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# A Multi-Phasic, Continuum Damage Mechanics Model of Mechanically Induced Increased Permeability in Tissues*

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## ABSTRACT

Recently, we have reported enhanced permeability of tissues due to *in vivo* treatment with pulsed high intensity focused ultrasound (pHIFU). This new therapy has shown promise as a way of increasing the penetration of large drug molecules, both out of the vasculature and through the tissue. To date, no clear physical model of tissue exists that can account for these effects.

A new model is proposed that clearly establishes the link between tissue structure and fluid flow properties on one hand, and the history of applied mechanical forces on the other. The model draws inspiration from two different theoretical fields of materials science, multi-phase theory and continuum damage mechanics. The theory differs from the traditional bi-phasic solid-fluid model of tissues in that the fluid part here is broken into trapped (moving with the solid) and free (moving through the solid) parts. A damage-like variable links the effective elasticity of the tissue to the ratio of the trapped to free fluids. As the damage increases, the tissue becomes, in effect, less stiff and more permeable. Release of elastic energy drives the process. A distribution of energy barriers opposes the process and governs how the fluid is released as damage increases.

## INTRODUCTION

Most current therapeutic applications of high intensity focused ultrasound (HIFU) involve continuous application, which promotes temperature elevations sufficient to cause tissue ablation in the focal zone [1]. Recently, more attention has been paid to pulsed mode high intensity focused ultrasound (pHIFU), which can introduce significant mechanical stresses without significant thermal elevation. Although instantaneous energy deposition remains high during each pulse, the time-average energy deposition is much lower. This means that the short timescale visco-elastic processes become more important than the long timescale thermal processes. Whereas very high intensity pulses (>4000 W/cm$^2$) are known to cause cavitation and subsequent pulverization and erosion of tissue [2], lower intensities (<1000 W/cm$^2$) have shown therapeutic promise unaccompanied by significant tissue destruction by either cavitation or heating. Pulsed-HIFU exposure of muscle and tumor tissue, followed by local or systemic administration, has been demonstrated to enhance the delivery of high molecular weight fluorophores [3], fluorescent nanoparticles [4], and plasmid DNA [5,6]. In related studies, pHIFU exposure has been shown to improve the penetration of tissue plasminogen activator (tPA) into blood clots *in vitro* [7], and subsequently increase the rate of thrombolysis *in vivo*, compared to tPA treatments alone. With these and other possible applications, the practical potential of this technology is evident. The physical mechanism behind pHIFU remains elusive,

however. Preliminary histological analysis seems to show that pHIFU exposures increase the permeability of both vasculature and tissue proper by increasing the flow through intercellular spaces. The purpose of this paper is to present a new tissue model that can help to explain this behavior. The simplest such model must incorporate, along with the standard visco-elastic tissue behavior, a model of fluid flow through the tissue and some mechanism for changing this flow. One way to do this, and still remain in the regime of continuum theories, is to treat the tissue as multi-phasic. Using mixture theory, the fluid flow properties are determined by the macroscopic 'permeability' of the solid portion. This permeability may be made dependent on the history of the tissue by introducing a 'damage' variable, analogous to that of continuum damage mechanics. This damage variable is a measure of the failure of the weaker structural elements of the tissue that block fluid flow. An increase in damage results in an increase in permeability as the intercellular spaces are opened to increased flow. The conclusion of this research is that the increased permeability may, in principle, be driven solely by a mechanical stimulus, such as pHIFU.

## MIXTURE THEORY FOR TISSUES

The basic idea of mixture theory is to treat each point in physical space as being simultaneously occupied by particles from each of the mixture phases. These particles are allowed to move and behave independently for the most part, but are mathematically connected via a few interaction equations. For biological materials, the standard mixture theory [8] consists of two phases, a solid phase with an inherent elasticity and permeability, and a fluid phase that is characterized locally by its average velocity field.

### A modified bi-phasic mixture theory for tissues

The standard bi-phasic model of tissue assumes that the fluid phase is monolithic and uniformly varying. This assumption works well for highly porous materials such as sponges, but is no longer valid when the pore connectivity is much lower, as is the case for tissue. In tissue, regions where the fluid velocity is significant are adjacent to regions where it is effectively zero (from one side of a cell membrane to the other). We propose to model the flow as having two components: one which moves with the solid tissue ('bound') and the other which moves through it ('free') (see Fig 1). The bound fluid does not contribute to the macroscopic flow. The effective permeability is therefore a variable, dependent on the free to bound fluid ratio. This ratio can be made dependent on the disease, thermal, and, in our case, mechanical history of the tissue. The addition of bound and free fluid phases, and a mechanism for converting from one to the other, is sufficient to model the link between tissue permeability and mechanical stress history.

