Modulation of interstitial fluid pressure by focused ultrasound - Supplementary Information

1. Mathematical Model

1.2 Basic Equations

The linear biphasic model implemented by Netti *et al.* (1995, 1997) is in the form originally formulated by Mow *et al.* (1980) for describing the load-bearing behavior of soft tissue and applied to articular cartilage. In this model, the density of the fluid and solid phases are defined as

$$\sigma_f(\boldsymbol{r},t) = \rho_f\phi, \text{ and } \sigma_s(\boldsymbol{r},t) = \rho_s(1-\phi), \tag{A1}$$

where ϕ is the volume fraction occupied by the fluid phase in the mixture, and ρ_f, ρ_s are respectively the mass density of the fluid and the solid phase considered intrinsically incompressible. The continuity equations (mass conservation) for the liquid and solid phases are

$$\frac{\partial}{\partial t}\sigma_f + \nabla\cdot\left(\sigma_f\boldsymbol{v}_f\right) = \mathrm{S}(\mathbf{r},\mathrm{t}), \text{ and } \frac{\partial}{\partial t}\sigma_s + \nabla\cdot(\sigma_s\boldsymbol{v}_s) = 0, \tag{A2}$$

where $\boldsymbol{v}_f$ is the fluid phase velocity, $\boldsymbol{v}_s$ is the solid phase velocity and S is the fluid source term. By substituting (A1) into (A2) and changing notation with $\boldsymbol{v} = \boldsymbol{v}_f, \boldsymbol{v}_s = \frac{\partial \boldsymbol{u}}{\partial t}$ with $\boldsymbol{u}$ is the tissue displacement

$$\frac{\partial\phi}{\partial t} = -\nabla\cdot(\phi\boldsymbol{v}) + \Omega(\boldsymbol{r},t), \tag{A3}$$

$$\frac{\partial\phi}{\partial t} = \nabla\cdot\left((1-\phi)\frac{\partial\boldsymbol{u}}{\partial t}\right), \tag{A4}$$

where $\Omega = \mathrm{S}/\rho_f$. Combining (A3) and (A4) we get

$$\nabla\cdot\left[\phi\boldsymbol{v} + (1-\phi)\frac{\partial\boldsymbol{u}}{\partial t}\right] = \Omega(\boldsymbol{r},t). \tag{A5}$$

The conservation of momentum for the liquid phase (generalized Darcy's law) is

$$\phi\left[\boldsymbol{v} - \frac{\partial\boldsymbol{u}}{\partial t}\right] = -K\nabla P_i, \tag{A6}$$

and for the solid phase

$$\nabla\cdot T = 0, \tag{A7}$$

with T second-order tensor

$$T = (-P_i + \lambda e)I + \mu[\nabla\boldsymbol{u} + \nabla\boldsymbol{u}^T], \tag{A8}$$

with P_i the interstitial pressure and λ, μ the Lamé coefficients of the solid matrix. In cylindrical polar coordinates and assuming axial symmetry, the terms in (A8) in explicit notation are as follows. Introducing the unit radial vector $\hat{\boldsymbol{e}}_r$ and the unit axial vector $\hat{\boldsymbol{e}}_z$, the displacement $\mathbf{u} = u_r(r,z,t)\hat{\boldsymbol{e}}_r + u_z(r,z,t)\hat{\boldsymbol{e}}_z$, and the nabla operator $\nabla = \hat{\boldsymbol{e}}_r\frac{\partial}{\partial r} + \hat{\boldsymbol{e}}_z\frac{\partial}{\partial z}$, we can write the dilatation, $e = \nabla\cdot\mathbf{u} = \frac{1}{r}\frac{\partial}{\partial r}(ru_r) + \frac{\partial u_z}{\partial z}$. The unit tensor is $\mathbf{I} = \hat{\boldsymbol{e}}_r\hat{\boldsymbol{e}}_r + \hat{\boldsymbol{e}}_z\hat{\boldsymbol{e}}_z$, $\nabla\mathbf{u}$ is the dyadic tensor $\nabla\mathbf{u} = \frac{\partial\mathbf{u}}{\partial r}\hat{\boldsymbol{e}}_r + \frac{\partial\mathbf{u}}{\partial z}\hat{\boldsymbol{e}}_z$ and $(\nabla\mathbf{u})^{\mathrm{T}}$ is the transpose of $\nabla\mathbf{u}$ with $(\nabla\mathbf{u})^{\mathrm{T}} = \hat{\boldsymbol{e}}_r\frac{\partial\mathbf{u}}{\partial r} + \hat{\boldsymbol{e}}_z\frac{\partial\mathbf{u}}{\partial z}$. Using tensor analysis:

