# Lung tissue viscoelasticity: a mathematical framework and its molecular basis

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**Suki, Béla, Albert-László Barabási, and Kenneth R. Lutchen.** Lung tissue viscoelasticity: a mathematical framework and its molecular basis. *J. Appl. Physiol.* 76(6): 2749–2759, 1994.—Recent studies indicated that lung tissue stress relaxation is well represented by a simple empirical equation involving a power law, $t^{-\beta}$ (where $t$ is time). Likewise, tissue impedance is well described by a model having a frequency-independent (constant) phase with impedance proportional to $\omega^{-\alpha}$ (where $\omega$ is angular frequency and $\alpha$ is a constant). These models provide superior descriptions over conventional spring-dashpot systems. Here we offer a mathematical framework and explore its mechanistic basis for using the power law relaxation function and constant-phase impedance. We show that replacing ordinary time derivatives with fractional time derivatives in the constitutive equation of conventional spring-dashpot systems naturally leads to power law relaxation function, the Fourier transform of which is the constant-phase impedance with $\alpha = 1 - \beta$. We further establish that fractional derivatives have a mechanistic basis with respect to the viscoelasticity of certain polymer systems. This mechanistic basis arises from molecular theories that take into account the complexity and statistical nature of the system at the molecular level. Moreover, because tissues are composed of long flexible biopolymers, we argue that these molecular theories may also apply for soft tissues. In our approach a key parameter is the exponent $\beta$, which is shown to be directly related to dynamic processes at the tissue fiber and matrix level. By exploring statistical properties of various polymer systems, we offer a molecular basis for several salient features of the dynamic passive mechanical properties of soft tissues.

stress relaxation; tissue viscance; tissue elastance; modeling; fractional derivatives; fibers; micromechanics; polymer systems

VISCOELASTICITY is a macroscopic property of matter. It is often referred to as a mechanical behavior that combines liquidlike and solidlike characteristics. In contrast to perfect elasticity, viscoelastic substances do not maintain a constant stress under constant deformation, but the stress in the material slowly relaxes, a phenomenon called stress relaxation. Alternatively, under constant stress the material undergoes a continuous deformation in time or creep. The relationship between stress and strain is called the constitutive equation, which contains information on the underlying mechanisms and structure contributing to such a behavior (8, 14).

Soft biological tissues are known to be highly viscoelastic in nature (14). In particular, lung tissues have been recognized to be viscoelastic as early as 1939 by Bayliss and Robertson (4) and later by Mount (38) in 1955. Subsequently several groups studied the stress relaxation and the hysteretic properties of the lungs (33, 44), and an attempt to explain the results using spring-dashpot networks was given by Sharp et al. (45). An extensive evaluation of lung viscoelasticity in human and in isolated cat lungs was presented in the early 1970s by Hildebrandt (26, 27) and Bachofen (1), respectively. Hildebrandt observed that the pressure (P) across the lung tissue in response to a step volume (V) change decreased almost perfectly linearly with the logarithm of time through at least two decades of time (26). Consequently he described the stress relaxation data in the lung as

$$P/V = A - B \ln(t) \quad (1)$$

where $t$ is time and $A$ and $B$ are parameters. He also measured the hysteresis area of the P-V curve (i.e., the amount of energy dissipation) during sinusoidal oscillations and found it to be nearly independent of frequency. Hildebrandt (27) and recently Mijailovic et al. (36) also pointed out that *Eq. 1* can only be an approximation to the true relaxation function. In a related modeling study, Hildebrandt (25) also found that for a rubber balloon the stress relaxation function followed a power law dependence on time

$$P/V = at^{-\beta} + b \quad (2)$$

where $a$, $b$, and $\beta$ are constants.

Recently similar models have been rediscovered mainly in the context of describing oscillatory behavior of lung tissue. Hantos et al. (23) fitted the following equation to the low-frequency input impedance (Z) of lung tissue measured in rats

$$Z(\omega) = \frac{G}{\omega^{\alpha}} - j\frac{H}{\omega^{\alpha}} \quad (3)$$

where $\omega = 2\pi f$ is the circular frequency, $f$ is the frequency, and $j$ is the imaginary unit. The parameters G and H represent the viscance and elastance, respectively, of the tissue at $\omega = 1$, and $\alpha$ is discussed below. They called the model a "constant-phase" model, since the phase of Z [i.e., $\tan^{-1}(-\mathrm{Im}\{Z\}/\mathrm{Re}\{Z\})$, where $\mathrm{Re}\{Z\}$ and $\mathrm{Im}\{Z\}$ denote the real and imaginary parts of Z, respectively] is independent of frequency, which implies a frequency-independent mechanical efficiency. In subsequent works Hantos and co-workers (19, 20, 22) showed that the Fourier transformation (FT) of *Eq. 2* used as a two-parameter model of lung tissue can fit Z from 0.125 to 5 Hz obtained in cat and dog lungs significantly better than a conventional Kelvin body or even the frequency domain equivalent of *Eq. 1*. They also pointed out that, in the frequency range applied, the asymptotic value $b$ in *Eq. 2* cannot be reliably estimated and that, when neglected, the FT of *Eq. 2* is exactly the constant-phase model with $\alpha = 1 - \beta$ in *Eq. 3*. In this case *Eq. 2* contains only two parameters ($a$ and $\beta$) and the following relationship holds between G, H, and $\alpha$

$$\alpha = \frac{2}{\pi} \tan^{-1}\left(\frac{H}{G}\right) \quad (4)$$

The parameter $\alpha$ is simply related to the hysteresivity index ($\eta$) recently introduced by Fredberg and Stamenovic (13) to characterize the hysteretic properties of the respiratory tissues. For the constant-phase model, $\eta$ is the ratio of G and H and hence is a trigonometric transform of $\alpha$ (see *Eq. 4*). The values of $\alpha$ for lung tissues may vary between 0.86 and 0.92, whereas for the chest wall tissues a range of 0.8–0.85 seems appropriate (3, 19, 22, 32). From the data of Gunst (17) one can derive an $\alpha$ range of 0.68–0.8 for tonically contracted airway smooth muscle. Thus $\alpha$ seems specific to the constituents as well as to the physiological state of the tissue in question. Because in most cases its value is close to unity, Re{Z} decreases almost hyperbolically with frequency. Thus, the dissipation or area of the hysteresis loop predicted by *Eq. 3* depends only slightly on frequency in accord with a number of observations (13, 14, 26, 27). Numerous studies have now used models based on *Eqs. 1–4* to describe viscoelastic properties of lung and respiratory tissues (3, 19, 20, 22, 23, 31, 32, 39, 41, 52). All these modeling efforts have confirmed that *Eqs. 1–4* are superior to the classic spring and dashpot systems.

