From Observation to Prediction: The up hill battle of Computational Surgery

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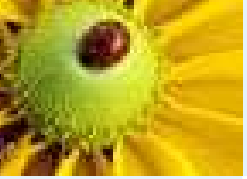


Multi Scale Modeling Questions

A. Hypothesis-driven research: how MSM can be used to

A.1. refine the hypothesis for experimental validation;

A.2. define a related hypothesis (a corollary) that can be more readily tested.

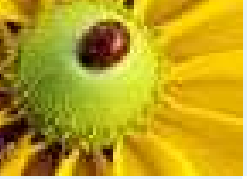
B. When can a virtual experiment be considered a reasonable way to test a clinical hypothesis?

C. How can we use models to optimize the experimental plan, design clinical trials, accelerate translation, reduce risk of therapeutic failure?

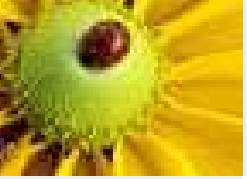
D. What are common bottlenecks in the MSM approach?

E. Effective strategies to ensure integration and consistency within and between models and model parts.

F. How to go from MSM demonstration of mechanism to clinically-relevant measures (imaging, heatmaps, physiologic variability, etc.) and back.



Breast Conservative Therapy: From Observation to Predictive Model ?



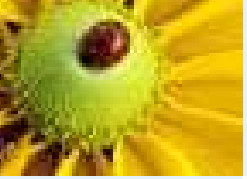
Background and Hypothesis

Background

The treatment of early breast stage carcinoma will usually involve mastectomy (complete breast removal) or alternatively lumpectomy (only tumor removal).
Lumpectomy followed by radiotherapy is labeled as Breast Conserving Therapy (BCT). The goal of BCT is to achieve local control of the cancer as well as to preserve a breast that satisfies the woman's cosmetic concerns. While most women undergo partial mastectomy with satisfactory cosmetic results, in many patients the remaining breast is left with major cosmetic defects

Hypothesis

The complex interplay between mechanical forces due to gravity, breast tissue constitutive law distribution, and internal stress generated by the healing process play a dominant role in determining the success or failure of lumpectomy in preserving the breast shape.



Aim

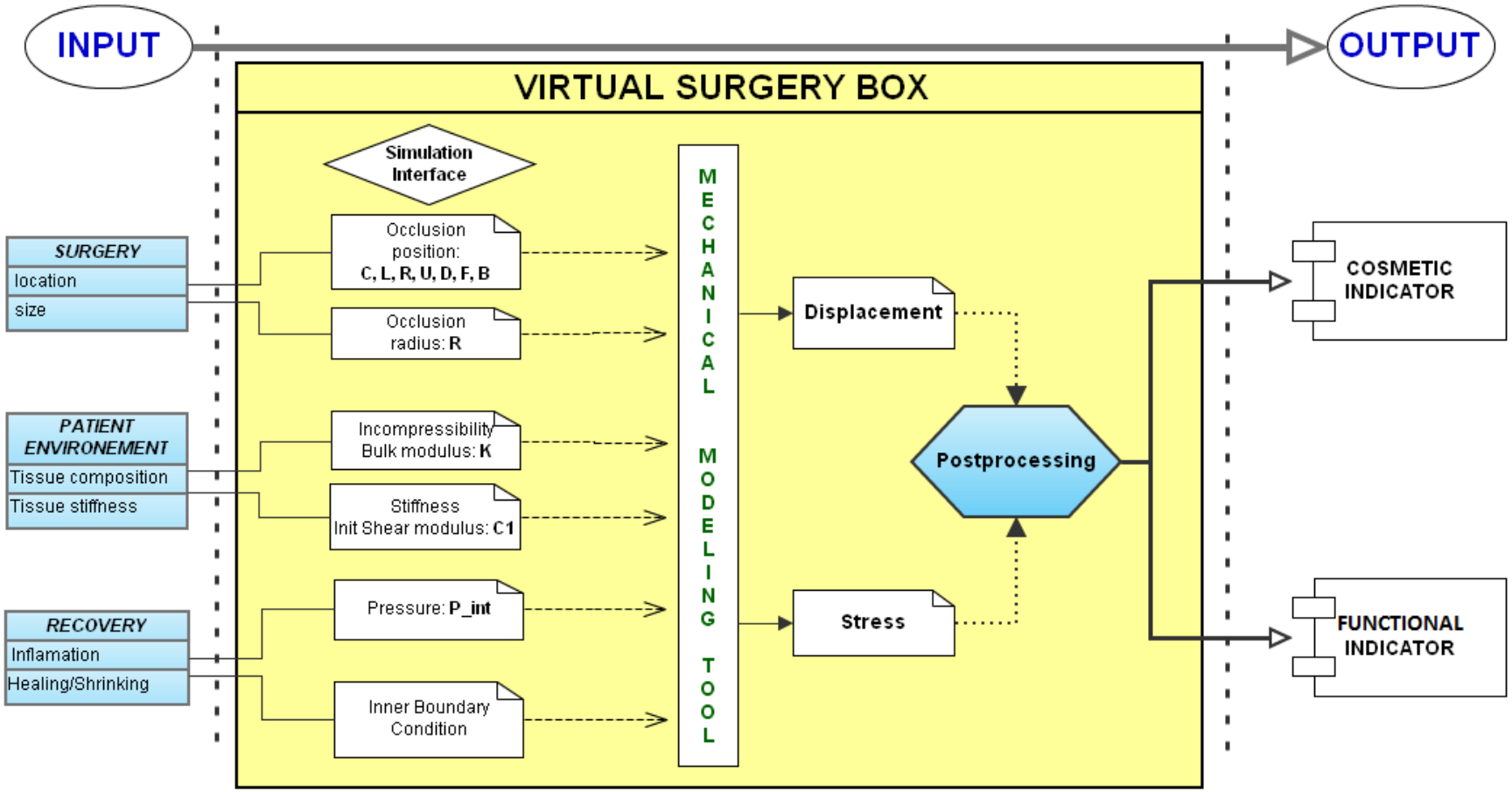
1. Define the immediate impact of tissue removal on breast deformation as a function of the tumor location and size.

2. Model the temporal interplay between the mechanical forces, the radiotherapy and the biology process involved in tissue formation and plasticity to predict long term effect of lumpectomy on breast shape recovery.