### Basic definitions and the continuity equations

In order to develop an appropriate mathematical structure for the modified tissue model, it is necessary to start by treating the medium as tri-phasic. The solid phase is defined as having a 'true' mass density, $\rho_T^S$, and a 'mixture' mass density of $\rho^S(\mathbf{x},t) = \phi^S(\mathbf{x},t)\rho_T^S$, where $\phi^S(\mathbf{x},t)$ is the local volume fraction of the solid. Similarly, the fluid phase has a true mass density $\rho_T^F$. The

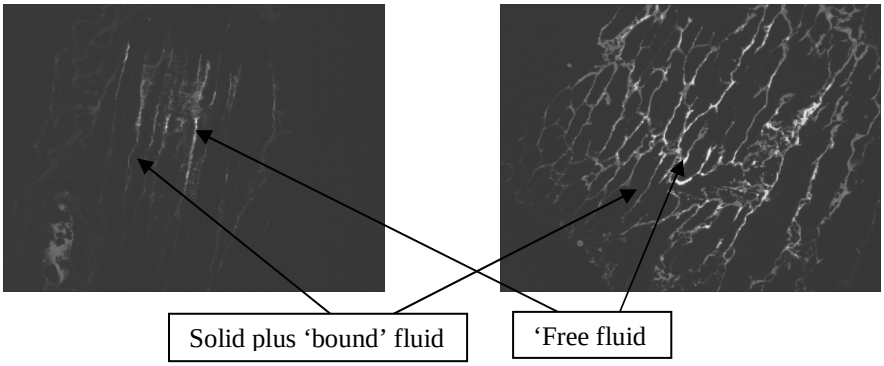


**Figure 1.** Following a single direct injection (100 μl) of 100 nm red fluorescent nanoparticles ($10^{10}$ $ml^{-1}$) into the flank muscle of a mouse. Light regions indicate high permeation (many particles), dark regions indicate little permeation. The micrograph height corresponds to 1.5 mm. Left: control, 200 ms digital camera exposure. Right: after standard treatment, 50 ms exposure.

'free' fluid mass density is then $\rho^f(\mathbf{x},t) = \phi^f(\mathbf{x},t)\rho_T^F$ and the 'bound' fluid mass density is $\rho^b(\mathbf{x},t) = \phi^b(\mathbf{x},t)\rho_T^F$. Assuming a continuous mixture implies $\phi^S + \phi^f + \phi^b = 1$ everywhere. In a tri-phasic theory, these phases may move independently, with velocities $\mathbf{v}^S(\mathbf{x},t)$, $\mathbf{v}^f(\mathbf{x},t)$ and $\mathbf{v}^b(\mathbf{x},t)$. In our model, the bound portion moves with the solid, therefore $\mathbf{v}^b = \mathbf{v}^S$. It is also necessary to accommodate the transfer of material from the bound fluid state to the free fluid state. If $M(\mathbf{x},t)$ is the rate of freeing of bound fluid mass density, the conservation of mass for the three phases may be written as:

$$\partial_t \rho^S + \nabla \cdot (\rho^S \mathbf{v}^S) = 0 \tag{1}$$

$$\partial_t \rho^b + \nabla \cdot (\rho^b \mathbf{v}^S) + M = 0 \tag{2}$$

$$\partial_t \rho^f + \nabla \cdot (\rho^f \mathbf{v}^f) - M = 0. \tag{3}$$

This system is equivalent to a modified bi-phasic model. Summing the first two continuity equations gives a continuity equation for the quasi-solid (solid plus bound fluid) system, without loss of information about fluid flow. With $\rho^{qS} = \rho^S + \rho^b$, this yields:

$$\partial_t \rho^{qS} + \nabla \cdot (\rho^{qS} \mathbf{v}^S) + M = 0. \tag{4}$$

Once the continuity equations are written, it is possible to derive sets of equations guaranteeing conservation of momentum and energy. For further information, see Refs. [8,9].

