PREDICITVE MULTISCALE MODELING FOR BREAST CONSERVING THERAPY

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Context and Motivations

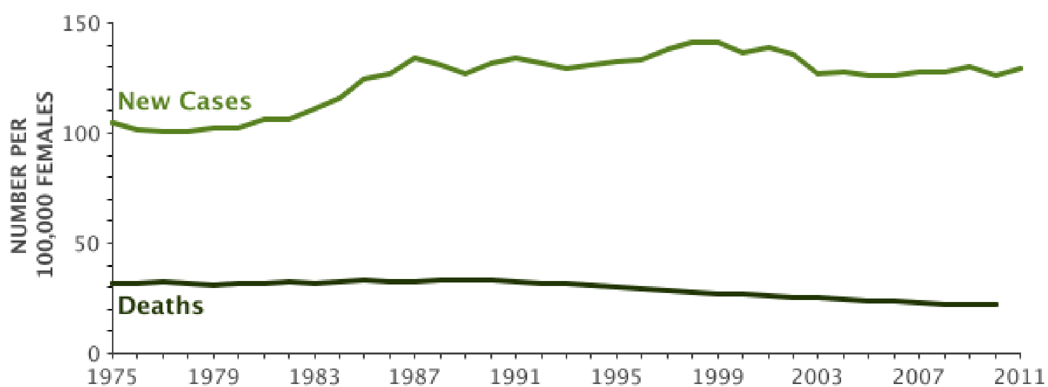
Surgery for early stage breast carcinoma is either:

- Total mastectomy (complete breast removal);

or

- Surgical lumpectomy (only tumor removal) coupled with radiotherapy, commonly known as **Breast Conserving Therapy (BCT)**

The goals of BCT are to *“achieve local control of the cancer as well as to preserve a breast that satisfies the woman's cosmetic, emotional and physical needs”*.



Context and Motivations

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Our objective: develop a model able to ***predict the contour of the breast following surgery.***

→ Help the dialogue between the surgeon and the patient: facilitates the decision process for the ***patient;***

→ Provides a virtual model of the breast of the patient after surgery: facilitates the surgical planning for the ***surgeons*** and optimizes the surgical outcome.

Our overall hypothesis is that:

i) The complex interplay among mechanical forces due to gravity;

ii) Breast tissue constitutive law distribution;

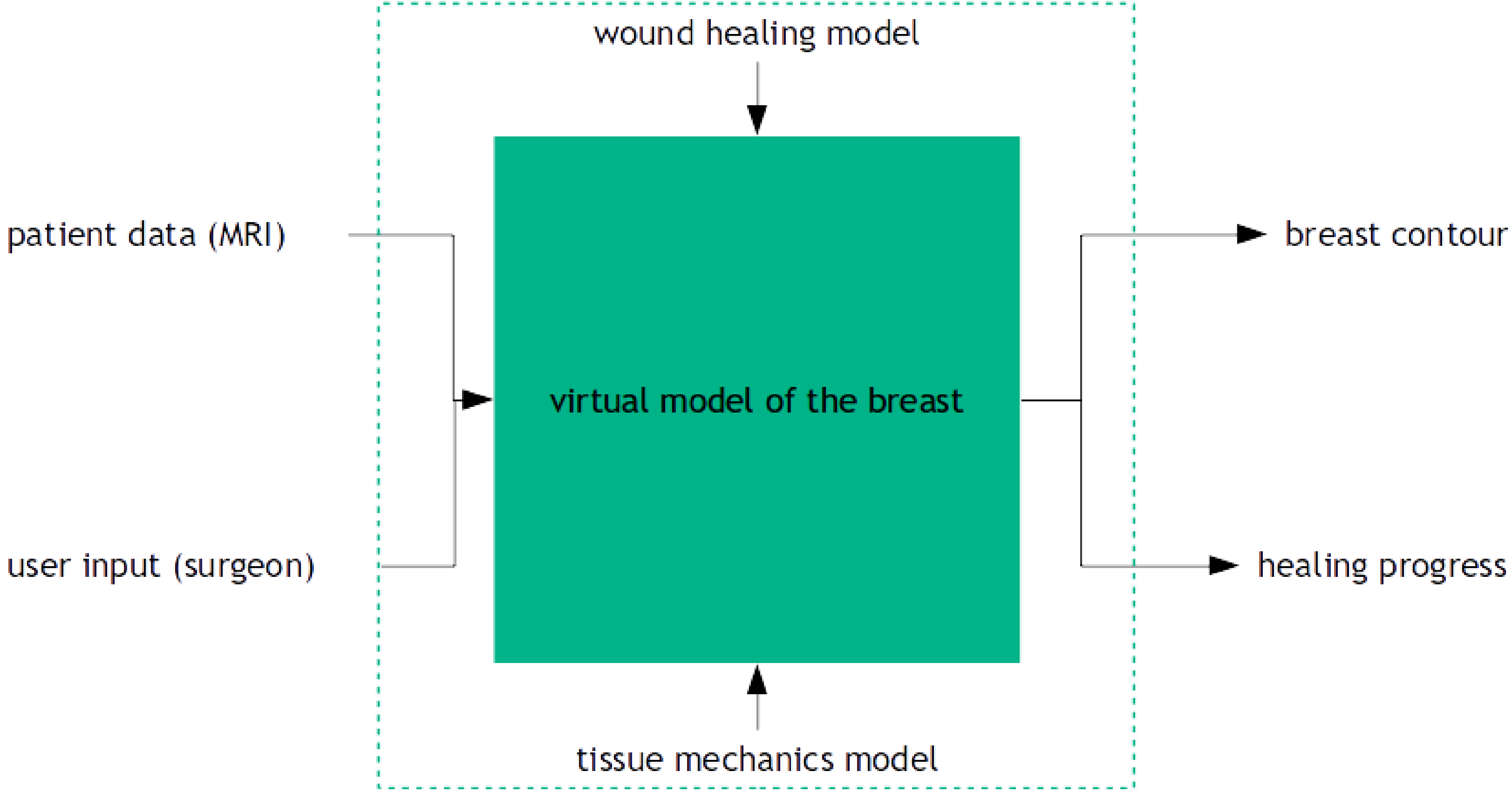
iii) Inflammation induced by radiotherapy;