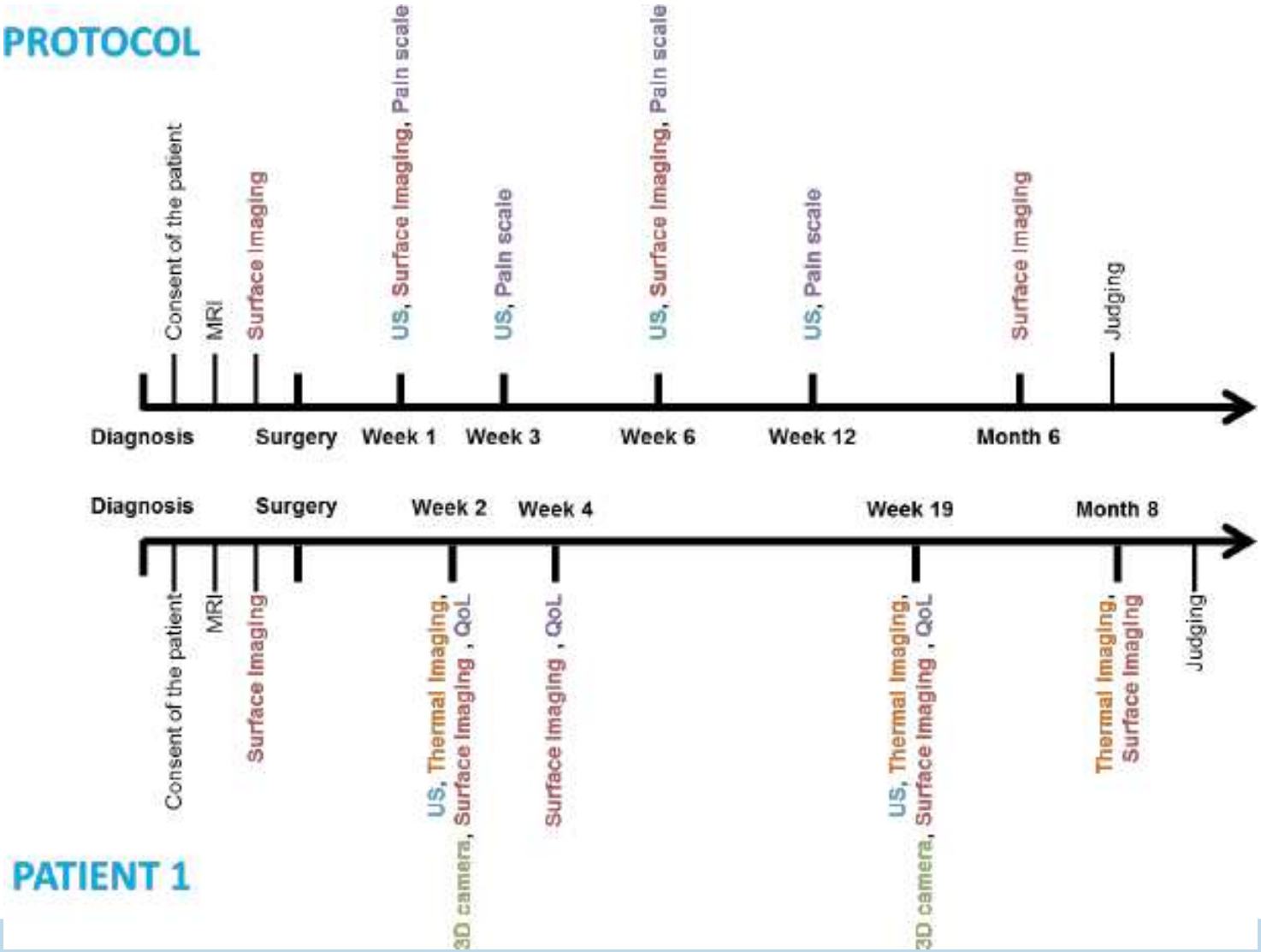
3. Test the predictive multiscale model of breast lumpectomy and healing in patients undergoing BCT for breast cancer and identify target for improvement in BCT.

Needs for an Interdisciplinary Team!