$$\nabla\cdot[(-P_i + \lambda e)\mathbf{I}] = -\nabla P_i + \lambda\nabla e + e\cdot\nabla\lambda. \tag{A9}$$

Usually $\nabla\lambda = 0$, and $\nabla\mu = 0$ if we consider domains with constant modulus, however, in our case these parameters are spatially varying. With

$$\nabla \cdot (\nabla \mathbf{u}) = \frac{\partial e}{\partial r}\hat{\boldsymbol{e}}_r + \frac{\partial e}{\partial z}\hat{\boldsymbol{e}}_z,$$

$$\nabla \cdot (\nabla \mathbf{u})^{\mathrm{T}} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial \mathbf{u}}{\partial r}\right) + \frac{\partial^2 \mathbf{u}}{\partial z^2},$$

together with the above equations, (A7) can be written as:

$$\mu\nabla^2\mathbf{u} + (\mu+\lambda)\nabla(\nabla\cdot\mathbf{u})) + e\cdot\nabla\lambda + [\nabla\mathbf{u} + \nabla\mathbf{u}^{\mathrm{T}}]\cdot\nabla\mu - \nabla P_i = 0 \quad \text{(A9)}$$

with $\nabla^2 = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\right) + \frac{\partial^2}{\partial z^2}$. In the hypothesis of axial symmetry, $\boldsymbol{u}$ is irrotational, i.e.: $\nabla \times \boldsymbol{u} = 0$ and since $\nabla^2\boldsymbol{u} = \nabla(\nabla\cdot\boldsymbol{u}) - \nabla\times(\nabla\times\boldsymbol{u})$, it follows that the condition of equilibrium given by (A9) can be also written in terms of the dilation as

$$H\nabla e + e\nabla H + [\nabla\mathbf{u} + \nabla\mathbf{u}^T - 2e\mathbf{I}]\cdot\nabla\mu = \nabla P_i, \quad \text{(A10)}$$

where $H = 2\mu + \lambda$ is the aggregate (pressure wave) modulus of the interstitial matrix. For simplicity, we ignore the third term, under the assumption that shear contributes little to the pressure and that $\nabla\mu$ is small. Under these conditions (A10) is just:

$$\nabla P_i = \nabla(He), \quad \text{(A10a)}$$

and the divergence is

$$\nabla^2 P_i = \nabla^2(He). \quad \text{(A11)}$$

(A6) can be written in terms of the dilatation by taking the divergence, as:

$$\frac{\partial \mathrm{e}}{\partial \mathrm{t}}\text{-}\mathrm{K}\nabla^2\mathrm{P_i} = \Omega(\mathrm{r},\mathrm{t}). \quad \text{(A12)}$$

Combining (A11) and (A12) we obtain

$$\frac{\partial \mathrm{e}}{\partial \mathrm{t}}\text{-}\mathrm{K}\nabla^2(\mathrm{He}) = \Omega(\mathrm{r},\mathrm{t}). \quad \text{(A13)}$$

