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Multiscale modeling and distributed computing to predict cosmesis outcome after a lumpectomy ☆

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ABSTRACT

Surgery for early stage breast carcinoma is either total mastectomy (complete breast removal) or surgical lumpectomy (only tumor removal). The lumpectomy or partial mastectomy is intended to preserve a breast that satisfies the woman's cosmetic, emotional and physical needs. But in a fairly large number of cases the cosmetic outcome is not satisfactory. Today, predicting that surgery outcome is essentially based on heuristic. Modeling such a complex process must encompass multiple scales, in space from cells to tissue, as well as in time, from minutes for the tissue mechanics to months for healing.

The goal of this paper is to present a first step in multiscale modeling of the long time scale prediction of breast shape after tumor resection. This task requires coupling very different mechanical and biological models with very different computing needs. We provide a simple illustration of the application of heterogeneous distributed computing and modular software design to speed up the model development. Our computational framework serves currently to test hypothesis on breast tissue healing in a pilot study with women who have been elected to undergo BCT and are being treated at the Methodist Hospital in Houston, TX.

1. Introduction

Breast cancer is currently the most prevalent form of cancer affecting women in developed as well as developing countries, according to the World Health Organization. In the US, more than 230,000 cases of breast cancers have been diagnosed in 2011, leading to more than 39,000 deaths. While the survival rate remains relatively high, over 80% in the US, the number of cases is still growing along with the increase of life expectancy [13,14,21].

From a clinical point of view, this reflects the need for a constant improvement of the way breast cancer is treated before and after the surgical act. First, early detection methods are becoming more accessible with large campaigns of screening. Second, much improvement has been done with post-surgery follow up. In the specific case of breast cancer, the physiological and psychological traumas can be important for the patient [19]. This question has been raised by the American Society of Breast Surgeons (http://www.breastsurgeons.org) that published in 2009 a statement on Breast Surgery Quality Initiatives. This report listed six initiatives that focused on quality of care and the impact on the emotional reaction of the patients.

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A large improvement in this direction is the introduction of lumpectomy (tumor removal) over mastectomy (complete breast removal) for the treatment of early stage of breast carcinoma. The objective is to preserve the breast of the patient and limit cosmesis defects. Lumpectomy is usually followed by radiotherapy in order to ensure a local control of the cancer. The combination of these two steps is called Breast Conservative Therapy (BCT). However, in many cases, the lumpectomy can produce asymmetry, distortion of nipple areolar complex or deformities of the shape of the breast [7,41]. There are currently no tools, other than surgical experience and judgment, that can predict the impact of lumpectomy on the contour and deformity of the treated breast.

Our long term objective is to provide a patient-specific computational model of BCT that can help the dialogue between the surgeon and the patient in order to reach a satisfactory decision on the surgery process options. While a great deal of work has been done on tissue deformation of the breast [4,37,5,32,12,29,35]; we are, up to our knowledge, the first team to investigate BCT outcomes with computational methods [42–44,17,18].

Our overall hypothesis is that the complex interplay among mechanical forces due to gravity, breast tissue constitutive law distribution [11,40], inflammation induced by radiotherapy [9], internal stress generated by the healing process [25,45,26,27,38,10] and angiogenesis [3,30,34] play a dominant role in determining the success or failure of lumpectomy in preserving the breast shape and cosmesis. Our initial work concentrated on the short time scale prediction of tissue resection: thanks to the use of well known tissue mechanic models [42], we are able to remove *virtually* the tumor and surrounding tissue to preserve the negative margin [31]. This tissue deformation simulation provides the immediate impact on breast shape under various gravity load. Our effort, then, focused on the design of a virtual surgery tool box that would translate in clinical conditions the value of modeling and simulations [44]. This design step must take into account the surgeon needs and experience. Modeling and simulation must be patient specific but the datas that one can access in real clinical conditions are limited. For example, while MRI provides detailed geometric information and can be well exploited by image analysis methods, one cannot expect to get spatially accurate patient breast tissue composition and mechanical properties. Further 3d surface reconstruction of breast shape provided by the model simulation prediction still requires subjective interpretation. A more realistic goal might be to provide cosmetic indicators and functional indicators related to mechanical stress that companion the results [43] and can be systematically documented in a clinical trial.

Lumpectomy has also a long term impact on breast shape. It may take about two years for the breast to heal, and for the wound to fully close. During that process tissue composition, stiffness and volume change significantly [7,41]. Cosmesis defects may appear or progress during that post-surgery period. The long term biological process of healing must be coupled, somehow, to tissue mechanics [17,18]. Much work on healing has been done starting with the pioneer work of Murray et al. with models of "cell population" based on Partial Differential Equations (PDE) [25,38]. On the other hand, Cellular Automata (CA) and Agent Base Model (ABM) provide a bottom up approach starting from basic biological principles [1,47,8,15,30,20]. While these models require usually more intense computing, modern parallel computer architectures allow simulation with realistic number of cells [8]. We have used, here, a CA model that mimics the biological process of healing in a very simplified way. We will show that our CA can reproduce some of the main results of Javierre et al. [22] that are based on PDEs like assumptions concerning the effect of curvatures at the wound edge on the dynamic of the process. However, our hypothesis is that mechanical stress next to the wound edge should influence significantly cell dynamic. We expect the wound progression to relax large local mechanical stress components added by the resection [23,26]. This assumption requires that we use a multiscale model with a two ways coupling that relates the CA dynamic of healing with the mechanical environment forces provided by tissue deformation. We will show that energy relaxation at the wound edge in our multiscale model emerges as a consequence of our basic CA' rules expressed at the cell level for tissue healing. Overall, we obtain a long term prediction modeling framework of breast lympectomy that will need to be carefully calibrated with patient data. This paper is a proof of concept that multiscaling modeling may eventually translate into a practical tool for clinical decisions with breast cancer surgical intervention. We are going next to describe in detail our modeling framework.

2. Multiscale model

The multiscale model is described in Fig. 1. For simplicity, we use a two dimensional simulation while the concept extends readily to three space dimensions. We start from the unloaded position of the breast, and virtually remove the tumor tissue and surrounding tissue to insure a negative margin [31]. We apply gravity to the new geometry shape that has, now, a cavity. The mechanical tissue deformation model should predict the deformation field and strain energy distribution. We may use several different gravity loads and combine the results with estimated weighting factors depending on the life style of the patient. This information is mapped back to the unloaded position of the breast that serves as a reference position [33]. The CA simulation for healing takes as input the mechanical load information and compute the progression of healing.

Fig. 2 shows the difference of time scale and space scale between the mechanical model of tissue deformation and the CA model of healing. Tissue deformation is almost instantaneous compared to the tissue healing time scale. Based on an average cell cycle of about 24 h, we let healing progress for a week, to update the new geometry. This geometry should progress toward a smaller internal wound than before. We compute, then, the new strain energy distribution under mechanical load for that new geometry (see Fig. 3).

This two time scale iterative process is advanced until eventually the wound gets completely filled by scar tissue. Our general method is simple but can have many variations depending on the choice of each sub-model. We use a modular