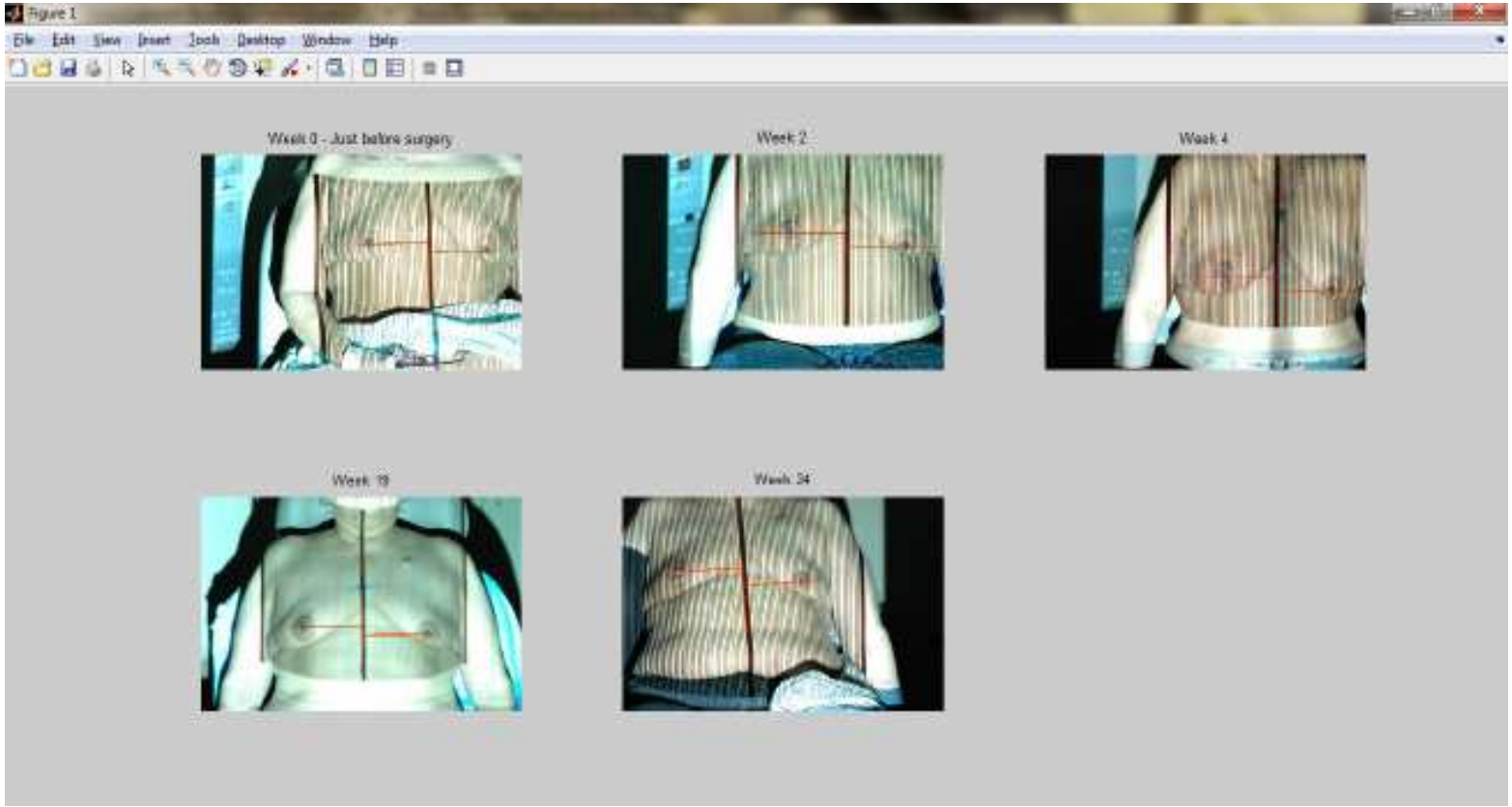
Tool Box



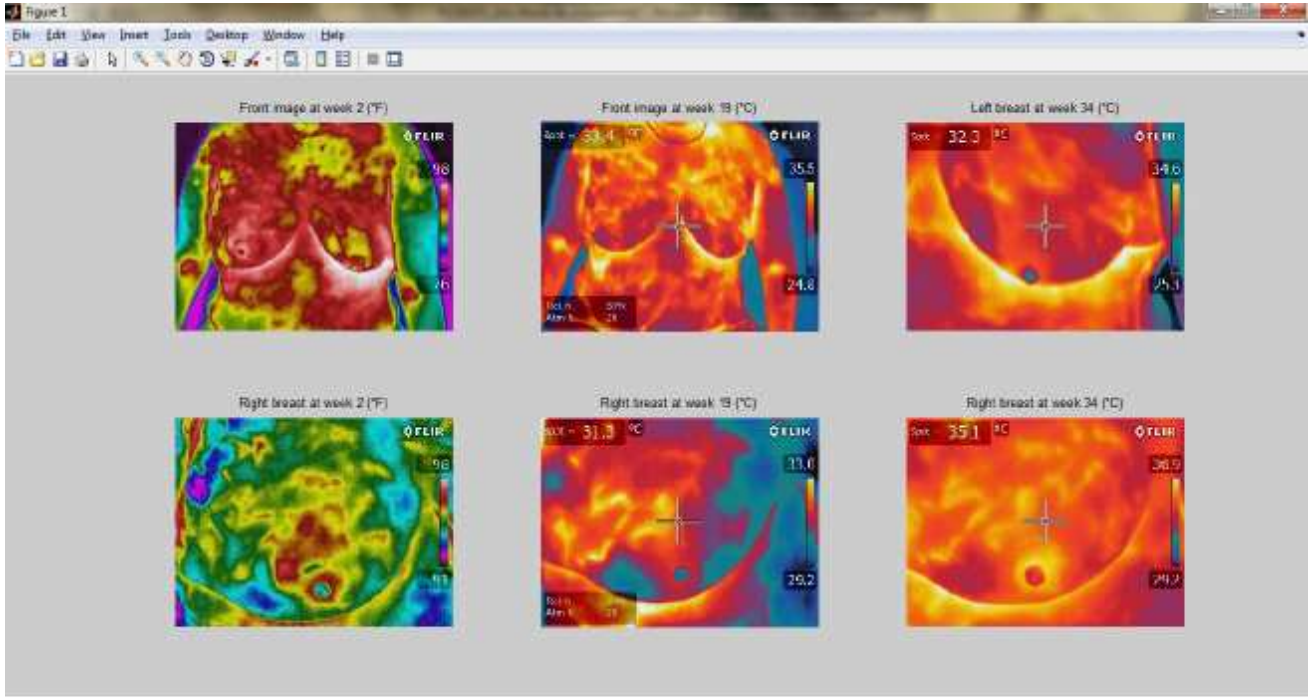
Clinical Protocol

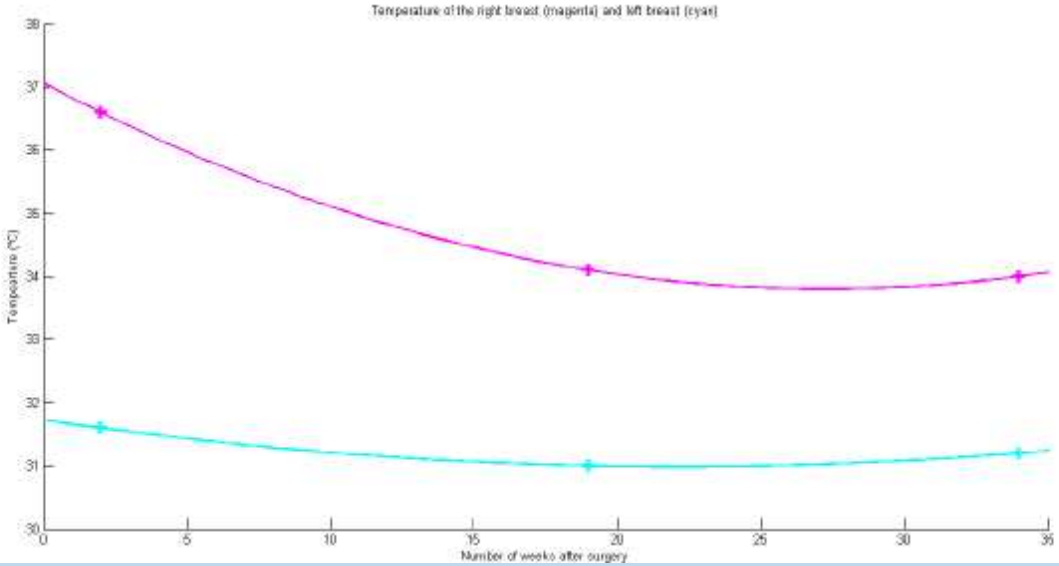


First Patient - Surface Reconstruction

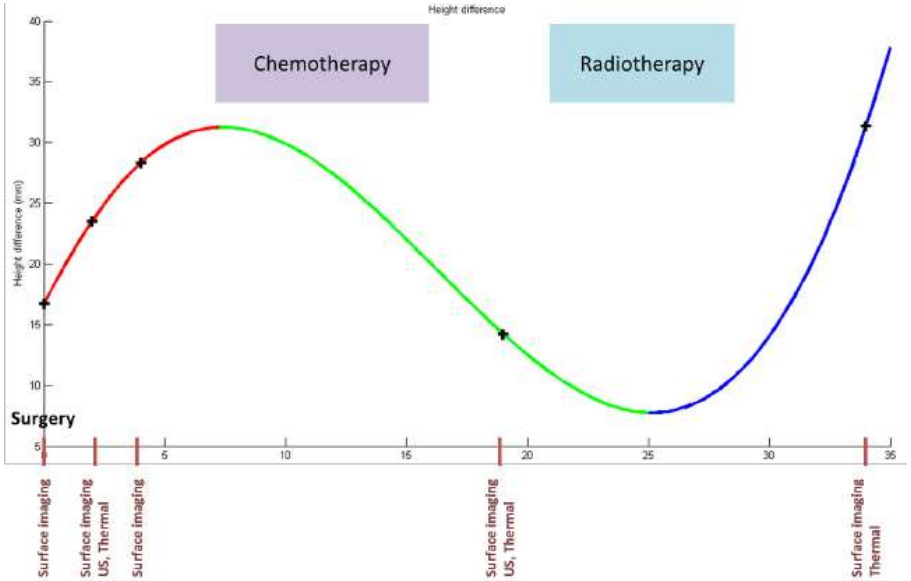


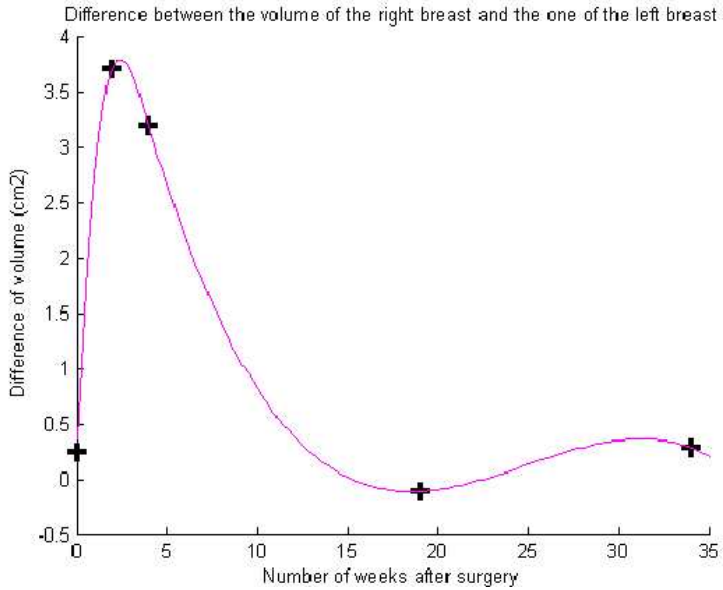
Thermal Imaging - Inflammation Indicator



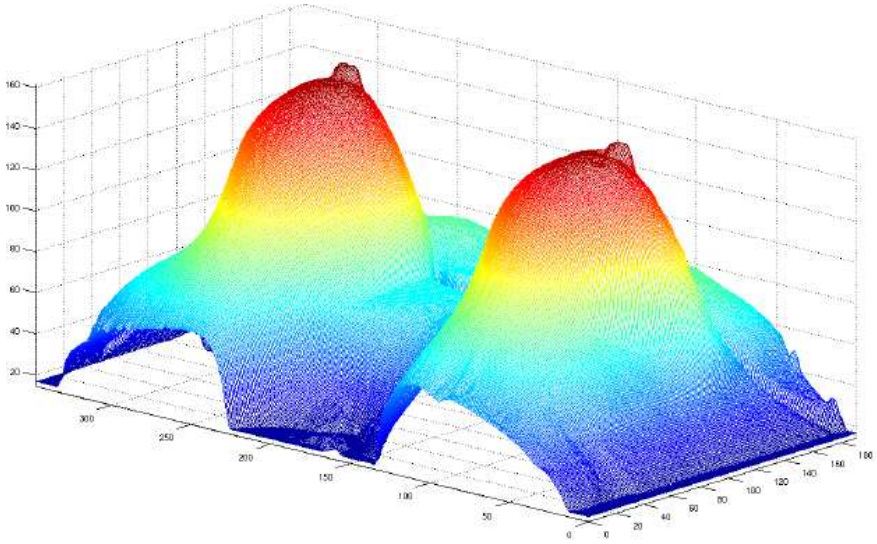