The substitution of $\Omega(\mathrm{r},\mathrm{t})$ given by (2) in Sec. 2.1 into (A13) yields

$$\frac{\partial e}{\partial t} - \mathrm{K}\nabla^2(He) + \left[\frac{L_pS}{V} + \frac{L_{PL}S_L}{V}\right]He = \frac{L_pS}{V}P_e + \frac{L_{PL}S_L}{V}P_L. \quad \text{(A14)}$$

This partial differential equation, with constant H, is the one solved by Netti *et al* (1995). At steady state and in completely homogeneous medium, the time derivatives and gradients are zero, so the solution is just:

$$P_{SS} = H_0e_0 = \left[\frac{L_pS}{V}P_e + \frac{L_{PL}S_L}{V}P_L\right] / \left[\frac{L_pS}{V} + \frac{L_{PL}S_L}{V}\right]. \quad \text{(A15)}$$

If the medium at steady state is not elastically homogeneous, H and e are functions of space (but not time). A trivial steady state solution that has continuity of $P_i(\mathbf{r})$ is $e(\mathbf{r}) = Pss/H(\mathbf{r})$.

Alternatively, we can change (A14) to make P_i our main variable. Integrating (A10a) with $P = P_{SS} = e_0H_0$ at $\boldsymbol{r} = \infty$ gives the general expression:

$$P_i = eH. \quad \text{(A16)}$$

Taking the partial derivative with time:

$$\frac{\partial P_i}{\partial t} = H\frac{\partial e}{\partial t} + e\frac{\partial H}{\partial t} \leftrightarrow \frac{\partial e}{\partial t} = \frac{1}{H}\frac{\partial P_i}{\partial t} - \frac{P_i}{H^2}\frac{\partial H}{\partial t},$$

so:

$$\frac{1}{H}\frac{\partial P_i}{\partial t} - \frac{P_i}{H^2}\frac{\partial H}{\partial t} = K\nabla^2 P_i - \left[\frac{L_p S}{V} + \frac{L_{PL} S_L}{V}\right] P_i + \left[\frac{L_p S}{V} P_e + \frac{L_{PL} S_L}{V} P_L\right]. \quad \text{(A17)}$$

The steady state solution is now clearly independent of H. This is why a change in modulus is not enough to explain permanently increased pressure in a tumor.

Defining $\alpha = \left[\frac{L_p S}{V} + \frac{L_{PL} S_L}{V}\right]$ and P_{SS} in (A15), the steady state is the trivial solution to:

$$K\nabla^2 P_i - \alpha P_i + \alpha P_{SS} = 0. \quad \text{(A18)}$$

Consistent with the boundary conditions at infinity used to derive (A16), $P_i = P_{SS}$ is the only possible solution to this steady state equation. For any transient change in H this expression implies that IFP must eventually return to the steady state condition at long times as $\frac{\partial H}{\partial t} \to 0$. To get the behavior during the transition, we need to solve the full PDE. This was set up in Comsol Multiphysics 3.5a using the thermal diffusion module with $T \sim P_i, C \sim \frac{1}{H}, k \sim K, \mathbf{u} = 0$, and $Q \sim \left(-\alpha + \frac{1}{H^2}\frac{\partial H}{\partial t}\right) P_i + \alpha P_{ss}$.

1.2 Analytical Approach

We can also approach this problem analytically using distinct domains in space and time. This is equivalent to approximating H as a step in space and time. Write:

$$H(\mathbf{r}, t) = H_0 + \Delta H h(t - t_0)(1 - h(\mathbf{r} - \mathbf{r}_i)), \quad \text{(A19)}$$

where h() is some step function that goes from 0 to 1 as the argument crosses 0 from –ve to +ve, $\Delta H = H_f - H_0$, and t_0, $\mathbf{r}_i$ are the coordinates of the interface in time and space. The relevant derivatives of H are:

$$\dot{H} = \Delta H \delta(t - t_0)(1 - h(\mathbf{r} - \mathbf{r}_i))$$

$$\nabla H = -\Delta H h(t - t_0)\delta(\mathbf{r} - \mathbf{r}_i)\hat{\mathbf{r}}_i \ ^{\dagger}$$

$$\nabla^2 H = -\Delta H h(t - t_0)\delta'(\mathbf{r} - \mathbf{r}_i) \ ^{\ddagger}$$

Here $\delta()$ is the Dirac delta function, the integral of which is a unit step, and $\delta'()$ is its derivative with respect to its argument; $\delta'(x) \propto x\delta(x)$.

