Clinical study and multiscale modeling to predict the esthetic outcome of Breast Conservative Therapy

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Abstract

Surgery for early stage breast cancer is either mastectomy (complete breast removal) or surgical lumpectomy (tumor removal only) coupled with radiotherapy, commonly known as Breast Conserving Therapy (BCT). The main goal of BCT is to preserve the breast contour in order to improve the quality of life of the patient after the surgery.

Our hypothesis is that the mechanical forces due to gravity, the breast density and tissue distribution, the inflammation induced by radiotherapy and the wound healing all play a role in determining the success or failure of BCT in preserving the contour of the breast.

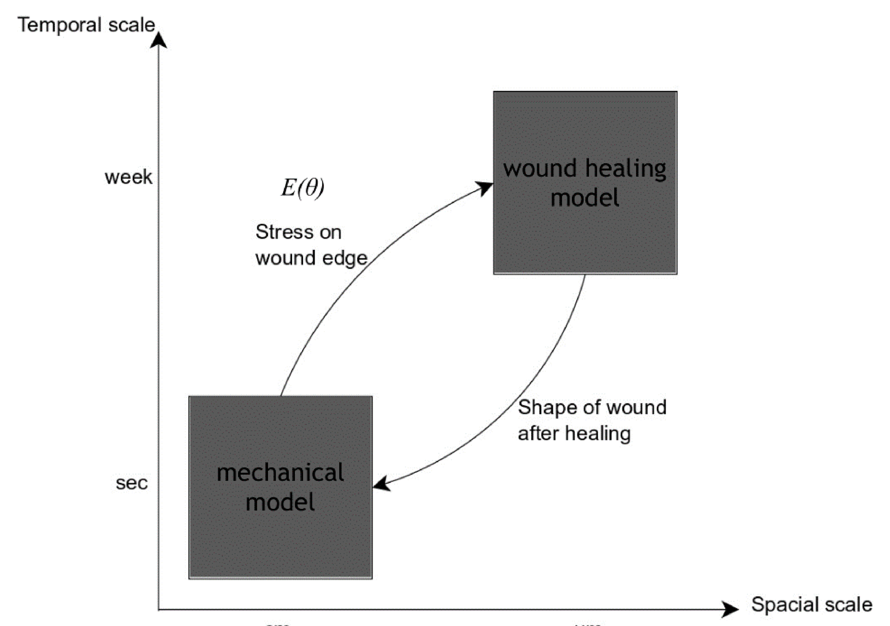
In order to predict and optimize the outcome of BCT, we are developing a patient-specific, multi-scale model aiming to:

1. Predict the immediate outcome of lumpectomy surgery based on the tumor size and location.
2. Predict at long term the healing of the surgical wound and the influence of inflammation, radiation therapy and scar tissues on the breast contour.
3. Test our predictive model on patients undergoing BCT and identify targets to help improve BCT outcome.

Introduction

Our model encompasses multiple scales in space from cells to tissue, and time from minutes for the tissue mechanics to months for the healing. We use a modular method coupling multi-modal imaging, mathematical modeling and finite element analysis to test our hypothesis and refine the model.

At the macroscopic (tissue) scale, a mechanical model of the breast tissue describes the effect of the gravity on the breast contour while at the microscopic (cell) scale, an agent-based model simulates the healing of the wound. Both models are inter-dependents: the mechanical stress resulting from the gravity influences the rate of scar tissue production during the healing, and the new scar tissue changes the mechanical properties of the breast.



Scales and inter-dependencies of the models.

Based on pre-operative imaging, our model aims to:

- Compute in three dimensions the cosmetic changes of the breast after surgery and during the healing.
- Provide an interactive, virtual model of lumpectomy surgery that can benefit the surgeon, both for surgical planning and with his discussion with the patient.

Methods

Our multi-scale model requires a robust initialization of a reference state of the breast. This pre-processing step involves a specific multi-modal registration algorithm that combines MRI and surface imaging of the breast in order to account for:

- The missing data that often results from breast imaging modalities (hidden surfaces on the surface imaging, compression of the breast compression on the MRI coils).
- The unknown parameters of the mechanical model of the breast (Young's modulus, density).

A clinical trial (NCT02310711) is currently underway at the Houston Methodist hospital in order to gather pre- and post-operative imaging of BCT patients; additional data will also be provided by clinical partners part of the Horizon 2020 DESIREE project. Finally, a graphical user interface is being developed to integrate our predictive model of BCT outcome within the DESIREE clinical decision system for breast cancer.