iv) Internal stress generated by the healing process play a dominant role in determining the success or failure of lumpectomy in preserving the breast shape and cosmesis.

Multiscale model of BCT

→We developed a *patient-specific, multi-scale* model that aims to:

- Compute in 3D the cosmetic aspect of the breast after surgery;
- Provide an interactive, virtual model of lumpectomy surgery based on user input.

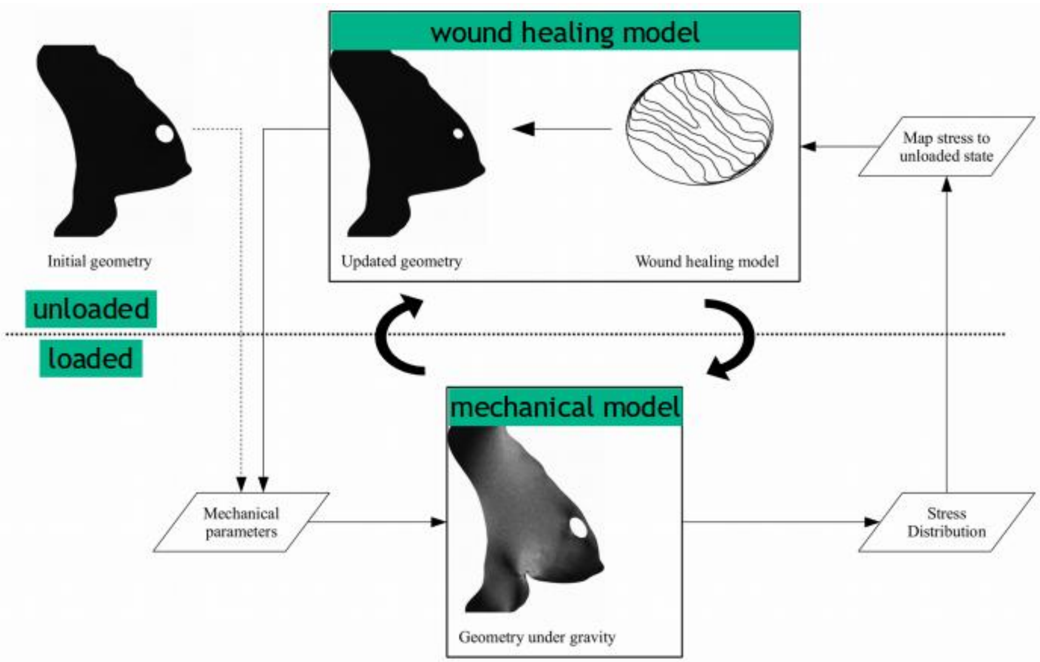


Multiscale model of BCT

Our model is based on the hypothesis that:

- The mechanical strain and stress in the breast under gravity influence the wound healing;
- The production of scar tissue during healing influences the contour of the breast.

In our multi-scale model the wound healing of the lumpectomy cavity is computed in a "stress-free" (gravity-free) reference position of the breast, assuming that, at a given time *t*, the cells topology is not modified by reversing the gravity on the breast.