Using these expressions, we can write (A18):

$$\frac{1}{H_0 + \Delta H h(t-t_0)(1-h(\mathbf{r}-\mathbf{r}_i))}\frac{\partial P_i}{\partial t} - \frac{P_i \Delta H \delta(t-t_0)\left(1-h(\mathbf{r}-\mathbf{r}_i)\right)}{\left(H_0 + \Delta H h(t-t_0)(1-h(\mathbf{r}-\mathbf{r}_i))\right)^2} = K\nabla^2 P_i - \alpha(P_i - P_{ss}), \quad \text{(A20)}$$

from which we have a domain $t < t_0$ with the steady state solution $P_i = P_{ss}$:

$$\frac{\partial P_i}{\partial t} = H_0\{K\nabla^2 P_i - \alpha(P_i - P_{ss})\}, \quad \text{(A21)}$$

and one for $t > t_0$:

$$\frac{\partial P_i}{\partial t} = (H_0 + \Delta H(1 - h(\mathbf{r} - \mathbf{r}_i))\{K\nabla^2 P_i - \alpha(P_i - P_{ss})\}, \quad \text{(A22)}$$

with matching condition at t_0 that the coefficient of the delta function goes to zero (because the delta goes to infinity):

$$\frac{P_i \Delta H(1 - h(\mathbf{r} - \mathbf{r}_i))}{(H_0 + \Delta H h(t - t_0)(1 - h(\mathbf{r} - \mathbf{r}_i)))^2} = 0. \quad \text{(A23)}$$

For $r > \boldsymbol{r}_i$, this is trivial since $1 - h(\mathbf{r} - \mathbf{r}_i) = 0$, and again $P_i = P_{SS}$. For $r < \boldsymbol{r}_i$, we have:

$$\frac{P_i \Delta H}{(H_0 + \Delta H h(t - t_0))^2} = 0. \quad \text{(A24)}$$

Approaching the transition from $t < t_0$ (before the change, where $P_i = P_{SS}$, $H = H_0$) and $t > t_0$ (after the change, where $H = H_f = H_0 + \Delta H$), this implies an "initial" condition at t_0:

$$\frac{P_i(\mathbf{r}<\mathbf{r}_i,t_0^+)}{H_f} = \frac{P_{ss}}{H_0}. \tag{A25}$$

That is, $e(\boldsymbol{r},t) = \frac{P_i(r,t)}{H(r,t)}$ is continuous across t_0, while the pressure "steps" from $H_0 e_0$ to $H_f \frac{P_{SS}}{H_0} = H_f e_0$.

Depending on K, one can assume all the gradients in (A21) remain localized to the boundary, that is, $K\nabla^2 P_i = 0$ at $\mathbf{r} \ll \mathbf{r}_i$, for small enough K. In that case, for example, near $\mathbf{r} = 0$, we have just $\frac{\partial P_i}{\partial t} = -H_f \alpha(P_i - P_{ss})$, with initial condition given above. The solution in spatial domains far from $\mathbf{r}_i$ is therefore:

$$P_i(\mathbf{r} \ll \mathbf{r}_i, t > t_0) = P_{ss}\left(1 + \frac{\Delta \mathrm{H}}{H_0} e^{-H_f \alpha(t-t_0)}\right);\; P_i(\mathbf{r} \gg \mathbf{r}_i, t) = P_{ss}. \tag{A26}$$