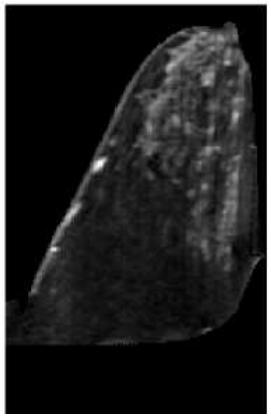
Anatomic Change

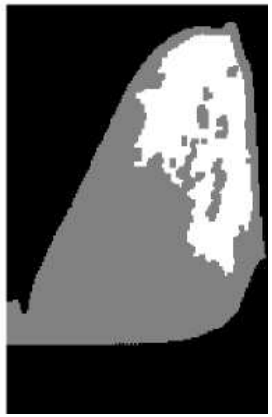




From MRI Scan to Tissue Mechanic I

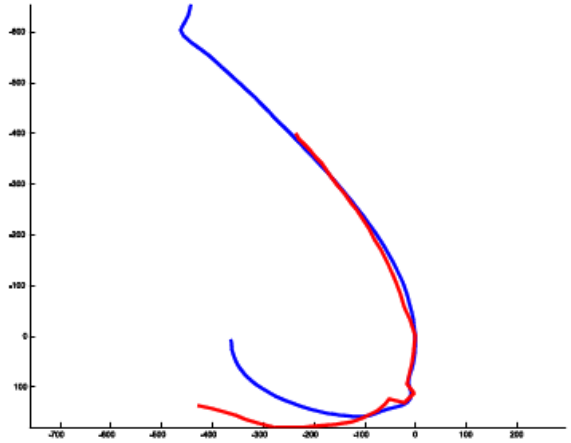




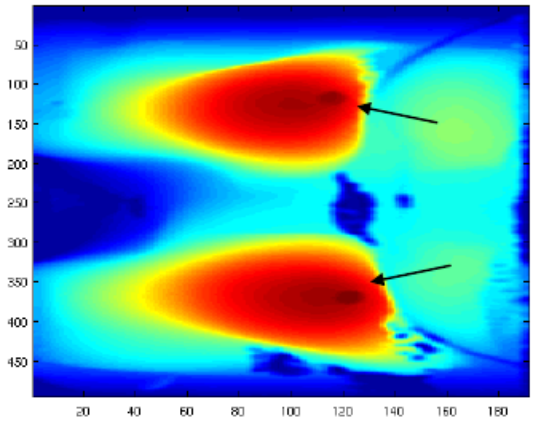


- First Reconstruct three D shape of the patient in prone position.
- Second Classify tissue in cluster of fat/glandular tissue.