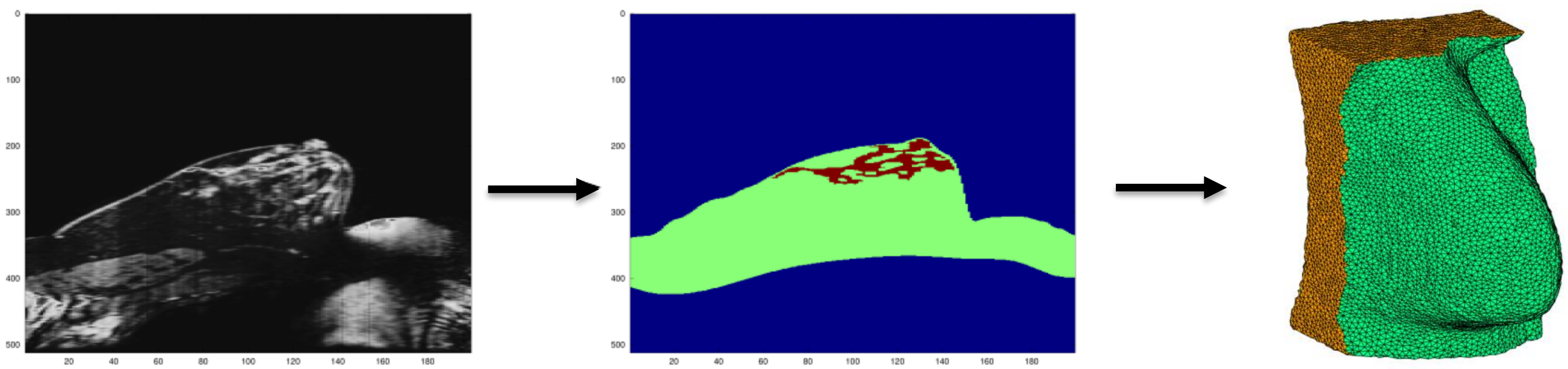
Multiscale model of BCT

Patients MRI data is acquired prior to the surgery and used as ground truth data to reconstruct a three dimensional virtual model of the breast:

- The background noise is segmented from the MRI data to extract the skin envelope;

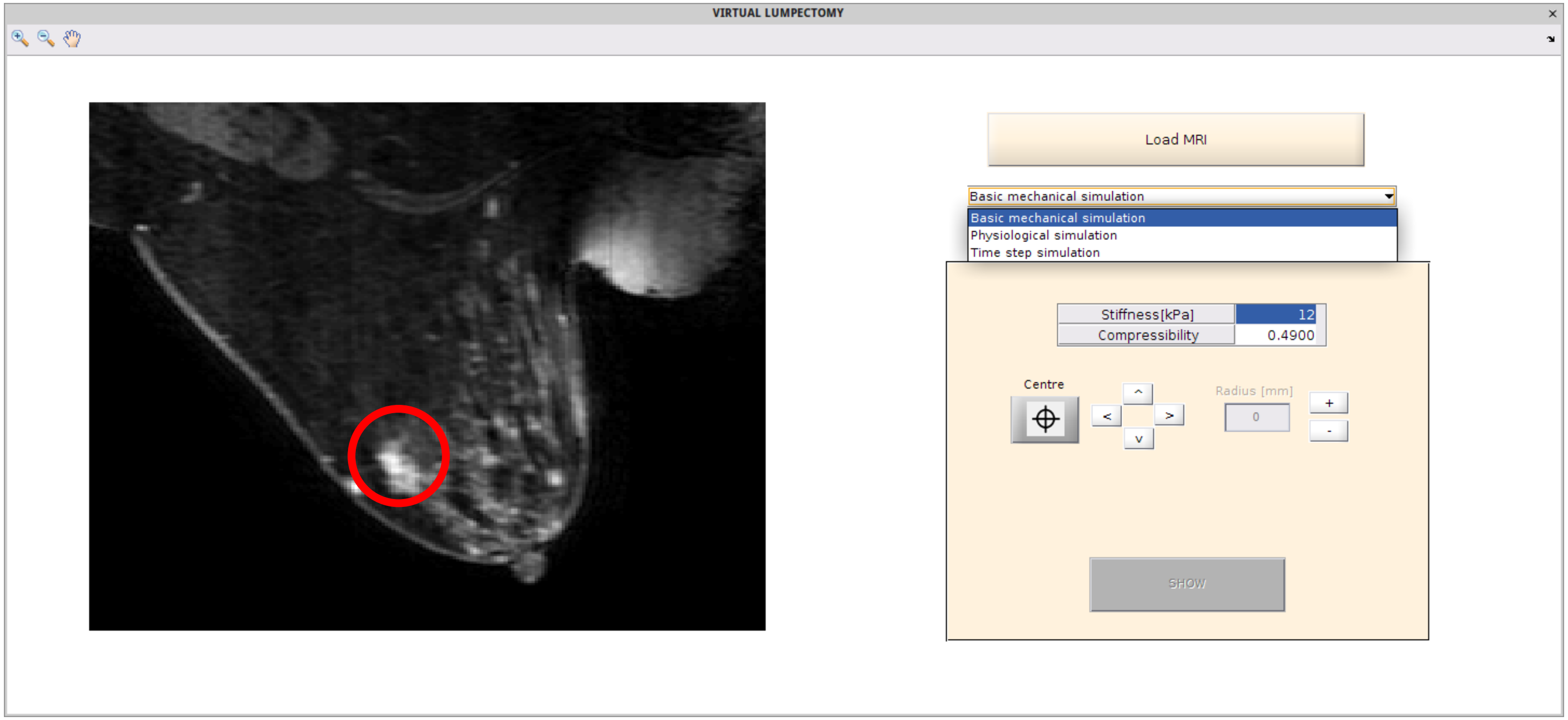
- The *pectoralis major* (chest wall) muscle separating the breast tissues from the rest of the MRI data is segmented using a 3D spline interpolated from user-defined points;