Most generally, the dynamics near the boundary require a numerical solution, however, it's possible to approximate what is happening there as well. It makes sense that an expression for P_i across the boundary will look like a generalization of the initial condition, that is, we can write:

$$P_i(\mathbf{r},t) = P_{ss}\left(1 + \frac{\Delta P_i(t)}{P_{ss}}\big(1 - h(\mathbf{r}-\mathbf{r}_i)\big)\right); \Delta P_i(t) = P_i(\mathbf{r} < \mathbf{r}_i, t) - P_{ss}. \tag{A27}$$

Then:

$$\nabla^2 P_i = -\Delta P_i(t)\delta'(\mathbf{r}-\mathbf{r}_i) \tag{A22}$$

and the PDE becomes:

$$\frac{\partial P_i}{\partial t} = -\Big(H_0 + \Delta H\big(1 - h(\mathbf{r}-\mathbf{r}_i)\big)\Big)\{K\delta'(\mathbf{r}-\mathbf{r}_i) + \alpha\}(P_i - P_{ss}), \tag{A28}$$

With formal solution for all space and time:

$$P_i(\mathbf{r},t) = P_{ss}\left(1 + \frac{\Delta H h(t-t_0)(1-h(\mathbf{r}-\mathbf{r}_i))}{H_0} e^{-(H_0+\Delta H(1-h(\mathbf{r}-\mathbf{r}_i)))\{K\delta'(\mathbf{r}-\mathbf{r}_i)+\alpha\}(t-t_0)}\right). \tag{A29}$$

† Proof of $\nabla H = -\Delta H h(t-t_0)\delta(\mathbf{r}-\mathbf{r}_i)\hat{\mathbf{r}}_i$:

$$\begin{aligned}\nabla H &= \nabla\{H_0 + \Delta H h(t-t_0)(1 - h(\mathbf{r}-\mathbf{r}_i))\}\\ &= -\Delta H h(t-t_0)\nabla h(\mathbf{r}-\mathbf{r}_i)\\ &= -\Delta H h(t-t_0)h'(\mathbf{r}-\mathbf{r}_i)\nabla(\mathbf{r}-\mathbf{r}_i)\\ &= -\Delta H h(t-t_0)\delta(\mathbf{r}-\mathbf{r}_i)\lim_{\mathrm{v}\to 0}\frac{(\mathbf{r}+\mathrm{v}\hat{\mathbf{r}}_i-\mathbf{r}_i)-(\mathbf{r}-\mathbf{r}_i)}{\mathrm{v}}\\ &= -\Delta H h(t-t_0)\delta(\mathbf{r}-\mathbf{r}_i)\hat{\mathbf{r}}_i\end{aligned}$$

since the limit is only non-zero if test vector, **v**, is across the boundary.

‡ Proof of $\nabla^2 H = -\Delta H h(t-t_0)\delta'(\mathbf{r}-\mathbf{r}_i)$:

$$\begin{aligned}\nabla^2 H &= \nabla\cdot\nabla H\\ &= -\Delta H h(t-t_0)\nabla\cdot(\delta(\mathbf{r}-\mathbf{r}_i)\hat{\mathbf{r}}_i)\\ &= -\Delta H h(t-t_0)\{\hat{\mathbf{r}}_i\cdot\nabla\delta(\mathbf{r}-\mathbf{r}_i) + \delta(\mathbf{r}-\mathbf{r}_i)\nabla\cdot\hat{\mathbf{r}}_i\}\\ &= \Delta H h(t-t_0)\{\delta'(\mathbf{r}-\mathbf{r}_i)\hat{\mathbf{r}}_i\cdot\hat{\mathbf{r}}_i\} = \Delta H h(t-t_0)\delta'(\mathbf{r}-\mathbf{r}_i)\end{aligned}$$

since: $\nabla\cdot\hat{\mathbf{r}}_i = \lim_{V\to 0}\int\nabla\cdot\hat{\mathbf{r}}_i\,dV = \lim_{V\to 0}\oint\hat{\mathbf{r}}_i\cdot d\boldsymbol{S} = \lim_{V\to 0}\int\hat{\mathbf{r}}_i\cdot\hat{\mathbf{n}}dS = 0$,

where the volume is taken across the interface, and the surface of this volume that contributes to the integral is only the part that parallels the interface where $\hat{\mathbf{n}} = \hat{\mathbf{r}}_i$.

