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Rheology of Irradiated Alginate-Gelatin Hydrogel

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ABSTRACT

3D bioprinted tumor models, composed of cells embedded in a hydrogel, are beginning to be used in radiobiology research. However, the impact of ionizing radiation on the rheological properties of hydrogel models remain largely unexplored. Hence, the purpose of this study is to investigate how high dose radiation alters the rheological properties of a hydrogel sample.

Hydrogels were prepared in the shape of a flat disc. One group served as the control (0 Gy), and the other was irradiated (60 Gy) using spatially fractionated or uniform dose. Rheological measurements of the storage (elastic) and loss (viscous) moduli of the hydrogel were made over frequency and amplitude sweeps. The moduli were plotted over each sweep and compared between experimental and control samples. The ratio of the loss modulus to the storage modulus, the tan(delta), was computed.

A decrease was found in the storage modulus for low and moderate oscillation amplitudes in experimental samples, $p < 0.01$. Additionally, a decrease in tan(δ) was found at a specific amplitude, $p < 0.05$.

These results indicate that high doses of x-ray radiation decrease the storage modulus of an alginate-gelatin hydrogel at moderate amplitudes, and that these high doses decrease the propensity of the hydrogel to become viscous under high stresses. To the extent to which hydrogels represent the tissue microenvironment, these results may extend to real tissues.

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INTRODUCTION

- Radiotherapy (RT) is a prominent cancer treatment modality, being used in ~50% of all cancer cases
- Advanced and emerging modalities such as stereotactic body radiotherapy (SBRT) spatially fractionated radiotherapy (SFRT), and FLASH deliver high doses of radiation per fraction
- These radiation doses could impact the viscoelastic properties of the tumor, which in turn could impact treatment effectiveness[1]
- Abundant research exists on the biological and chemical effects of radiation on 2D monolayer and 3D spheroid tumor models.[1] However, no study has reported on the rheological effects of radiation
- This study examines the rheological effects of x-ray radiation on hydrogel models. Conventional and SFRT radiation types were used

METHODS AND MATERIALS

- Hydrogel was made by mixing 1% alginate and 7% gelatin powders in Dulbecco's phosphate-buffered saline (DPBS)[2,3]
- It was stored overnight and pipetted into a well-plate lid acting as a mold, forming disks
- The discs were crosslinked in the wells with 3% calcium chloride for 8 minutes
- Samples were divided randomly into control and experimental samples
- Experimental samples were irradiated to a uniform 60 Gy dose while control samples rested at room temperature
- Storage modulus (G') and loss modulus (G'') were measured over frequency and amplitude sweeps using a DHR-3 Digital Hybrid Rheometer
- We also computed tan(δ) = G''/G'
- X-ray doses confirmed by film dosimetry