- The tissue classification of the actual breast tissues into adipose and glandular tissues is performed using Fuzzy C-Means classification, combined with morphological operation in order to isolate the bulk of glandular tissue from the remaining adipose tissue.



Multiscale model of BCT

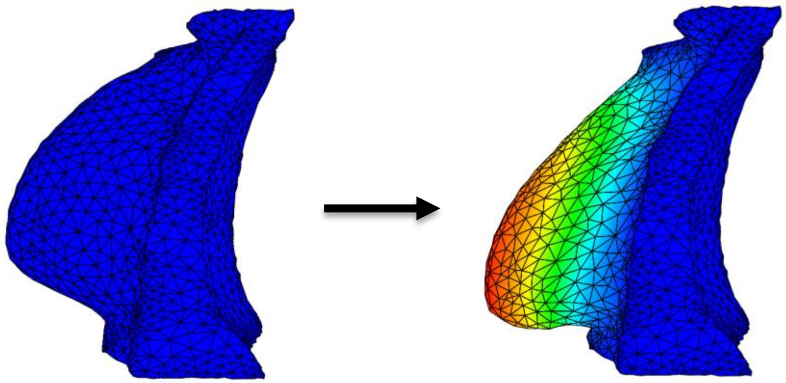
The virtual surgery is performed by removing a volume of tissue from the reconstructed breast according to the size and location of the tumor estimated by the surgeon:



Multiscale model of BCT

The mechanic of breast tissues is modeled using a Neo-Hookean hyper-elastic model, parameterized by the Young's modulus, Poisson ratio and density of the adipose, glandular, skin and scar tissues.

No-displacement boundary conditions (BC) are used on the *pectoralis major* muscle, and on the top and bottom surfaces of the virtual breast.

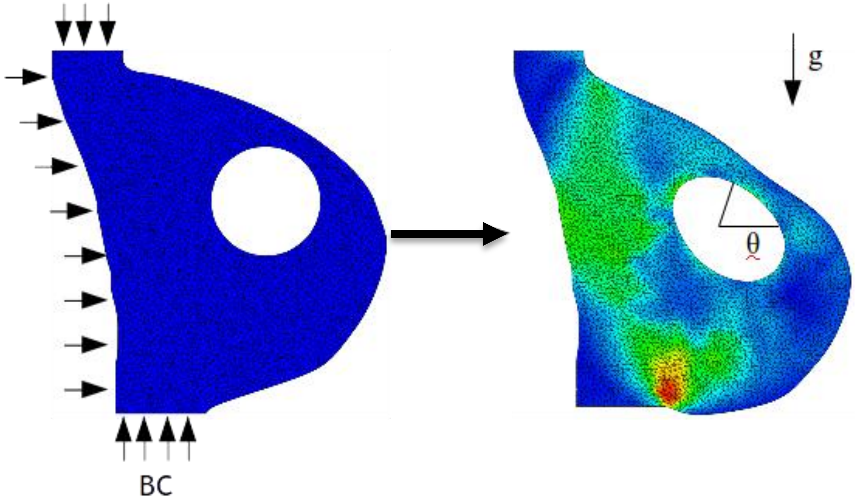


Effect of the gravity on the breast tissues

→ Contour of the breast

Multiscale model of BCT

A mechanical stress/strain density function $E(\theta)=\varepsilon_{xx}\sigma_{xx}+\varepsilon_{yy}\sigma_{yy}+\varepsilon_{xy}\sigma_{xy}$ is defined as a metric of the internal mechanical energy in the breast tissues due to gravity and is derived from the mechanical model of the breast (function of the stress and strain tensors σ,ε).