### *Systems Admitting Power Law Relaxation or Constant-Phase Impedance*

The above arguments compel the question of why the simple power law relaxation (*Eq. 2*) and the constant-phase impedance (*Eqs. 3* and *4*) provide such superior descriptions of lung tissue dynamics. Is there a universality reflected in the form of the relaxation function and the value of $\alpha$ close to unity that is appropriate for many biological tissues? What kind of physical systems admit solutions similar to *Eqs. 2* and *3*? We present five different (but not necessarily exclusive) classes of input-output systems that can potentially lead to power law type of relaxation or constant-phase impedance.

*Class 1: nonlinear constitutive equation.* A nonlinear differential equation may have an $at^{-\beta}$ solution to a step input. Indeed, lung and respiratory tissues have been shown to behave nonlinearly, and several models have been proposed to account for their nonlinear mechanical behavior (14, 27, 39, 48, 49). However, because *Eq. 3* provided such a faithful fit to Z measured with small-amplitude forced oscillations (19, 22), it is unlikely that nonlinearity would be the primary mechanism responsible for the constant-phase behavior.

*Class 2: differential equations with time-dependent coefficients.* The mechanical properties of living tissues can change in time. However, the stress in excised lobes (26, 41) as well as in isolated tissue pieces (39) relaxes almost linearly on a logarithmic time scale. With an appropriate value of $\beta$, *Eq. 2* can also provide a linear decrease of P/V over many time decades (28). In fact, for rat lungs *Eq. 2* fits the stress relaxation better than *Eq. 1* (see below, Fig. 3). All these suggest that the power law relaxation and the constant-phase impedance are not due to time-varying processes.

*Class 3: continuous distribution of time constants that are solutions to integral equations.* Fung (14) introduced a linear model composed of many Kelvin bodies with a continuous distribution of their time constants. By appropriately choosing the distribution function he was able to mimic the constancy of the hysteresis loop area over many decades of frequency, from which it also followed that the stress relaxation function decreased linearly with the logarithm of time. Although this class of systems seems attractive, the form of the time constant distribution function is arbitrary and lacking a microstructural basis.

*Class 4: complex dynamic systems exhibiting self-similar properties.* Recently Bates and Suki (3) argued that the lung tissue might be viewed as a complex dynamic system. Because the scale-invariant behavior is so ubiquitous in nature, the stress relaxation is a consequence of the rich dynamic interactions among the different constituents of the tissues irrespective of their individual properties. Although such a theory is useful to capture aspects of the system that are difficult to describe by conventional tools, it does not immediately suggest which are the specific mechanisms that produce the particular behavior.

*Class 5: input-output relationships that include fractional derivates.* Although fractional calculus has not been applied in tissue biomechanics, there have been numerous attempts in a variety of fields to use it to describe viscoelastic properties of matter, especially those of polymers (2, 8, 10, 28, 42, 53). It has been shown that the relaxation function associated with a stress-strain relationship that involves a fractional derivative is of the form of *Eq. 2* (28). Although it may seem to be an unusual way of representing viscoelastic phenomena, when one limits the analysis to the linear case, it is possible to borrow many useful analogies from the theory of ordinary or integer-order differential equations (28, 42). In this paper one of our aims is to provide a mathematical framework for using relaxation functions and impedance models such as given by *Eqs. 2* and *3*. Hence, we resorted to the differential equations of fractional order because their solutions naturally lead to such functions. Finally, for certain polymer systems there exists a mechanistic basis of fractional derivatives in viscoelasticity arising from the microscopic behavior of polymers embedded in a solution or matrix (2).

### *Origins of Viscoelasticity*

The models of *Eqs. 2–4* provide very good macroscopic descriptions of soft tissue relaxation and impedance data. Nevertheless, they are currently perceived as empirical and therefore provide limited insight into the origins of viscoelastic behavior. We argue, however, that these relationships (*Eqs. 2–4*) may not be strictly empirical, as tissue viscoelasticity might be a consequence of the structural similarities between soft tissues and certain polymer systems. The molecular theories developed for the constitutive equations of polymers take into account the complexity and the statistical nature of the system at the molecular level. Such a description is especially attractive, because for polymer systems Bagley and Torvik (2) established the link between the empirical fractional cal-

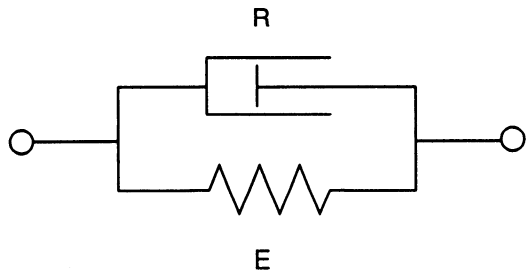


FIG. 1. Voigt body. $R$, dashpot coefficient; $E$, spring constant.

culus of viscoelasticity and molecular theories that can predict macroscopic stress relaxation. Interestingly, the stress relaxation function in many polymer systems is similar to *Eq. 2* with $\alpha$ ranging from 0.4 to 0.9 (2, 10), which covers the values of $\alpha$ (0.7–0.9) that are appropriate for the various tissues in the respiratory system. This is, however, not entirely surprising, since soft biological tissues are also composed of long and complicated biopolymers, which, in solutions, display similar rheological properties to synthetic polymers (34). Thus, we felt that exploring the universal properties of polymer systems may suggest a basis for the molecular origins of the dynamic passive mechanical properties of soft tissues.

In this paper we first summarize the basic concepts of linear viscoelasticity in terms of ordinary differential equations. Then we develop viscoelasticity in the framework of fractional calculus. Finally, we overview the most relevant theories of polymer dynamics that lead to constitutive equations involving fractional derivatives and show how the variables in these models are related to parameters arising from the molecular theories.

## EMPIRICAL THEORIES OF VISCOELASTICITY

### *Ordinary Derivatives in Viscoelasticity*

The simplest viscoelastic behavior occurs in a system possessing a perfectly elastic element, i.e., an elastic spring, mechanically in parallel with a purely viscous element, a dashpot. This model is called the Voigt body (Fig. 1) in which the stress ($\sigma$) across the system is the sum of the individual stresses across the spring and the dashpot (14)

$$\sigma(t) = E\,\epsilon(t) + R\,\dot{\epsilon}(t) \tag{5}$$

where $\epsilon$ is the strain, $E$ is the spring constant, $R$ is the viscosity coefficient of the dashpot, and the overdot denotes differentiation with respect to time. In the frequency domain such a relationship is expressed by multiplying the FT of the strain with $j\omega$; thus *Eq. 5* becomes

$$\sigma(\omega) = E\,\epsilon(\omega) + j\omega R\,\epsilon(\omega) \tag{6}$$

where the argument $\omega$ denotes the FT of the quantity. This system can store as well as dissipate energy, i.e., it is viscoelastic, but it does not show relaxation. An alternative is the Maxwell body in which the two elements are arranged in series so that the overall strain is the sum of the strains of the spring and the dashpot. The constitutive equation now includes the derivatives of both stress and strain (14), and this model is able to mimic stress relaxation. The relaxation function, however, contains only a single exponential, and the model does not show a realistic creep, the counterpart of relaxation. A more versatile arrangement is obtained by adding another spring in parallel with the Maxwell body. The result is the standard linear solid or Kelvin body (14), which is still inferior to the constant-phase model (*Eqs. 3* and *4*) in accounting for lung tissue impedance (19, 20, 22).

