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On the influence of microscopic architecture elements to the global viscoelastic properties of soft biological tissue

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ABSTRACT

In this work we introduce a 2D minimal model of random scale-invariant network structures embedded in a matrix to study the influence of microscopic architecture elements on the viscoelastic behavior of soft biological tissue. Viscoelastic properties at a microscale are modeled by a cohort of basic elements with varying complexity integrated into multi-hierarchic lattice obeying self-similar geometry. It is found that this hierarchy of structure elements yields a global nonlinear frequency dependent complex-valued shear modulus. In the dynamic range of external frequency load, the modeled shear modulus proved sensitive to the network concentration and viscoelastic characteristics of basic elements. The proposed model provides a theoretical framework for the interpretation of dynamic viscoelastic parameters in the context of microstructural variations under different conditions.

1. Introduction

Dynamic elastography can non-invasively measure the distribution of viscoelastic constants in biological soft tissues [1,2]. Time-harmonic dynamic stimuli of body tissue are primarily used by magnetic resonance elastography (MRE) for the measurement of the complex shear modulus G^* and its dispersion-relation to frequency [3,4]. There is growing evidence that G^* measured by elastography is sensitive to the tissue's architecture on multiple scales from single-cell rigidity up to larger tissue building blocks and their engagement into the macroscopic morphology of organs and tissues [5–8].

The mathematical description of microscopically heterogeneous media, such as biological tissue, is challenging. First, solving equations with spatially distributed parameters is generally difficult. Second, and most importantly, it is usually impossible to even specify the constitutive equations based on the precise geometric configuration of the viscoelastic network. Even if local solutions to the constitutive equations can be found, the high number of free parameters would render such a solution impractical. Instead, the description of tissue viscoelasticity on a statistical basis might better remodel the origin of the signal in elastography.

In a previous study, we used a multi-scale effective-medium model inspired by random micro-structures in soft biological tissues to analyze the viscoelasticity parameter dispersion observed in biorheology and elastography [9]. Our current work expands this theoretical framework on different local constitutive models to provide a link between the macroscopical viscoelastic properties [10–13] to viscoelastic constants and network geometry on the microscale.

The theoretical fundamentals of our approach were originally developed to describe effective physical properties in disordered media (see, for example, [14–16]). Adopting these methods, we assume that randomness is presented throughout all scales of tissue structure. Although tissues are clearly not randomly organized (e.g. brain, muscle), the topology of their viscoelastic elements (connective tissue immersed in the body fluids) can be considered random with respect to specific positions and local properties. The principle of local randomness at multiple scales implies the applicability of mathematical methods within the realm of self-similar geometries.

In this study, a general coarse-graining (CG) multi-scale approach is used to integrate basic viscoelastic elements (BE), namely the *Voigt and Maxwell*; *fractional springpot* and *fractional Voigt*; *generalized Maxwell* and *standard linear solid* into self-similar networks, and the global viscoelastic response of the effective medium was analyzed. Therewith we aim to predict results of dynamic elastography and to provide an interconnection between effective-medium viscoelastic constants and structure-related

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parameters such as network density and small-scale basic matrix properties.

2. Physical model of viscoelasticity

The complexity of the microscopic structure of biological tissues given by the heterogeneity of viscoelastic properties and geometrical irregularity of the mechanical network results in nonlinear constitutive laws and nontrivial dynamics. Still, the local relationship between the tensors of stress σ_{fk} and strain ε_{fk} is given by Hook's law [17]

$$\sigma_{fk} = G^{*}\left(\omega, \vec{r}\right)\varepsilon_{fk}, \tag{1}$$

where the real-valued elastic modulus was transformed to the complex-valued G^{*} according to principles of correspondences:

$$G^{*}\left(\omega, \vec{r}\right) = G'\left(\omega, \vec{r}\right) + i\,G''\left(\omega, \vec{r}\right). \tag{2}$$

$G'\left(\omega, \vec{r}\right)$ and $G''\left(\omega, \vec{r}\right)$ denote the storage and loss moduli, respectively, with ω and $\vec{r}$ being the angular drive frequency and the position vector.

A fundamental question is how specific complexity features manifest themselves in the global dispersive dynamics. Studying dispersive viscoelasticity therefore, is a way to characterize the type of structural disorder of network in a composite sample. Here we consider a class of viscoelasticity, caused by extended networks which regulate the stiffness of biological tissue, and the possibility of elastic wave propagation. Networks can introduce significant long-range correlations into the biological sample. These correlations give rise to distinct viscoelastic features, qualitatively different from those due to short-range disorder, which is a default assumption in the traditional models of small perturbations [18].

We assume that the external stationary shear load is periodically applied along one border surface and zero displacement on the opposite side is considered. The load is characterized by a frequency $\omega = 2\pi/T$ with period of motion T. The balance of all forces in the vicinity of the location $\vec{r}$, and in the absence of external body forces, assumes a conservation law [19] which may be solved by numerical methods if boundary condition and material constants are known. If we introduce a regular square mesh to a set of nodes $\left\{\vec{r}_k\right\}$, located in $2D$ Euclidean space at distances $a = \left|\vec{r}_l - \vec{r}_m\right|$, $a =$ const and with (lm) chosen as closest neighbors, then the conservation law expressed in finite differences yields a system of linear equations of displacements $u_l = u\left(\vec{r}_l\right)$ at nodes $\vec{r}_l$:

$$\mathbf{G}\cdot\vec{u} = \vec{c}. \tag{3}$$

$\vec{c}$ denotes the external force which is zero but on the boundary, $\vec{u} = (u_1, \ldots, u_l, \ldots, u_m, \ldots, u_N)^{*}$ is a vector-column of displacements. Eq. (3) in a bra-and-ket notation [20] may be expressed as