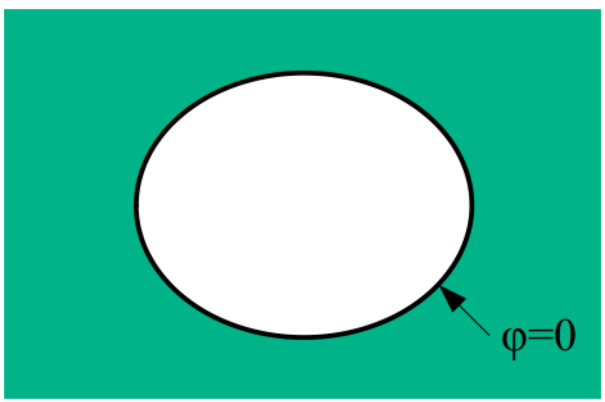
Effect of a virtual surgery on the breast tissues

→ Stress/strain map

Multiscale model of BCT

The wound healing at the cellular level is modeled using a level-set algorithm to describe the production of scar tissues (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 adds to the normal velocity of the wound edge. This velocity is finally modulated by a concentration of growth factor produced in an active layer around the wound edge.



$$\frac{\partial \varphi}{\partial t} + v_n \|\nabla \varphi\| = 0$$

$$v_n = G_b(\alpha_0^{\varphi} + \alpha_1^{\varphi} K + \alpha_2^{\varphi} E)$$

biological model

mechanical model

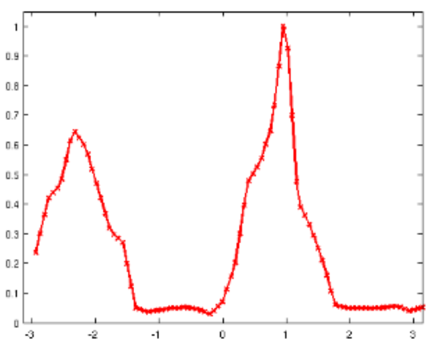
curvature (wound geometry)

$$\frac{\partial G_b}{\partial t} - D \Delta G_b + \Lambda G_b = \chi_{a.l.}$$

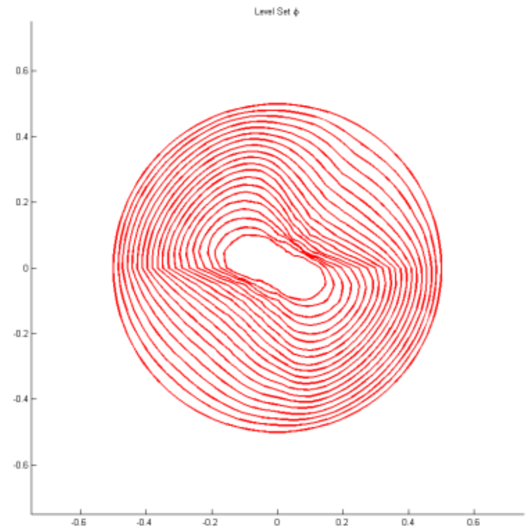
$$K = \nabla \cdot n, \text{ with } n = \frac{\nabla \varphi}{\|\nabla \varphi\|}$$

Multiscale model of BCT

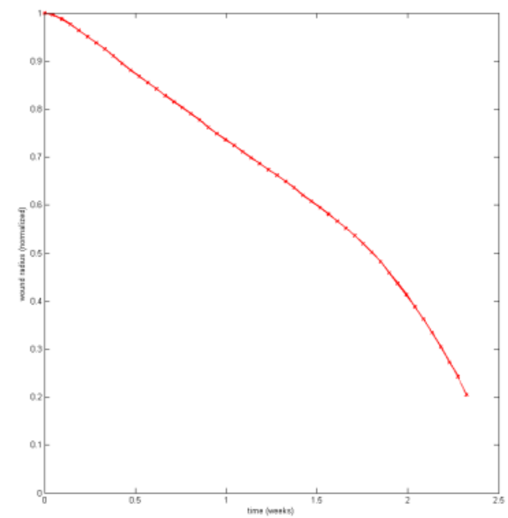
The result is a non-linear (in time), non isotropic (in space) closure of the wound:



E(θ)



Wound shape over time

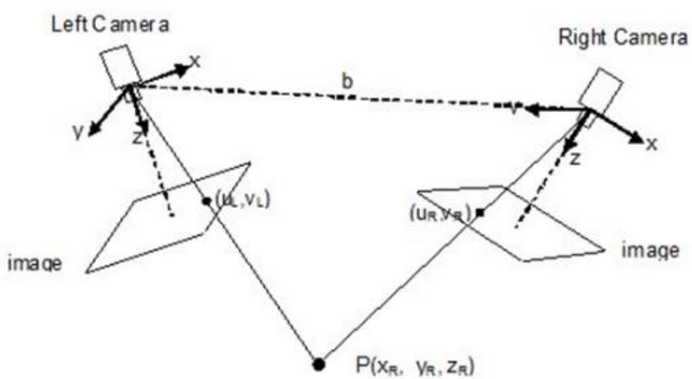


Average wound radius over time

Validation and clinical trial

A first validation of the model was performed through the follow-up 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 provide non-invasive measurements of the evolution of the inflammation and stiffness of the breast tissues after the surgery.