From MRI Scan to Tissue Mechanic II



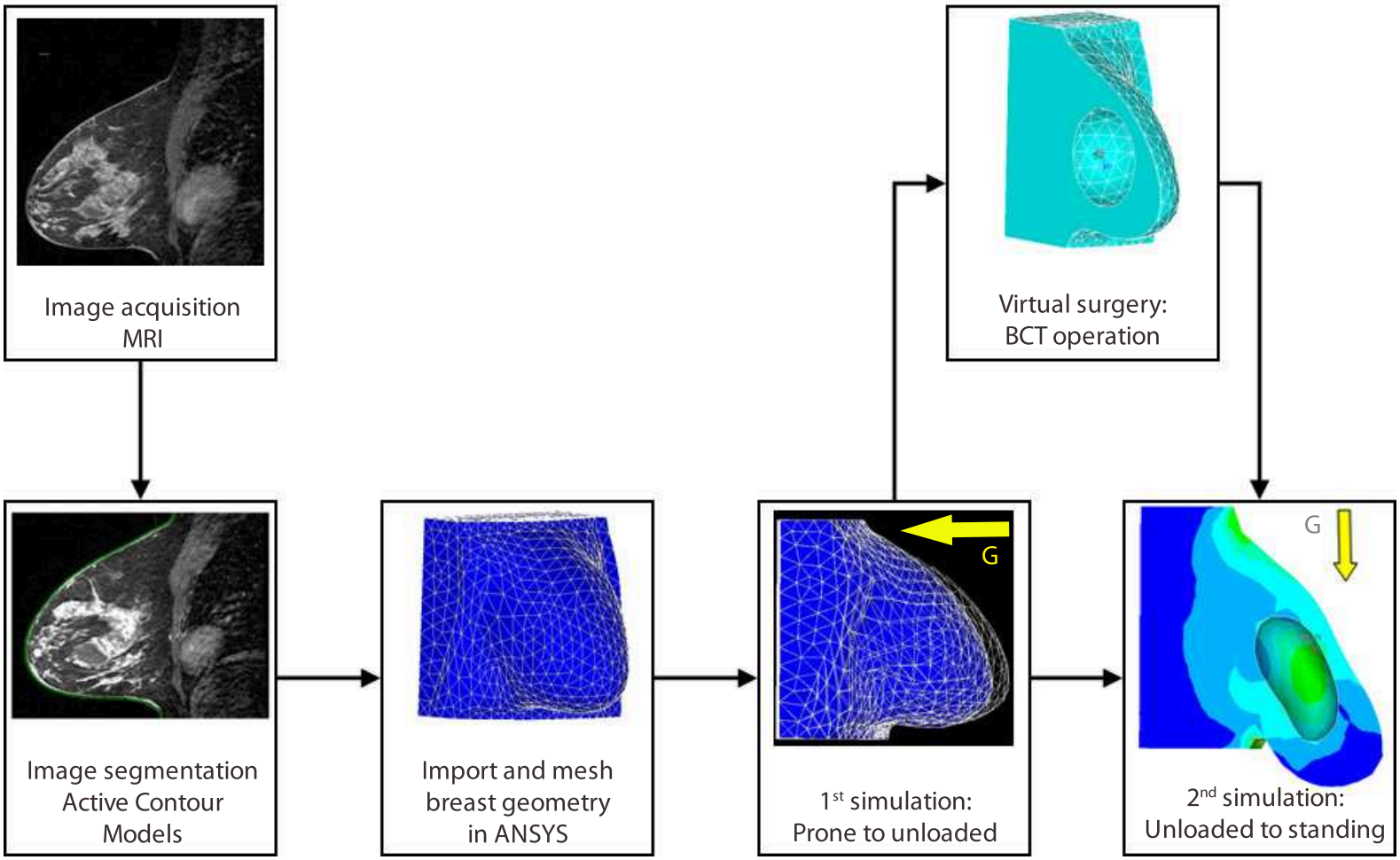
Comparison between actual outline (red) and simulation (blue)



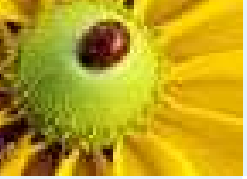
MRI height map showing missing MRI data in lower part of the breasts.

- Third Get the shape in standing position thanks to an hyper-elastic model of tissue deformation.
- Fourth Validate the tissue deformation model.

3D Image Base Simulation



Basic Principal of Virtual Lumpectomy

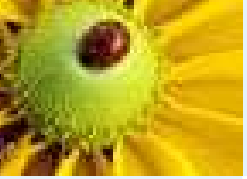


Healing process

Simplified three step process:

- Inflammation:
  - ☐ blood clot providing homeostasis.
  - ☐ recruiting of macrophage
  - ☐ cavity fill up with liquid and pressure build up
- Tissue Formation
  - ☐ cells (fibroblast for example) recruiting at the boundary of the wound due to the loss of contact inhibition.
  - ☐ production of collagen that polymers into fibers which help contracting the wound.
- Tissue Remodeling
  - ☐ combination of cell migration and cell mitosis activated by Growth Factor (GF) in a boundary layer.
  - ☐ collagen fibers reorganized as a function of mechanical factors.

Add Chemotherapy + Radiotherapy Effect



Level set model

Goal

Phenomenological model that ignores the detailed biology and keep the essential on wall remodeling and wound healing as a function of local mechanical conditions.

Input: Wound healing normal velocity law

Output: Dynamic of healing and wound closing

Example: from Javierre, Vermolen, Vuik and Van der Zwaag in Al J.Math. Biol. 2009.

Ref Garbey, Thanoon, Salom, Bass, JSSCM 2011.

Remark: analogous technique on vein graft remodeling (ref Tran Son Tay, Hwang, Garbey, Jiang, Osaki and Berceli, Annal Biomed 2008 and ongoing work)