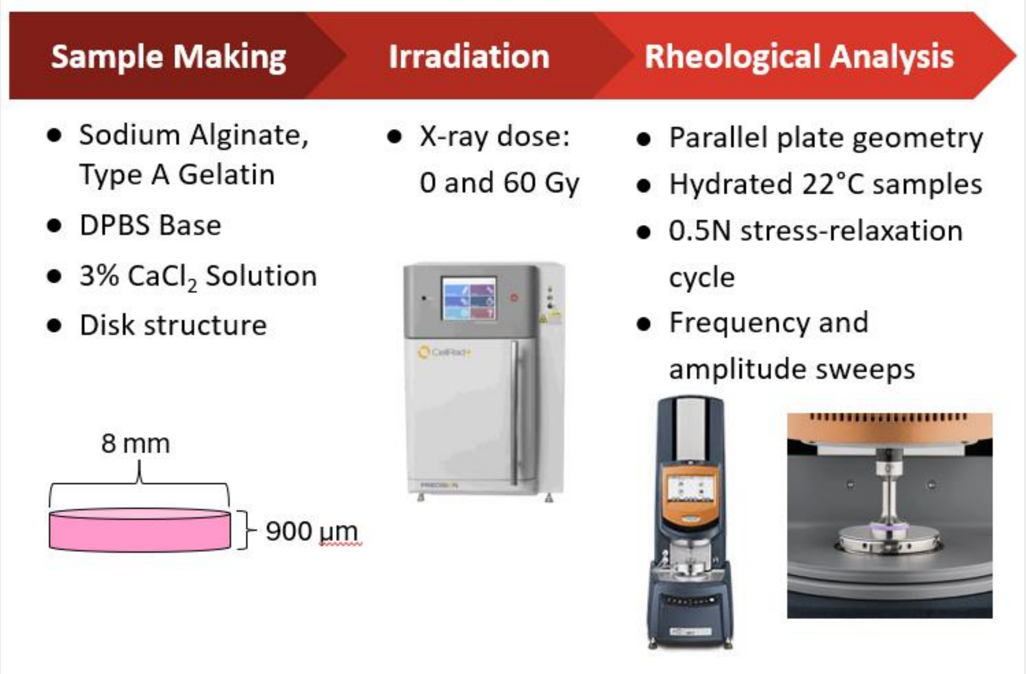

Figure 1. Workflow

RESULTS

- Plots of the storage modulus and tan(δ) against the amplitude of the oscillations are shown in Figs. 2 & 3
- Frequency sweeps were not found to contain statistically significant differences between the irradiation and control samples
- Results are from a total of 9 control and 11 experimental samples and three distinct biological replicates

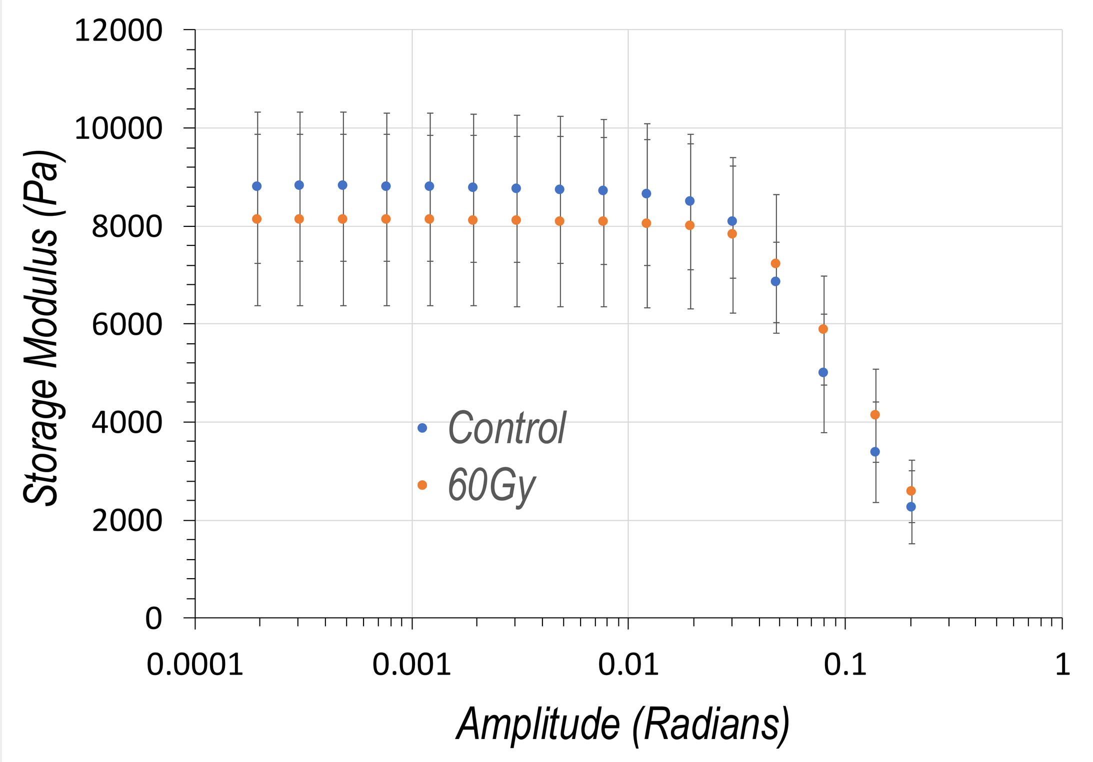

Figure 2. Storage modulus as a function of oscillation amplitude. Bars represent standard deviation from the mean.