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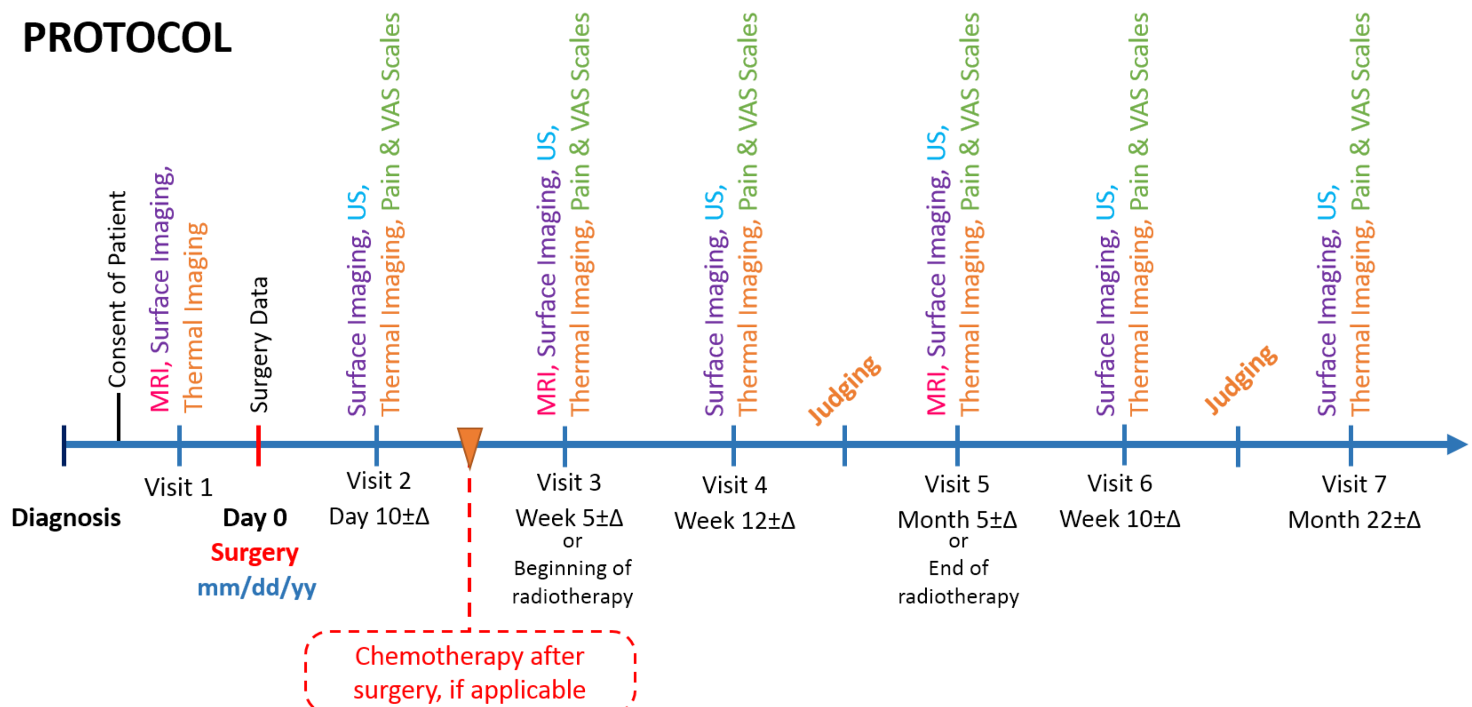

Δ: All study visits should occur as close as clinically possible to the visit days described.

