Constitutive Models for Tumor Classification

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For centuries, palpation has been an important medical diagnostic tool. The efficacy of palpation is based on the fact that many diseases change the mechanical properties of tissues. These changes are caused either by exudation of fluids from the vascular into the extra- and intracellular space or by loss of lymphatic systems, as in the case of cancer. The result is an increase in stiffness or elastic modulus of the tissue. Even today it is common for surgeons to feel lesions during surgery that have been missed by CT, magnetic resonance (MR), or ultrasound. None of these modalities provide the information about the elastic properties of tissue elicited by palpation. The elastic moduli of various human soft tissues are known to vary over a wide range, more than four orders of magnitude. In contrast, most of the physical properties depicted by conventional medical imaging modalities are distributed over a much smaller numerical range. These observations have provided the motivation for many researchers to seek a medical imaging technology that can estimate or assess the elastic moduli of tissues. The approaches to date have been to use conventional imaging methods to measure the mechanical response of tissue to mechanical stress. The resulting strains have been measured using ultrasound, CT, or MRI and the related elastic modulus has been computed from biomechanical models of tissues. In particular, the MR elastography method (MRE) using harmonic shear waves offers direct visualization and quantitative measurement of tissue displacements, high sensitivity to very small motions, a field of view unencumbered by acoustic window requirements, and the ability to obtain full three dimensional displacement information throughout a volume.

In order to recover the mechanical properties of biological tissues we need to invert the displacement data measured by the MRE method. This inversion process requires the use of an accurate biomechanical model for tissues. It was noticed experimentally that most biological tissues have incompressible viscoelastic features: they have a certain amount of rigidity that is characteristic of solid bodies, but, at the same time, they flow and dissipate energy by frictional losses as viscous fluids do. The incompressibility assumption for soft tissues is based on the fact that most tissues are made primarily of water. In addition, since the displacements in MRE are very small (on the order of microns), a linear constitutive law is usually assumed. However, despite the richness of the data set, the variety of processing techniques and the simplifications made in the biomechanical model, it remains a challenge to extract accurate results at high resolution in complex, heterogeneous tissues from the intrinsically noisy data. Therefore, any

improvement in the MRE data processing with the help of biomechanics and computational methods will be of significant importance to modern medicine. MRE can help in tumor detection, determination of characteristics of disease, and in assessment of rehabilitation.

The aim of this proposal is to formulate new constitutive models that will be able to differentiate not only between normal and abnormal tissues, but may be more importantly, between benign and malignant tumors. As it can be seen in Fig.1, benign tumors tend to be more isotropic, and look more regularly-shaped due in part to the presence of the fibrous connective tissue shells that separate the benign tumors from the surrounding healthy tissue. On the other hand, malignant tumors are diffuse, anisotropic and irregularly-shaped.

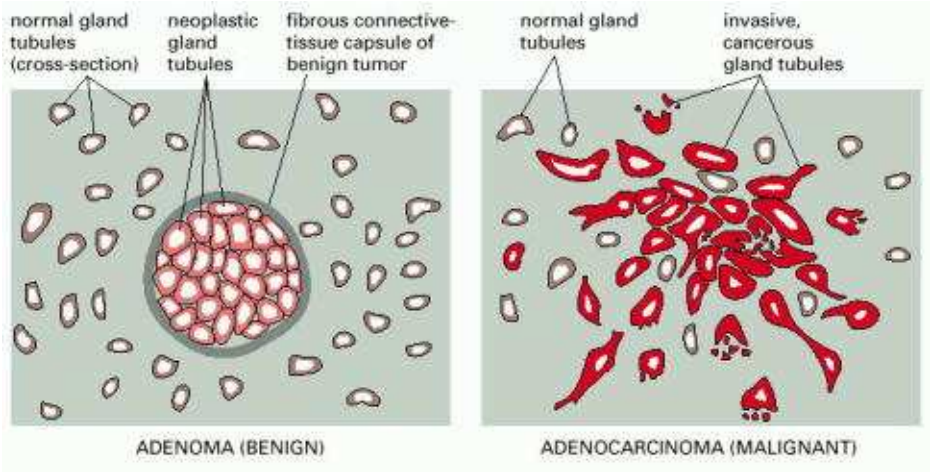

Fig.1: Benign and malignant tumors of the breast tissue.

In order for the MRE method to correctly classify the tumors of a given tissue in benign and malignant, the constitutive models of these two classes of tumors need to incorporate the differences between them. We believe that a more accurate formulation of the direct problem of MRE will help us not only to gain a better understanding of the tumors' biomechanics but also to obtain more reliable elastic moduli by solving the inverse problem.

A very rough summary of my current thoughts on this are:

1. The normal tissue is mainly a viscoelastic solid until a malignant tumor starts to develop when, due to the diffusive effect of the tumor, the surrounding, still healthy, tissue changes properties into a poro-elastic material. A benign tumor should not change the mechanical properites of the surrounding normal tissue.

2. Malignant tumors should probably be modeled as a viscoelastic fluid, due to the increasing presence of blood vessels.

3. Benign tumors can be modelled as viscoelastic solids, separated from the normal tissue by a fibrous connective tissue capsule (that holds in the tumor) which can be modelled as a thin hyper-elastic membrane.

So my list of tentative goals for the study group are:

1. Are the above macroscopic models a reasonable, and easy way to start in re-formulating the direct problem of MRE?

2. How can we incorporate relevant clinical information about tumors (which are usually microscopic measurements) into these macroscopic constitutive models?

3. Ideas on how to model distinct growth processes for normal, benign, and malignant tissues.

References

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2. J.F. Greenleaf, M. Fatemi, M. Insana, Selected Methods for Imaging Elastic Properties of Biological Tissues, Annu. Rev. Biomed. Eng. vol. 5, pg. 57-78, 2003 (wonderful review of the research done in elastography; Greenleaf does ultrasound elastography at Mayo and he is one of the world leaders in this field).

3. J.D. Humphrey, Continuum Biomechanics of Soft Biological Tissues, Proc.R.Soc.Lond.A, vol. 459, pg. 3-46, 2003. (review paper on macroscopic models for biological tissues; excellent review).

4. S. Suresh, Biomechanics and Biophysics of cancer cells, Acta Biomaterialia, vol. 3, pg. 413-438, 2007 (although the paper focusses only on cancer cells, I think it gives very useful information that we can possibly use in achieving goals 2 and 3 listed above).