Multi Scales Model

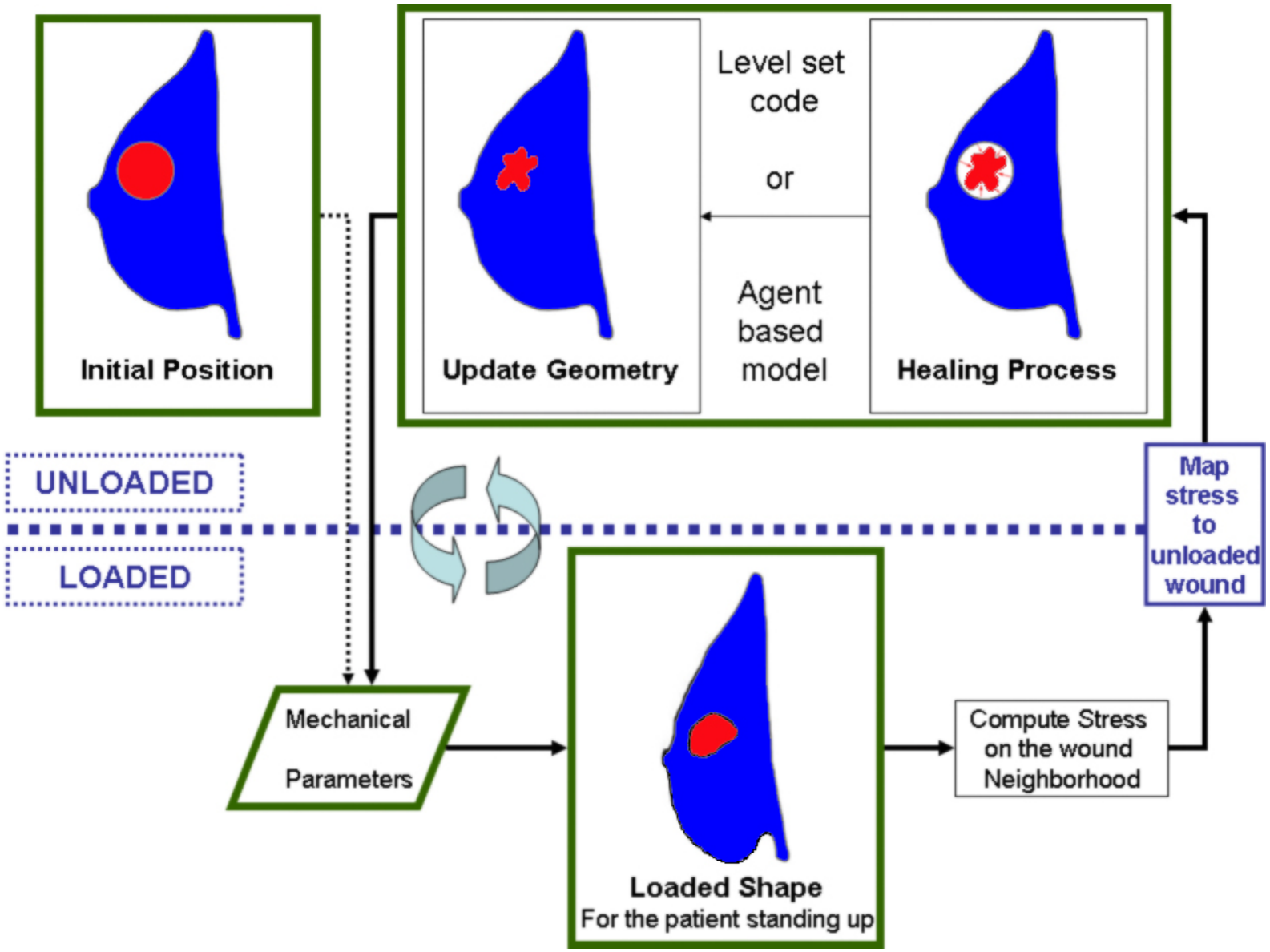
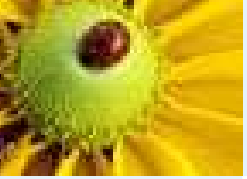


Figure 1: *Illustration of the two steps Algorithm.*



On Going Validation

To get the "constitutive normal velocity law" of the wound and calibrate all parameters in the model relies on experimental data.

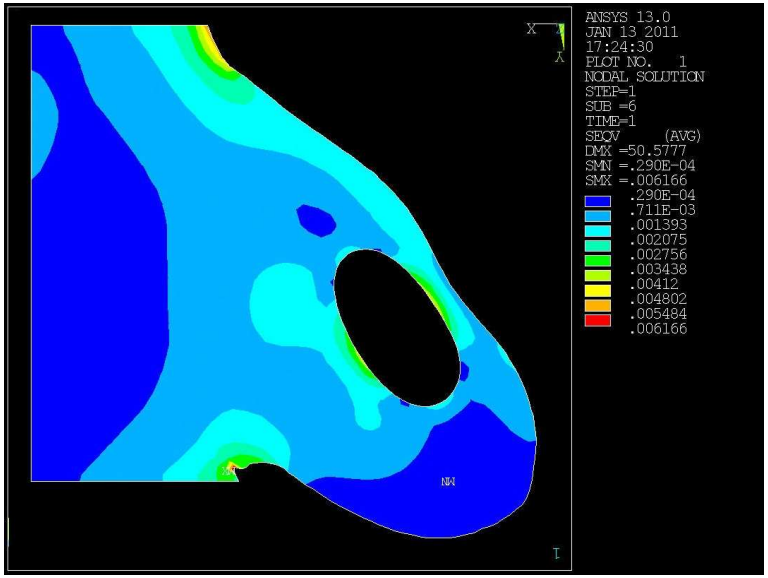
We follow two complementary methods:

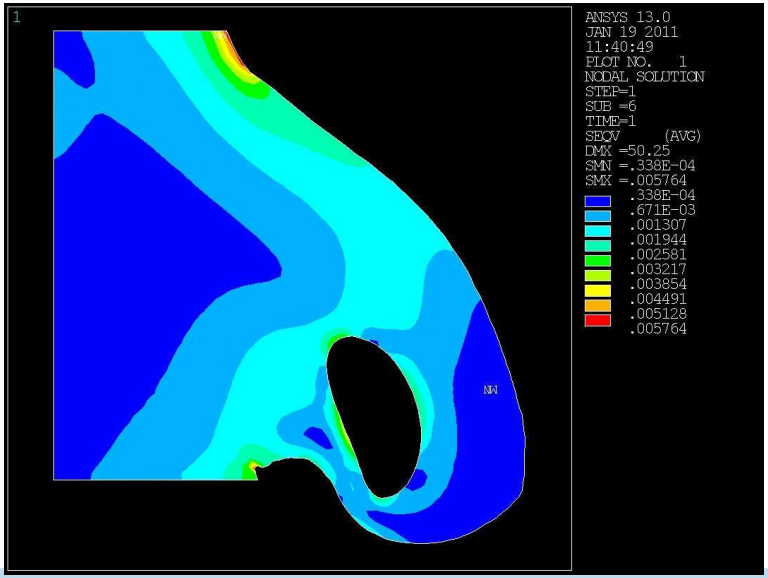
(1) Fitting the model on clinical data with a carefully designed protocol.

(2) Fitting the model to an in silico experiment that mimic wound healing with a bottom approach starting from basic principles in biology; this is the so-called agent base model.

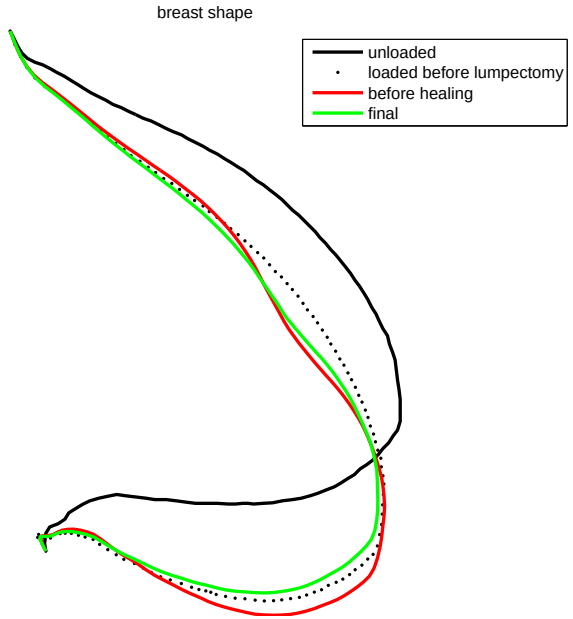
In this feasibility theoretical study, we will only look qualitatively at the influence of each component of the model.
The result will be how to simplify further the model, so it might be feasible to calibrate it in clinical conditions.