Validation and clinical trial

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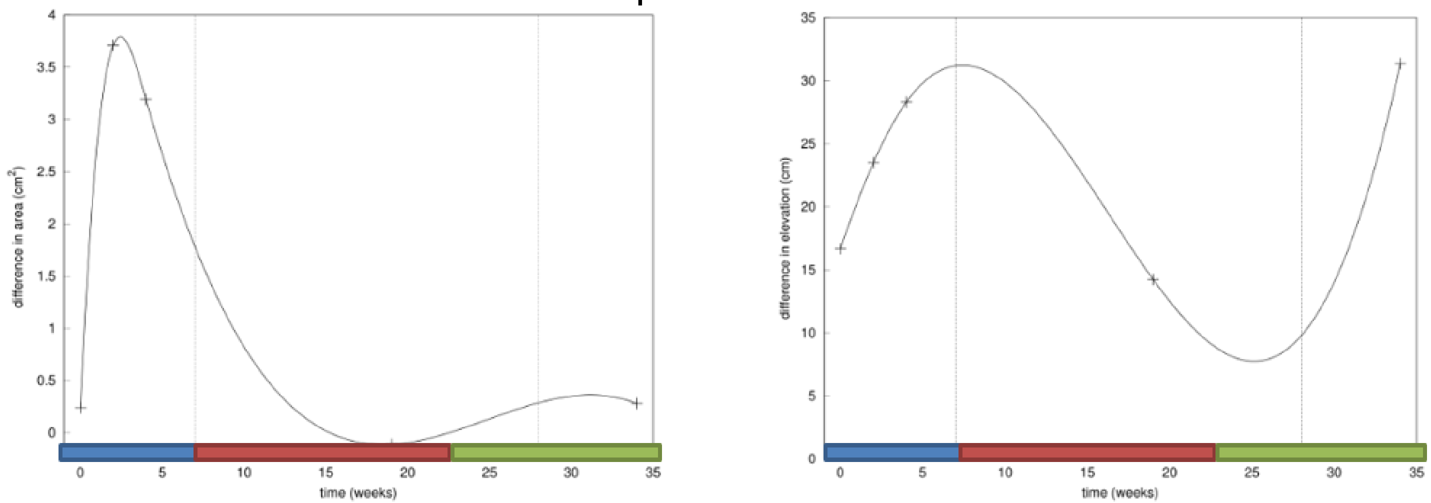
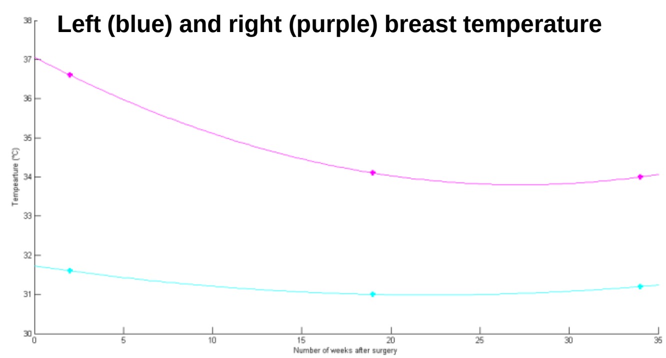
After identification of three distinct phases of healing at 2, 19 and 34 weeks after surgery (inflammation, healing and radiation therapy), we fit selected mechanical and biological parameters of the multiscale model to the patient data.



Measure of difference in area (left) and difference in elevation (right) between left and right breast.



Validation and clinical trial

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Parameter	Value	
Mechanical model of breast tissues:		
E_{fat}	$2 - 15kPa$ (Rzymski et al, 2011)	
$E_{glandular}$	$5 - 15kPa$ (Rzymski et al, 2011)	
First phase of healing:		
λ_1	$1.0 - 3.0$	$E^{*}_{\text{adipose,glandular}} = \lambda_1 E_{\text{adipose,glandular}}$
P	$0.0 - 500.0Pa$	
Second phase of healing:		
λ_2	$1.0 - 3.0$	$E^{*}_{\text{adipose,glandular}} = \lambda_2 E_{\text{adipose,glandular}}$
Third phase of healing:		
λ_3	$1.0 - 3.0$	$E^{*}_{\text{adipose,glandular}} = \lambda_3 E_{\text{adipose,glandular}}$
E_{scar}	$10 - 80kPa$	
Biological model of wound healing:		
α_0	0-0.6	$p_i^{mitosis} = F(G)\left(\alpha_0 + \alpha_1 \frac{E(i)}{E_{max}}\right)$ with $F(G) = \begin{cases} 1 & \text{if } G>0 \\ 0 & \text{else} \end{cases}$

Third step: optimize the targeted parameters of the model using a surface response algorithm:

$$f(\alpha, s) = \sum_{i,j} \| C_{i,j}^{model}(\alpha) - s * C_{i,j}^{groundthruth} \|$$

derived from the multiscale model   derived from imaging of the patient

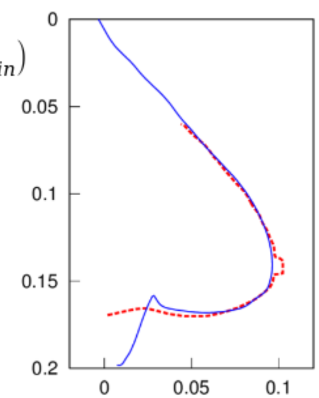
Validation and clinical trial

This case study was able to identify the main parameters that impact cosmetic defect and provided new guidelines for the current clinical trial underway at the Houston Methodist Hospital (NCT02310711).

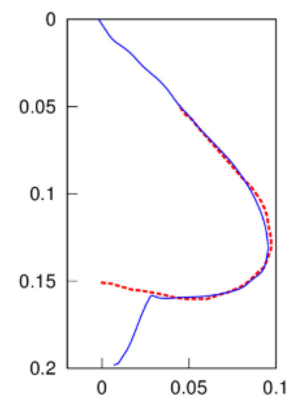
$\alpha = (E_{fat}, E_{glandular}, E_{skin})$