The standard linear solid can further be generalized to include $N$ discrete Maxwell bodies in parallel or Voigt bodies in series (8, 14). The corresponding differential equation contains time derivatives of both the stress and strain up to orders $N$ and $M$, respectively. Thus

$$\sum_{n=0}^{N} a_n D^n[\sigma(t)] = \sum_{m=0}^{M} b_m D^m[\epsilon(t)] \tag{7}$$

where $a_n$ and $b_m$ are parameters expressing the viscoelastic properties of the material and $\mathrm{D}^i(t) = \mathrm{d}^i/\mathrm{d}t^i$ is the differential operator of integer order $i$. In *Eq. 7* one parameter can be chosen arbitrarily. For example, by dividing both sides by $a_0$, we can introduce the equilibrium elasticity as $\mathrm{G_e} = b_0/a_0$. The complex modulus defined as the ratio of the stress to the strain in the frequency domain is the ratio of two ordinary polynomials in $j\omega$

$$\mathrm{g}(\omega) = \frac{\mathrm{G_e} + \sum_{m=1}^{M} c_m(j\omega)^m}{1 + \sum_{n=1}^{N} d_n(j\omega)^n} \tag{8}$$

where $c_m = b_m/a_0$, $d_n = a_n/a_0$, and $M \leq N$ for the modulus to behave properly at high frequencies. The relaxation function, $\mathrm{g}(t)$, associated with this complex modulus is the sum of $N$ decaying exponentials. The impedance of the system is then defined as

$$\mathrm{Z}(\omega) = \frac{\mathrm{g}(\omega)}{j\omega} \tag{9}$$

To characterize a given viscoelastic material one can fit *Eq. 8* or *9* directly to measured modulus or impedance data. This involves the determination of the orders $N$ and $M$, as well as the coefficients $\mathrm{G_e}$, $c_m$, and $d_n$. Another method is to match $\mathrm{g}(t)$ to describe the measured stress relaxation data. Both approaches require the estimation of multiple exponentials, which is usually an ill-posed problem. Moreover, neither case leads to power law type of relaxation (*Eq. 2*) or impedance (*Eq. 3*).

### *Fractional Derivatives in Viscoelasticity*

In this brief summary of the fractional calculus and its application to viscoelasticity we follow the lines of Bagley and Torvik (2), Koeller (28), and Rogers (42). These authors extensively discuss the tensorial formalism of both relaxation and creep. Because the currently available data on lung tissue mechanics are invariably in the form of pressure relaxation or volumetric impedance, we restrict our development to the one-dimensional case of relaxation and impedance. We start with the simplest form, which is analogous to *Eq. 5*, but with the time derivative of $\epsilon$ replaced by its fractional derivative of order $\beta$

$$\sigma(t) = \mathrm{E}\,\epsilon(t) + \mathrm{Q}\mathrm{D}^{\beta}[\epsilon(t)] \qquad (10)$$

where the second term is called a fractional calculus element, with Q being a viscoelastic parameter of the system that is examined later. The fractional derivative operator $\mathrm{D}^{\beta}$ is defined by (28)

$$\mathrm{D}^{\beta}[x(t)] = \frac{1}{\Gamma(1-\beta)}\frac{\mathrm{d}}{\mathrm{d}t}\int_0^t \frac{x(\tau)}{(t-\tau)^{\beta}}\,\mathrm{d}\tau \quad (0 \le \beta \le 1) \qquad (11)$$

where $\Gamma$ is the gamma function. For causality reasons it is required that $x(t)$ is zero for negative times. *Equation 11* seems rather complicated. It is instructive to compare *Eq. 11* to an ordinary derivative that provides information about the rate of change of the function $x(t)$ only at time $t$, i.e., the local slope of $x(t)$. In contrast, the physical meaning of *Eq. 11* is that the fractional derivative is proportional to the local slope of the convolution of $x(t)$ with a kernel function of the form $t^{-\beta}$. Because a convolution involves some kind of influence of the past into the present, we can already anticipate some memory function associated with the fractional derivative, i.e., it involves not only local properties in time. Indeed, on the one hand, for $\beta = 0$ *Eq. 11* reduces to $x(t)$ and the second term in *Eq. 10* would be another elastic part with no memory. On the other hand, when $\beta \to 1$, one can show that *Eq. 11* becomes an ordinary derivative $\mathrm{d}/\mathrm{d}t$ (28) and the second term in *Eq. 10* reduces to a dashpot with perfect memory. Thus *Eq. 10* expresses that the stress is composed of an elastic part and a "viscoelastic" part determined by a fractional derivative. Let us now examine more closely how the latter contributes to the viscoelastic behavior. First, we calculate the FT of *Eq. 11*. The $\mathrm{d}/\mathrm{d}t$ operator introduces a $j\omega$ factor. The rest is a convolution so that its FT is the product of the FT of $x(t)$ and the FT of function of the form $t^{-\beta}$. The FT of the function $t^{-\beta}$ is $\Gamma(1-\beta)/(j\omega)^{1-\beta}$. Hence the FT of *Eq. 10* is

$$\mathrm{FT}\{\mathrm{D}^{\beta}[x(t)]\} = (j\omega)^{\beta}\mathrm{FT}[x(t)] \qquad (12)$$

which is completely analogous to the FT of an ordinary derivative of $x(t)$. From *Eq. 12* the impedance of the fractional derivative system defined by *Eq. 10* is obtained as

$$\mathrm{Z}(\omega) = \frac{E}{j\omega} + \frac{\mathrm{Q}}{(j\omega)^{\alpha}} \qquad (13)$$

where we have also used *Eq. 9*. Note that in the following both $\alpha$ and $\beta$ are used, keeping in mind that $\alpha = 1 - \beta$. Observing that $1/j$ can be expressed as $\exp(-j\pi/2)$, *Eq. 13* can be written as

$$\mathrm{Z}(\omega) = \frac{\mathrm{G}}{\omega^{\alpha}} - j\frac{\mathrm{H}}{\omega^{\alpha}} - j\frac{E}{\omega} \qquad (14)$$

where G and H are defined as

$$\mathrm{G} = \mathrm{Q}\cos\left(\frac{\pi}{2}\alpha\right) \qquad \mathrm{H} = \mathrm{Q}\sin\left(\frac{\pi}{2}\alpha\right) \qquad (15)$$

The dynamic or equivalent viscance (Vdyn) and elastance (Edyn) from *Eq. 14* are defined as

$$\mathrm{Vdyn}(\omega) = \mathrm{G}\omega^{\beta} \qquad E\mathrm{dyn}(\omega) = E + \mathrm{H}\omega^{\beta} \qquad (16)$$

Notice that the first two terms in *Eq. 14* are exactly those in *Eq. 3*. Furthermore, the inverse FT of Z is the impulse response in strain rate or the step response in strain; thus the relaxation function associated with *Eq. 10* is

$$\mathrm{g}(t) = \left[E + \frac{\mathrm{Q}}{\Gamma(1-\beta)}t^{-\beta}\right]\mathrm{h}(t) \qquad (17)$$

where $\mathrm{h}(t)$ denotes the unit step function. Now *Eq. 17* is formally the same as *Eq. 2*.[1] We note that, for any $t$ or $\omega$, when $\beta \to 1$ the second term approaches the delta function and hence *Eq. 17* reduces to the relaxation function of the Voigt body defined by *Eq. 5* (28). Thus the fractional derivative formalism also contains, as a special case, the classical spring-dashpot systems.