$$\vec{u} = \sum_{m=\overline{1,N}} |1_m\rangle\, u_m \tag{4}$$

and

$$\mathbf{G} = \sum_{l,m=\overline{1,N}} |1_l\rangle \otimes \langle 1_m| \left(\delta_{lm}\sum_{k=1}^{z} G^{*}_{(lk)} - G^{*}_{(lm)}\right), \tag{5}$$

where δ_{lm} is the Kronecker delta and $\otimes$ denotes the outer product. In Eq. (5) $G^{*}_{(lm)}$ is the shear modulus of viscoelastic element between the closest nodes l and m. We define the node coordination number, z, as the number of links involved in the node, which is e.g. in a regular square mesh $z = 4$ for bulk nodes and $z = 3$ for surface nodes. N is the number of nodes within the lattice excluding boundaries. In Eqs. (4), (5) orthonormal properties for the basis bra-and-ket functions are taken into account.

The distribution of displacements at nodes in a random network may be due to both global external and local internal fields [21] where the first increases the displacements regularly by a constant amount per row of nodes, while the second imposes random displacements whose average over significantly large regions converges to zero. Thus a solution of (3) can be found as

$$\vec{u} = \mathbf{G}^{-1}\cdot\vec{c} \tag{6}$$

with $\mathbf{G}$ split into regular and irregular parts as $\mathbf{G} = \mathbf{G}_{\rm reg} - \mathbf{G}_{\rm irreg}$. Factoring out $\mathbf{G}_{\rm reg}$ we obtain:

$$\mathbf{G} = \mathbf{G}_{\rm reg}\left(\mathbf{I} - \mathbf{G}_{\rm reg}^{-1}\cdot\mathbf{G}_{\rm irreg}\right), \tag{7}$$

with $\mathbf{I}$ being the unit matrix. Suppose that shear modulus of the uniform medium characterized by $\mathbf{G}_{\rm reg}$ is $G^{*,\rm eff}$. Then the bra-and-ket notation of $\mathbf{G}$ in a closest neighbor approximation gives:

$$\mathbf{G}_{\rm reg} = \sum_{l,m=\overline{1,N}} |1_l\rangle \otimes \langle 1_m|\, G^{*,\rm eff}\left(z\delta_{lm} - (1-\delta_{lm})\,\Delta_{lm}\right), \tag{8}$$

where $\Delta_{lm} = \{0, 1\}$ (if nodes l and m are nearest neighbors $\Delta_{lm} = 1$, otherwise $\Delta_{lm} = 0$) and

$$\mathbf{G}_{\rm irreg} = \sum_{l,m=\overline{1,N}} \left(G^{*,\rm eff} - G^{*}_{(lm)}\right)\left(|1_l\rangle - |1_m\rangle\right)\otimes\left(\langle 1_l| - \langle 1_m|\right). \tag{9}$$

In Eq. (9) only not paired terms, e.g. $|1_l\rangle\otimes\langle 1_m|$ with $l \neq m$, give contribution to exclude self-coupled effects.

If fluctuations of irregular displacements are small and the matrix norm satisfies $\left\|\mathbf{G}_{\rm reg}^{-1}\cdot\mathbf{G}_{\rm irreg}\right\| < 1$ the series expansion for evaluation of $\mathbf{G}^{-1}$ can be represented as:

$$\mathbf{G}^{-1} = \mathbf{G}_{\rm reg}^{-1}\left(\sum_{n=\overline{0,\infty}}\left(\mathbf{G}_{\rm reg}^{-1}\mathbf{G}_{\rm irreg}\right)^{n}\right). \tag{10}$$

From (7) and (10) we see that $\left\langle\mathbf{G}^{-1}\right\rangle$ is given by $\mathbf{G}_{\rm reg}^{-1}$ with corrections and the optimal choice of $G^{*,\rm eff}$ can be done only if

$$\left\langle\mathbf{G}_{\rm irreg}\right\rangle = 0, \tag{11}$$

where spatial averaging $\langle\ldots\rangle$ is performed over a large region of a sample of size L.

For large fluctuations the condition of expansion (10) is violated. In this case we assume a scale hierarchy in irregular part, $\mathbf{G}_{\rm irreg}$, and perform a sequence of scale averages to achieve condition Eq. (11) with best fitted $G^{*,\rm eff}$. After a number of coarse-graining steps:

$$\left\langle\mathbf{G}_{\rm irreg}\right\rangle\Big|_{l_1} > \cdots > \left\langle\mathbf{G}_{\rm irreg}\right\rangle\Big|_{l_k} > \cdots > \left\langle\mathbf{G}_{\rm irreg}\right\rangle\Big|_{l_n} \to 0, \tag{12}$$

where l_k is a current k-th scale within the sample for averaging and $L > \cdots > l_k > \cdots > l_1 > a$.

Such an approach defines a multiscale effective medium approximation to represent the average effects of the randomly built network. Thus, according to our hypothesis, the extra field fluctuations possess scaling properties and tend to zero after a number of averages depending on the network concentration. The mathematical technique of successive scale by scale averaging on the basis of recurrent laws is discussed below.

Suppose that for a local link binary probability density function, we can use [22]

$$\rho\left(G^{*}_{(lm)}\right) = p\,\delta\left(G^{*}_{(lm)} - G^{(1)}\right) + (1-p)\,\delta\left(G^{*}_{(lm)} - G^{(2)}\right), \tag{13}$$

as appropriate to the random network models. $G^{(1)}$ is a local network parameter and $G^{(2)}$ is a parameter characterizing a matrix,