MULTISCALE COMPUTATIONAL MODELS FOR PREDICTING HYDROGEL VISCOELASTIC PROPERTIES

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Introduction

Predicting hydrogel mechanical behaviour is essential to precisely control and guide cell behaviour [1]. Since hydrogel viscoelastic behaviour is strongly related to the interaction of liquid molecules with the solid network, different mathematical models have been proposed to simulate transport phenomena in gels. However, most of them present limitations such as the lack of correlation with gel viscoelastic properties or do not provide experimental validation [2]. We propose a versatile computational model to predict agarose hydrogel viscoelastic behaviour with tunable liquid phases thanks to the presence of soluble polysaccharides such as dextran, which is known to react mainly with water molecules [3], and hyaluronic acid (HA), a component of the extracellular matrix which also binds to polymeric network [4].

Methods

Agarose hydrogels were modelled as a homogeneous porous system, while the viscous phase (with dextran or HA) was considered as a spherical agglomerate linked to the water molecules and the agarose fibres in the case of HA. The liquid phase movement was described using the reaction-diffusion equation (eq.1), introducing an apparent diffusion coefficient D_{app} (eq.2) which adapts the Einstein-Stokes coefficient D_0 through additional coefficients: • β considers the obstacle imposed by the porous matrix using the permeability (κ) and the hydrodynamic radius (R_h); • δ includes the correlation between diffusive and mechanical properties through the average mesh size ξ_{avg}. They were derived by combining Brinkmann's theory of hindered diffusion in porous media [5], Flory's theory of rubber elasticity and the Amsden obstructing-scaling model [6].

$$\frac{\partial c}{\partial t} = D_{app} \cdot \nabla^2 c - c \cdot \nabla v - v \cdot \nabla c - k_r c_{vm} \quad (1)$$

$$D_{app} = \beta(R_h, \kappa) \cdot \delta(\xi_{avg}) \cdot D_0 \quad (2)$$

Modified Maxwell Standard Linear Solid (SLS, fig.1A-B) lumped parameter models were used to describe hydrogel mechanics reflecting dextran and HA interaction respectively with the viscous phase and with both solid and liquid phase. The model equations in the time domain were used to fit the experimental data obtained from the hydrogel mechanical characterisation using the epsilon dot method, deriving the instantaneous and equilibrium elastic modulus, and the relaxation time (τ_{rel}) [3]. The dextran/HA-water reaction was expressed as a first-order equation as a function of the free polysaccharide concentration (c_{vm}). The model was implemented on Matlab 2022a and Simulink, and the results were optimised on the experimental data, using the least squares method.

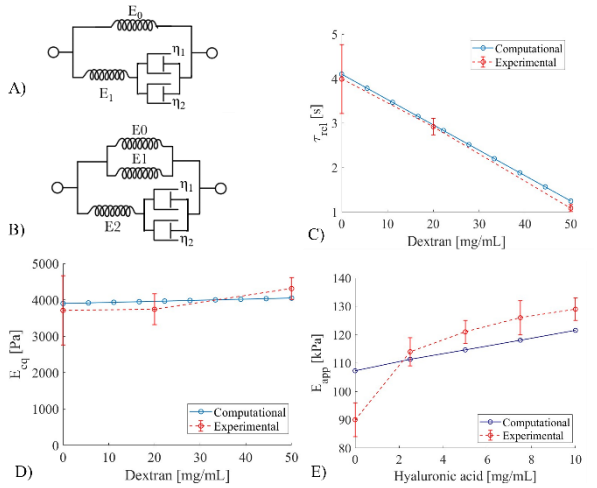

Figure 1. SLS models for A) dextran and B) HA-agarose hydrogels; C) τ_{rel} and D) E_{eq} of dextran-agarose hydrogels; D) HA-agarose gel apparent elastic modulus.

Results

The comparison of computational and experimental E_{eq} and τ_{rel} data confirmed the model capability to predict the hydrogel mechanical behaviour in the presence of different c_{vm} in the liquid phase. Despite the increase in dextran concentration and hence liquid phase viscosity, the mesh size ξ_{avg} increases leading to the decrease of τ_{rel} (fig.1C), while the E_{eq} constant trend (fig.1D) assesses the dextran effect only on the viscous properties' modulation. Mechanical analyses are ongoing to validate the model in the case of HA; however, preliminary tests (fig.1E) suggested that the predicted values for E_{app} are comparable with the experimental ones [5].

Conclusion

The presented computational framework resulted effective in predicting gel transport properties' effect on viscoelastic features. In the future, the model will be adapted to other material combinations and coupled with in silico descriptions of cell response to the mechanical stimuli [1] to provide a useful tool for the design of hydrogels for regenerative medicine applications and advanced in-vitro models.

References

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