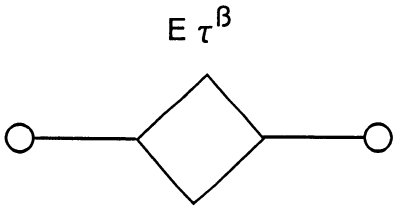


FIG. 2. Spring-pot (diamond shape; obeys *Eq. 18*) with its 3 parameters: $E$, characteristic time constant ($\tau$), and parameter describing memory of element ($\beta$).

The above brief introduction of the fractional derivatives to viscoelasticity is important in several ways. The fractional derivative constitutive equations have simple expressions for the relaxation function and impedance, yet they represent a fairly complicated rheological behavior that is often difficult to mimic with spring-dashpot systems. The previously discovered simple empirical relations thought to best describe stress relaxation (*Eq. 2*) and frequency dependence of lung tissue impedance (*Eq. 3*) are in fact natural solutions to the simplest differential equation of fractional order. Thus, fractional derivatives provide us a relatively simple concise mathematical framework for using the power law relaxation and the constant-phase impedance.

### *Fractional Derivative Models and Their Application to Lung Tissue*

It is instructive now to introduce a distinct fractional calculus element as defined by Koeller (28). By use of the dashpot coefficient $R$ and the spring constant $E$, the constitutive equation can be defined by

$$\sigma(t) = E\tau^{\beta}\mathrm{D}^{\beta}[\epsilon(t)] \qquad (0 \le \beta \le 1) \qquad (18)$$

where $\tau = R/E$ is a characteristic time constant of the system. The element obeying *Eq. 18* in Fig. 2 was termed a spring-pot because it contains both an ideal spring and a pure dashpot (28). Indeed, in the limiting cases when $\beta$ goes to 0 or 1, the stress-strain relationship is precisely that of a spring (e.g., the first term in *Eq. 5*) and that of a dashpot (e.g., the second term in *Eq. 5*), respectively. For any intermediate value of $\beta$ we obtain the constant-phase model (*Eq. 3*) or the second term of *Eq. 13* with $\mathrm{Q} = E\tau^{\beta}$.

[1] In the limit of $t = \infty$, *Eq. 17* reduces to its first term, which gives rise to solidlike behavior for long times. In the frequency domain, the limit $t = \infty$ is equivalent to $\omega = 0$ and a constant term $E$ appears in expression of dynamic elastance in *Eq. 16*. The second term in *Eq. 17* provides time-dependent features of relaxation function $\mathrm{g}(t)$. When $t \to 0$ (or $\omega \to \infty$), a single fractional element behaves as newtonian fluid, i.e., its contribution to $\mathrm{g}(t)$ approaches delta function.

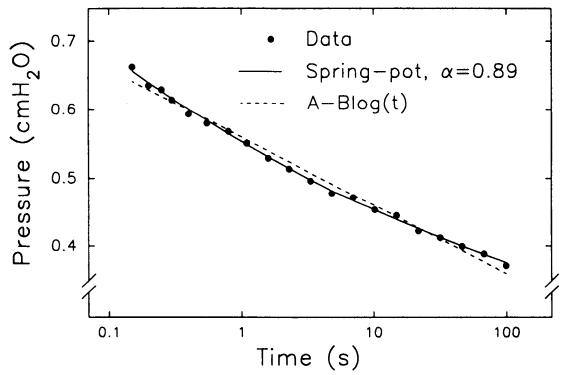


FIG. 3. Fits of power law relaxation (*Eq. 2*) and relaxation predicted by *Eq. 1* to stress relaxation in a rat lung taken from Peslin et al. (41). *A*, *B*, and $\alpha$, parameters; *t*, time.

In this case the material exhibits memory depending on the value of $\beta$; for example, when $\beta$ is ~0.1 (a value appropriate for lung tissue) the stress relaxes in the material almost linearly with the logarithm of time that extends over at least 10 decades of times (28). Figure 3 demonstrates that the fit provided by the spring-pot to stress relaxation data obtained in rat lung is excellent and superior to that provided by *Eq. 1* (root mean square errors of the spring-pot and *Eq. 1* are $3.69 \times 10^{-3}$ and $9.02 \times 10^{-3}$, respectively).

Because the dynamic viscance changes as a small power of frequency (*Eq. 16*), the underlying phenomenon also produces a hysteresis area of the stress-strain curve that is almost independent of frequency over several frequency decades. This is in agreement with published data in various tissues (1, 13, 14, 19–23, 26, 32, 39, 51, 52). Similarly, the dynamic elastance increases slowly and steadily with frequency over many decades (*Eq. 16*), giving rise to the apparent observation that lung tissue elastance increases quasi-linearly with the logarithm of frequency (13, 19–23, 26, 32, 39, 51, 52). Examples of the quality of the fits of the constant-phase model to the resistances and elastances of the lung tissue measured in a dog are shown in Fig. 4. In the control case $\alpha = 0.9$. In the histamine-challenged lung, however, $\alpha$ drops down to 0.74, indicating that it is sensitive to the physiological state of the tissue. In summary, in the time domain $\beta$ can be identified as a parameter controlling the memory of the material, whereas it is also the parameter that determines the frequency dependence of the dynamic elastance. The other parameters such as G, H, and *E* in *Eq. 14* or Q in *Eq. 17* must depend on the amount as well as the type of tissue involved. Finally, we also note that, in accord with the structural damping hypothesis postulated by Fredberg and Stamenovic (13), the formalism above inherently leads to an elementary coupling of elasticity and dissipation through *Eq. 15* in a frequency-independent manner. This postulate is supported by the molecular theories of stress relaxation described next because they lead to power law type of macroscopic relaxation functions.

## MOLECULAR THEORIES OF VISCOELASTICITY

Next we summarize several molecular theories of polymer viscoelasticity. We provide only the underlying basic assumptions on which these theories are built. It was not our intention to reproduce the mathematical derivations of the stress relaxation functions from the different theories. However, we report their final forms and critically discuss their relevance and implications to lung tissue mechanics.