$E_{fat} = 3.7\,kPa$
$E_{glandular} = 9.5\,kPa$
$E_{skin} = 25\,kPa$

pre-surgery



2 weeks post-surgery



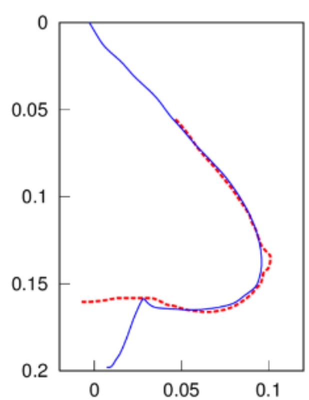
$\alpha = (P, \lambda_1)$

$P = 120\,Pa$
$\lambda_1 = 2.0$

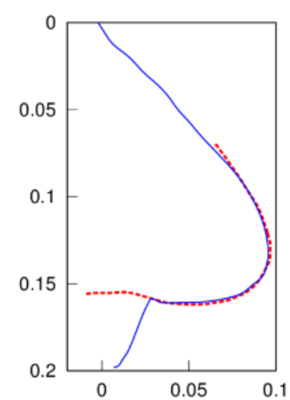
$\alpha = (\alpha_0, \lambda_2)$

$\alpha_0 = 0.17$
$\lambda_2 = 1.2$

19 weeks post-surgery



34 weeks post-surgery

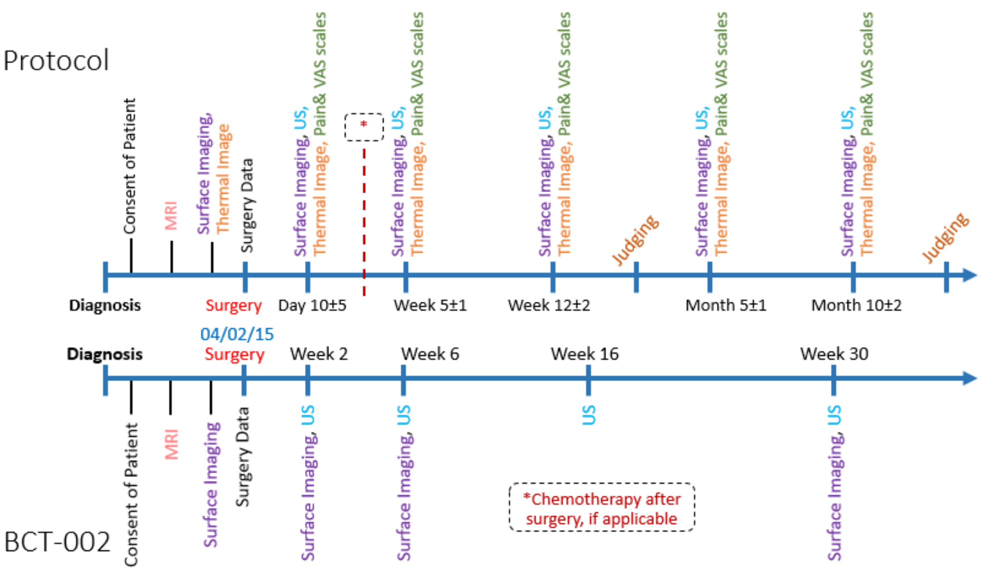


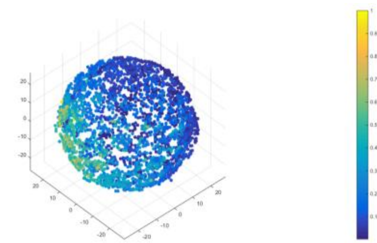
$\alpha = (E_{scar}, \lambda_1)$

$E_{scar} = 24\,kPa$
$\lambda_3 = 1.7$

Future work

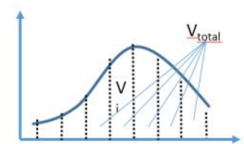
Following this pilot study, we were able to identify the main parameters that impact cosmetic defect and provided new guidelines for the current clinical trial underway at the Houston Methodist Hospital (NCT02310711).

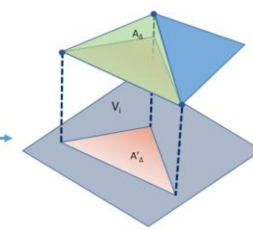


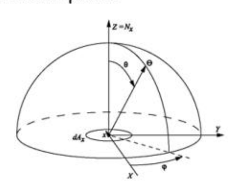


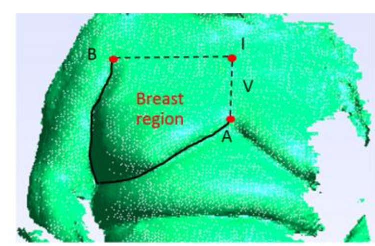
Volume Difference

- Approximately Volume sum up
- Validated successfully
  - Real 3D printing hemisphere
  - Kinect surface
  - V-Calculate *vs.* V-real with error < 2%
- Next step:
  - Now applying all Breast data after validation of reference point









Team and thanks

PIs:
Dr. Barbara Bass, Dr. Marc Garbey (Houston Methodist)

Residents & Instructors:
Diana Hwang, Linda Moore (Houston Methodist)

Past internships:
Marlene Gilles, Nicole Lepoutre, Valentina Simonetti (University of Houston, University of Strasbourg, Polytechnic University of Milan)

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