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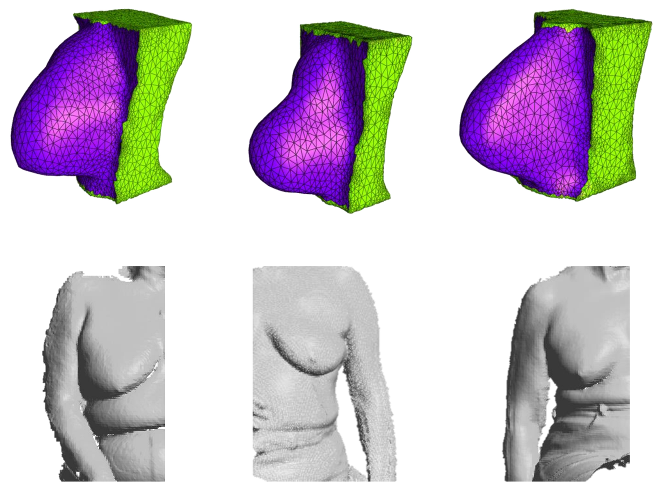
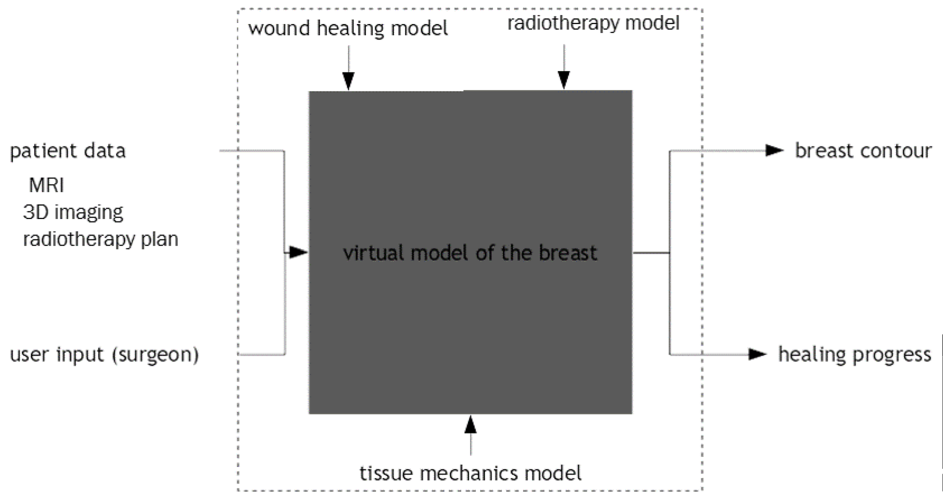
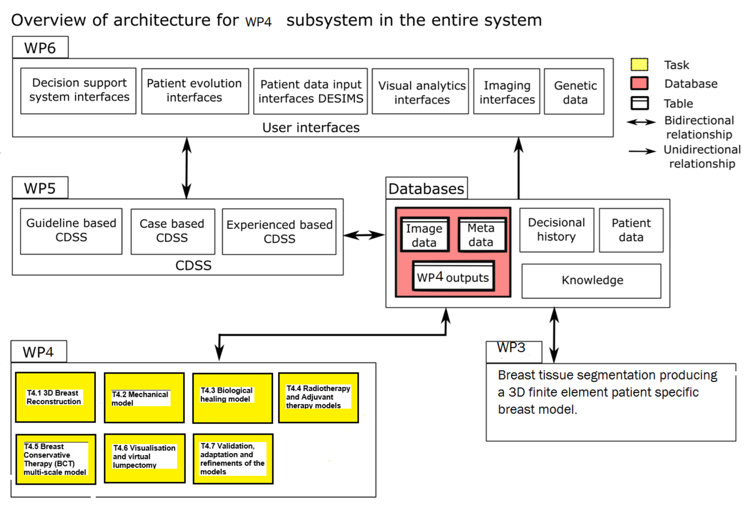


MRI (top) and surface imaging (right) of BCT patients.



Modules and input/output of the multi-scale model.

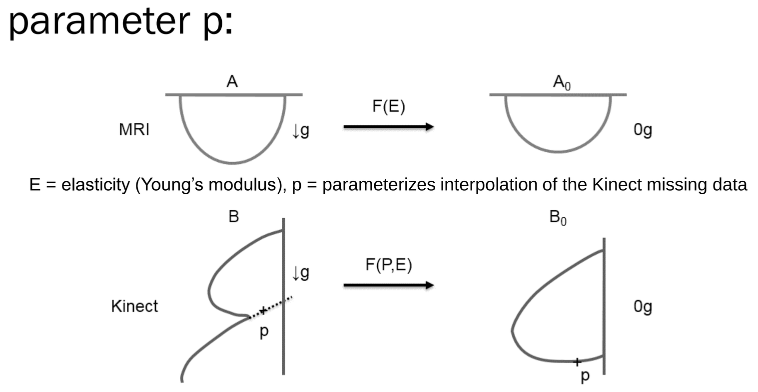


Integration of the multi-scale model in the DESIREE project (yellow).