### *Viscoelastic Properties of Polymer Systems: Rouse Theory*

The classic picture of random motion of long flexible chains in a solvent and the macroscopic viscoelastic properties of such solutions were first described by Rouse in 1953 (43). The basis of the theory is that a velocity gradient induced in the solution by external forces continuously alters the equilibrium distribution of the configurations of the polymer molecules. The long molecules are assumed to be composed of submolecules that are still long enough that the separation of their ends in space follows a three-dimensional gaussian probability distribution. These submolecules can be thought of as elastic springs consisting of a sequence of polymer monomers. The submolecules are in a coordinated thermal or Brownian motions, the driving force of which is the thermal energy (Fig. 5). In the presence of the velocity gradient the equilibrium distribution of the configurations is disturbed by pulling, squeezing, or bending the molecules. The Brownian motion, however, keeps going on, and the molecules try to drift back toward their equilibrium distribution. This represents an opposing effect against the external forces. Because the molecules are no longer dis-

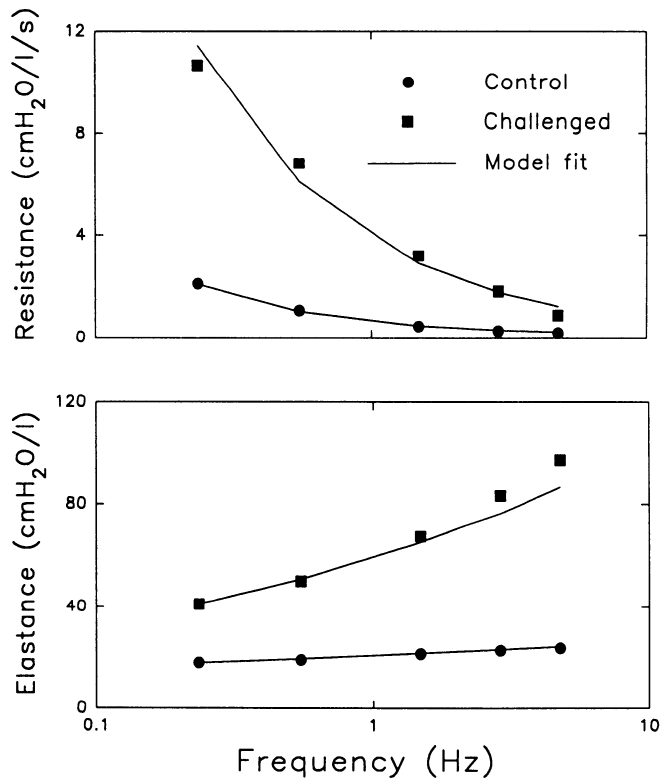


FIG. 4. Lung tissue resistance (*top*) and elastance (*bottom*) of anesthetized paralyzed dog as function of frequency in control state (●) and after 4 min of intravenous administration of constant infusion of histamine (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$; ■) from Lutchen et al. (32). Data points, average resistance and elastance values measured in 4 alveolar capsules. Solid line, fit of constant-phase model (*Eq. 3*).

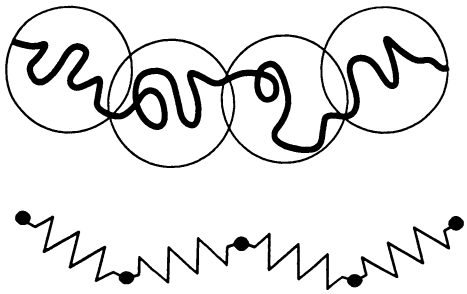

FIG. 5. Representation of random coiled macromolecule (*top*) by spring-bead model (*bottom*).

tributed over all possible configurations, the entropy is decreased and free energy is stored in the system. This is why the submolecules are also called entropy springs. The influence of the fluid is concentrated at the junctions of the submolecules, and the coordination of the motion of the entire polymer is achieved by requiring that the motion of the atom that joins the two submolecules changes the configuration of both submolecules. Because the junctions as spherical beads are moving in a viscous newtonian fluid while stretching elastic springs, one can anticipate energy storage as well as dissipation, i.e., a viscoelastic behavior. Rouse obtained a solution for the complex shear modulus of the system of $L$ number of submolecules in terms of $L$ normal or independent modes. Observing that the notion of a submolecule is somewhat arbitrary and artifactual, Bagley and Torvik (2) showed that Rouse's solution can be transformed into continuous form as

$$\sigma(t) = \mu_s \epsilon(t) + \left[\frac{3}{2}(\mu_0 - \mu_s)nkT\right]^{1/2} \mathrm{D}^{1/2}[\epsilon(t)] \quad (19)$$

where $\mu_0$ is the steady-flow viscosity of the solution, $\mu_s$ is the viscosity of the solvent, $T$ is absolute temperature, $k$ is Boltzmann's constant, and $n$ is the number of molecules per unit volume of the solution. *Equation 19* thus expresses that the stress in a dilute polymer solution is the sum of a newtonian term characteristic only of the solvent and a fractional derivative of order $\beta = 0.5$ of the strain history that provides the contribution of the long-chain molecules to the macroscopic stress.

Although the Rouse theory describes the dynamics of an isolated chain in a solution, it is instructive to examine the impedance of such a system. According to *Eq. 9* we obtain an exponent of $\alpha = 0.5$, whereas the evidence for lung tissue is that $\alpha$ is $\sim$0.9. The theory, however, was developed for polymer solutions, and it does not take into account *1*) interactions among far segments of the molecule; *2*) processes involving segments shorter than a submolecule; *3*) the self-avoiding character, which means that the molecules cannot cross each other; and *4*) polydispersity where the molecular weight distribution is not sharp; that is, all the molecules in the Rouse theory were assumed to possess exactly the same $L$ submolecules. There are a number of extensions of the Rouse theory, and they are summarized in the book by Ferry (8). The various corrections of the theory all lead to similar expressions of the shear modulus, but the different mechanisms (e.g., solvent features, cross-linking, intermolecular hydrostatic forces) may result in slightly different values of $\alpha$. Indeed, when the interactions among the submolecules are not limited to the two neighbors of each submolecule, the analysis leads to the Zimm (54) theory. In this model the exponent $\alpha$ depends on the solvent quality and takes the values of $^2/_3$ for a chain without interaction with the solvent and $^5/_9$ for a chain in a good solvent. Inserting a Rouse-like chain into a cross-linked polymer solid with a fixed network of cross-links adds a constant term (such as $E$ in *Eq. 17*) to the stress-strain relationship of *Eq. 19*, thereby providing the material a solidlike behavior (37). Finally, according to an alternative description by Hearst et al. (24), in which the polymer molecules can also resist bending forces (similar to the bending elasticity of flexible beams), $g(\omega)$ displays several decades of $\omega$ where both $\mathrm{Re}\{g\}$ and $\mathrm{Im}\{g\}$ are proportional to $\omega^{0.25}$. Combining this with the model of fixed cross-links (37) leads to macroscopic impedance and relaxation expressions similar to *Eqs. 13–17*, with $\alpha = 0.75$ and G and H (or Q) being dependent on the viscosity of the solution or matrix, the concentration of the fibers, and the temperature. This value of $\alpha$ is closer to 0.9, which is characteristic of lung tissue, and near the value of 0.8, which was found for the chest wall tissue (19).