1.2 Fluid flow and solute transport

Of particular interest is the amount of excess drug that may be transported during this process. The amount of excess fluid entering the tissue from the vasculature per second is given by Ω. The amount that comes in from neighboring tissue is given by $-\mathrm{K}\nabla^2\mathrm{P_i}$. The excess from these two sources is the cause of the swelling, $\frac{\partial \mathrm{e}}{\partial \mathrm{t}}$. Finally, the total amount of excess fluid can be found by integrating over time, that is, the excess fluid is just the change in e. We already know that e goes from $e_0 = \frac{P_{SS}}{H_0}$ to $\frac{P_{SS}}{H_f}$, so:

$$\Delta e = \frac{P_{SS}}{H_f} - \frac{P_{SS}}{H_0} = \frac{P_{SS}}{H_0}\left[\frac{H_0}{H_f} - 1\right] = -\frac{P_{SS}}{H_0}\frac{\Delta H}{H_f}. \quad \text{(A30)}$$

Solute transport is governed by:

$$\frac{\partial C_i}{\partial t} + \boldsymbol{\nabla}\cdot(-D\boldsymbol{\nabla}C_i + r_F\boldsymbol{v}C_i) = \phi_S - \phi_R \quad \text{(A31)}$$

Ignoring the loses due to reactive binding, the source term is:

$$\begin{aligned}\phi_S &= \frac{\xi_d S}{V}\left(C_p - C_i\right) + \frac{L_p S}{V}(P_e - P_i)(1-\sigma)C_p - \frac{L_{pL}S_L}{V}(P_i - P_L)(1-\sigma_L)C_p \\ &= \frac{\xi_d S}{V}\left(C_p - C_i\right) + \Omega(1-\sigma)C_p + \frac{L_{pL}S_L}{V}(P_i - P_L)(\sigma-\sigma_L)C_p \end{aligned} \quad \text{(A32)}$$

Ω is given by (2). We are really interested in the excess solute so we rewrite this in terms of $C_i = C_{i0} + C_{ex}$, and $P_i = P_{SS} + P_{ex}$ where C_{ex} is the excess concentration that arises due to non-steady state pressures, P_{ex}. Using the expressions above,

$$\begin{aligned}\frac{\partial C_{ex}}{\partial t} = \boldsymbol{\nabla}\cdot(-D\boldsymbol{\nabla}C_{ex} + r_F\boldsymbol{v}C_{ex}) - \frac{\xi_d S}{V}C_{ex} - \frac{L_p S}{V}P_{ex}(1-\sigma)C_p \\ -\frac{L_{pL}S_L}{V}P_{ex}(1-\sigma_L)C_p.\end{aligned} \quad \text{A33)}$$

Recalling that $\Omega = -\alpha(P_i - P_{ss}) = -\alpha P_{ex}$, we can write this as:

$$\frac{\partial C_{ex}}{\partial t} = \nabla\cdot(-D\nabla C_{ex} + r_F\mathbf{v}C_{ex}) - \frac{\xi S}{V}C_{ex} + (1-\Sigma)\Omega C_p, \quad \text{(A34)}$$

where $1-\Sigma = \frac{1}{\alpha}\left[\frac{L_p S}{V}(1-\sigma) + \frac{L_{PL}S_L}{V}(1-\sigma_L)\right]$ is an effective reflection coefficient. The first term on the right describes solute transfer from neighboring regions. The second term is the loss of diffused solute from the vasculature due to the reduction in the concentration gradient. The third term is excess solute brought in from the vasculature due to convection. The initial condition for C_{ex} is clearly $C_{ex}(t_0) = 0$.