## Constitutive equations

Unlike the conservation equations, which are derived from first principles, constitutive equations need only to satisfy the second law of thermodynamics and agree with the observed experimental behavior. In this case, four constitutive equations are needed (thermal effects are

considered negligible): one each to control the elastic behavior of the quasi-solid and the fluid, one that governs the flow of the free fluid relative to the solid, and one that governs the release of the bound fluid. The fluid may be assumed to be incompressible:

$$\sigma_{ij}^{f} = -p\phi^{f}\delta_{ij}, \tag{5}$$

where $\sigma_{ij}^{f}$ is the mechanical stress in the free fluid phase, $p$ is the hydraulic pressure, and $\delta_{ij}$ is the unit tensor. Assuming that the solid plus bound fluid behaves as an elastic solid, with modulus dependent on the relative volume fraction of bound fluid,

$$\sigma_{ij}^{qS} = -p\phi^{qS}\delta_{ij} + \left(S_{ijkl} + \Phi Q_{ijkl}\right)\varepsilon_{kl}, \tag{6}$$

where $\Phi = \phi^{b}/\phi^{S}$, and $\varepsilon_{kl}$ is the elastic strain (a viscous term may be added to this if necessary). Presumably, the solid filled with fluid is stiffer than without so the elastic stiffening tensor, $Q_{ijkl}$, should be positive definite, as should the solid stiffness, $S_{ijkl}$. The governing equation for the fluid flow is somewhat more complicated:

$$\boldsymbol{\pi}^{qS} = -D\left(\mathbf{v}^{S} - \mathbf{v}^{f}\right) + pR\nabla\phi^{S} - p\left(1-\phi^{S}\right)\nabla R, \tag{7}$$

where $\boldsymbol{\pi}^{qS}$ is the body force (force per unit volume) on the quasi-solid due to the fluid flowing through it; $D$ is a material constant (the 'diffusive drag coefficient') related to the Darcy's law permeability, $K = R/D$; and $R = \phi^{f}/\phi^{F} = 1 - \left(\phi^{S}/(1-\phi^{S})\right)\Phi$ is a dimensionless 'damage' variable. For uniform tissue, only the first term survives; this provides the viscous character of the tissue, as it does in the bi-phasic model. Finally, assuming a barrier energy per unit fluid mass, $\mu$, that acts to bind the 'bound' portion of the fluid, a reasonable expression for the rate of conversion is

$$M = A\Phi\left[\frac{Q_{ijkl}\varepsilon_{ij}\varepsilon_{kl}}{2\rho_{T}^{F}\phi^{S}} - \frac{\left(\mathbf{v}^{f}\right)^{2} - \left(\mathbf{v}^{S}\right)^{2}}{2} - \mu\right]. \tag{8}$$

where *A* is some positive material constant. It is possible to show from the continuity equations that $M = -\phi^{S}\left(\partial_{t} + \mathbf{v}^{S}\cdot\nabla\right)\Phi$, resulting in a reasonably simple differential equation. A similar expression may be applicable for the reverse process (healing). Eq. (8) states that the rate of change of fluid from bound to free is: (i) proportional to the current bound fluid fraction; (ii) driven by the decrease of elastic 'free' energy; and (iii) opposed by the barrier energy.

## BARRIER ENERGY DISTRIBUTIONS

In the above expression, a single barrier energy was defined. In real tissues, however, there exist many different structures that create barriers to fluid flow, and even similar structures may have dissimilar strengths. It makes much more sense, therefore, to use a distribution of bound

fluid volumes governed by a continuous range of barrier potentials. Since $\phi^S$ is a constant, this implies,

$$\Phi = \int \hat{\Phi}(\mu)\mathrm{d}\mu, \tag{10}$$

where $\hat{\Phi}(\mu)$ is the barrier distribution function, which remains to be determined from experiment. Since $\Phi$ is linearly related to $M$, a similar expression holds:

$$M = \int \hat{M}(\mu)\mathrm{d}\mu. \tag{11}$$

Then analogous to Eq. (8),

$$\hat{M}(\mu) = A\hat{\Phi}(\mu)\left[\frac{Q_{ijkl}\varepsilon_{ij}\varepsilon_{kl}}{2\rho_T^F\phi^S} - \frac{\left(\mathbf{v}^f\right)^2 - \left(\mathbf{v}^S\right)^2}{2} - \mu\right], \tag{12}$$

from which the net conversion rate may be found by using Eq. (11).