### *Viscoelasticity of Polymers by Reptation*

The next significant step in the modeling of the dynamic properties of long linear polymers was due to de Gennes (15) in 1971, who released the non-self-avoiding condition of the Rouse model. He proposed that the chief relaxation mechanism in concentrated polymer melts is not due to Rouse-like modes but the so-called reptation. This process consists of the gradual disengagement of one long flexible chain from its environment by performing "wormlike displacements" inside a strongly cross-linked polymeric gel. The constrainments on the motion of the molecule consist of obstacles made up of the neighboring molecules that form a tubelike environment that the chain cannot intersect (Fig. 6). The only motion allowed is the curvilinear diffusion along its own contour associated with "defects" propagating through the chain.

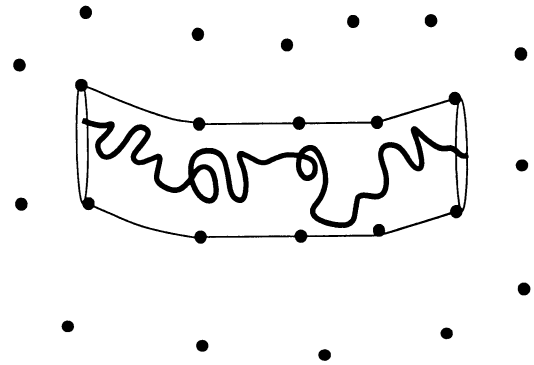

FIG. 6. Chain trapped in fixed network of obstacles created by other chains. Circles, topological constraints imposed on motion of chain by other molecules. Thin lines, effective tube in which chain is free to move.

Several predictions of the theory were in very good agreement with experimental results whenever the chain was longer than a critical length ($L_c$). For much shorter chains, the topological constraints on the motion are not important and the dominant relaxation mechanism is Rouse-like. For chains longer than $L_c$, the motion is extremely slow and gives rise to a different macroscopic relaxation process. In other words, for short time scales (or higher frequencies) the conformational changes of the chain are Rouse-like, whereas at longer times (or lower frequencies) the important behavior is that of reptation.

The macroscopic stress relaxation function due to reptation was derived by Doi and Edwards (7). When a polymer system undergoes a unit step change in deformation, the strain induces a distortion in the molecular conformation that creates stress that relaxes with time as the chains go back to their equilibrium state. As a result of the strain, the tube in which a chain is confined will also be deformed. At first the chain has to find its new internal conformation; this short time behavior is described by Rouse dynamics. Later, however, this motion is not important because it is constrained by the tube and reptation starts. The idea is that because the process of reptation takes over in a deformed environment or tube the remaining stress at any time $t$ will be proportional to the fraction of the chain that has not escaped by reptation from the deformed tube by time $t$. In other words, only those segments of the chain can support stress that are still in the orientation of the strain. The exact calculation yields the following relaxation function

$$g(t) = n\left(\frac{e}{d}\right)^2 kT \sum_{p;\text{odd}} \frac{8}{p^2\pi^2} \exp(-p^2 t/\tau_d) \qquad (20)$$

where the parameter $d$ is the effective tube diameter that depends on the meshwork size and is proportional to the square root of the density (7), the parameter $e$ is the distance between the submolecules, and $\tau_d$ is the principal relaxation time and is a function of $d$ and $e$.

Although the reptation theory successfully accounted for many aspects of polymer viscoelasticity, several features remained unexplained. For example, the theory does not agree with the experimentally obtained molecular weight dependence of $\mu_0$. Another problem is that the higher order terms do not contribute significantly to $g(t)$ because of their quickly decreasing amplitude (proportional to $1/p^2$). Although it has not been shown that *Eq. 20* can be transformed to a fractional derivative, simulation studies demonstrate (7) that there is a significant portion of the time scale where $g(t)$ decreases much slower than $t^{-0.5}$. Again one may speculate that the combination of reptation with bending rigidity of the chains would perhaps make $\alpha$ increase toward the 0.9 value appropriate for lung tissues. We believe that in the collagen-elastin network of lung parenchyma reptation can certainly contribute to macroscopic viscoelasticity. In this picture the G and H in *Eq. 14* would depend on meshwork size, fiber concentration, and the temperature.

*Further Mechanisms Contributing to Macroscopic Viscoelasticity*

The shortcomings of the above theories may be attributed to the assumption that the tube constraints imposed on the motion of a chain are fixed, i.e., the chains constituting the tube preserve their position on the time scale of reptation. This is, however, not obvious because the neighboring chains themselves continue reptation within their own tubes. Another important assumption is that the distribution of the molecular weight in the polymer system is very narrow, which is certainly not true for the lung (Fig. 7). The above limitations have been examined and released in a model proposed by Cates (5). He showed that polydispersity leads to a slow macroscopic stress relaxation, the analytic form of which is a highly complicated integral. He chose to approximate this integral by a stretched exponential so that the stress relaxation $g(t)$ was proportional to $\exp[-(t/\tau_d)^{0.25}]$. However, the stretched exponential is almost indistinguishable from the power law relaxation function over many decades of frequency when $\beta$ is appropriately chosen. The approximation of the above stretched exponential requires a $\beta$ of 0.1, which is in good agreement with the values reported for the lung (3, 19, 22). Because stereological measurements show a wide distribution of the length and diameter of the fibers in the collagen and elastin network of the lung (35, 46), reptation with high polydispersity is certainly a good candidate for being at least partly responsible for lung tissue properties.

The molecular theories presented so far are all limited to long coiled but nonbranching polymers. From the works of Mercer and Crapo (35) and Sobin et al. (46), it appears, however, that the collagen and elastin networks of the lung contain many branches (Fig. 7). The static and dynamic properties of branched polymers (often called star-shaped polymers) have been extensively studied both experimentally and theoretically (7, 9, 16, 40). For a star-shaped polymer simple reptation is not possible among fixed obstacles because the arm of the polymer is attached to and fixed at the branching point. It was de Gennes (16) who first pointed out that for such a polymer to relax when stretched in one direction the polymer has to retract its arm along itself. The process is shown in Fig. 8. In equilibrium position all three arms are in their own tube. When the polymer is stretched the branch point is displaced. This is opposed by a strong elastic force trying to bring back the branch point to its original position. This reduces the entropy of the system by storing elastic energy in it. To find its new minimum energy configuration the arm first has to be withdrawn from its tube via Brownian motion to the branch point from where it can form its new tube. When this is completed the entropy defect associated with the side chain is removed. The time required to do so, however, is extremely long because the probability that the end of the arm moves back along itself via Brownian motion is very small. According to de Gennes, the time required to achieve this is exponentially growing with the length of the arm. If the network containing branches and free ends was strained at time $t = 0$, then the time $t$ required