With a solution to (A13) or (A17), the source term of (A34) may be expressed in terms of e or P_i and solved. Employing the analytical solution far from the boundaries, where $H = H_f$, and using (A26), we can write:

$$\frac{\partial C_{ex}}{\partial t} = -\frac{\xi S}{V}C_{ex} + (1-\Sigma)\frac{1}{H_f}\frac{\partial \mathrm{P_i}}{\partial t}C_p = -\frac{\xi S}{V}C_{ex} - (1-\Sigma)\mathrm{P_{SS}}\frac{\Delta H}{H_0}\alpha e^{-H_f\alpha(t-t_0)}C_p. \quad \text{(A35)}$$

Assuming the plasma decay rate is very low compared to $H_f\alpha$, a solution to this equation is:

$$C_{ex}(t-t_0) = \frac{(1-\Sigma)C_p\alpha P_{SS}\frac{\Delta H}{H_0}}{H_f\alpha - \frac{\xi S}{V}}\left[e^{-H_f\alpha(t-t_0)} - e^{-\frac{\xi S}{V}(t-t_0)}\right]$$

$$= (1-\Sigma)C_p\Delta e\left[1-e^{-(H_f\alpha-\frac{\xi S}{V})(t-t_0)}\right]\frac{e^{-\frac{\xi S}{V}(t-t_0)}}{1-\frac{\xi S}{VH_f\alpha}}, \tag{A36}$$

where we used the expression derived above for the total change in strain.

2. Derivation of the function $H(\mathbf{r},t)$ from MRI data

All the results presented here and in the paper hinge on some estimate of $H(r,t)$. Clearly there is no easy way to directly measure a change in H over time in living tissue. Based on the theory above, however, it is possible to estimate it indirectly from the relative change in fluid content, which may be obtained from MRI. The most accurate method for doing this would probably be to obtain a proton density map. Unfortunately, the best data we have are T2-weighted images. Other factors being equal, T2-weighted signal intensity is correlated to fluid fraction, although the dependence is not strictly linear. Nevertheless, for the sake of illustration, the relative increase in fluid fraction in tissue was estimated from a T2 weighted image of the focal plane taken at 2.5 minutes after the HIFU exposure under the assumption that the signal intensity is approximately linearly related to fluid fraction. The same approach would work for proton density maps. Here, we have considered a particular set of data obtained during and after a pulsed HIFU treatment of rabbit thigh. More details about this experiment can be found in O'Neill *et al* (*2013*). The T2 weighted image intensity map and the corresponding thermal dose map (see O'Neill *et al (2013)* for details) are plotted in Fig. A1. Cylindrically averaged plots of the same are shown in Fig. A2, where the center pixel was chosen as the peak of the cumulative effective thermal dose obtained according to Sapareto and Dewey (1984). The T2-weighted image has a resolution 0.5 mm per pixel. Fig. A3 shows the same data with pixel value plotted vs. distance from the peak pixel in Fig. A2. Also shown is averaged data derived by lumping pixel values in ranges $i-0.25$ mm $< R \le i+0.25$ mm where $i = 0, 0.5, 1.0, 1.5, \ldots$. The background intensity (excluding everything R≤3.5 mm) is 412.4±53.6. Therefore, the averaged image intensity relative to the background goes from a peak of about 1.83±0.24 at the center of the treated spot to just over 1.0±0.15 at a distance of about 3 mm. The relative increase in image intensity is approximately equal to the relative increase in the water content and therefore is proportional to the dilatation. The unknown parameters in (10), ΔH and σ were adjusted to match this behavior at the 2.5 minute timepoint (see Fig. 3).

