 134.1 (01/2012), p. 011005.

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