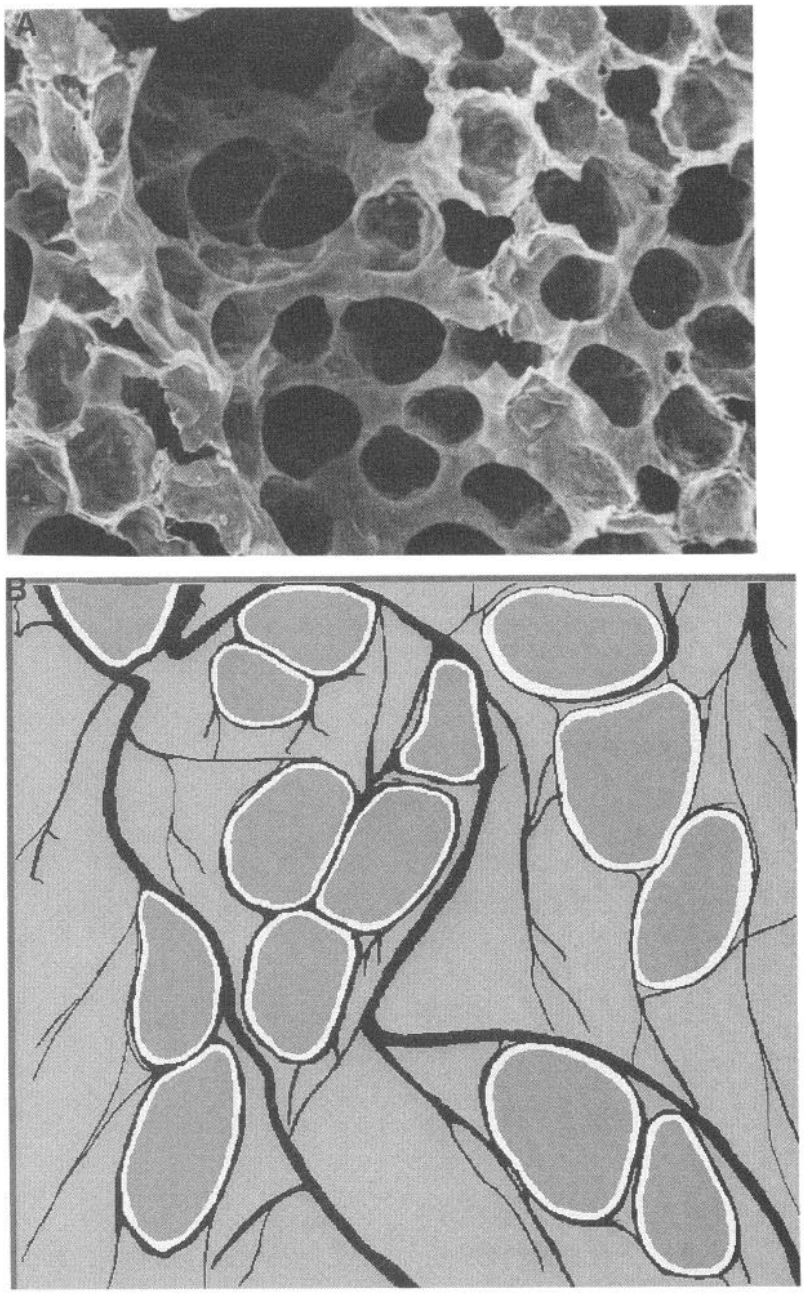

FIG. 7. Arrangement of connective tissue fibers in alveolar openings and surrounding tissues adjacent to alveolar duct. *A*: scanning electron micrograph of vascular perfusion-fixed rat lung (courtesy of Dr. R. R. Mercer). *B*: schematic diagram of connective tissue fiber arrangement [redrawn from Mercer and Crapo (35)]. Elastin fibers (white) form continuous rings encircling each alveolar entrance ring. Collagen fibers (black) form meshlike arrangement. Note variety of fiber lengths and widths as well as many branchings and free ends of fibers.

for $L$ submolecules and hence the total length associated with these side chains to relax by time $t$ is an exponential function of $L$, i.e., $t \cong t_1 \exp(qL)$ where $t_1$ and $q$ are constants. Then $L(t)$ is given by

$$L(t) = q^{-1} \ln \left( \frac{t}{t_1} \right) \tag{21}$$

It is conceivable that the stress remaining in the material after time $t$ is proportional to $L(t)$, giving rise to a relaxation function of the form

$$g(t) = E_0 - F \ln (t) \tag{22}$$

where $E_0$ is an initial elastic modulus and F is proportional to the concentration of the branches or the free ends in the polymer system. The precise calculation of $g(t)$ is rather complicated and can be found elsewhere (40). Although *Eq. 22* is only an approximation, it is still noteworthy that it has exactly the form of *Eq. 1*, which is again indistinguishable from *Eq. 2* over many time decades if the exponent $\beta$ has an appropriate value. We conclude that, based on the architecture of the microstructure of the lung (Fig. 7), slow relaxation of branched polymers is most probably one of the main contributors to lung tissue dynamic properties.

## DISCUSSION

The viscoelastic properties of soft biological tissues and in particular of lung tissues have been reexamined. The simple empirical equations describing stress relaxation (*Eq. 2*) and mechanical impedance (*Eq. 3*) have been put in a concise mathematical framework. We have chosen to describe viscoelasticity in terms of fractional

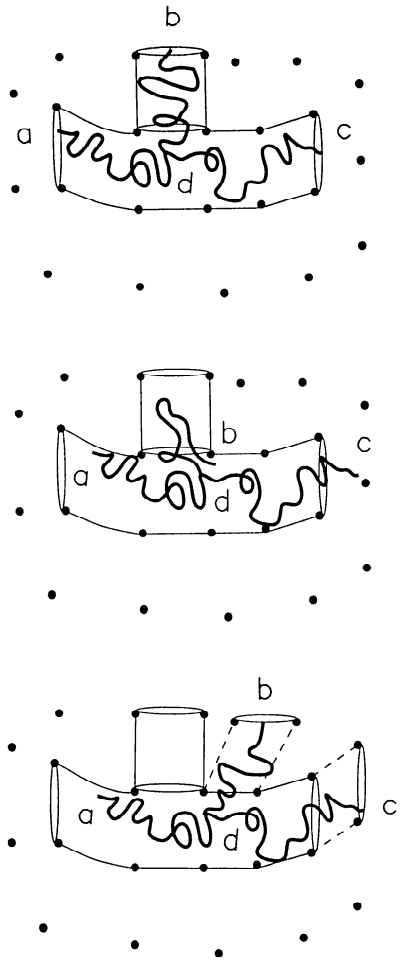


FIG. 8. Reptation of star-shaped polymer in network of obstacles created by other polymers. *Top*: equilibrium configuration. Note positions of 3 ends of arms (*arms a, b, c*) and branch point (*d*). *Middle*: configuration of molecule after applying unit step in strain at end of *arm c*. First, *points c* and *d* are displaced, and then later *point b* is slowly moving backward along itself, which is mechanism providing stress relaxation. *Bottom*: final equilibrium configuration of molecule. *Arm b* has established its new tube.