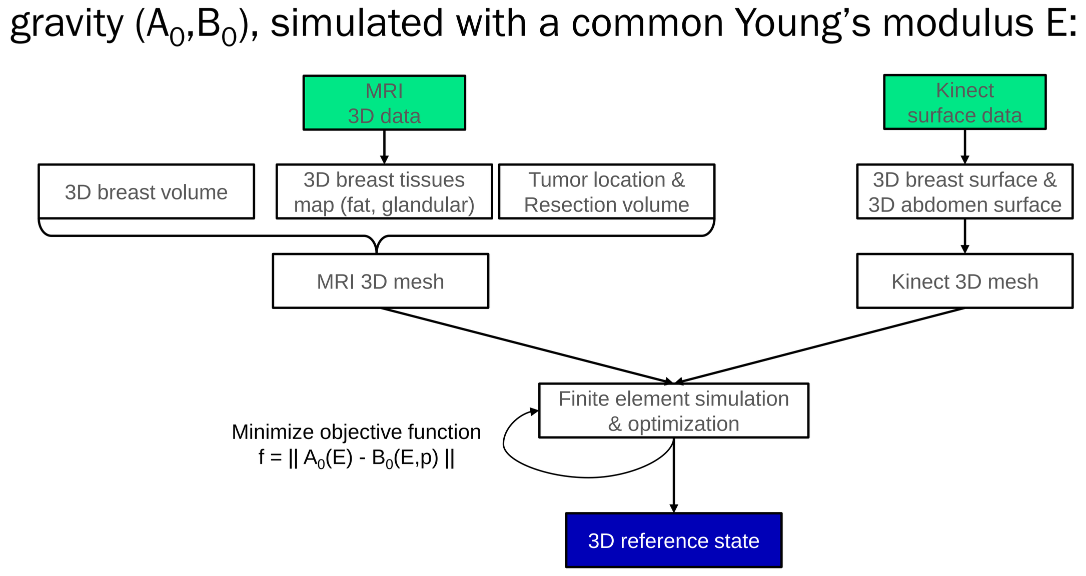
Reference State of the Breast

We use as ground truth data both MRI and surface imaging of the breast, acquired with the patient in prone position (A) and standing position (B), respectively. A finite element mesh of the breast is then constructed for both modalities.

In order to account for the missing surface data in (B), we extrapolate the surface data in order to reconstruct a complete finite element mesh of the breast, parameterized by a unique parameter p:



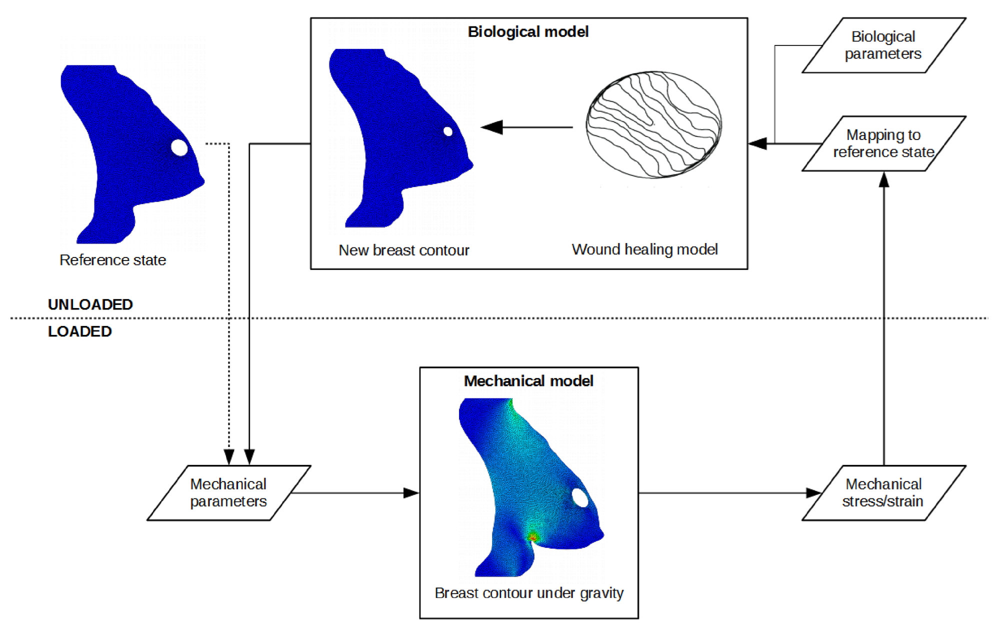
Starting from the finite element meshes of both breast models, we use an optimization algorithm minimizing the difference between the two meshes after inversion of the gravity (A_0,B_0), simulated with a common Young's modulus E:



Multi-Scale Model

In our multi-scale model, the wound healing and the mechanical stress resulting from the gravity are simulated from the "stress-free" (gravity-free) reference state of the breast, assuming that the cells topology is not modified by applying the gravity on the reference model of the breast.