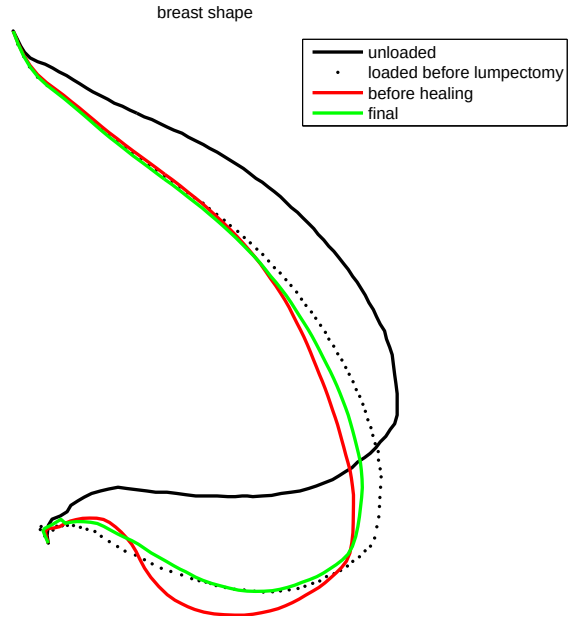
2d - Simulation - Initial Wound

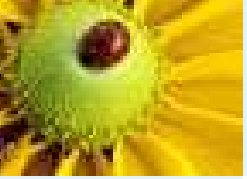




2d - Simulation 0 - Wound - History







Agent Base Model

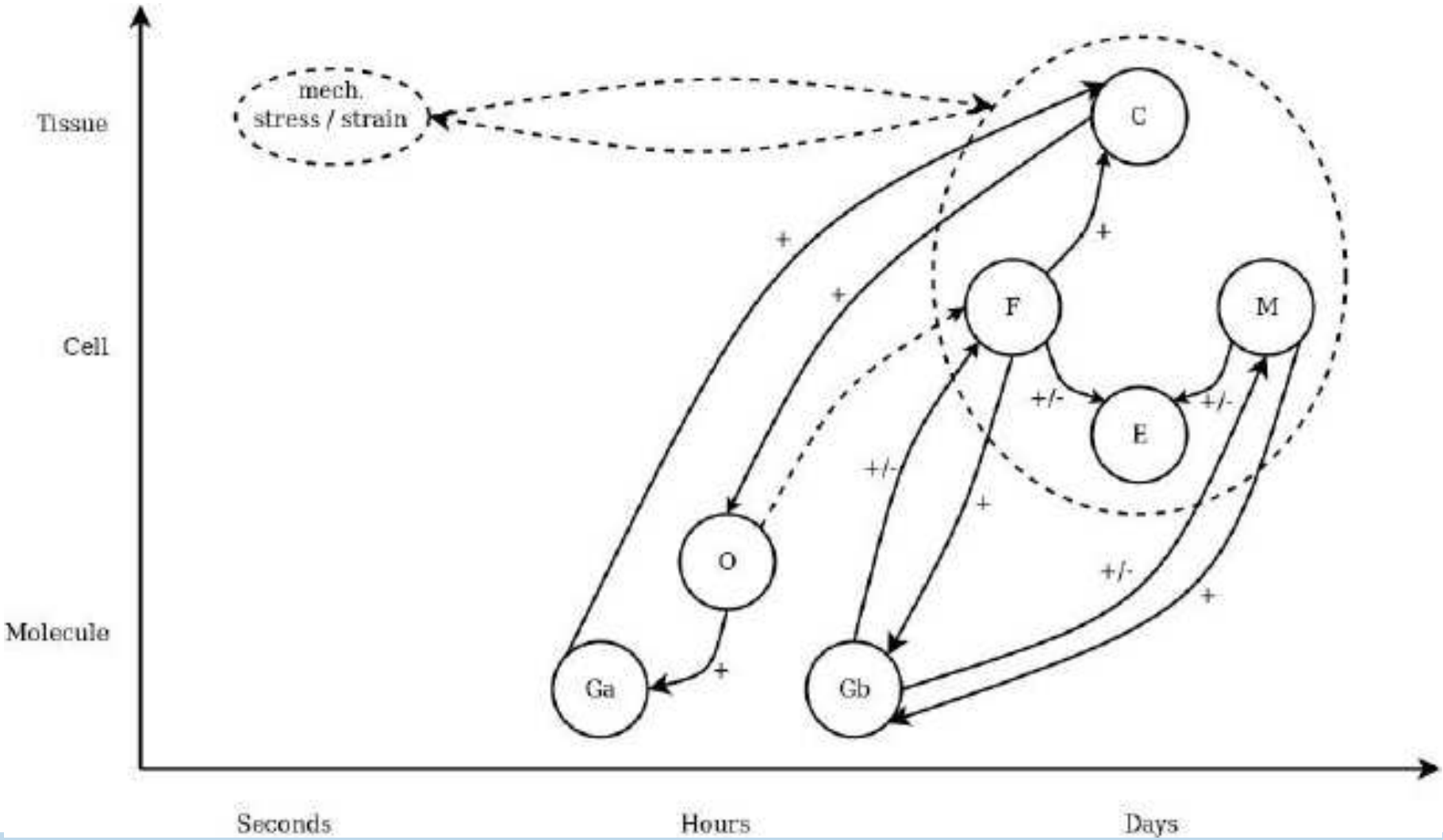
Bottom up approach with modeling at the cell level

- Explicit mapping of cells to grid location.
- Basic set of rules to drive cell division, apoptosis, extra cellular matrix production/degeneration
- Production/Absorbtion of key molecules + diffusion
- Random walk of macrophage
- Motion of cells driven by gradient of some "concentration"
- NEW: Mechanical environment set up
- NEW: Multi-scale
- Possibly Angiogenesis -ref Peirce et Al.

Ref Garbey, Thanoon, Salom, Bass, JCP Special issue MSM 2012.

MSM Schema

Players Oxygen, Capillaries, VEGF, TGF-β, PDGF, Fibroblast, Myofibroblast, Extra-cellular matrix .... Fat Cells.