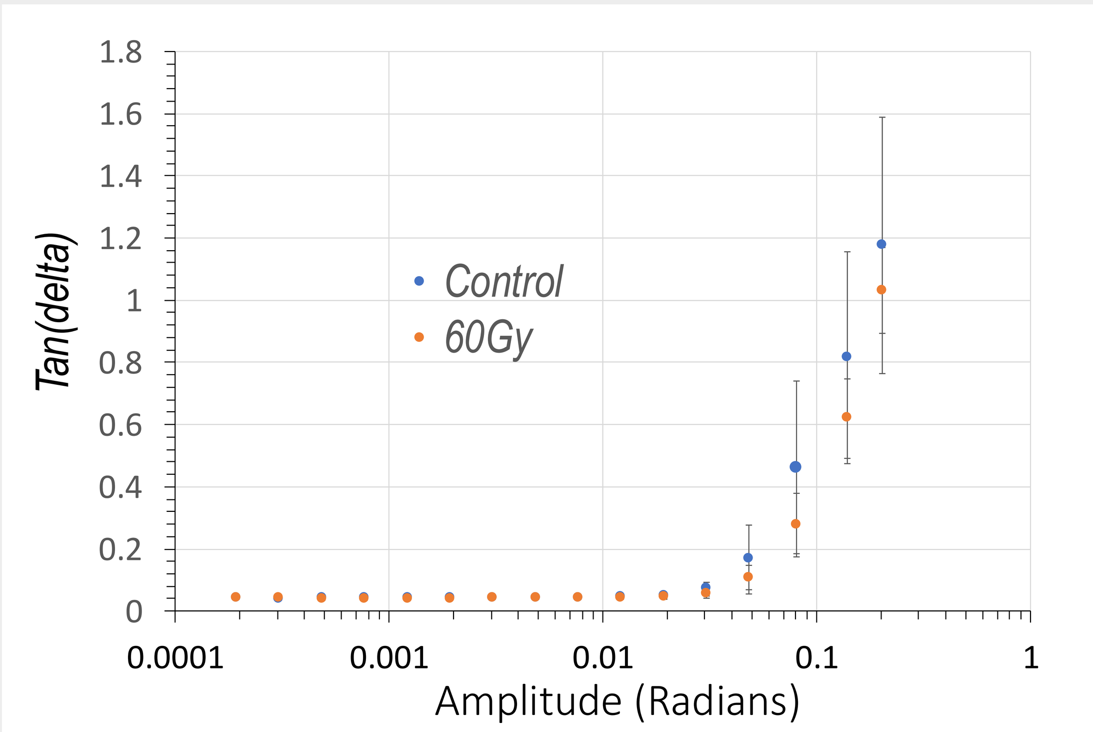

Figure 3. Tan(δ) as a function of oscillation amplitude. Bars represent standard deviation from the mean.

Sample type	Storage modulus, G' (Pa)	Loss modulus, G'' (Pa)	Tan(δ)
Control	8540 ± 440	400 ± 30	0.047 ± 0.004
60 Gy	8270 ± 590	370 ± 30	0.045 ± 0.005

Table 1. Average rheological parameters over frequency sweeps. Values are reported as mean ± standard error.

DISCUSSION

- Storage modulus of irradiated samples decreased at low and moderate amplitudes ($p < 0.01$) between amplitudes of 3.0×10^{-4} radians and 1.2×10^{-2} radians (Fig. 2)
- Average magnitude: 8.1% or 680 Pa
- Decrease seen in tan(δ) at the specific amplitude 1.9×10^{-2} radians ($p < 0.05$) and by average magnitude 13% (fourth point from the right on Fig. 2)
- Fig. 3 indicates that this trend is a result of delayed response to increasing amplitude in irradiated samples seen in adjacent points
- Limitations of our methodology include lack of spatial measurement, and some inter-sample variation in construction

CONCLUSIONS

- X-ray radiation leads to a decrease in the storage modulus of the alginate-gelatin hydrogel under moderate amplitude oscillations
- This radiation leads to a sample that is slower to deform and become viscous-dominant under high-amplitude oscillations
- Findings may extend to real tissues

FUTURE WORK

- Cells will be incorporated into the hydrogel models
- Validation will be performed using real tumors

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