derivatives, since the solutions of differential equations of fractional order naturally admit functional forms of *Eqs. 2* and *3*. Compared with ordinary differential equations, e.g., that of a Kelvin body, the number of parameters in *Eq. 2* is two and in the spring-pot (*Eq. 18*) is three; yet the description of observed viscoelastic properties is much superior. One of the reasons is that the fractional derivative elements naturally contain a continuous distribution of time constants. One can show that the associated distribution function is proportional to $t^{-\alpha}$. As Fung (14) demonstrated in his theory, a distribution of time constants proportional to $t^{-1}$ over a finite range of time constants is appropriate for many tissues and gives rise to the observed phenomenon that the hysteresis area of the stress-strain curve is quasi-independent of frequency. Because the value of $\alpha$ in the constant-phase model is close to unity, the mechanical behaviors predicted by *Eqs. 2* and *3* and Fung's theory are virtually the same. Thus it may seem that the distinction between the two approaches is unimportant. However, conceptually there is a significant difference between them. Fung's stress relaxation function and dynamic modulus are a consequence of the specific form of the time constant distribution function that was chosen in a rather ad hoc manner. In contrast, the power law stress relaxation and the constant-phase impedance are solutions to equations of motions that, for simple systems such as large solid objects moving in viscous fluid, can be derived from the Navier-Stokes equations (53). Furthermore, these constitutive equations share the common form of stress-strain relationships with those of polymer systems derived from first principles of statistical mechanics and thermodynamics. Thus, we conjecture that the time constant distribution of the constant-phase model for the lung tissues is not arbitrarily chosen but rather a consequence of the specific forms of the equations of motion describing the dynamics at the tissue fiber level.

There have been several attempts to account for the linear and nonlinear elastic behaviors of various soft tissues on their structural basis (29, 30, 47). However, we are aware of only one recent study by Mijailovic et al. (36) that related the macroscopically observed viscoelastic properties of tissues to events at the tissue fiber level. They proposed that the chief mechanism responsible for the macroscopic behavior is the slip of fibers on each other, which results in a plasticlike material behavior. This mechanism can certainly be important in connective tissue dynamics. In this paper we overview several additional mechanisms borrowed from the statistical description of polymer viscoelasticity. Clearly, in view of the limited experimental data in this direction, it would be too speculative to propose a single mechanism fully responsible for the rheological behavior of soft tissues. Nevertheless, we mention one fact to support our ideas. Recently, Debes and Fung (6) found that the Young's and the shear moduli of lung tissue increased by 6% when the tissue was cooled from 40 to 10°C. For low frequencies, the Rouse theory with its extensions and the reptation theory reduce to a form in which the shear modulus is proportional to $1/T$ (7), which predicts that the shear modulus increases by ~10% in the above temperature range.

By examining various aspects of the above molecular theories we can speculate on the origins of several additional observed tissue mechanical properties. For example, one interesting property of the Rouse model is that it predicts that the relaxation function has a term proportional to strain rate and solvent viscosity (*Eq. 19*). In impedance terms it means that the real part of tissue impedance should have a newtonian component. The existence of such a component has been confirmed for the chest wall tissues (19) but not for the lung tissue. It is possible that the newtonian component of lung tissue resistance is negligible compared with the resistance component hyperbolically decreasing with frequency in the frequency range where tissue resistance is usually measured (<5 Hz). The newtonian component of airway wall resistance is, however, measurable by using data at much higher frequencies. Indeed, a newtonian component for the airway wall resistance is relatively well accepted (12). Furthermore, recently it was hypothesized that for the tracheal wall such a newtonian component represents the viscosity of the ground substance (50). This hypothesis is consistent with the Rouse model (43), which pro-

vides it a molecular basis. Another important observation borrowed from polymer systems is that, when one end of the macromolecules is fixed, a term appears in the modulus expression that is purely elastic (37). In the lung such a fixed boundary that maintains the integrity of the structure can be the pleural membrane, which was estimated to give an important ~20% contribution to the quasi-static elasticity of the lung (18, 47). The dynamic contribution of the pleural membrane to lung impedance was shown to be predominantly elastic (51), which is in accord with the above molecular notion. Finally, the last point is related to the relaxation of star polymers. We have seen that after a unit step deformation the stress relaxes quasi-linearly on a logarithmic time scale. However, the entropy defect associated with the trapped side chain disappears as soon as the far end of the side chain completely reverted its way along itself (see Fig. 8). If the strain is now eliminated, the star polymer still maintains its new equilibrium configuration. This then represents a permanent deformation because the arm is displaced with respect to its microenvironment. Such a mechanism therefore leads to static hysteresis and would appear as plasticity at the macroscopic level (48).

*Concluding Remarks*

In this paper we introduced the differential equations of fractional order to provide a concise mathematical framework for using recent empirical equations in lung tissue mechanics (19, 22, 23). The fractional derivative formalism offers simple forms for the relaxation function and impedance, yet they naturally incorporate complicated rheological behavior and thereby remove the single time constant constraint embedded in the classic spring-dashpot systems (e.g., Maxwell or Kelvin bodies). On the basis of molecular theories of polymer viscoelasticity, we also showed that the fractional derivative models are not only empirical. We presented several candidate mechanisms involving linear and branching fibers moving in various environments that all contribute to the macroscopically observable stress-strain relationship in a similar manner: each microscopic mechanism results in a power law relaxation or constant-phase impedance behavior. The proportionality factor in the relaxation function seems to depend on the fiber concentration and meshwork characteristics, whereas the exponent is perhaps more specific to the mechanism most contributing to the relaxation. Soft tissues, however, are also composed of long flexible biopolymer molecules. Moreover, there is morphological evidence that in the lung tissue there are many branching fibers with a wide distribution of their width and length (35, 46). Thus, mechanisms such as reptation in highly polydisperse systems or the relaxation of star-shaped fibers, for example, most probably also exist. This suggest a mechanistic basis for the viscoelasticity of lung tissues as represented by the fractional derivative models.

In addition to the above processes, there are, of course, several other important mechanisms such as the fiber-fiber interactions (36), the absorption-desorption of surface-active molecules (13), or the mechanics of the contractile elements within the parenchyma (11), all of which produce an apparently similar dynamical behavior. To date, unfortunately, no experiments have been reported that would combine macroscopic mechanical testing with microscopic measurements (e.g., light scattering) that could follow the dynamics at the fiber level. Future studies should thus focus on the experimental aspects of soft tissue mechanics to elucidate which are the chief molecular mechanisms contributing to the macroscopic mechanics in the normal and the pathological lung.

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