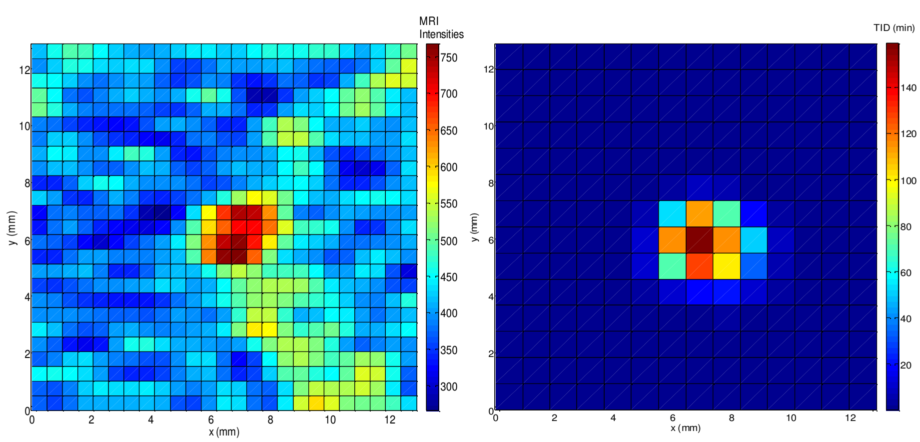

Fig. A1. Left: T2-weighted MR image intensity map. Right: Corresponding map of thermal dose at this location.

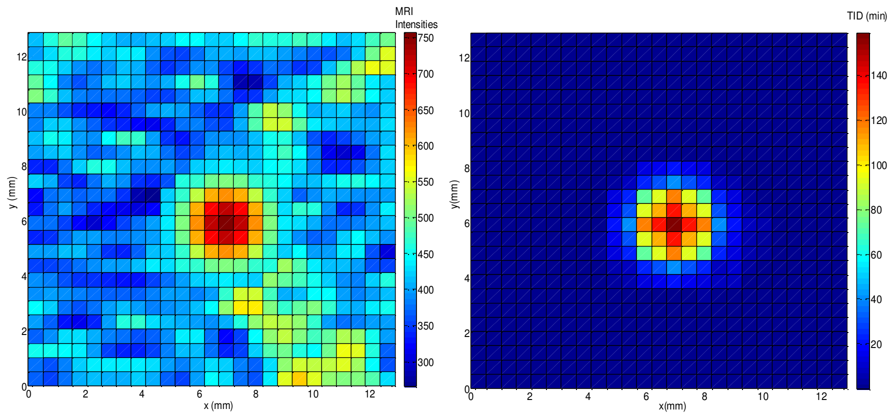

Fig. A2. Left: T2 weighted image cylindrically averaged around the peak of the thermal dose. Right: Cylindrically averaged thermal dose.

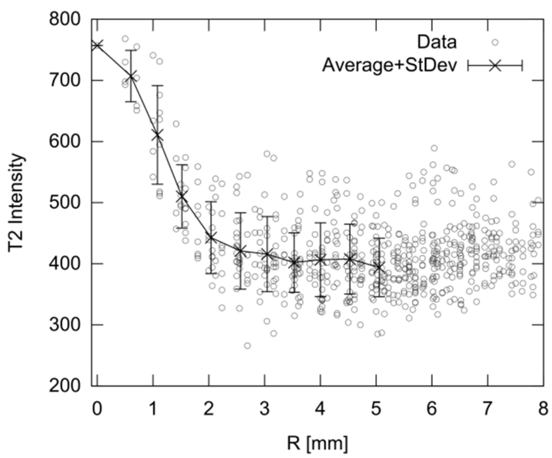

Fig. A3. T2-weighted signal vs. radial distance from the center of treatment. Shown is raw data and moving average data over 0.5 mm, the normalized version of which appears in Fig. 3.

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