# Simulation of MRI Related Tissue Changes Occurring during Formaldehyde Fixation of Human Brain Hemispheres

**R. J. Dawe[1], D. A. Bennett[2], J. A. Schneider[2], and K. Arfanakis[1]**

[1]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, United States, [2]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, United States

**Introduction:** Postmortem MRI of the human brain allows for invasive examination of the tissue specimen immediately following the MR scan, a practice that is not possible with living subjects. An increasing number of researchers have exploited this opportunity, correlating MR results from cadaveric brains with the findings of histological examination. However, previous investigations have shown that MR properties of the tissue vary with both time and position as fixation progresses, causing misinterpretation of MRI results.[1] In this study, computer simulation was used to model the fixation process in cadaveric brain hemispheres immersed in formaldehyde solution. The resulting changes in the simulated $T_2$ values were compared with previous experimental observations.[2]

**Methods:** A realistically shaped 3D hemisphere model was created by masking an available $T_2$ map from Reference 2. This tissue was treated as a homogeneous mass and was assumed to initially consist of 100 percent unfixed tissue (UT). A pool of formaldehyde formed a boundary around the tissue and diffused into the hemisphere in a Fickian manner (finite differences, voxel size = 1.25 × 1.25 × 1.5 $mm^3$, timestep = 1.0 s), with a diffusion coefficient of $8.0 \times 10^{-7}$ $cm^2 \cdot s^{-1}$, which is within the range of reported values.[3,4] In each timestep, a portion of UT in each voxel was allowed to transform into either decomposed tissue (DT) or fixed tissue (FT) via autolysis[5] and protein cross-linking[6], respectively. The rates of these processes were governed by rate constants and depended on the local concentrations of UT, FT, DT, formaldehyde, and autolytic enzyme. The $T_2$ of each voxel was then calculated based on the state of the tissue (UT, FT, and DT composition) for each point in time. The simulated changes in $T_2$ throughout the hemisphere were then compared to the actual $T_2$ changes that had been observed previously.[2]

**Results & Discussion:** The simulated patterns of $T_2$ change were very similar to experimental results[2] (Fig. 1). The main difference was that the changes occurred approximately twice as fast in the simulations compared to experiments, probably because the simulations treated the hemisphere as a homogeneous mass and also did not account for changes in the diffusion coefficient over time. However, experimental results and simulations showed the same behaviors for $T_2$ values both near the edge of the hemisphere and in deep tissue. Near the edge of the hemisphere, $T_2$ values dropped rapidly and then stabilized within days postmortem (Fig. 2). In the deep tissue of the hemisphere, $T_2$ values also decreased, but took approximately two weeks rather than days to reach a minimum. According to simulation results, the $T_2$ decrease was caused by the conversion of UT to FT (i.e., formation of protein cross-links) shortly after death (Fig. 3). The protein cross-links confer rigidity to the tissue, reducing the mobility of water molecules[7] and reducing $T_2$ values. Simulations also showed that formaldehyde was delayed in reaching the deepest parts of the tissue because of its relatively far distance from the surface, and consumption of the fixative by more superficial tissue. Therefore, the rate of fixation in deep tissue was slow compared to tissue near the surface. Additional decomposition during this slow fixation led to an increase in DT (Fig. 3) and allowed the water molecules to become more mobile, leading to the gradual increase in $T_2$ (Fig. 2). This $T_2$ increase has also been observed experimentally (Fig. 1). Finally, the deep tissue $T_2$ values reached a plateau by approximately six weeks of fixation (Fig. 2), after the simulated values of UT, FT, and DT had largely stabilized (Fig. 3). The models used to simulate formaldehyde fixation in this study provide insight to the possible mechanisms of $T_2$ change at different locations in the hemisphere over time. Therefore, in studies that combine histology and postmortem MR imaging of human brain hemispheres, it may be possible to account for the time dependent and location dependent variations of the MR properties of the tissue using models such as this one.