## APPLICATION TO pHIFU

The above theory was applied to the mechanical stimulation in the focal zone of the pHIFU beam. The model tissue we used was liver, which is assumed to be isotropic and homogenous. Quasi-static material parameters were taken from Lizzi, *et al.* [10]. Since, at high frequencies, it is the fluid viscosity that dominates the stress, the quasi-static elastic moduli were used in all the equations above, while the high frequency constants were used only in the ultrasonic wave equations. Standard pHIFU treatment was assumed to be 40 W, 50 ms pulses applied with a repetition rate of 1 Hz. The ultrasonic beam was modeled as a longitudinal plane wave, of frequency 1 MHz, with a 2 mm beam-waist Gaussian profile in the focal zone. Two sources of damage were considered: the longitudinal strain energy from the wave itself, and the shear strain energy due to the radiation force. From our experimental work and the literature [3-6], it is clear that the changes due to pHIFU are limited to opening of the intercellular spaces and minor changes in elastic constant. In the absence of significant experimental evidence to the contrary, the barrier distribution was assumed to be bi-modal, with the bulk of the fluid trapped behind the high energy barriers of the cell membrane well beyond the reach of the pHIFU, and a smaller portion in the intercellular space with a much lower barrier potential. Based upon evidence from micrographs, such as Fig. 1, the free volume fraction is changed from about 1 % to about 10 % by the application of a full treatment of 100 pHIFU pulses. This is assumed to represent the bulk of the bound fluid available to be freed by this process, and thus gives the bounds on the barrier energy distribution in the low energy region. Much less information is available regarding the changes in elastic constant due to the damage evolution. A 10 % decrease in both the shear and bulk moduli might be reasonable, but this remains to be verified. With these assumptions, the rate constant in Eq. (12) may be estimated. It is then possible to predict the evolution of the free fluid volume fraction, which is proportional to the tissue permeability, due to application of pHIFU. Fig. 2 shows the evolution of the free fluid volume fraction predicted in and near the pHIFU focal zone due to the longitudinal wave itself, and due to the radiation force. Because the radiation force is proportional to the square of the wave amplitude, this component becomes

increasingly important at higher acoustic power. This explains why, in our case, the dominant effect is due to the radiation force (Fig. 2 on the right) rather than the action of the wave itself.

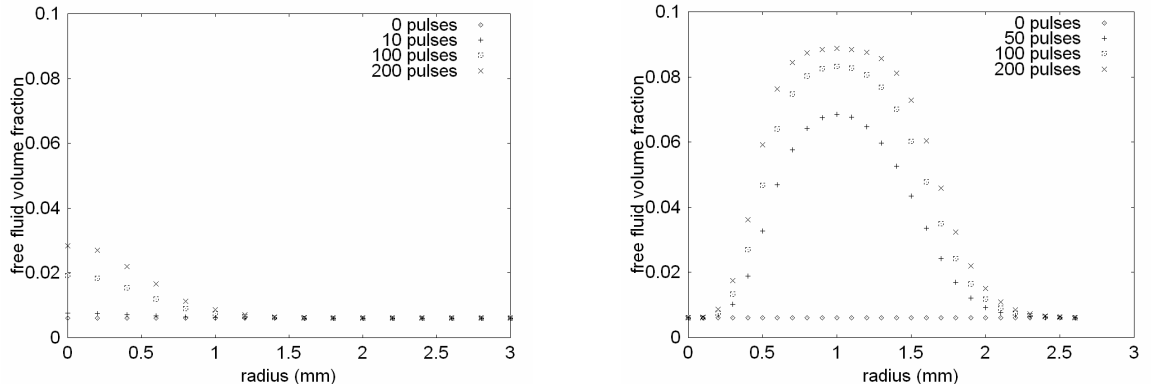


**Figure 2.** Increases in free fluid volume fraction (permeability) as a function of off-axis distance, for a longitudinal pHIFU wave of Gaussian profile. Left: increase due to direct action of the wave. Right: increase due to action of the radiation force.

## CONCLUSION

In this paper, we have outlined a new material model for tissue which may be useful in explaining changes observed during pHIFU exposures. This provides us with a fundamental understanding of the process, even as further research is needed to fill in the details. With further experiments, we hope to better define the tissue parameters needed for accurate mathematical modeling. Ultimately, these considerations will assist in rapid optimization of pHIFU exposure parameters across different tissue types and for different drug therapies.

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