The virtual surgery can also be performed from the reference state of the breast by removing breast tissues according to the size and location of the tumor and negative margin defined by the surgeon and by generating a new finite element mesh.

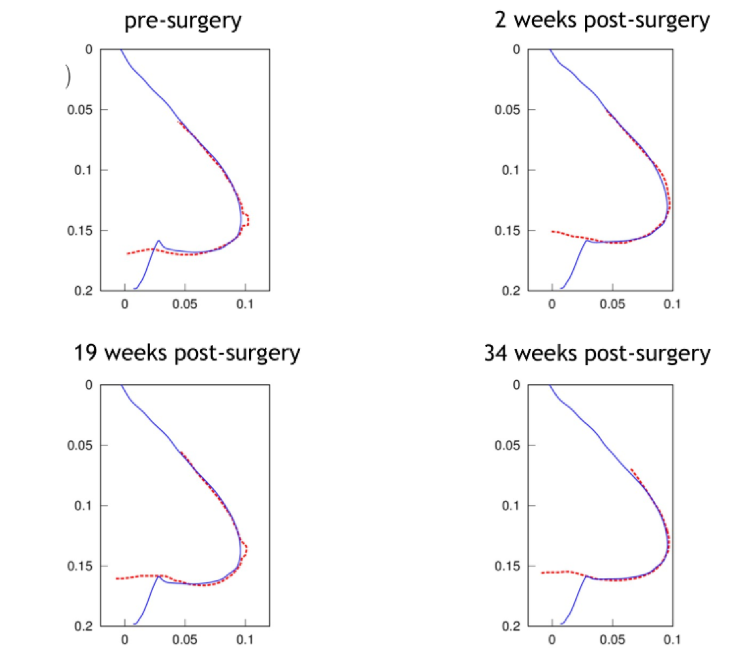


Flowchart of the mutli-scale model starting from the reference state of the breast.

The wound healing at the cellular level is modeled using an agent-based model that describes the production of scar tissue (fibroblasts, ECM) at the wound edge. We model the velocity of the wound closure as a function of the mechanical energy *E* and the wound curvature *K* that add to the normal velocity of the wound edge. We define the mechanical energy density function $E(\theta)=\varepsilon_{xx}\sigma_{xx}+\varepsilon_{yy}\sigma_{yy}+\varepsilon_{xy}\sigma_{xy}$ as a metric of the internal stress an strain in the breast tissues under the effect of gravity, function of the stress and strain tensors σ,ε retrieved from the mechanical model of the breast.

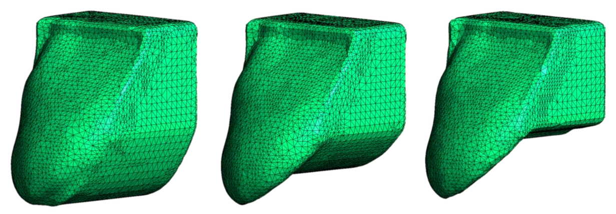
Results

A first validation of our multi-scale model was conducted with the case study of a patient presenting an ideal configuration of tumor centered in the sagittal plane of the nipple. Additional thermal and surface imaging of the breast provided non-invasive measurements on the evolution of the inflammation and stiffness of the breast tissues after the surgery. After identification of 3 distinct phases of healing at 2, 19 and 34 weeks after surgery (inflammation, healing and radiation therapy), we were able to fit selected mechanical and biological parameters of the multi-scale model to the patient data.

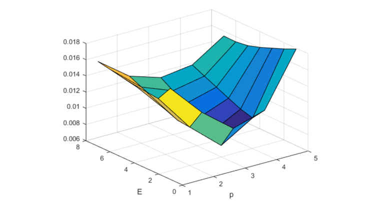


Patient surface imaging (red) and fitted model (blue) in 2D for each phase of healing.

We are extending the validation of our model on our patient population. We first retrieve the reference state of the breast in 3D by optimizing both the geometrical and mechanical parameters (p,E) of the model:



3D mesh interpolated from surface imaging data (B), with 3 different values of *p*.



Evaluation of the objective function f(p,E).

Conclusion

We have successfully identified and calibrated critical parameters of our multi-scale model on a case study at multiple phases of the healing process. Our next goal is to reproduce this optimization process on a statically significant patient population using 3D multi-modal imaging in order to derive relevant indicators for the cosmetic outcome of BCT.

References

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