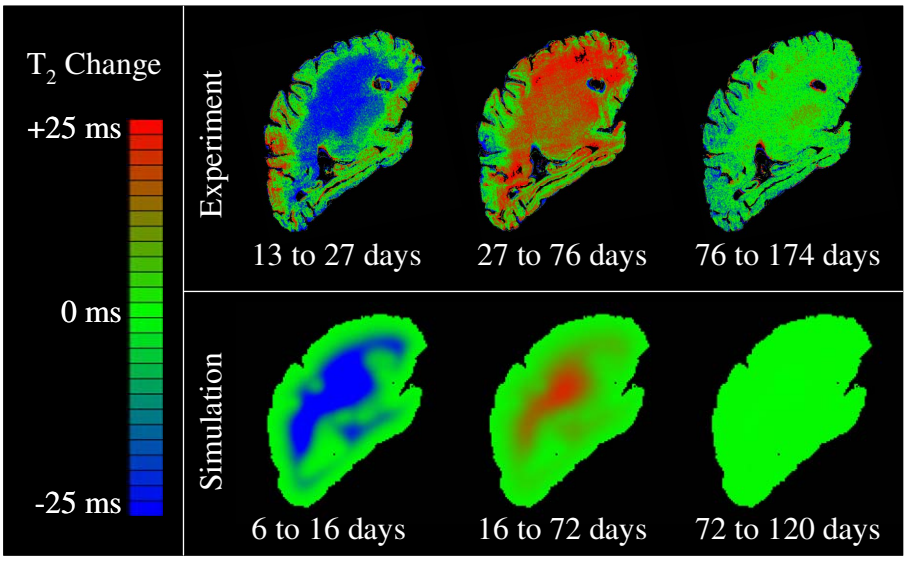


**Figure 1.** $T_2$ difference maps for experiment[2] versus simulation in the same hemisphere. The color blue is used to indicate a decrease in $T_2$ over the time period of interest, while red shows $T_2$ increase and green shows little or no change in $T_2$, according to the scale at left. The time period of interest appears below each image in days postmortem. For example, from 6 to 16 days postmortem, the simulated $T_2$ values decreased by at least 25 ms in the deep tissue regions of the hemisphere. Although the timescales differ, the patterns of $T_2$ change are similar between the experimental and simulated results.

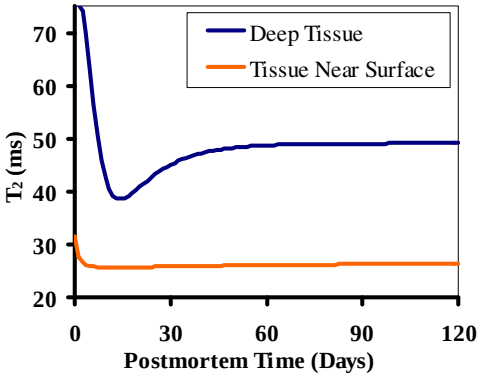


**Figure 2.** Simulated changes in $T_2$ over time at locations near the surface of the hemisphere and in the deep tissue.

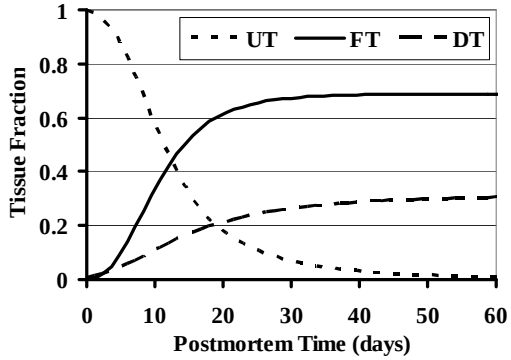


**Figure 3.** Simulated changes in unfixed tissue (UT), fixed tissue (FT), and decomposed tissue (DT) over time at a deep location in the hemisphere.

**References:**

[1] Yong-Hing CJ, et al., MRM 2005;54:324-332. [2] Dawe RJ, et al., Proc. ISMRM 2008, 882. [3] Start RD, et al., J Clin Pathol 1992;45:1120-1121 [4] Baker JR, The reactions of fixatives with proteins, 1958. [5] D'Arceuil H, de Crespigny A, NeuroImage 2007;36:64-68. [6] Puchtler H and Meloan SN, Histochemistry 1985;82:201-204. [7] Kennan RP, et al., J Magn Reson 1996;110:267-277.