Distributed Computing

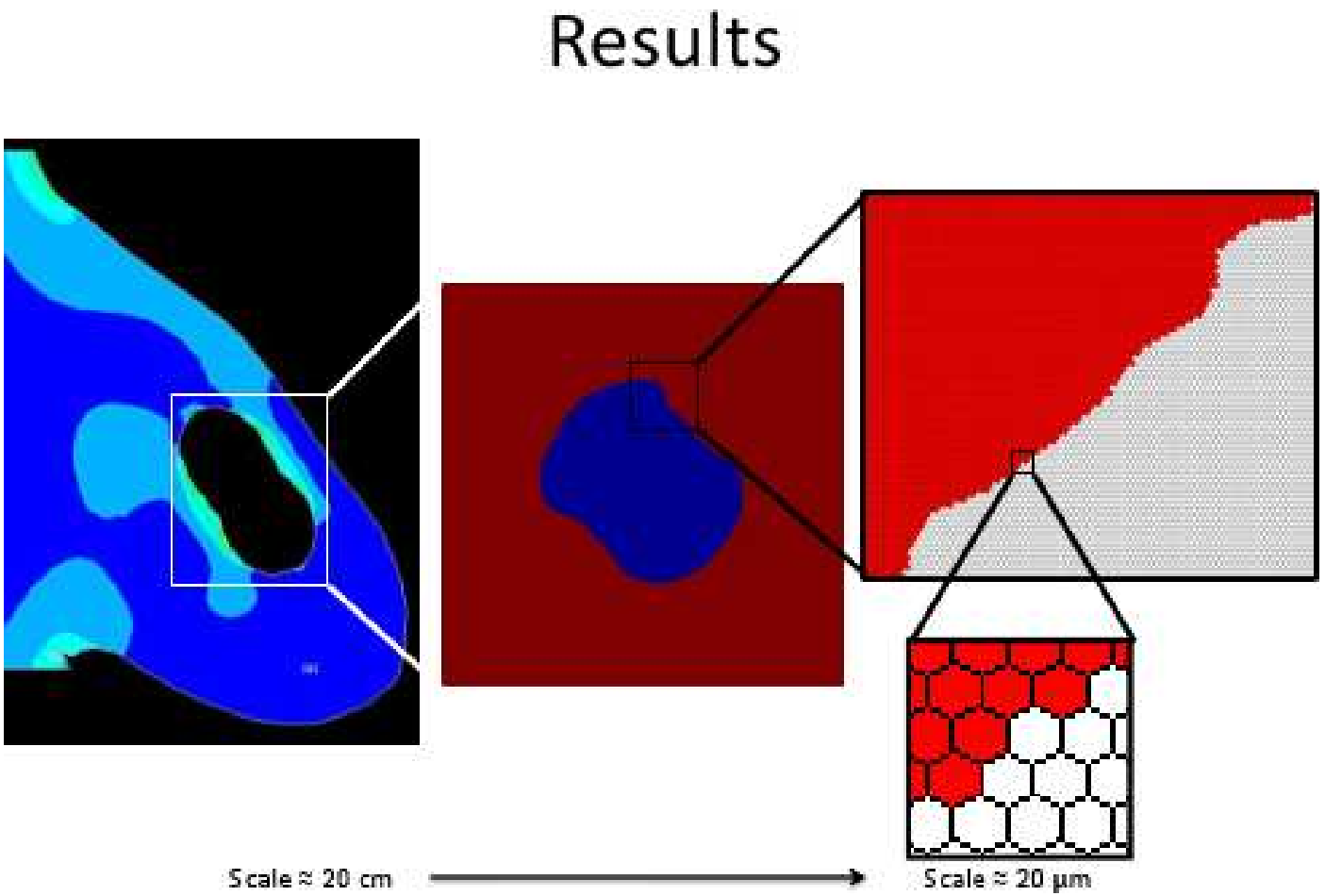
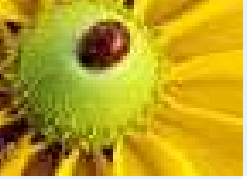


Figure 2: Distributed Architecture.



Architecture

	Server PC	Sicortex
OS	Windows Server 2003	Gentoo Linux 2.6.18
CPU number	4	1434
CPU speed	2GHz	600Mhz

Table 1: Machines specifications.

Distributed Computing Framework

Implementation

- Heterogeneous network for multiscale computing

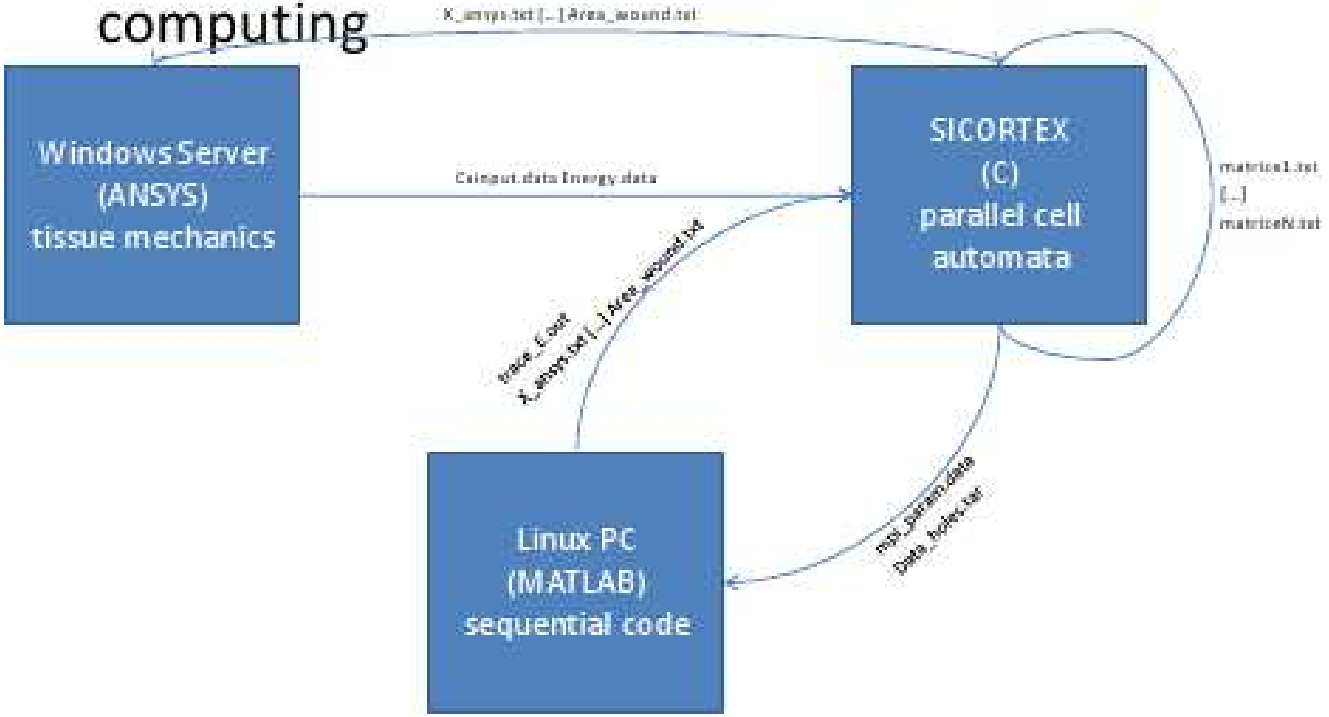
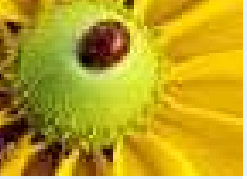


Figure 3: Distributed Architecture.



Conclusion

Fujiyama

Figure 4: At Sea

Some Good Perspective on where we stand!
`http://www.computationalsurgery.org`